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of OBSTETRICIANS
and GYNAECOLOGISTS

Bacterial meningitis and meningococcal septicaemia in children

June 2010

NICE Clinical Guideline

National Collaborating Centre for Women's and Children's Health

Bacterial meningitis and meningococcal septicaemia

management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

National Collaborating Centre for
Women's and Children's Health

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Implementation of this guidance is the responsibility of local commissioners and/or providers.

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Appendices E–G are in separate files.

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1 Summary of recommendations and care pathway

Under the Health Protection (Notification) Regulations 2010 (see http://www.opsi.gov.uk/si/si 2010/uksi 20100659 en 1) registered medical practitioners in England have a legal requirement to notify the proper officer of the local authority urgently when they have reasonable grounds for suspecting that a patient has meningitis or meningococcal septicaemia.

The guideline will assume that prescribers will use a drug's summary of product characteristics (SPC) to inform their decisions for individual patients.

1.1 Key priorities for implementation

Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 3.3.

- Be aware that:
  - some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
  - children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia, and the symptoms and signs may become more severe and more specific over time.

Recognise shock (see table 3.3) and manage urgently in secondary care.

Healthcare professionals should be trained in the recognition and management of meningococcal disease.

Management in the pre-hospital setting

Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Diagnosis in secondary care

Investigation and management in children and young people with petechial rash

Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):

- petechiae start to spread
- the rash becomes purpuric
- there are signs of bacterial meningitis (see table 3.3)
- there are signs of meningococcal septicaemia (see table 3.3)
- the child or young person appears ill to a healthcare professional.

Polymerase chain reaction

Perform whole blood real-time PCR testing (ethylenediaminetetraacetic acid [EDTA] sample) for *N. meningitidis* to confirm a diagnosis of meningococcal disease.

Lumbar puncture

In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:

- signs suggesting raised intracranial pressure
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - relative bradycardia and hypertension
  - focal neurological signs
  - abnormal posture or posturing
  - unequal, dilated or poorly responsive pupils
  - papilloedema
  - abnormal 'doll's eye' movements
- shock (see table 3.3)
- extensive or spreading purpura
- after convulsions until stabilised
- coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 10^9/litre
  - receiving anticoagulant therapy
- local superficial infection at the lumbar puncture site
- respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

Management in secondary care

Fluids for bacterial meningitis

Do not restrict fluids unless there is evidence of:

- raised intracranial pressure, **or**
- increased antidiuretic hormone secretion.*

Intravenous fluid resuscitation in meningococcal septicaemia

In children and young people with suspected or confirmed meningococcal septicaemia:

- If there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards.
- If the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes.
- If the signs of shock still persist after the first 40 ml/kg:
  - immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
  - start treatment with vasoactive drugs
  - be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume
  - consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on

* See National Patient Safety Agency (2007) Patient Safety Alert 22: Reducing the Risk of Hyponatraemia when Administering Intravenous Infusions to Children. Available from www.nrls.npsa.nhs.uk

clinical signs and appropriate laboratory investigations including urea and electrolytes.
- Discuss further management with a paediatric intensivist.

Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' [NICE technology appraisal 166]).

Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate services. The following morbidities should be specifically considered:

- hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)
- orthopaedic complications (damage to bones and joints)
- skin complications (including scarring from necrosis)
- psychosocial problems
- neurological and developmental problems
- renal failure.

1.2 Recommendations

Chapter 3 Bacterial meningitis and meningococcal septicaemia in children and young people — symptoms, signs and initial assessment

This guideline assumes that fever in children younger than 5 years will be managed according to 'Feverish illness in children' (NICE clinical guideline 47) until bacterial meningitis or meningococcal septicaemia is suspected.

Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 3.3.

- Be aware that:
  - some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
  - children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia, and the symptoms and signs may become more severe and more specific over time.
- Recognise shock (see table 3.3) and manage urgently in secondary care.

Table 3.3. Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Symptom/sign	Bacterial meningitis (meningococcal meningitis and meningitis caused by other bacteria)	Meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia)	Meningococcal septicaemia	Notes
Common non-specific symptoms/signs				
Fever	✓	✓	✓	Not always present, especially in neonates
Vomiting/nausea	✓	✓	✓	
Lethargy	✓	✓	✓	

Irritable/unsettled	✓	✓	✓	
Ill appearance	✓	✓	✓	
Refusing food/drink	✓	✓	✓	
Headache	✓	✓	✓	
Muscle ache/joint pain	✓	✓	✓	
Respiratory symptoms/signs or breathing difficulty	✓	✓	✓	
Less common non-specific symptoms/signs				
Chills/shivering	✓	✓	✓	
Diarrhoea, abdominal pain/distension	✓	✓	NK	
Sore throat/coryza or other ear, nose and throat symptoms/signs	✓	✓	NK	
More specific symptoms/signs				
Non-blanching rash	✓	✓	✓	Be aware that a rash may be less visible in darker skin tones – check soles of feet, palms of hands and conjunctivae
Stiff neck	✓	✓	NK	
Altered mental state	✓	✓	✓	Includes confusion, delirium and drowsiness, and impaired consciousness
Capillary refill time more than 2 seconds	NK	✓	✓	
Unusual skin colour	NK	✓	✓	
Shock	✓	✓	✓	
Hypotension	NK	✓	✓	
Leg pain	NK	✓	✓	
Cold hands/feet	NK	✓	✓	
Back rigidity	✓	✓	NK	
Bulging fontanelle	✓	✓	NK	Only relevant in children aged under 2 years
Photophobia	✓	✓	X	
Kernig's sign	✓	✓	X	
Brudzinski's sign	✓	✓	X	
Unconsciousness	✓	✓	✓	
Toxic/moribund state	✓	✓	✓	
Paresis	✓	✓	X	
Focal neurological deficit including cranial nerve involvement and abnormal pupils	✓	✓	X	
Seizures	✓	✓	X	

Signs of shock

- Capillary refill time more than 2 seconds
- Unusual skin colour
- Tachycardia and/or hypotension
- Respiratory symptoms or breathing difficulty

• Leg pain • Cold hands/feet • Toxic/moribund state • Altered mental state/decreased conscious level • Poor urine output
✓ symptom/sign present X symptom/sign not present NK not known if a symptom/sign is present (not reported in the evidence)

Be alert to the possibility of bacterial meningitis or meningococcal septicaemia when assessing children or young people with acute febrile illness.

Healthcare professionals should be aware that classical signs of meningitis (neck stiffness, bulging fontanelle, high-pitched cry) are often absent in infants with bacterial meningitis.*

Be aware that children and young people with bacterial meningitis commonly present with non-specific symptoms and signs, including fever, vomiting, irritability, and upper respiratory tract symptoms. Some children with bacterial meningitis present with seizures.*

Consider other non-specific features of the child's or young person's presentation, such as:

- the level of parental or carer concern (particularly compared with previous illness in the child or young person or their family),
- how quickly the illness is progressing, **and**
- clinical judgement of the overall severity of the illness.

In children and young people with suspected bacterial meningitis or meningococcal septicaemia, undertake and record physiological observations of heart rate, respiratory rate, oxygen saturations, blood pressure, temperature, perfusion (capillary refill) and neurological assessment (for example the Alert, Voice, Pain, Unresponsive [AVPU] scale) at least hourly.

Healthcare professionals should be trained in the recognition and management of meningococcal disease.

Notify a proper officer of the local authority urgently on suspicion of meningitis or meningococcal septicaemia. This is a legal requirement under the Health Protection (Notification) Regulations 2010.†

Be aware of 'Guidance for Public Health Management of Meningococcal Disease in the UK' (Health Protection Agency Meningococcus Forum, 2006).‡

Chapter 4 Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Suspected bacterial meningitis without non-blanching rash

Transfer children and young people with suspected bacterial meningitis without non-blanching rash directly to secondary care without giving parenteral antibiotics.

If urgent transfer to hospital is not possible (for example, in remote locations or adverse weather conditions), administer antibiotics to children and young people with suspected bacterial meningitis.

* This recommendation is from 'Feverish illness in children' (NICE clinical guideline 47). See www.nice.org.uk/guidance/CG47

† See www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health Protection Legislation Guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH_114510

‡ See www.hpa.org.uk

Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia)

Give parenteral antibiotics (intramuscular or intravenous benzylpenicillin) at the earliest opportunity, either in primary or secondary care, but do not delay urgent transfer to hospital to give the parenteral antibiotics.

Withhold benzylpenicillin only in children and young people who have a clear history of anaphylaxis after a previous dose; a history of a rash following penicillin is not a contraindication.

Chapter 5 Diagnosis in secondary care

Perform a very careful examination for signs of meningitis or septicaemia in children and young people presenting with petechial rashes (see table 3.3).

Investigation and management in children and young people with petechial rash

Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):

- petechiae start to spread
- the rash becomes purpuric
- there are signs of bacterial meningitis (see table 3.3)
- there are signs of meningococcal septicaemia (see table 3.3)
- the child or young person appears ill to a healthcare professional.

If a child or young person has an unexplained petechial rash and fever (or history of fever) carry out the following investigations:

- full blood count
- C-reactive protein (CRP)
- coagulation screen
- blood culture
- whole-blood polymerase chain reaction (PCR) for *N. meningitidis*
- blood glucose
- blood gas.

In a child or young person with an unexplained petechial rash and fever (or history of fever) but none of the high-risk clinical manifestations (see table 3.3):

- Treat with intravenous ceftriaxone immediately if the CRP and/or white blood cell count (especially neutrophil count) is raised, as this indicates an increased risk of having meningococcal disease.
- Be aware that while a normal CRP and normal white blood cell count mean meningococcal disease is less likely, they do not rule it out. The CRP may be normal and the white blood cell count normal or low even in severe meningococcal disease.
- Assess clinical progress by monitoring vital signs (respiratory rate, heart rate, blood pressure, conscious level [Glasgow Coma Scale and/or APVU], temperature), capillary refill time, and oxygen saturations. Carry out observations at least hourly over the next 4–6 hours.
- If doubt remains, treat with antibiotics and admit to hospital.

If the child or young person is assessed as being at low risk of meningococcal disease and is discharged after initial observation, advise parents or carers to return to hospital if the child or young person appears ill to them.

Be aware that in children and young people who present with a non-spreading petechial rash without fever (or history of fever) who do not appear ill to a healthcare professional, meningococcal disease is unlikely, especially if the rash has been present for more than 24 hours. In such cases consider:

- other possible diagnoses
- performing a full blood count and coagulation screen.

Investigation and management in children and young people with suspected bacterial meningitis

In children and young people with suspected bacterial meningitis, perform a CRP and white blood cell count:

- If the CRP and/or white blood cell count is raised and there is a non-specifically abnormal cerebrospinal fluid (CSF) (for example consistent with viral meningitis), treat as bacterial meningitis.
- Be aware that a normal CRP and white blood cell count does not rule out bacterial meningitis.
- Regardless of the CRP and white blood cell count, if no CSF is available for examination or if the CSF findings are uninterpretable, manage as if the diagnosis of meningitis is confirmed.

Polymerase chain reaction (PCR) tests for bacterial meningitis and meningococcal disease

Perform whole blood real-time PCR testing (ethylenediaminetetraacetic acid [EDTA] sample) for *N. meningitidis* to confirm a diagnosis of meningococcal disease.

The PCR blood sample should be taken as soon as possible because early samples are more likely to be positive.

Use PCR testing of blood samples from other hospital laboratories if available, to avoid repeating the test.

Be aware that a negative blood PCR test result for *N. meningitidis* does not rule out meningococcal disease.

Submit CSF to the laboratory to hold for PCR testing for *N. meningitidis* and *S. pneumoniae*, but only perform the PCR testing if the CSF culture is negative.

Be aware that CSF samples taken up to 96 hours after admission to hospital may give useful results.

Skin samples and throat swabs for meningococcal disease

Do not use any of the following techniques when investigating for possible meningococcal disease: skin scrapings, skin biopsies, petechial or purpuric lesion aspirates (obtained with a needle and syringe), or throat swabs.

Performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis

Perform a lumbar puncture as a primary investigation unless this is contraindicated.

Do not allow lumbar puncture to delay the administration of parenteral antibiotics.

CSF examination should include white blood cell count and examination, total protein and glucose concentrations, Gram stain and microbiological culture. A corresponding laboratory-determined blood glucose concentration should be measured.

In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:

- signs suggesting raised intracranial pressure
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - relative bradycardia and hypertension
  - focal neurological signs
  - abnormal posture or posturing
  - unequal, dilated or poorly responsive pupils
  - papilloedema
  - abnormal 'doll's eye' movements
- shock (see table 3.3)
- extensive or spreading purpura

- after convulsions until stabilised
- coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 10^9/litre
  - receiving anticoagulant therapy
- local superficial infection at the lumbar puncture site
- respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

In children and young people with suspected bacterial meningitis, if contraindications to lumbar puncture exist at presentation consider delaying lumbar puncture until there are no longer contraindications. Delayed lumbar puncture is especially worthwhile if there is diagnostic uncertainty or unsatisfactory clinical progress.

CSF white blood cell counts, total protein and glucose concentrations should be made available within 4 hours to support the decision regarding adjunctive steroid therapy.

Start antibiotic treatment for bacterial meningitis if the CSF white blood cell count is abnormal:

- in neonates at least 20 cells/microlitre (be aware that even if fewer than 20 cells/microlitre, bacterial meningitis should still be considered if other symptoms and signs are present – see table 3.3)
- in older children and young people more than 5 cells/microlitre or more than 1 neutrophil/microlitre, regardless of other CSF variables.

In children and young people with suspected bacterial meningitis, consider alternative diagnoses if the child or young person is significantly ill and has CSF variables within the accepted normal ranges.

Consider herpes simplex encephalitis as an alternative diagnosis.

If CSF white cell count is increased and there is a history suggesting a risk of tuberculous meningitis, evaluate for the diagnosis of tuberculous meningitis in line with 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' (NICE clinical guideline 33).

Perform a repeat lumbar puncture in neonates with:

- persistent or re-emergent fever
- deterioration in clinical condition
- new clinical findings (especially neurological findings) or persistently abnormal inflammatory markers.

Do not perform a repeat lumbar puncture in neonates:

- who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery
- before stopping antibiotic therapy if they are clinically well.

Cranial computed tomography in suspected bacterial meningitis

Use clinical assessment and not cranial computed tomography (CT) to decide whether it is safe to perform a lumbar puncture. CT is unreliable for identifying raised intracranial pressure.

If a CT scan has been performed, do not perform a lumbar puncture if the CT scan shows radiological evidence of raised intracranial pressure.

In children and young people with a reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more) or with focal neurological signs, perform a CT scan to detect alternative intracranial pathology.

Do not delay treatment to undertake a CT scan.

Clinically stabilise children and young people before CT scanning.

If performing a CT scan consult an anaesthetist, paediatrician or intensivist.

Chapter 6 Management in secondary care

Antibiotics for suspected bacterial meningitis or meningococcal disease

Treat children and young people aged 3 months or older with suspected bacterial meningitis without delay using intravenous ceftriaxone.

Treat children younger than 3 months with suspected bacterial meningitis without delay using intravenous cefotaxime plus either amoxicillin or ampicillin.

Treat suspected meningococcal disease without delay using intravenous ceftriaxone.

Treat children and young people with suspected bacterial meningitis who have recently travelled outside the UK or have had prolonged or multiple exposure to antibiotics (within the past 3 months) with vancomycin in addition to the above antibiotics.

Where ceftriaxone is used, do not administer it at the same time as calcium-containing infusions. Instead, use cefotaxime.[*]

In children younger than 3 months, ceftriaxone may be used as an alternative to cefotaxime (with or without ampicillin or amoxicillin), but be aware that ceftriaxone should not be used in premature babies or in babies with jaundice, hypoalbuminaemia or acidosis as it may exacerbate hyperbilirubinaemia.

If tuberculous meningitis is part of the differential diagnosis use antibiotic treatment appropriate for tuberculous meningitis in line with 'Tuberculosis' (NICE clinical guideline 33).

If herpes simplex meningoencephalitis is part of the differential diagnosis give appropriate antiviral treatment.

Treatment for specific infections in confirmed bacterial meningitis

Children and young people aged 3 months or older

Treat *H. influenzae* type b meningitis with intravenous ceftriaxone for 10 days in total unless directed otherwise by the results of antibiotic sensitivities.

Treat *S. pneumoniae* meningitis with intravenous ceftriaxone for 14 days in total unless directed otherwise by the results of antibiotic sensitivities.

Children younger than 3 months

Treat Group B streptococcal meningitis with intravenous cefotaxime for at least 14 days. If the clinical course is complicated[†] consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Treat bacterial meningitis due to *L. monocytogenes* with intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first 7 days.

Treat bacterial meningitis due to Gram-negative bacilli with intravenous cefotaxime for at least 21 days unless directed otherwise by the results of antibiotic sensitivities. If the clinical course is complicated[†] consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Treatment of unconfirmed bacterial meningitis

In children and young people aged 3 months or older with unconfirmed, uncomplicated but clinically suspected bacterial meningitis, treat with intravenous ceftriaxone for at least 10 days depending on symptoms and signs and course of the illness.

In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. If

[*] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update: Volume 3, Issue 3. Available from www.mhra.gov.uk

[†] For example, if there is poor response to antibiotic therapy, effusion or abscess, or concomitant intraventricular haemorrhage in a premature baby.

the clinical course is complicated,* consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Meningococcal disease

In children and young people with confirmed meningococcal disease, treat with intravenous ceftriaxone for 7 days in total unless directed otherwise by the results of antibiotic sensitivities.

In children and young people with unconfirmed but clinically suspected meningococcal disease, treat with intravenous ceftriaxone for 7 days in total.

Other aspects of management in bacterial meningitis and meningococcal septicaemia

Metabolic disturbances

In children and young people with suspected or confirmed meningococcal septicaemia, anticipate, monitor and correct the following metabolic disturbances using local or national protocols:

- hypoglycaemia
- acidosis
- hypokalaemia
- hypocalcaemia
- hypomagnesaemia
- anaemia
- coagulopathy.

Seizures

Use local or national protocols for management of seizures in children and young people with suspected bacterial meningitis or meningococcal septicaemia.

Raised intracranial pressure

Use local or national protocols to treat raised intracranial pressure.

Fluid management in suspected or confirmed bacterial meningitis

Assess for all of the following:

- signs of shock (see table 3.3)
- raised intracranial pressure
- signs of dehydration.

Refer to 'Diarrhoea and vomiting in children' (NICE clinical guideline 84) for assessment of shock and dehydration.

If present, correct dehydration using enteral fluids or feeds, or intravenous isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with dextrose 5%).

Do not restrict fluids unless there is evidence of:

- raised intracranial pressure, **or**
- increased antidiuretic hormone secretion.*

Give full-volume maintenance fluids to avoid hypoglycaemia and maintain electrolyte balance.

Use enteral feeds as maintenance fluid if tolerated.

If intravenous maintenance fluid is required, use isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with dextrose 5%). In neonates, use glucose 10% and added sodium chloride for maintenance.

* See National Patient Safety Agency (2007) Patient Safety Alert 22: Reducing the Risk of Hyponatraemia when Administering Intravenous Infusions to Children. Available from www.nrls.npsa.nhs.uk

Monitor fluid administration and urine output to ensure adequate hydration and avoid overhydration.

Monitor electrolytes and blood glucose regularly (at least daily while the child or young person is receiving intravenous fluids).

If there are signs of raised intracranial pressure or evidence of shock, initiate emergency management for these conditions and discuss ongoing fluid management with a paediatric intensivist.

Intravenous fluid resuscitation in meningococcal septicaemia

In children and young people with suspected or confirmed meningococcal septicaemia:

- If there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards.
- If the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes.
- If the signs of shock still persist after the first 40 ml/kg:
  - immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
  - start treatment with vasoactive drugs
  - be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume
  - consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes.
- Discuss further management with a paediatric intensivist.

Vasoactive therapy for shock in meningococcal septicaemia

If shock persists despite fluid resuscitation (more than 40 ml/kg) and treatment with either intravenous adrenaline or intravenous noradrenaline, or both, consider potential reasons (such as persistent acidosis, incorrect dilution, extravasation) and discuss further management options with a paediatric intensivist.

Use local or national protocols for the administration of vasoactive agents in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

Respiratory support in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia

In self-ventilating children and young people with signs of respiratory distress, administer 15-litre face mask oxygen via a reservoir rebreathing mask.

If there is a threatened loss of airway patency, implement airway-opening manoeuvres, and start bag–valve mask ventilation in preparation for tracheal intubation.

A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

Be aware that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are very ill and at grave risk of sudden deterioration during intubation. Anticipate aspiration, pulmonary oedema or worsening shock during intubation.

Ensure that they are nil by mouth from admission to hospital and that the following are available before intubation:

- facilities to administer fluid boluses
- appropriate vasoactive drugs
- access to a healthcare professional experienced in the management of critically ill children.

Undertake tracheal intubation and mechanical ventilation for the following indications:

- threatened (for example, loss of gag reflex), or actual loss of airway patency
- the need for any form of assisted ventilation, for example bag–mask ventilation
- clinical observation of increasing work of breathing
- hypoventilation or apnoea
- features of respiratory failure, including:
  - irregular respiration (for example, Cheyne–Stokes breathing)
  - hypoxia (PaO_2 less than 13 kPa or 97.5 mmHg) or decreased oxygen saturations in air
  - hypercapnia ($PaCO_2$ greater than 6 kPa or 45 mmHg)
- continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- signs of raised intracranial pressure
- impaired mental status:
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - moribund state
- control of intractable seizures
- need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit or another hospital.

Use local or national protocols for intubation.

Corticosteroids

Bacterial meningitis

Do not use corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis.

Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[*] for suspected or confirmed bacterial meningitis as soon as possible if lumbar puncture reveals any of the following:

- frankly purulent CSF
- CSF white blood cell count greater than 1000/microlitre
- raised CSF white blood cell count with protein concentration greater than 1 g/litre
- bacteria on Gram stain.

If tuberculous meningitis is in the differential diagnosis, refer to 'Tuberculosis' (NICE clinical guideline 33) before administering steroids, because steroids may be harmful if given without antituberculous therapy.

If dexamethasone was not given before or with the first dose of antibiotics, but was indicated, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics.

After the first dose of dexamethasone discuss the decision to continue dexamethasone with a senior paediatrician.

Meningococcal septicaemia

Do not treat with high-dose corticosteroids (defined as dexamethasone 0.6 mg/kg/day or an equivalent dose of other corticosteroids).

[*] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice. The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Dexamethasone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

In children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 0.25 mg/m^2 four times daily)[*] should be used only when directed by a paediatric intensivist.

Adjunctive therapies

Do not use activated protein C or recombinant bacterial permeability-increasing protein in children and young people with meningococcal septicaemia.

Monitoring for deterioration for meningococcal disease

Monitor children and young people closely after admission to hospital for signs of deterioration (monitor respiration, pulse, blood pressure, oxygen saturation and Glasgow Coma Scale score).

Be aware that children and young people with meningococcal disease can deteriorate rapidly, regardless of the results of any initial assessment of severity.

Retrieval and transfer to tertiary care

Children and young people who need resuscitation should be discussed with a paediatric intensivist as soon as possible.

Transfer of children and young people to tertiary care should be undertaken by an experienced paediatric intensive care retrieval team comprising medical and nursing staff.

Chapter 7 Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

Before discharging children and young people from hospital:

- consider their requirements for follow-up, taking into account potential sensory, neurological, psychosocial, orthopaedic, cutaneous and renal morbidities, **and**
- discuss potential long-term effects of their condition and likely patterns of recovery with the child or young person and their parents or carers, and provide them with opportunities to discuss issues and ask questions.

Offer children and young people and their parents or carers:

- information about and access to further care immediately after discharge, **and**
- contact details of patient support organisations including meningitis charities that can offer support, befriending, in-depth information, advocacy, counselling, and written information to signpost families to further help, **and**
- advice on accessing future care.

Offer a formal audiological assessment as soon as possible, preferably before discharge, within 4 weeks of being fit to test.

Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' [NICE technology appraisal 166]).

Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate services. The following morbidities should be specifically considered:

- hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)

[*] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice. The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Hydrocortisone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

- orthopaedic complications (damage to bones and joints)
- skin complications (including scarring from necrosis)
- psychosocial problems
- neurological and developmental problems
- renal failure.

Inform the child's or young person's GP, health visitor and school nurse (for school-age children and young people) about their bacterial meningitis or meningococcal septicaemia.

Healthcare professionals with responsibility for monitoring the child's or young person's health should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects of bacterial meningitis and meningococcal septicaemia.

Immune testing

Test children and young people for complement deficiency if they have had either:

- more than one episode of meningococcal disease, **or**
- one episode of meningococcal disease caused by serogroups other than B (for example, A, C, Y, W135, X, 29E), **or**
- meningococcal disease caused by any serogroup and a history of other recurrent or serious bacterial infections.

Children and young people with recurrent episodes of meningococcal disease should be assessed by a specialist in infectious disease or immunology.

Do not test children and young people for complement deficiency who have had either:

- a single episode of meningococcal disease caused by serogroup B meningococcus, **or**
- unconfirmed meningococcal disease.

Discuss appropriate testing for complement deficiency with local immunology laboratory staff.

If a child or young person who has had meningococcal disease has a family history of meningococcal disease or complement deficiency, test the child or young person for complement deficiency.

If a child or young person who has had meningococcal disease is found to have complement deficiency, test their parents and siblings for complement deficiency.

Refer children and young people with complement deficiency to a healthcare professional with expertise in the management of the condition.

Do not test children and young people for immunoglobulin deficiency if they have had meningococcal disease, unless they have a history suggestive of an immunodeficiency (that is, a history of serious, persistent, unusual, or recurrent infections).

1.3 Key priorities for research

Symptoms and signs of bacterial meningitis and meningococcal disease

What are the symptoms and signs of bacterial meningitis and meningococcal disease in children and young people aged under 16 years that differentiate between these conditions and minor self-limiting infections (including those characterised by fever)?

Why this is important

Research is needed from primary and secondary care settings on the diagnostic accuracy of symptoms and signs suggestive of bacterial meningitis and meningococcal disease in children and young people. The research should focus on identifying individual symptoms and signs, or groups of symptoms and signs that are effective as predictors of bacterial meningitis and meningococcal disease. These symptoms and signs should also differentiate effectively between these conditions and minor self-limiting infections. The research should include consideration of the effectiveness of symptoms and signs of acute feverish illness as

predictors of meningococcal disease. Consideration should also be given to the age of the child or young person (in terms of the relevance of particular symptoms and signs) and the clinical setting at presentation. Suitable study designs would include diagnostic accuracy studies as well as observational studies (such as case–control studies), and the research could include a systematic review of studies that have already been published.

Predictive value of blood test results and CSF findings

What are the normal ranges for blood and CSF parameters in children and young people in the UK?

Why this is important

Bacterial meningitis is a rare disease that is not easily distinguishable clinically from aseptic meningitis. It is, however, important to recognise those children who are most likely to have bacterial meningitis to direct appropriate management of the condition and to avoid inappropriate treatment of aseptic meningitis. Since the introduction of vaccines to protect against Hib, meningococcus serogroup C and pneumococcus, no high-quality studies involving previously healthy children and young people have been conducted in the UK to determine normal ranges for blood test results or CSF findings in bacterial and aseptic meningitis. Such studies are needed to provide reference values to help interpret blood test results and CSF findings in children (especially neonates) and young people with suspected bacterial meningitis.

Albumin and crystalloid solutions for fluid resuscitation

How effective is albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock?

Why this is important

There are theoretical reasons why albumin solution may be more effective than crystalloid solution in children and young people with septic shock. However, no clinical studies have evaluated the effectiveness of albumin solution in children and young people with meningococcal disease. Concerns about the safety of colloids such as albumin solution led to a widespread change in clinical practice in the 1990s to using crystalloid solutions, despite a lack of evidence of equivalent effectiveness. Although albumin solution is considerably more expensive than crystalloid solution, a small additional benefit of albumin over crystalloid (one death prevented in more than 14,000 treated cases) would make the use of albumin solution cost effective. Randomised controlled trials are therefore needed to compare the effectiveness of albumin and crystalloid solutions in children and young people with septic shock.

Adjunctive corticosteroid treatment

What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis?

Why this is important

Neonatal bacterial meningitis is associated with high morbidity, despite the availability of antibiotics that are highly effective against the leading causes of bacterial meningitis in this age group. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms. Corticosteroids are effective as an adjunct to antibiotic treatment in older children with meningitis caused by Hib, and in adults with bacterial meningitis. However, there is insufficient evidence to support a recommendation for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the spectrum of organisms causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same. A large-scale randomised controlled trial is therefore needed to compare the effectiveness of antibiotic treatment plus corticosteroids with antibiotic treatment alone in neonates with suspected or confirmed bacterial meningitis.

Steroid replacement treatment

How effective is steroid replacement treatment in children and young people with vasopressor-unresponsive shock caused by septicaemia, including meningococcal septicaemia?

Why this is important

Well-conducted but relatively small randomised controlled trials involving adults only suggest that low-dose corticosteroid replacement treatment may ameliorate haemodynamic failure and inflammatory dysregulation associated with severe sepsis. Such treatment may also improve outcomes following septic shock. Severe sepsis in children and young people differs from that in adults, in that multiple-organ dysfunction is less common in children and young people, and mortality is lower. A randomised controlled trial involving children and young people is needed to evaluate the effectiveness of corticosteroid replacement treatment. Studies involving adults only suggest that those with normal adrenal function have worse outcomes if they receive steroids than those with adrenal dysfunction, and so the proposed trial should consider whether testing for adrenal dysfunction before starting steroid replacement treatment improves outcomes.

1.4 Research recommendations

Chapter 3 Bacterial meningitis and meningococcal septicaemia in children and young people — symptoms, signs and initial assessment

What are the symptoms and signs of bacterial meningitis and meningococcal disease in children and young people aged under 16 years that differentiate between these conditions and minor self-limiting infections (including those characterised by fever)?

Why this is important

Research is needed from primary and secondary care settings on the diagnostic accuracy of symptoms and signs suggestive of bacterial meningitis and meningococcal disease in children and young people. The research should focus on identifying individual symptoms and signs, or groups of symptoms and signs that are effective as predictors of bacterial meningitis and meningococcal disease. These symptoms and signs should also differentiate effectively between these conditions and minor self-limiting infections. The research should include consideration of the effectiveness of symptoms and signs of acute feverish illness as predictors of meningococcal disease. Consideration should also be given to the age of the child or young person (in terms of the relevance of particular symptoms and signs) and the clinical setting at presentation. Suitable study designs would include diagnostic accuracy studies as well as observational studies (such as case–control studies), and the research could include a systematic review of studies that have already been published.

Chapter 4 Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

Does the administration of pre-hospital antibiotics improve outcomes in children and young people with suspected meningococcal disease?

Why this is important

The GDG has recommended administration of antibiotics (benzylpenicillin) for children and young people with suspected meningococcal disease in the pre-hospital setting, in accordance with advice issued by the Chief Medical Officer (PL/CMO/99/1). However, no evidence was identified to indicate whether such practice improves outcomes. Research is needed to evaluate the effectiveness of administering antibiotics in the pre-hospital setting. Suitable research designs would include observational studies (e.g. cohort studies or case–control studies) to compare outcomes in children and young people with suspected meningococcal disease according to whether or not they receive antibiotics before admission to hospital. The studies could evaluate the effect of immediate versus delayed administration of antibiotics and comparison of outcomes in children and young people in whom

meningococcal disease is confirmed after hospital admission, and those in whom an alternative diagnosis is made.

Chapter 5 Diagnosis in secondary care

Performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis

What are the normal ranges for blood and CSF parameters in children and young people in the UK?

Why this is important

Bacterial meningitis is a rare disease that is not easily distinguishable clinically from aseptic meningitis. It is, however, important to recognise those children who are most likely to have bacterial meningitis to direct appropriate management of the condition and to avoid inappropriate treatment of aseptic meningitis. Since the introduction of vaccines to protect against Hib, meningococcus serogroup C and pneumococcus, no high-quality studies involving previously healthy children and young people have been conducted in the UK to determine normal ranges for blood test results or CSF findings in bacterial and aseptic meningitis. Such studies are needed to provide reference values to help interpret blood test results and CSF findings in children (especially neonates) and young people with suspected bacterial meningitis.

Does repeat lumbar puncture in neonates with bacterial meningitis alter the prognosis?

Why this is important

Bacterial meningitis in neonates differs from bacterial meningitis in older children in several ways, including the causative organisms and the risk of relapse even after a long course of antibiotics (with the risk being greater in neonates). This has led some healthcare professionals to repeat lumbar puncture before stopping antibiotic treatment to ensure that the CSF is sterile. The GDG found no evidence from which to evaluate the effectiveness of repeat lumbar puncture for preventing relapse of bacterial meningitis in neonates. A study is required in neonates with documented bacterial meningitis to determine what factors are associated with relapse and whether repeat lumbar puncture alters the prognosis. All neonates included in the study would need to receive a specified antibiotic regimen (tailored to the causative pathogen), involving similar dosages, dosing intervals and duration of treatment. The following data should be collected for each neonate in the study: signs and symptoms, blood test results (inflammatory markers), CSF findings (microbiology and chemistry) and central nervous system imaging. All variables should be measured at the start and end of treatment. Follow up should continue for 1 month after stopping antibiotic treatment, and longer-term follow-up (at 2 years) should also be conducted. Any deterioration in clinical condition should prompt a full clinical assessment, blood analysis, lumbar puncture, and imaging, from which it will be possible to evaluate the risk of relapse according to whether or not repeat lumbar puncture is undertaken.

Chapter 6 Management in secondary care

Antibiotics for suspected bacterial meningitis or meningococcal disease

In children and young people what are the risk factors for meningitis and septicaemia caused by cephalosporin-resistant strains of pneumococcus?

Why this is important

Although serious invasive disease due to cephalosporin-resistant pneumococci is rare in the UK, the recommended regimen for empiric antibiotic treatment of suspected meningitis and septicaemia in children and young people will not treat cephalosporin-resistant pneumococci adequately. A delay in starting suitable alternative treatment (vancomycin with or without rifampicin) may result in worse outcomes. The ability to identify at presentation those children and young people who are likely to be infected with cephalosporin-resistant strains of pneumococcus would ensure that optimal antibiotic treatment could be started as soon as possible. Additionally, the ability to confidently exclude the possibility of cephalosporin-

resistant pneumococci would mean that potentially toxic empiric antibiotic treatment could be avoided. Resistance of pneumococcus to penicillin is generally higher in: countries other than the UK; children who have been exposed to oral or parenteral antibiotics recently (for example, in the previous 3 months), over a prolonged period of time, or on multiple occasions; and children with underlying health problems. The current evidence base is insufficient to determine accurately the risks of cephalosporin-resistant pneumococcal infection according to the duration, number, or type of antibiotic treatment, or the time period over which previous antibiotic exposure or foreign travel is relevant. Large-scale epidemiological studies (for example, cohort studies or case–control studies) are needed to evaluate these risks.

Intravenous fluid resuscitation in meningococcal septicaemia

How effective is albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock?

Why this is important

There are theoretical reasons why albumin solution may be more effective than crystalloid solution in children and young people with septic shock. However, no clinical studies have evaluated the effectiveness of albumin solution in children and young people with meningococcal disease. Concerns about the safety of colloids such as albumin solution led to a widespread change in clinical practice in the 1990s to using crystalloid solutions, despite a lack of evidence of equivalent effectiveness. Although albumin solution is considerably more expensive than crystalloid solution, a small additional benefit of albumin over crystalloid (one death prevented in more than 14,000 treated cases) would make the use of albumin solution cost effective. Randomised controlled trials are therefore needed to compare the effectiveness of albumin and crystalloid solutions in children and young people with septic shock.

Corticosteroids

Bacterial meningitis

What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis?

Why this is important

Neonatal bacterial meningitis is associated with high morbidity, despite the availability of antibiotics that are highly effective against the leading causes of bacterial meningitis in this age group. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms. Corticosteroids are effective as an adjunct to antibiotic treatment in older children with meningitis caused by Hib, and in adults with bacterial meningitis. However, there is insufficient evidence to support a recommendation for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the spectrum of organisms causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same. A large-scale randomised controlled trial is therefore needed to compare the effectiveness of antibiotic treatment plus corticosteroids with antibiotic treatment alone in neonates with suspected or confirmed bacterial meningitis.

Meningococcal septicaemia

How effective is steroid replacement treatment in children and young people with vasopressor-unresponsive shock caused by septicaemia, including meningococcal septicaemia?

Why this is important

Well-conducted but relatively small randomised controlled trials involving adults only suggest that low-dose corticosteroid replacement treatment may ameliorate haemodynamic failure and inflammatory dysregulation associated with severe sepsis. Such treatment may

also improve outcomes following septic shock. Severe sepsis in children and young people differs from that in adults, in that multiple-organ dysfunction is less common in children and young people, and mortality is lower. A randomised controlled trial involving children and young people is needed to evaluate the effectiveness of corticosteroid replacement treatment. Studies involving adults only suggest that those with normal adrenal function have worse outcomes if they receive steroids than those with adrenal dysfunction, and so the proposed trial should consider whether testing for adrenal dysfunction before starting steroid replacement treatment improves outcomes.

Adjunctive therapies

Does early intervention with anti-endotoxin treatments such as recombinant bactericidal permeability-increasing protein improve outcomes in children and young people with severe meningococcal septicaemia?

Why this is important

Disease progression in meningococcal septicaemia is rapid and so anti-endotoxin treatment is likely to be effective only if it is given early in the course of disease. A multi-centre randomised controlled trial involving children and young people with severe sepsis reported that the mean time of delivery of recombinant bactericidal permeability-increasing protein rBPI21 was 5.9 hours after receiving initial antibiotic treatment. The results of the trial suggest that rBPI21 might be more effective if given earlier in the course of the disease, such as when meningococcal septicaemia is first diagnosed and treated in the emergency department, or within 2 hours of giving intravenous antibiotics. A further randomised controlled trial is needed to evaluate the effectiveness of such practice in children and young people with severe meningococcal septicaemia.

Monitoring for deterioration for meningococcal disease

Are severity scoring systems useful for directing clinical management of suspected or confirmed meningococcal disease in children and young people?

Why this is important

Scoring systems are used widely in clinical research to classify the severity of suspected or confirmed meningococcal disease in children and young people. They are also used in clinical practice in some areas of the UK. Such systems can be applied relatively easily at presentation, and sequentially thereafter. If severity scoring systems can be used to identify changes in clinical condition that would direct clinical management to improve outcomes they could have widespread applicability in clinical practice. Studies are, therefore, needed to evaluate the usefulness of severity scoring systems for meningococcal disease in children and young people. The outcomes evaluated in the studies should include mortality and morbidity; they could also include satisfaction with care among children and young people, their parents or carers and other family members.

Chapter 7 Long-term management

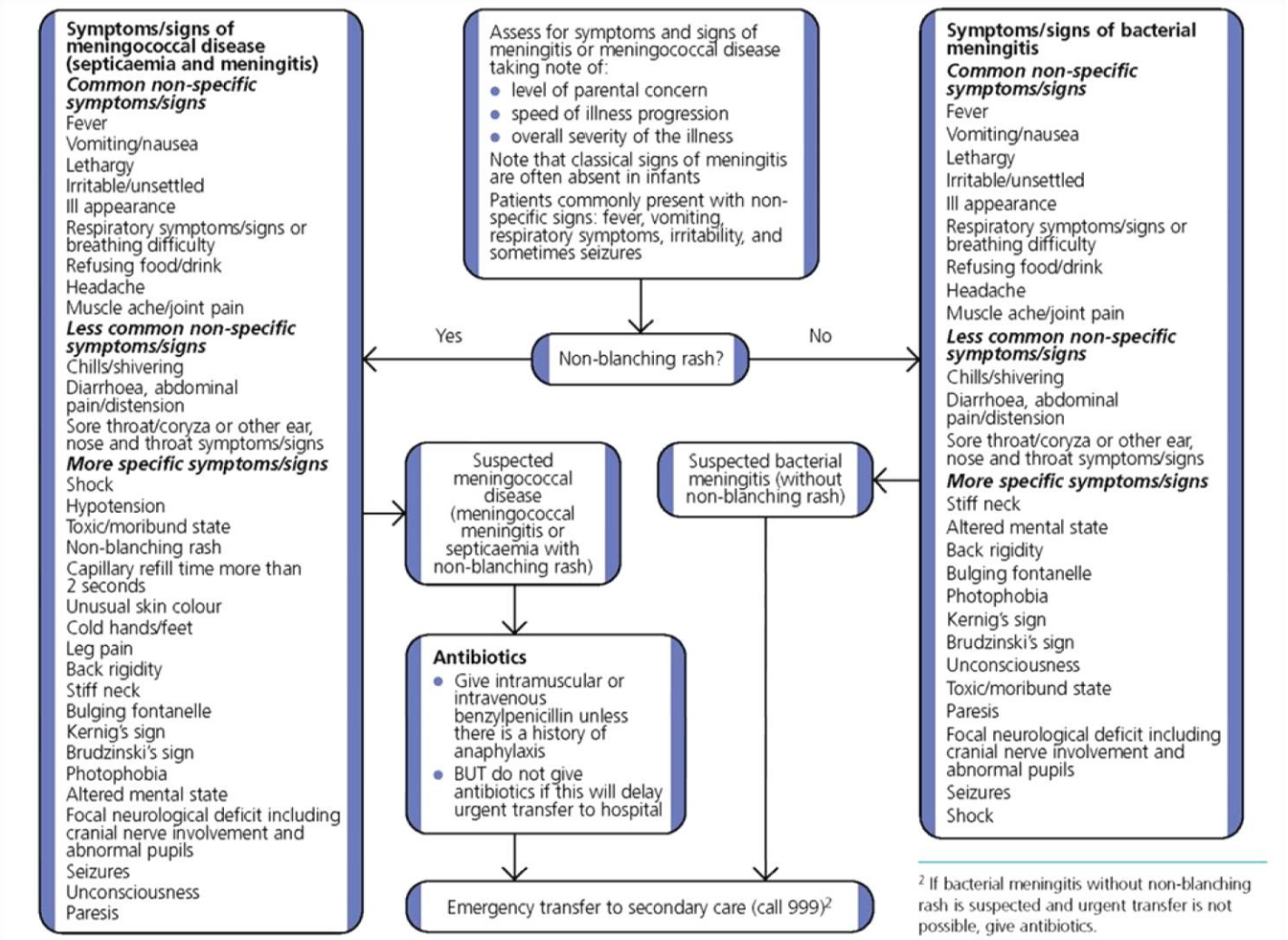
Does routine follow-up reduce the incidence of psychosocial stress and long-term morbidity in children and young people who have had bacterial meningitis or meningococcal septicaemia and their families?

Why this is important

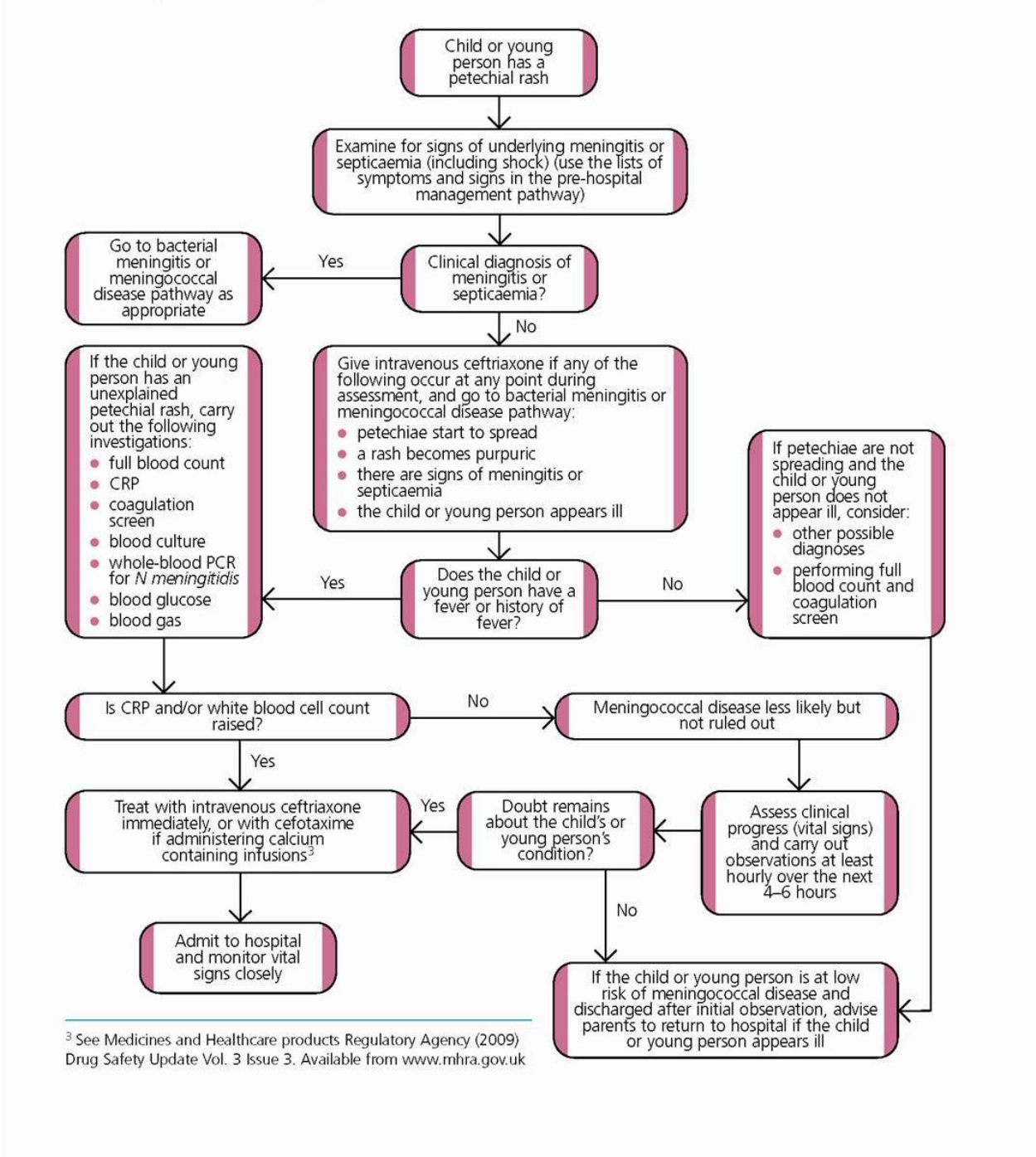
Access to follow-up therapies (such as occupational therapy) and other services for children and young people who have had bacterial meningitis or meningococcal septicaemia is recommended. Qualitative research is needed to evaluate the effectiveness of this practice. The research should seek to elicit views and experiences of the children and young people themselves and the impact on their parents or carers and other family members.

1.5 Care pathway

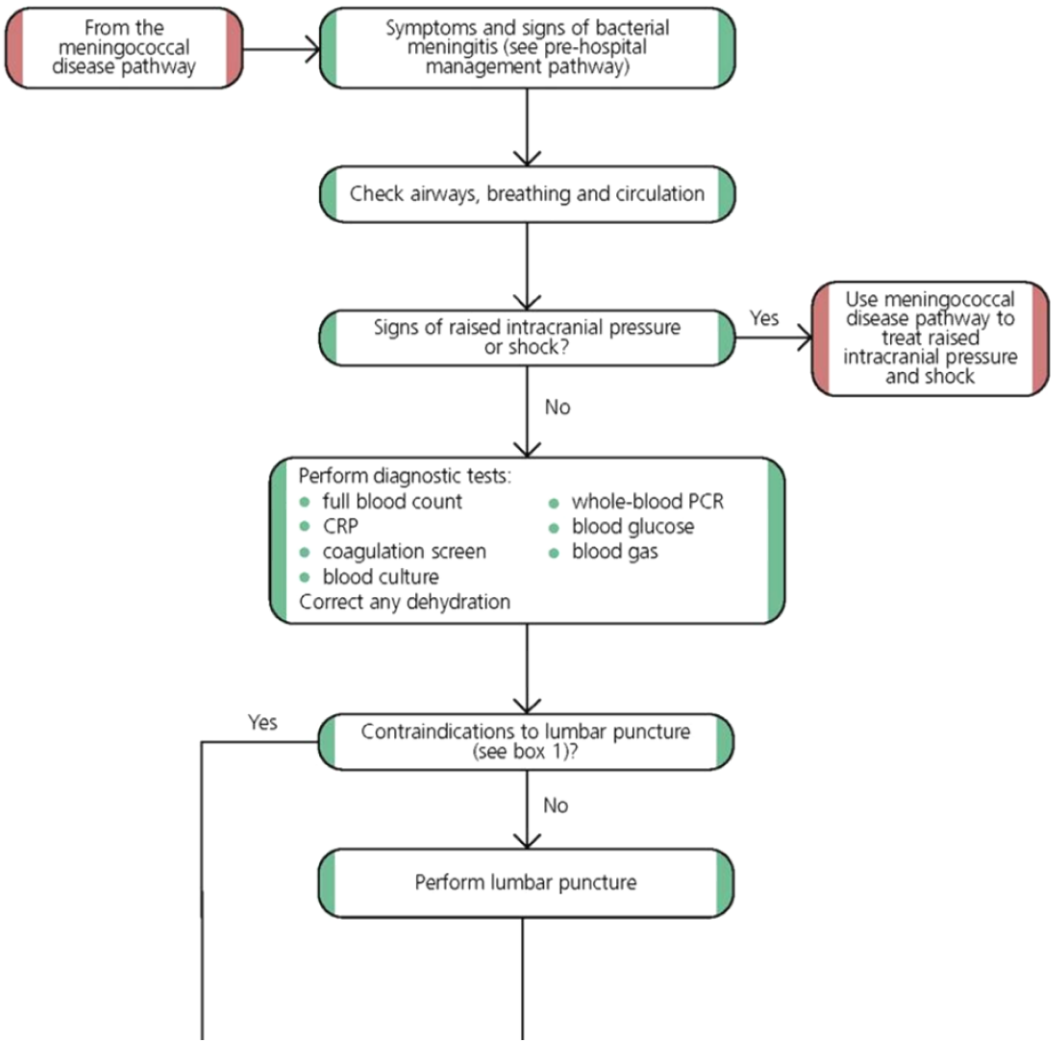
Pre-hospital management – meningococcal disease and bacterial meningitis

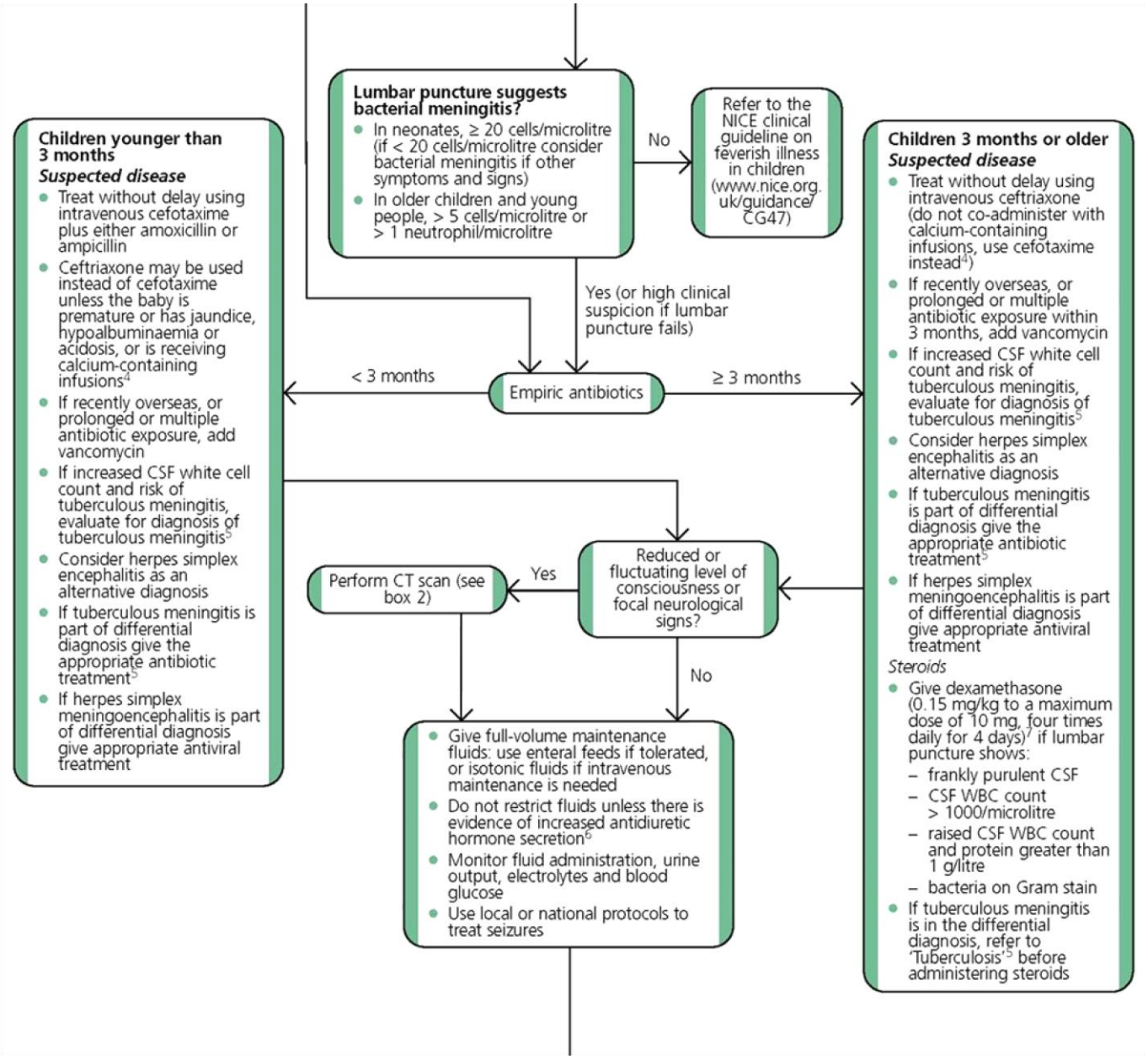


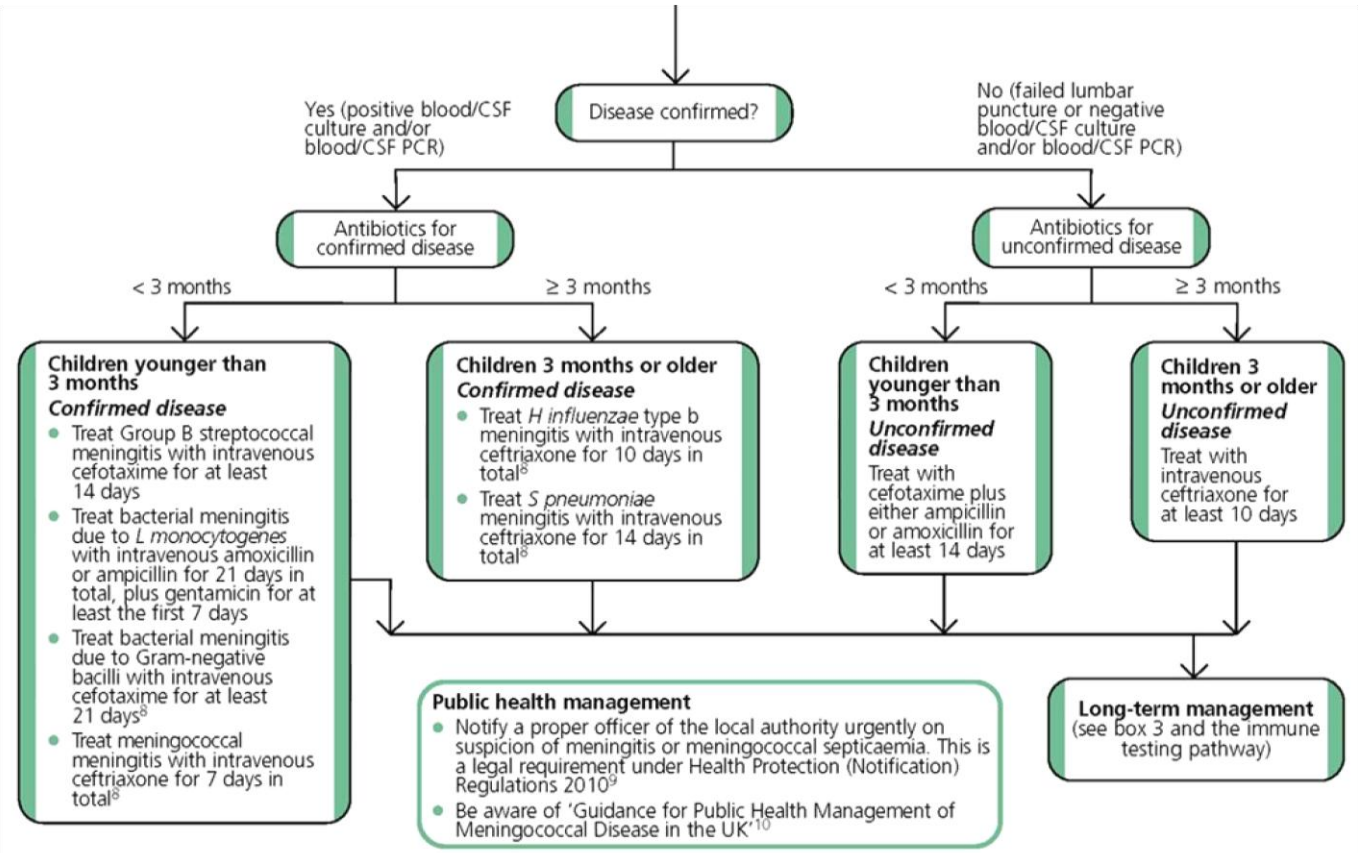
Management of petechial rash



Bacterial meningitis pathway

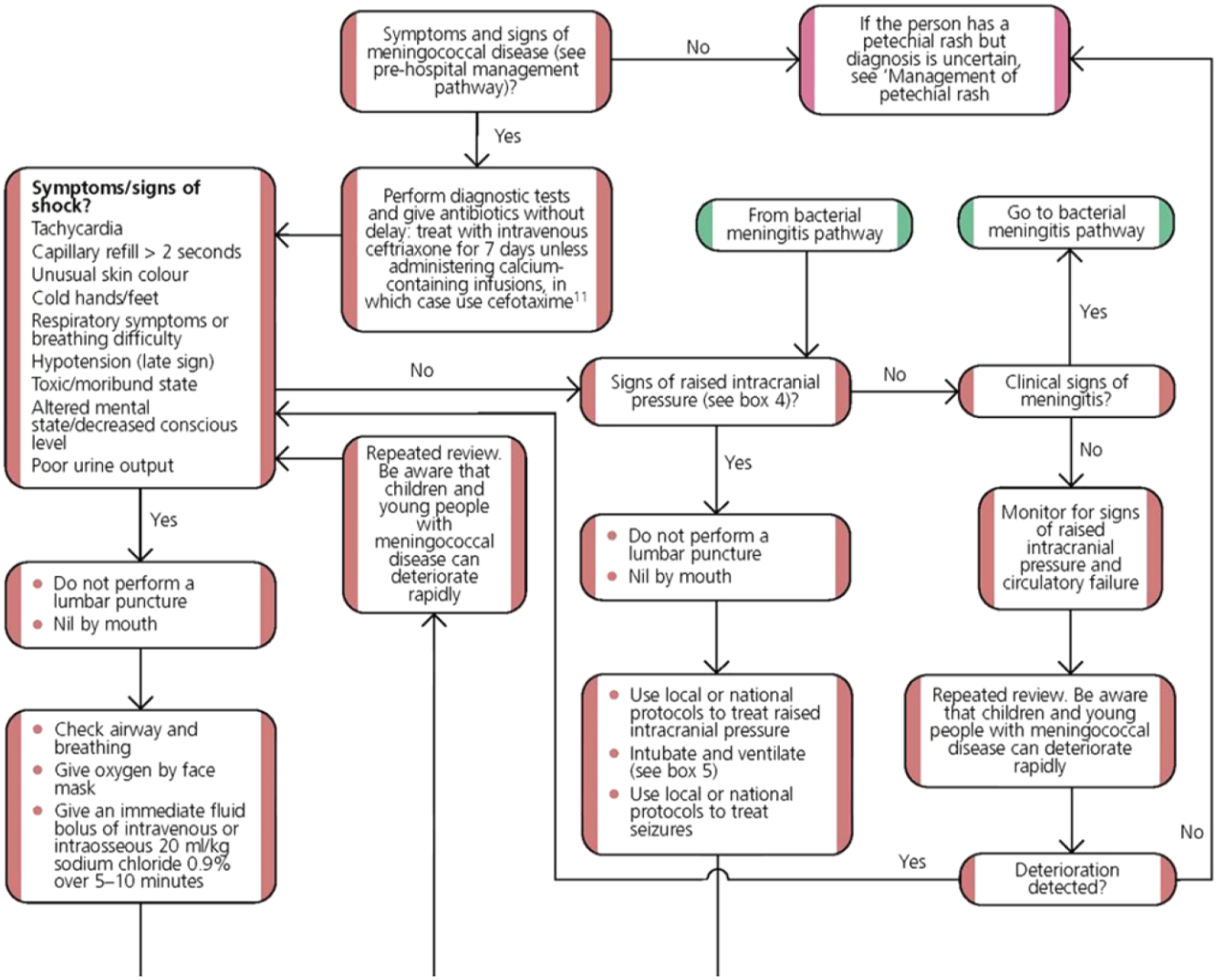


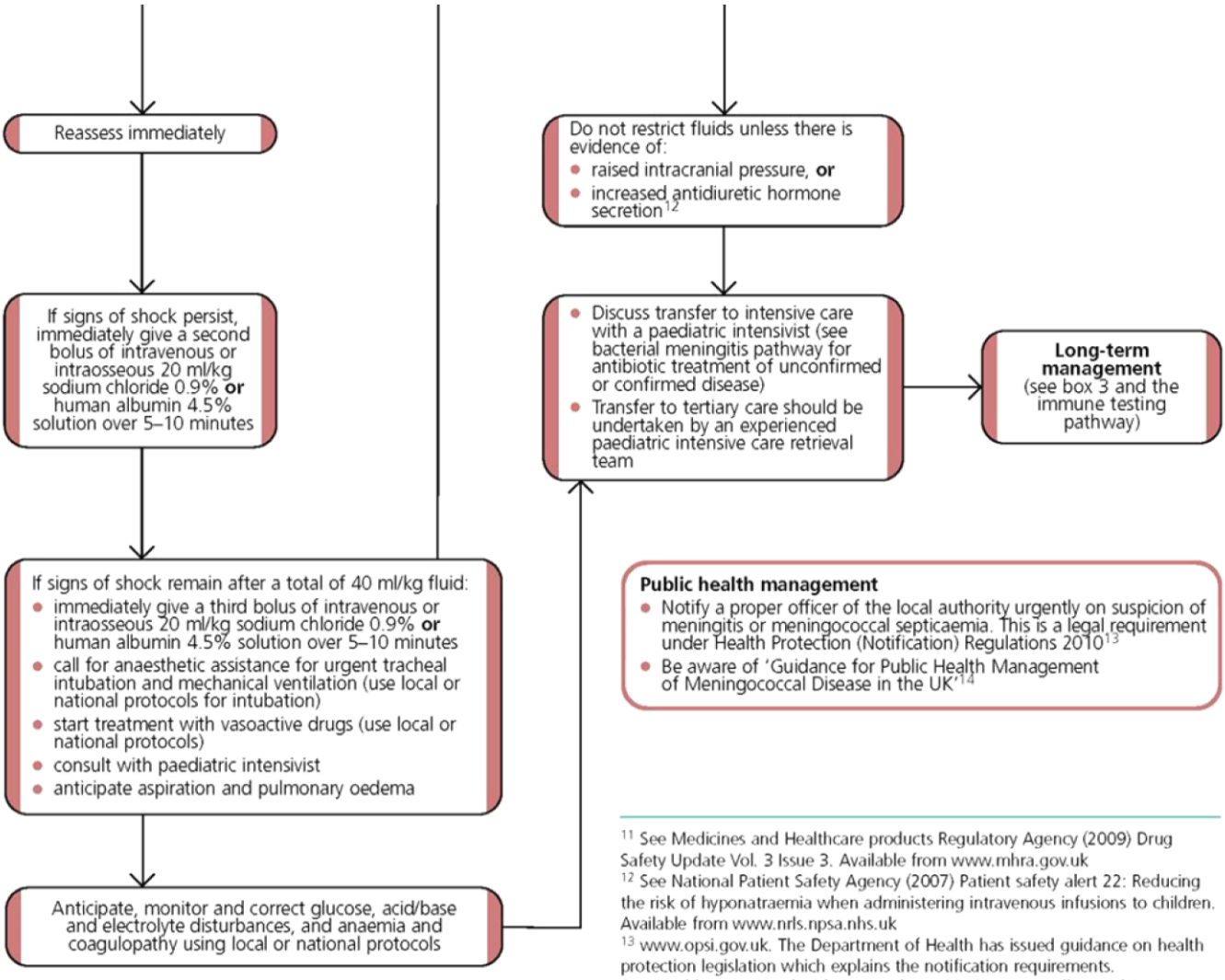

Lumbar puncture suggests bacterial meningitis?
In neonates, ≥ 20 cells/microlitre (if < 20 cells/microlitre consider bacterial meningitis if other symptoms and signs)
In older children and young people, > 5 cells/microlitre or > 1 neutrophil/microlitre
No
Refer to the NICE clinical guideline on feverish illness in children (www.nice.org.uk/guidance/CG47)
Yes (or high clinical suspicion if lumbar puncture fails)
< 3 months
Empiric antibiotics
≥ 3 months
Children younger than 3 months
Suspected disease
Treat without delay using intravenous cefotaxime plus either amoxicillin or ampicillin
Ceftriaxone may be used instead of cefotaxime unless the baby is premature or has jaundice, hypoalbuminaemia or acidosis, or is receiving calcium-containing infusions[4]
If recently overseas, or prolonged or multiple antibiotic exposure, add vancomycin
If increased CSF white cell count and risk of tuberculous meningitis, evaluate for diagnosis of tuberculous meningitis[5]
Consider herpes simplex encephalitis as an alternative diagnosis
If tuberculous meningitis is part of differential diagnosis give the appropriate antibiotic treatment[5]
If herpes simplex meningoencephalitis is part of differential diagnosis give appropriate antiviral treatment
Children 3 months or older
Suspected disease
Treat without delay using intravenous ceftriaxone (do not co-administer with calcium-containing infusions, use cefotaxime instead[4])
If recently overseas, or prolonged or multiple antibiotic exposure within 3 months, add vancomycin
If increased CSF white cell count and risk of tuberculous meningitis, evaluate for diagnosis of tuberculous meningitis[5]
Consider herpes simplex encephalitis as an alternative diagnosis
If tuberculous meningitis is part of differential diagnosis give the appropriate antibiotic treatment[5]
If herpes simplex meningoencephalitis is part of differential diagnosis give appropriate antiviral treatment
Steroids
Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[7] if lumbar puncture shows:
– frankly purulent CSF
– CSF WBC count > 1000/microlitre
– raised CSF WBC count and protein greater than 1 g/litre
– bacteria on Gram stain
If tuberculous meningitis is in the differential diagnosis, refer to 'Tuberculosis'[5] before administering steroids
Reduced or fluctuating level of consciousness or focal neurological signs?
Yes
Perform CT scan (see box 2)
No
Give full-volume maintenance fluids: use enteral feeds if tolerated, or isotonic fluids if intravenous maintenance is needed
Do not restrict fluids unless there is evidence of increased antidiuretic hormone secretion[6]
Monitor fluid administration, urine output, electrolytes and blood glucose
Use local or national protocols to treat seizures



[4] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk
[5] See 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control'. Available from www.nice.org.uk/guidance/CG33
[6] See National Patient Safety Agency (2007) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk
[7] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice (see the full guideline for further details). The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Dexamethasone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.
[8] Unless directed otherwise by the results of antibiotic sensitivities.
[9] www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health protection legislation guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510
[10] Health Protection Agency Meningococcus Forum, 2006; see www.hpa.org.uk

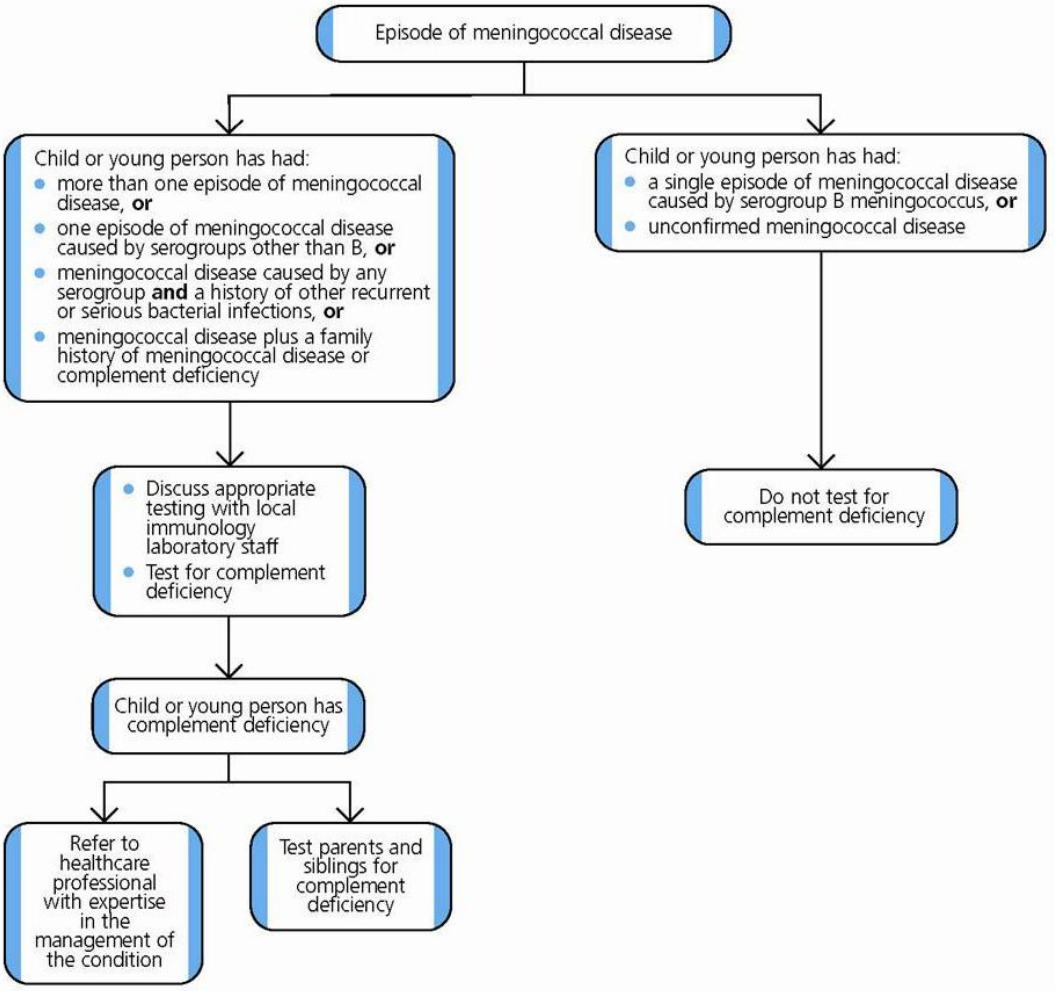
Meningococcal disease pathway





[11] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk
[12] See National Patient Safety Agency (2007) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk
[13] www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health protection legislation guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510
[14] Health Protection Agency Meningococcus Forum, 2006; see www.hpa.org.uk

Immune testing in children and young people who have had meningococcal disease



- Children and young people with recurrent episodes of meningococcal disease should be assessed by a specialist in infectious disease or immunology.
- Do not test children and young people for immunoglobulin deficiency if they have had meningococcal disease, unless they have a history suggestive of an immunodeficiency.

Supplementary information for bacterial meningitis and meningococcal disease pathways

Box 1 Contraindications to lumbar puncture

- Signs suggesting raised intracranial pressure (see box 4)
- Shock
- Extensive or spreading purpura
- After convulsions until stabilised
- Coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 10^9/litre
  - receiving anticoagulant therapy
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency)
- Radiological evidence of raised intracranial pressure

Box 2 Cranial CT scanning

- Perform a CT scan to detect alternative intracranial pathology if consciousness is reduced or fluctuating, or there are focal neurological signs.
- Do not delay treatment to undertake a CT scan.
- Clinically stabilise children and young people before CT scanning.
- If performing a CT scan consult an anaesthetist, paediatrician or intensivist.

Box 3 Long-term management

- Consider requirements for follow-up before discharge.
- Discuss likely patterns of recovery and potential long-term effects with the child or young person and their parents or carers.
- Offer information about further care and contact details of patient support organisations.
- Inform the child's or young person's GP, health visitor and school nurse about their bacterial meningitis.
- Healthcare professionals should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects.
- Offer a formal audiological assessment as soon as possible, within 4 weeks of being fit to test.
- Offer children and young people with severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing.*
- Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after hospital discharge to discuss morbidities associated with their condition and offered referral to the appropriate services.

* Further guidance on the use of cochlear implants for sever to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' (NICE technology appraisal 166)

Box 4 Signs suggesting raised intracranial pressure

- Reduced or fluctuating level of consciousness
- Relative bradycardia and hypertension
- Focal neurological signs
- Abnormal posture or posturing
- Unequal, dilated or poorly responsive pupils
- Papilloedema
- Abnormal 'doll's eye' movements

Box 5 Intubation and ventilation

A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

Indications for tracheal intubation and mechanical ventilation:

- threatened or actual loss of airway patency
- the need for any form of assisted ventilation
- clinical observation of increasing work of breathing
- hypoventilation or apnoea
- features of respiratory failure
- continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- signs of raised intracranial pressure
- impaired mental status
- control of intractable seizures
- need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit/another hospital.

Preparation for intubation

Ensure that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are nil by mouth from admission to hospital and that the following are available before intubation:

- facilities to administer fluid boluses
- appropriate vasoactive drugs
- access to a healthcare professional experienced in the management of critically ill children.

2 Development of the guideline

2.1 Bacterial meningitis and meningococcal septicaemia in children and young people

This guideline covers bacterial meningitis and meningococcal septicaemia, focusing on management of these conditions in children and young people aged younger than 16 years in primary and secondary care, and using evidence of direct relevance to these age groups where available.

Bacterial meningitis

Bacterial meningitis is an infection of the surface of the brain (meninges) by bacteria that have usually travelled there from mucosal surfaces via the bloodstream. In children and young people aged 3 months or older, the most frequent causes of bacterial meningitis include *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib; see table 2.1). These organisms occur normally in the upper respiratory tract and can cause invasive disease when acquired by a susceptible person. In neonates (children younger than 28 days), the most common causative organisms are *Streptococcus agalactiae* (Group B streptococcus), *Escherichia coli, S. pneumoniae* and *Listeria monocytogenes* (see table 2.2). These organisms are likely to be acquired around the time of birth from the maternal genital and gastrointestinal tract.[1]

Table 2.1. Incidence of and mortality from bacterial meningitis in children aged under 16 years in England and Wales by causative organism

Organism (period of data collection, source of isolate)	Number of cases	Number of deaths (case fatality rate %)
[a]*Neisseria meningitidis* (mid 2006 to mid 2007, all invasive)	790 (aged < 16 years; includes 38 aged < 3 months)	25 (3.2%)
[b]*Streptococcus pneumoniae* (2005, meningitis: cerebrospinal fluid/blood)	232 (aged < 15 years; includes 9 aged < 2 months)	n/a (6% to 11%) varies by age and is an amalgamation of data from 1998 to 2005
[a]*Haemophilus influenzae* type b (Hib) (mid 2006 to mid 2007, all invasive)	53 (aged < 15 years; includes 6 aged < 3 months)	1 (1.9%)

Source: [a] Health Protection Agency; [b] Johnson et al. (2007)[2]

Table 2.2. Incidence of bacterial meningitis in neonates (aged < 28 days) in England and Wales by causative organism, 1996–1997

Organism	Percentage of cases (n=144 culture-proven cases of meningitis)
Group B streptococcus	48
Escherichia coli	18
Streptococcus pneumoniae	6
Listeria monocytogenes	5
Neisseria meningitidis	4
Haemophilus influenzae	<1
Other Gram-positive organisms	12
Other Gram-negative organisms	8

Source: Holt et al (2001)[3]

The most recent UK national surveillance study of bacterial meningitis in neonates (aged under 28 days) was conducted in 1996–1997 and identified a case fatality rate of 10% in bacteriologically proven cases.[3] Comparison with the previous national surveillance study (which was conducted in 1985–1987)[4] revealed little change in the overall incidence of neonatal bacterial meningitis (0.22 cases per 1,000 live births in 1985–1987 versus 0.21 cases per 1,000 live births in 1996–1997). Although mortality has fallen significantly there has been no change in the rate of sequelae.[5] A recent national study focusing specifically on Group B streptococcus in children in the first 90 days of life was conducted in 2000–2001 and reported a meningitis case fatality rate of 12.4%.[6] Infection with *L. monocytogenes* is rare, accounting for approximately 5% of cases of neonatal meningitis; most cases involve early onset (age under 7 days), occur predominantly in premature infants and are related to maternal infection. Traditionally, pregnancy-associated *L. monocytogenes* has been considered capable of causing meningitis and sepsis in infants aged up to 3 months, but current epidemiological data indicate that nearly all pregnancy-associated cases present clinically in the first month of life: for example, of 72 cases of *L. monocytogenes* meningitis diagnosed between 1990 and 2007, only one occurred in an infant aged more than 4 weeks (source: Health Protection Agency [HPA], London).

The epidemiology of paediatric bacterial meningitis in the UK has changed dramatically in the past two decades following the introduction of vaccines developed to control the bacteria that cause meningitis. Hib was the main cause of bacterial meningitis in children aged under 5 years before the introduction of the Hib conjugate vaccine in 1992.[7] It is now the third most common causative organism after *N. meningitidis* and *S. pneumoniae* (see table 2.1). Reduction in the incidence of disease caused by serogroup C meningococcus in the UK after the introduction of the meningococcal C (MenC) conjugate vaccine in 1999 has been equally marked.[8] A reduction in the incidence of pneumococcal disease is already evident following the introduction of the pneumococcal conjugate vaccine in 2006[*] and is likely to decline further. The pneumococcal conjugate vaccine covers only seven serotypes of pneumococcus, although 91 have been described.[9] As no vaccine is currently licensed against serogroup B meningococcus, this pathogen is now the most common cause of bacterial meningitis (and septicaemia) in children and young people aged 3 months or older (see HPA guidance[†]).

The incidence of pneumococcal meningitis in children younger than 3 months may decline as a result of vaccination through population (or 'herd') immunity. However, serotypes not included in the current vaccine (for example ST1), appear to be more likely to cause disease in this age group than in older age groups. For example, the percentage of invasive pneumococcal disease serotypes found in the seven-valent vaccine before widespread vaccination was 47% for those aged under 1 month compared with 88% for children aged 1

[*] www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1207821645727

[†] www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859712887?p=1201094595391

to 4 years.[10] Thus, population immunity with the current pneumococcal conjugate vaccine may have minimal impact on pneumococcal meningitis in children younger than 3 months.

This guideline does not consider meningitis associated with tuberculosis (TB), because tuberculous meningitis (or meningeal TB) is covered in 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control', National Institute for Health and Clinical Excellence (NICE) clinical guideline 33.[11] However, some features of the presentation of tuberculous meningitis are indistinguishable from bacterial meningitis.

Meningococcal disease

Most *N. meningitidis* colonisations are asymptomatic, but occasionally the organism invades the bloodstream (usually within a few days of a susceptible person acquiring the organism) to cause meningococcal disease. Meningococcal disease most commonly presents as bacterial meningitis (15% of cases) or septicaemia (25% of cases), or as a combination of the two syndromes (60% of cases).[12] Rarely the disease presents as pneumonia, arthritis, osteomyelitis, pericarditis, endophthalmitis or conjunctivitis.[13] Meningococcal disease is the leading infectious cause of death in early childhood,[14] making its control a priority for clinical management (as well as public health surveillance and control; see below). The disease can be fatal within hours of the first symptoms appearing, and many experts believe that lives could be saved by earlier recognition and prompt and appropriate emergency management. This view is supported by research in adults on the 'golden hours' that suggests that the initial management of patients with meningococcal disease may be critical in determining outcome[*].

Disease-causing meningococci are encapsulated with polysaccharides, the chemical nature of which determines the serogroup of the organism. Serogroups A, B, C, W135 and Y are the main causes of invasive meningococcal disease.[15] Most meningococcal disease in Europe is caused by serogroups B and C, but the serogroup distribution varies over time: following the introduction of the MenC conjugate vaccine (which protects against serogroup C meningococcus), almost all cases of meningococcal disease in England and Wales are now caused by serogroup B.[15]

The highest incidence of meningococcal disease occurs among children aged under 2 years; another period of increased risk occurs in adolescence and early adulthood.[15] The disease is more frequent in winter months[15] and is associated with smoking, crowding and recent viral respiratory illness.[16-19] The case fatality rate is about 10%,[20] with the highest mortality rates occurring in people with fulminant meningococcal septicaemia (meningococcal septicaemia that strikes suddenly and with great severity).[21]

Notification and public health management

Under the Health Protection (Notification) Regulations 2010,[†] registered medical practitioners in England have a legal requirement to notify the proper officer of the local authority in which the patient resides when they have reasonable grounds for suspecting that the patient has a notifiable disease as listed in Schedule 1 of the Regulations. From October 2010, the Regulations will place a duty on diagnostic laboratories to notify the HPA when they identify evidence of infection caused by specified causative agents. Prior notification by a diagnostic laboratory does not remove the registered medical practitioner's responsibility to notify a notifiable disease.

The Regulations identify those diseases which should be notified urgently. Urgent notifications are to be made orally, usually by telephone, as soon as is reasonably practicable and always within 24 hours. Oral notification should be followed by a written notification to be received by the proper officer within 3 days of the clinical suspicion being formed. This is the case for clinical and laboratory diagnoses. Acute meningitis (including bacterial meningitis) and meningococcal septicaemia are notifiable diseases requiring urgent notification. From the laboratory perspective, *N. meningitidis* should be reported urgently.

[*] See, for example, www.acep.org/publications.aspx?id=37782

[†] www.opsi.gov.uk/si/si2010/uksi_20100659_en_1

The Department of Health has issued guidance[22] explaining the notification requirements on registered medical practitioners and diagnostic laboratories that test human samples, and health protection powers available to local authorities and justices of the peace.*

The purposes of notification are to prompt local investigation and public health action to control these diseases, including prevention of nosocomial (healthcare associated) transmission and transmission in the community. The resulting data are also used for analysis of local and national trends. The HPA has issued guidance on public health management of meningococcal disease in the UK[15] which covers laboratory investigation of suspected cases, local and national public health surveillance, and public health action after a case to prevent secondary infection, including chemoprophylaxis (using antibiotics and/or vaccines) in close contacts, the wider community and healthcare settings.† Specific recommendations contained in the HPA guidance include:

- isolation of the index case during the first 24 hours of treatment with antibiotics (after this the index case ceases to be infectious)[23]
- use of surgical masks by healthcare professionals during initial management to reduce the possibility of exposure to large particle droplets (especially during airway management procedures), so avoiding the need for chemoprophylaxis
- use of chemoprophylaxis only for those healthcare professionals whose mouth or nose is directly exposed to large particle droplets or secretions from the respiratory tract of a probable or confirmed case of meningococcal disease during acute illness until 24 hours of systemic antibiotics has been completed: general medical or nursing care of cases is not an indication for prophylaxis.

2.2 Aim and scope of the guideline

This clinical guideline concerns the management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. It has been developed with the aim of providing guidance in the following areas:

- diagnosis of bacterial meningitis and meningococcal septicaemia (covering symptoms and signs, identification of levels of risk based on probabilities of combinations of signs and symptoms, and differentiating between meningococcal septicaemia and other causes of non-blanching rash)
- management of suspected bacterial meningitis and meningococcal septicaemia in primary care and in the pre-hospital setting
- management of bacterial meningitis and meningococcal septicaemia in secondary care, covering:
  - choice of antibiotics
  - fluid resuscitation
  - timing and role of intubation and the decision to initiate it
  - corticosteroids for the treatment of meningitis
  - use of scoring systems such as the Glasgow meningococcal septicaemia prognostic score (GMSPS) in diagnosis and management
  - the role of recombinant bacterial permeability increasing protein (Bpi) and activated protein C
- retrieval and transfer to secondary and tertiary care
- choice and timing of investigations:
  - blood tests, aspirates and swabs
  - lumbar puncture
  - radiology and immunological testing

* www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510

† See HPA guidance at www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261

- information that should be given to parents and carers (at the time of initial presentation and after diagnosis, regarding short- and long-term effects, and including significant psychological and physical morbidities).

The following groups are specifically excluded from the guideline:

- children and young people with known immunodeficiency
- children and young people with brain tumours, existing hydrocephalus or intracranial shunts
- neonates already receiving care in neonatal units.

Further information about the areas covered in the guideline is available in the 'scope' of the guideline (reproduced in appendix A).

2.3 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England, Wales and Northern Ireland, in particular:

- healthcare professionals involved in the care of children and young people with bacterial meningitis or meningococcal septicaemia, including paediatricians, general practitioners (GPs) and nurses
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers
- parents and carers of children and young people with bacterial meningitis or meningococcal septicaemia.

A version of this guideline for patients and their parents and carers is available from the NICE website (www.nice.org.uk/CG102) or from NICE publications on 0845 003 7783 (quote reference number N2202).

2.4 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including the following guidance published by NICE:

- 'Diarrhoea and vomiting in children under 5', NICE clinical guideline 84[24]
- 'Feverish illness in children', NICE clinical guideline 47[25]
- 'Tuberculosis', NICE clinical guideline 33[11]
- 'Cochlear implants for children and adults with severe to profound deafness', NICE technology appraisal (TA) 166[26]

This guideline also draws on clinical questions and searches developed for the Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline on management of invasive meningococcal disease in children and young people.[27] The Department of Health guidance on health protection legislation in England*[22] and the HPA guidance on public health management of meningococcal disease in the UK[15] should also be considered in conjunction with this guideline (see section 3).

* See www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510

2.5 Who has developed the guideline?

The guideline was developed by a multi-professional and lay Guideline Development Group (GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- eight paediatricians (including paediatricians specialising in emergency medicine and infectious diseases)
- a GP
- two nurses specialising in paediatric critical care
- a public health physician
- two patient/carer members.

NCC-WCH staff provided methodological support for the guideline development process, undertook systematic searches, retrieved and appraised the evidence, developed health economic models and wrote successive drafts of the guideline.

Two external advisers were appointed by the GDG to advise on topics relevant to the guideline.

All GDG members' and external advisers' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in appendix B). None of the interests declared by GDG members constituted a material conflict of interest that would influence recommendations developed by the GDG.

Organisations with interests in the management of bacterial meningitis and meningococcal septicaemia in children and young people aged under 16 years were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process. The types of organisations eligible to register as stakeholders included:

- national patient and carer organisations that directly or indirectly represent interests of children and young people aged under 16 years with bacterial meningitis or meningococcal septicaemia and their families
- national organisations that represent healthcare professionals who provide services for children and young people aged under 16 years with bacterial meningitis or meningococcal septicaemia
- companies that manufacture preparations and/or products used in the management of bacterial meningitis or meningococcal septicaemia in children and young people aged under 16 years
- providers and commissioners of health services in England, Wales and Northern Ireland
- statutory organisations such as the Department of Health and the Welsh Assembly Government
- research organisations that have undertaken nationally recognised research in relation to the topics covered in the guideline.

A list of registered stakeholder organisations for this guideline is presented in appendix C.

2.6 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the process outlined in successive editions of 'The guidelines manual'.[*] Table 2.3 summarises the key stages of the process and which version of the guidelines manual was followed at each stage. In accordance with NICE's Equality Scheme[†], ethnic and cultural considerations and factors relating to disabilities were considered by the GDG at every stage of the process and addressed specifically in individual recommendations where relevant.

[*] www.nice.org.uk/guidelinesmanual

[†] www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp

Table 2.3. Stages in the NICE guideline development process and versions of `The guidelines manual' followed at each stage

Stage	2007 version	2009 version
Scoping the guideline (determining what the guideline would and would not cover)	✓	
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution, etc.)	✓	
Forming and running the GDG	✓	
Developing clinical questions	✓	
Identifying evidence	✓	
Reviewing and grading evidence	✓	
Incorporating health economics	✓	
Making group decisions and reaching consensus	✓	
Linking guidance to other NICE guidance	✓	
Creating guideline recommendations	✓	
Writing the guideline	✓	
Stakeholder consultation on the draft guideline		✓
Finalising and publishing the guideline (including pre-publication check)		✓
Declaring and dealing with conflicts of interest	✓	✓

Developing clinical questions and identifying evidence

The GDG formulated clinical questions based on the scope (see appendix D). These formed the starting point for subsequent evidence reviews. Relevant published evidence to answer the clinical questions was identified by applying systematic search strategies (see appendix E) to the following databases:

- Medline (1950 onwards)
- Embase (1980 onwards)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards using the Ovid platform and 1987 onwards using the Ebsco platform)
- three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects).

PsycInfo (1967 onwards) was also searched for evidence related to long-term sequelae of bacterial meningitis and meningococcal disease and the NHS Economic Evaluation Database (NHS EED) was also searched to identify economic studies. Except where specifically stated, the searches were not limited by date or language of publication (although publications in languages other than English were not reviewed). Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials) and hand searching of journals not indexed on the databases was not undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed, to include evidence published and indexed in the databases by 1 June 2009.

Reviewing and grading evidence

Evidence relating to clinical effectiveness was reviewed and graded using the hierarchical system presented in table 2.4. This system reflects the susceptibility to bias inherent in particular study designs.

Table 2.4. Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of evidence, each study was assigned a quality rating coded as `++', `+' or `−'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of RCTs (EL = 1++) or an individual RCT (EL = 1+). Studies of poor quality were rated as `−'. Studies rated as `−' should not be used as a basis for making a recommendation, but they may be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL = 2).

For each clinical question, the highest available level of evidence was sought. Where appropriate (for example, if a systematic review, meta-analysis or RCT was identified to answer a question), studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the effectiveness (accuracy) of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated or quoted where possible (see table 2.5). Likelihood ratios (LRs) were also quoted where reported.

Table 2.5. '2 × 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Test positive	a (true positive)	b (false positive)	a+b
Test negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d)

The hierarchical system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting accuracy of diagnostic tests. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy of evidence that takes into account various factors likely to affect the validity of such studies (see table 2.6).

Table 2.6. Levels of evidence for studies of the accuracy of diagnostic tests

Level	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are minor or no variations in the directions and degrees of results between individual studies that are included in the systematic review.
[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.
[c] Level-2 studies are studies that have only one of the following:
- •narrow population (the sample does not reflect the population to whom the test would apply)
- •use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- •the comparison between the test and reference standard is not blind
- •case–control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

Some studies were excluded from the reviews after obtaining copies of the corresponding publications because they did not meet inclusion criteria specified by the GDG (see appendix F). Clinical evidence from included studies was extracted into evidence tables for each question (see appendix G), and a brief summary of each study was included in the guideline text. Where possible, dichotomous outcomes are presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs).

The body of evidence identified for each clinical question was synthesised qualitatively in clinical evidence statements. Quantitative synthesis (meta-analysis) was also undertaken for specific areas of the guideline, with results being presented in the text as pooled RRs, pooled ORs or weighted mean differences (WMDs). By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used. Forest plots are presented for the effectiveness of empiric antibiotics for the treatment of suspected bacterial meningitis and effectiveness of corticosteroids for the treatment of bacterial meningitis (see appendix H).

Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to the management of bacterial meningitis and meningococcal septicaemia in children and young people aged under 16 years, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits or harms (ideally in terms of quality adjusted life years [QALYs]) and costs of different care options.

The GDG prioritised a number of clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. For this guideline the areas prioritised for economic analysis were:

- polymerase chain reaction (PCR) for confirming diagnosis in suspected meningococcal disease (see section 5.3 and appendix I for details of a health economic model developed to address this issue)
- antibiotics for treatment of bacterial meningitis and meningococcal disease (see sections 6.1 and 6.2 and appendix J for details of a health economic model developed to address this issue)
- crystalloid versus colloid intravenous fluid for resuscitation in suspected meningococcal septicaemia (see section 6.5 and appendix K for details of a 'what-if' analysis developed to address this issue)

- complement deficiency screening in survivors of meningococcal disease (see section 7.3 and appendix L for details of a 'what-if' analysis developed to address this issue).

GDG interpretation of the evidence and creating recommendations

For each clinical question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree clinical and, where appropriate, cost-effectiveness evidence statements. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process.

In areas where no substantial clinical research evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost-effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer its clinical questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified ten 'key priorities for implementation' (key recommendations) and five high priority research recommendations. The key priorities for implementation were those recommendations likely to have the biggest impact on patients' care and outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were selected in a similar way.

Stakeholder involvement in the guideline development process

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. Stakeholder organisations were also invited to undertake a pre-publication check of the final guideline to identify factual inaccuracies. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently for NICE by a guideline review panel, are published on the NICE website.

2.7 Specific considerations for this guideline

For this guideline, the effectiveness of interventions was assessed against the following broad outcome categories:

- mortality
- incidence of seizures
- loss of limbs
- relapse of infection
- duration of hospital stay
- need for rehabilitation
- adverse effects of antibiotic treatment
- immediate, short-term and long-term neurological complications including:
  - hearing loss
  - visual impairment
  - mobility and ambulation problems
  - psychosocial/behavioural problems.

Some of the clinical questions developed for the SIGN guideline* on management of invasive meningococcal disease in children and young people[27] were sufficiently similar to clinical questions developed for this guideline that SIGN search strategies could be updated and

* See SIGN guideline at www.sign.ac.uk/pdf/sign102.pdf

used as search strategies for this guideline. For other questions, the GDG developed original search strategies. Some searches were restricted by year of publication, for example to target studies conducted after the introduction of the Hib conjugate vaccine, or by country of study, for example to target studies conducted in high-income (developed) countries, so that the pathogens and clinical settings reported in the studies were relevant to current epidemiology and NHS clinical practice in England in Wales (see individual chapters for further details). Studies involving adults as well as children and young people were included where data were presented separately for children and/or young people.

Where the evidence supported it, the GDG made separate recommendations for the management of different conditions (bacterial meningitis, meningococcal septicaemia and, in some cases, meningococcal disease). Unless otherwise specified, the recommendations refer to all children and young people aged under 16 years. The GDG also used the term neonate in some recommendations.

2.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

3 Bacterial meningitis and meningococcal septicaemia in children and young people — symptoms, signs and initial assessment

3.1 Symptoms and signs of bacterial meningitis

Introduction

It is important for healthcare professionals to be aware of clinical features that can be used to help identify children and young people presenting with possible bacterial meningitis. Meningitis involves inflammation of the meninges and spinal cord, so it is typically associated with symptoms and signs that result from this inflammation. Meningitis can be caused by several types of infective organisms, including bacteria (see section 2.1) and viruses: identifying infection due to bacterial meningitis is particularly important because prompt recognition and referral for emergency admission are essential in order to initiate antibiotic treatment.

Clinical question

In children and young people under 16 years of age, what symptoms and signs or combinations of symptoms and signs are predictive of bacterial meningitis?

Previous UK guidelines

'Feverish illness in children', NICE clinical guideline 47[25] contains the following recommendations on meningitis.

Meningitis should be considered in a child with fever and any of the following features:

- neck stiffness
- bulging fontanelle
- decreased level of consciousness
- convulsive status epilepticus.

Healthcare professionals should be aware that classical signs of meningitis (neck stiffness, bulging fontanelle, high-pitched cry) are often absent in infants with bacterial meningitis.

Studies considered in this section

All study designs evaluating symptoms and signs, or combinations of symptoms and signs, predictive of meningitis (bacterial and/or aseptic [where no bacteria are detected on testing]) were considered for this section. Studies providing diagnostic accuracy values (or sufficient information to derive diagnostic accuracy values) were included; however, the majority of the studies were retrospective. Only research conducted in high-income countries was included.

Studies involving adults as well as children and young people were included where data were presented separately for children and/or young people. Findings were presented for three age groups: children aged 0 to 18 years, children under 2 years and neonates. Studies relating to meningococcal disease were excluded (although some of them would have included data on children and young people with bacterial meningitis).

Overview of available evidence

There were three prospective cohort studies[28-30] of children with diagnosed bacterial meningitis and nine retrospective studies, of which eight were cohort studies[31-38] and one was a cross-sectional study.[39] Baseline data at presentation were used to estimate the frequency of clinical symptoms and signs of bacterial meningitis. Eight studies[29;30;33-37;39] provided information for children aged up to 18 years, five studies[28;31;32;37;38] provided information for children under 2 years and one study provided information for neonates.[40] Two studies compared the prevalence of symptoms and signs in viral (aseptic) and bacterial meningitis in 'all children'[28;35] and one in children under 2 years.[28] All of the studies obtained information on the frequency of clinical symptoms and signs from hospital records. No studies were identified in relation to the frequency of clinical features in primary care settings or in the pre-hospital phase of illness. No studies were identified that allowed calculation of diagnostic characteristics of any of the clinical features.

Review findings

Prevalence of individual signs and symptoms of bacterial meningitis

All children

Results from eight studies were included.[29;30;33-37;39] In all but one study[37] the results for 'all children' were not reported in a form that allowed separation into children under 2 years and those over 2 years, and so the results reported here are for all children aged 0 to 18 years.

Although specific outcome measures varied, evidence from six studies[29;30;33-35;39] [EL 3 and III] suggested that most children with meningitis presented with a temperature over 38°C or fever (prevalence range 85% to 95%). Two cohort studies[29;33] and one cross-sectional study[39] reported that just under three-quarters of children with meningitis had vomiting (prevalence range 70% to 73%), although one cohort study[35] reported that only 52% of children had vomited and 48% had nausea. Prevalence rates for headache varied from 3% to 58% in the four cohort studies[30;33-35] reporting this symptom.

The findings of all eight studies[29;30;33-37;39] [EL 3 and III] suggested that under a third of children with meningitis presented having a seizure (13% to 30%). Evidence from three cohort studies[28;36;37] [EL 2+ to 3] identified shock as a less common finding at presentation (8% to 17%). All except one study[35] reported conscious state, although definitions and data categories varied across studies. Evidence from four cohort studies[29;30;33;34] suggested that over two-thirds of children with meningitis experienced impaired consciousness (60% to 87%), with 8% to 12% presenting with coma in one cross-sectional study[39] and one cohort study.[37] Between 20% and 53% of children were described as 'irritable' or 'agitated' in three cohort studies[33;34;36] and one cross-sectional study.[39]

Photophobia was identified in 5% of participants in the one cohort study[35] that reported this symptom. In another cohort study36, in which 110 out of 159 participants were aged under 2 years, 71 children (32%) had a bulging fontanelle. Six cohort studies[28;29;33-35;37] and one cross-sectional study[39] reported the prevalence of neck stiffness, which ranged from 62% to 75%. One cohort study[30] reported that back rigidity was present in 46% of children.

Brudzinski's sign was elicited in 66% of children and Kernig's sign in 53% of children in one cohort study[28] which also reported that 83% of participants had one of three signs (neck stiffness, Kernig's sign, Brudzinski's sign) present.

Respiratory symptoms were estimated using different measures in five studies. The prevalence of respiratory symptoms was estimated as 25% and 32% in two cohort studies[29;33]; one cohort study[36] reported that 41% of children had catarrh, another cohort study[34] reported that 12% of children had a chest infiltrate on X-ray, and one cohort study[37] found that 34% were in respiratory distress. The prevalence of otitis media was reported as 14% and 49% in two cohort studies[29;34] and 12% of children exhibited focal neurological abnormalities in one cohort study.[34]

Children under 2 years

Results from five cohort studies were included.[28;31;32;37;38]

Three cohort studies[31;32;38] [EL=3] reported that 69% to 96% of children with meningitis presented with temperature over 38°C or fever. The same studies found that over one-third of children vomited (60%, 31% and 55.2%), while poor feeding was commonly reported (45% and 76%) in two studies.[31;32] The prevalence of seizures ranged from 22% to 55.2% in four cohort studies [EL=3].[31;32;37;38] Details of the child's conscious state were provided in all five studies, but definitions and data capture categories were not consistent. In two cohort studies[31;32] over half of children were described as 'irritable' and in three cohort studies between 28% and 54% of children were described as 'lethargic'.[31;32;37] One cohort study[38] reported that 96% of children were 'lethargic or irritable' and another cohort study[28] [EL=2] found that 80% were 'lethargic or comatose'. Two studies[31;37] reported that 3% and 6% of children respectively were comatose.

Prevalence of the 'classical' signs of meningitis varied across the studies. All five studies reported neck stiffness (prevalence range 13% to 56%), three[28;31;32] reported bulging fontanelle (prevalence range 41% to 45%), one[31] reported photophobia (7%) and two[28;38] reported Brudzinski's sign (11% and 68%) and Kernig's sign (10% and 36%). One study[28] reported that 72% of children exhibited at least one of three 'classical' signs of meningitis (neck stiffness, Brudzinski's sign or Kernig's sign). However, in another study[32] over half (55%) of children did not exhibit neck stiffness or bulging anterior fontanelle. Approximately one-third of children (prevalence 29% and 38%) in two studies[31;37] were in respiratory distress.

Neonates

One retrospective cohort study conducted in the USA[40] [EL=3] examined hospital case notes of 24 'older' neonates (aged 2 to 6 weeks) who were diagnosed with bacterial meningitis (by cerebrospinal fluid [CSF], blood and urine culture and bacterial antigen detection). Fever and irritability were noted in 79% of the neonates: however, the classical symptoms of nuchal rigidity and bulging fontanelle were not usually evident (17% and 13%, respectively). In the study 25% of participants were described as lethargic and 17% had seizures. Non-specific gastrointestinal symptoms (anorexia and/or vomiting, diarrhoea and abdominal distension) were more frequent (reported in 50%, 29% and 17% of participants, respectively) than respiratory symptoms (respiratory distress [17%] and apnoea [13%]).

Symptoms and signs of bacterial meningitis versus those of viral or aseptic meningitis

All children

Two cohort studies compared the symptoms and signs of bacterial meningitis to those found in viral[35] [EL=III] and aseptic[28] [EL=2+] meningitis in children aged under 16 years. In only one study[28] were the results for 'all children' were reported in a form that allowed separation into children under 2 years and those over 2 years, and so the results reported here are for all children aged 0 to 16 years.

One retrospective cohort study[35] reported that more children with bacterial meningitis presented with fever and seizures than did those with viral meningitis (bacterial versus viral: fever: 90% versus 82%, $P = 0.026$; seizures: 19% versus 3%, $P = 0.01$). However, in viral meningitis nausea, vomiting, headache and neck stiffness were more common than in

bacterial meningitis (viral versus bacterial: nausea: 79% versus 48%, *P* = 0.005; vomiting: 81% versus 52%, *P* = 0.009; headache: 78% versus 10%, *P* < 0.0001; neck stiffness: 88% versus 62%, *P* = 0.006). There was no significant difference in the prevalence of photophobia between the two groups.

One prospective cohort study[28] reported that each of the recorded signs and symptoms was observed significantly more frequently in children with bacterial meningitis compared to those with aseptic meningitis (shock: 17% versus 7%, *P* = 0.04; lethargic or comatose state: 87% versus 45%, *P* < 0.0001; toxic/moribund state: 87% versus 45%, *P* < 0.0001; neck stiffness: 74% versus 32%, *P* < 0.0001; Brudzinski's sign: 66% versus 26%, *P* < 0.0001; Kernig's sign: 53% versus 15%, *P* < 0.0001; at least one of three 'classical' signs of meningitis [neck stiffness, Brudzinski's sign or Kernig's sign]: 83% versus 44%, *P* < 0.0001).

Children under 2 years

One prospective cohort study[28] reported that in children under 2 years most signs and symptoms were observed more frequently with bacterial meningitis compared to those with aseptic meningitis (lethargic or comatose state: 80% versus 46%, *P* < 0.03; toxic/moribund state: 40% versus 12%, *P* < 0.006; bulging fontanelle: 44% versus 12%, P = 0.0002; neck stiffness: 52% versus 5%, *P* = 0.0001; Brudzinski's sign: 68% versus 16%, *P* < 0.001; Kernig's sign: 36% versus 7%, *P* = 0.0008; at least one of three 'classical' signs of meningitis (neck stiffness, Brudzinski's sign or Kernig's sign): 72% versus 17%, *P* = 0.0001). The prevalence of shock was not significantly different between the two groups (16% versus 8%, *P* = ns).

Evidence statement

Prevalence of individual symptoms and signs of bacterial meningitis

All children

The observational studies identified for inclusion did not present diagnostic accuracy characteristics (sensitivity, specificity, etc.) of clinical features of meningitis. Furthermore, the studies were heterogeneous in terms of study populations, years in which the studies were conducted (in relation to availability of Hib conjugate vaccine, pneumococcal conjugate vaccine, etc.), and types of setting. Only one small study was identified which described clinical features in children referred from primary care: no other data from primary care or emergency departments were identified. The findings may, therefore, apply more to hospitalised children than those seen at first contact.

There is consistent evidence that the vast majority of children with bacterial meningitis presented with high fever (six studies). Two-thirds of children experienced 'impaired consciousness' (six studies). Over half the children studied had vomited (four studies) and less than one-third had a first seizure at presentation (eight studies). The prevalence of an irritable or agitated state varied from 20% to 53% (four studies). Shock was reported in 8% to 17% of cases (three studies). Neck stiffness was experienced by 60% to 75% of children (seven studies) and evidence from one study suggested that over 80% of children experienced Brudzinski's sign, Kernig's sign or neck stiffness. Reporting of respiratory symptom outcomes varied, but depending on definition, respiratory symptoms were reported in 12% (X-ray chest infiltrate) to 40% (catarrh) (five studies). Prevalence of otitis media varied in the two studies that reported this outcome. Focal neurological abnormalities were identified in about 10% of children in a further study.

Children under 2 years

In children under 2 years, conscious state was reported mostly in terms of irritability, lethargy or comatose state in single or grouped categories. The evidence suggests that more children were irritable than lethargic, although both states were common and a comatose state occurred in about 5% of children (five studies). Bulging fontanelle was reported in over 50% of cases (three studies), although the prevalence of other typical signs of meningitis (Brudzinski's sign, Kernig's sign or neck stiffness) varied across studies reporting these outcomes, suggesting that these signs would be less reliable in children under 2 years (neck stiffness, six studies; Brudzinski's and Kernig's sign, two studies). One-third of children presented in respiratory distress (two studies).

Neonates

Evidence from one small study suggests that most 'older' neonates with bacterial meningitis present with symptoms of fever and irritability, and half have anorexia and/or vomiting. Seizures, bulging fontanelle and neck stiffness were reported in less than 20% of neonates.

Symptoms and signs of bacterial meningitis versus those of viral or aseptic meningitis

All children

Clinical findings from two studies were available for this age group. The studies identified compared the frequency of clinical features between children who were evaluated for possible meningitis and those who were subsequently identified as having bacterial or viral meningitis based on spinal fluid examinations. The evidence was limited for several reasons. First, the studies were small (n=119 and n=92, respectively). Second, the spectrum of viral meningitis was likely to be more severe than that in a 'typical' group of children with viral meningitis because all the children had spinal fluid examinations (so they must have been sufficiently suggestive clinically of meningitis to require invasive testing). Third, neither of the studies included clinical features identified before admission to hospital, and so they were likely to represent a more severe spectrum. Finally, diagnostic characteristics (for example sensitivity and specificity) of clinical features were not reported in the studies.

Symptoms and signs of bacterial meningitis were compared to those of viral meningitis in one study and aseptic meningitis in the other study. Although nausea, vomiting, headache and neck stiffness were reported more frequently with viral meningitis, more children with bacterial meningitis presented with the more serious symptoms of fever and seizures. Photophobia was not a predictor of meningitis type.

The second study captured more serious clinical outcomes (shock, lethargic or comatose state, and toxic or moribund state) and these were reported more frequently in children with bacterial meningitis than in those with aseptic meningitis. Typical meningitis signs (Brudzinski's sign, Kernig's sign and neck stiffness) were reported more frequently in bacterial meningitis in contrast to the first study.

Children under 2 years

One study showed that in children under 2 years there was no difference in the prevalence of shock between those with bacterial and aseptic meningitis. All other symptoms recorded (lethargic or comatose state, toxic or moribund state, bulging fontanelle, neck stiffness, Brudzinski's sign, Kernig's sign) were reported more frequently in bacterial meningitis.

All the evidence identified in relation to prevalence of symptoms and signs of bacterial meningitis and meningococcal septicaemia is summarised in table 3.2 (see section 3.2). The GDG interpretation of the evidence and recommendations relating to symptoms and signs of bacterial meningitis are presented at the end of section 3.2.

3.2 Symptoms and signs of meningococcal septicaemia

Introduction

Identifying children and young people who may have meningococcal disease can be difficult. In some patients the illness may be obvious, while in others it may be difficult to differentiate from more common self-limiting infections. There are several reasons why meningococcal disease can present a diagnostic challenge in clinical settings providing first contact care, such as primary care or emergency departments. First, the disease is very rare and so most healthcare professionals will see only one or two cases in their entire career. It is, therefore, difficult for many healthcare professionals to gain much experience in recognising the disease. Second, patients may present at an early stage of the disease, before obvious features have had time to emerge. At this stage clinical features may be vague and non-specific. Third, the disease progresses very rapidly, with most children being admitted to hospital within about 24 hours of the illness starting. This can leave little time to 'wait and

see' if clinical features are evolving. Finally, the frequency of clinical features varies between children of different ages.

Clinical question

In children and young people under 16 years of age, what symptoms and signs, or combination of symptoms and signs, are predictive of meningococcal septicaemia?

Previous UK guidelines

'Feverish illness in children', NICE clinical guideline 47[25] contains recommendations relating to signs and symptoms of meningococcal disease which were based on three prospective studies and one retrospective study. Any child presenting with fever and rash may have meningococcal disease if any of the following features are present:

- ill-looking child
- lesions larger than 2mm in diameter
- capillary refill time of 3 seconds or longer
- neck stiffness.

The SIGN guideline on management of invasive meningococcal disease in children and young people[27] recommends that the following features in an ill child should prompt consideration of diagnosis of invasive meningococcal disease:

- petechial rash
- altered mental state
- cold hands and feet
- extremity pain
- fever
- headache
- neck stiffness, and
- skin mottling.

Studies considered in this section

All study designs evaluating symptoms and signs, or combinations of symptoms and signs, which may be predictive of meningococcal septicaemia were considered for this section. Where possible, the diagnostic accuracy of symptoms and signs was reported. In most studies, there were insufficient data to calculate such values. Only studies from high-income settings were included because of differences in the patterns of presentation of meningococcal disease in countries where primary care is unavailable and children present late to secondary care. Retrospective studies with more than 50 cases were included.

Overview of available evidence

Ten studies were included, of which one was a systematic review[41] [EL=2+], three were prospective cohort studies[42-44] [EL=2+ and II] and six were retrospective case series[45-50] [EL=3]. The three prospective cohort studies investigated the prevalence of meningococcal disease in children presenting with a petechial or haemorrhagic rash. The retrospective review studies involved children and young people with confirmed or probable meningococcal disease and described the prevalence of presenting symptoms. Only one study specifically reported symptoms and signs of meningococcal septicaemia[46] [EL=3].

Review findings

A systematic review of mainly descriptive studies[41] (1998) [EL=2+] examined current knowledge on symptoms and signs of meningococcal disease. The review included a total of eight studies; all except two reported clinical findings from the time of hospital admission, although some also included information from GP referral letters. All except two studies were conducted retrospectively. Only one study used primary care data for the recognition of meningococcal disease. The sample size in the studies ranged from 69 to 298. Three studies included in the review involved adults (20% or less of the study population).

Presentation with *N. meningitidis* colonisations ranged from non-specific acute febrile illness through meningitis to fulminant septicaemia with purpuric rash and shock. Fever was present in 71% to 100% of cases, vomiting in 34% to 76% of cases and lethargy in 28% to 89% of cases. Non-specific upper respiratory tract symptoms were reported in up to half of patients in the week before admission to hospital.

For some symptoms the range of prevalence was very wide: neck stiffness was reported in six studies and ranged from 11% to 79% of cases; convulsions were reported in five studies and ranged from 4% to 21%; and lethargy, reported in three studies, ranged from 21% to 89%.

Features specific for meningococcal disease (petechial or purpuric rash) were reported in seven studies and ranged from 48% to 80% of cases. The presence of neck stiffness and rash was reported in only one study and was recorded in 26% of cases. Details of signs and symptoms reported in each study included in the review are presented in table 3.1.

A prospective cohort study[43] (1982–1983) [EL=2+] sought to determine the prevalence of meningococcal disease in children with fever and petechiae presenting to the emergency department of a tertiary care hospital in the USA. The study included 190 patients enrolled with the following selection criteria: presence of fever or history of fever (above 38°C); petechial rash; and age less than 21 years. The number of petechiae was measured using a scale of 0 to 2 (for example 0 indicated less than 10 petechiae and 2 indicated generalised petechiae). The age range of patients was 3 months to 15 years. Of children who presented with fever and petechiae, 7% (13 out of 190) had meningococcal disease (eight children had meningococcal meningitis; five had bacteraemia caused by *N. meningitidis*). Two children had bacteraemia caused by other organisms. Patients with invasive bacterial disease (bacteraemia without meningitis) and patients with meningitis only appeared more ill, were more likely to have signs of meningeal irritation and were more likely to have petechiae below the nipple line compared with patients with non-bacteraemic disease.

A prospective cohort study[42] (1993–1996) [EL=II] determined criteria for early distinction between meningococcal disease and other conditions with similar clinical features, and aimed to identify other causes for haemorrhagic rashes accompanied by fever. The study included 264 infants and children admitted to paediatric departments in five Danish hospitals . Inclusion criteria were: presence of haemorrhages in the skin, irrespective of size, detected at admission or during the stay in hospital; rectal temperature above 38°C at some time within the 24 hours before inclusion; and age greater than 1 month and less than 16 years. An aetiological agent was identified in 28% subjects. Thirty-nine children (15%) had meningococcal disease. Two percent had another type of invasive bacterial infection. The study reported that five clinical features (presence of characteristic skin haemorrhages, universal distribution of skin haemorrhages, maximum diameter of skin haemorrhages more than 2 mm, poor general condition and nuchal rigidity) independently predicted meningococcal disease (see table 3.1). CIs were wide, reflecting the small numbers of children included in the analysis.

Table 3.1. Clinical features of meningococcal disease

Clinical feature	OR	95% CI
Characteristic skin haemorrhages	11.2	2.5 to 50.7
Universal distribution of skin haemorrhages	5.1	1.1 to 23.7
Maximum diameter of skin haemorrhages >2 mm	7.0	1.5 to 32
Poor general condition	14	3.1 to 62.6
Nuchal rigidity	6.9	1.1 to 44.0

Of children with meningococcal disease, 97% had two or more of the clinical features listed in table 3.1. The sensitivity and false positive rates were reported for combinations of the five clinical features listed. The sensitivity and false positive rates for a child or young person with one or more clinical features were 97% and 49% respectively; for two or more clinical features, they were 97% and 12% respectively; and for three or more clinical features they were 82% and 5% respectively.

A prospective cohort study[44] (1998–1999) [EL=II] examined which clinical features and investigations in children with a non-blanching rash predicted meningococcal infection. The study included 233 infants and children aged 15 years and younger with a non-blanching rash admitted to a paediatric accident and emergency department in the UK. Petechiae were defined as non-blanching spots in the skin, less than 2 mm in diameter, known to be new in onset. The lesions were classed as purpura if they were more than 2 mm in diameter. Fifteen children with obvious alternative diagnoses (including Henoch–Schonlein purpura, idiopathic thrombocytopenic purpura, acute leukaemia and a known clotting disorder) were excluded. Twenty-four children (11%) had proven meningococcal disease.

Compared to children who did not have meningococcal infection, children with meningococcal infection were more likely to be 'ill' (OR 16.7, 95% CI 5.8 to 47.6), to have an axillary temperature more than 38.5°C (OR 8.0, 95% CI 2.7 to 23.8), purpura (OR 37.2, 95% CI 11.7 to 118.3) and a capillary refill time of more than 2 seconds (OR 29.4, 95% CI 9.4 to 92.6). The sensitivities, specificities, PPVs and NPVs were:

- appearing 'ill': sensitivity 79%, specificity 81%, PPV 35%, NPV 97%
- purpura: sensitivity 83%, specificity 88%, PPV 47% and NPV 98%
- fever of more than 38.5°C: sensitivity 58%, specificity 81%, PPV 27%, NPV 94%
- fever of more than 37.5°C: sensitivity 79%, specificity 55%, PPV 18%, NPV 95%
- capillary refill more than 2 seconds: sensitivity 83%, specificity 85% PPV 42%, NPV 98%.

A retrospective case series[50] [EL=3] conducted in a UK hospital investigated clinical features of meningococcal disease in children and young people under 16 years. The study included 69 children (31 males [mean age 1.75 years] and 38 females [mean age 2.73 years]). On presentation, 56 of the children (81%) had a temperature higher than 38˚C and 41 (60%) had shock and/or an abnormal neurological sign. Twenty-three children over the age of 3 years presented with a headache, although the total number of children over 3 years was not specified. On admission, 34 children (49%) had a petechial rash, compared to 13 (39%) with a non-petechial rash. Among five deaths reported, all five children were severely ill at presentation and three (60%) had petechial rash on admission.

A retrospective case series[46] conducted in New Zealand [EL=3] examined the predominant presenting features of patients notified with probable or suspected meningococcal disease in the Auckland area in the 18 months from January 1998 (n=248, median age 4 years, range 1 month to 88 years). The study analysed all probable cases of meningococcal disease (clinically compatible but without serological or bacteriological confirmation) and confirmed cases (those clinically compatible cases where laboratory tests isolated *N. meningitidis* from a normally sterile site, or meningococcal antigen in CSF, or a positive polymerase chain reaction [PCR]). Presenting features were extracted from initial admission notes, GP referral letters or ambulance observer sheets by age group (child if under 10 years, young person if 10 years or older) and discharge diagnosis (septicaemia or meningitis or both).

In children, fever was present in 96% of cases, rash in 66% of cases, lethargy in 64%, vomiting and nausea in 59%, irritability in 45%, refusing food and drink in 42%, headache in 27% and cough in 27% of cases. In young people fever was present in 92% of cases, headache in 81%, vomiting and nausea in 77%, muscle ache or joint pain in 65%, rash in 64%, lethargy in 57%, neck stiffness in 53% and chills in 39%. The most common presenting features of meningococcal disease in those who had septicaemia at discharge were fever (98%), rash (70%), vomiting and nausea (64%) and lethargy (60%). Those who had meningitis as the diagnosis at discharge most commonly presented with fever (93%), vomiting and nausea (66%), lethargy (64%) and rash (58%).

A retrospective case series conducted in the UK[47] (1997) [EL=3] used a telephone questionnaire to study 103 cases of all ages with a clinical diagnosis of meningococcal meningitis. Patients were classified as having meningitis in 46 cases (45%) and meningitis with septicaemia in 57 cases (55%). In the age group 0 to 4 years the most common presenting features for meningococcal meningitis and septicaemia were fever (98% of cases), rash (83%), drowsiness (80%), vomiting (67%) and neck stiffness (57%). Among children aged 5 to 14 years the most common clinical features were fever (94% of cases), rash (94%), neck stiffness (82%), headache (76%) and drowsiness and vomiting (53% each). Among cases aged

15 to 24 years the most common clinical features were fever (100% of cases), rash and neck stiffness (72%), headache (67%) drowsiness (50%) and intensive care admission (50%). Shock was reported in 31% of children aged 0 to 4 years, and in 35% of children aged 5 to 14 years. Nine percent of patients died, 14% (8 out of 57) had meningitis and septicaemia and 4% (2 out of 46) had predominantly meningitis.

A retrospective case series[45] [EL=3] sought to determine the frequency of extremity pain or refusal to walk in children with meningococcal disease. Medical records of 274 people with invasive meningococcal disease who were aged under 20 years were reviewed. Patients with signs or symptoms of extremity pain or refusal to walk were identified on the basis of history or physical examination. A total of 45 patients (16%) had extremity symptoms as part of their presenting histories and/or at physical examination. Children with meningococcal disease who presented with extremity symptoms were significantly older than those without extremity symptoms (mean age 77.9 months versus 44 months, $P < 0.001$).

A retrospective case series[48] (1995–2000) [EL=3] reviewed admission records of 407 children with invasive meningococcal disease in two paediatric tertiary referral centres and two regional paediatric units in Ireland. Symptoms that occurred before hospitalisation included fever (present in 97–99% of cases), rash (present in 84–88% of cases), irritability (present in 35–36% of cases) and neck stiffness (present in 5-6% of the cases). All the values reported were dependent on serotype.

A retrospective case series[49] [EL=3] aimed to determine the frequency and time of onset of clinical features of meningococcal disease to enable clinicians to make an early diagnosis before admission to hospital. The study included 448 children aged 16 years or younger. Most children had only non-specific symptoms in the first 4 to 6 hours, but almost all were admitted to hospital within 24 hours. The most common early features were cold hands and feet (35–47%), leg pain (31–63%, excluding infants) and abnormal colour (17–21%, described as pallor or mottling). Haemorrhagic rash was reported in 42–70% of cases. Meningism was reported in about half the children aged over 5 years (46–53%), and about half of these children presented with photophobia. The most common late feature was confusion or delirium (43–49% of cases).

In all age groups symptoms progressed in the following order: fever, symptoms of sepsis, haemorrhagic rash, impaired consciousness and meningism. Three features of sepsis occurred earlier in the illness: these were leg pain (median 7 hours, 37%), abnormal skin colour (10 hours, 18.6%) and cold hands and feet (12 hours, 43.2%). The classical features of haemorrhagic rash, meningism and impaired consciousness developed later (median onset 13–22 hours). Seventy-two percent of children had earlier symptoms (leg pains, cold hands and feet, and abnormal skin colour) that developed first at a median time of 8 hours.

Evidence statement

The diagnostic accuracy of symptoms and signs (individually or in combination) for identifying meningococcal septicaemia (or disease) in primary and secondary care settings was not reported in most of the studies included in the review. Children and young people with meningococcal disease present with a wide variety of clinical features, depending on their age, the duration of illness, and whether they have focal infection (for example meningitis) or septicaemia. Evidence shows that in the initial stages of meningococcal disease, children and young people have non-specific features of a febrile illness which may be similar to those seen with minor respiratory or gastrointestinal illnesses, such as coryza and diarrhoea. Thus meningococcal disease is not always obvious at the child's or young person's initial presentation to primary or emergency care. The vast majority of children and young people with meningococcal disease present with fever, nausea and vomiting, drowsiness and irritability, and decreased appetite, but these are relatively non-specific clinical features.

All the evidence identified in relation to prevalence of symptoms and signs of bacterial meningitis and meningococcal septicaemia is summarised in table 3.2.

Table 3.2. Prevalence of symptoms and signs in children and young people with bacterial meningitis, meningococcal disease and meningococcal septicaemia[a]

Symptom or sign	Prevalence range (number of studies)		
	Bacterial meningitis	**Meningococcal disease**	**Meningococcal septicaemia**
Fever	66–97% (10)	58–97% (7)	98% (1)
Vomiting or nausea	18–70%(10)	44–76% (6)	64% (1)
Rash[b]	9–62% (6)	59–100% (9)	70% (1)
Headache	3–59% (7)	16–49% (5)	40% (1)
Lethargy	13–87% (6)	36–65% (3)	59% (1)
Coughing	n/a (0)	15–27% (2)	33% (1)
Irritable or unsettled	21–79% (8)	36–67% (3)	32% (1)
Runny nose	n/a (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7–65% (3)	30% (1)
Refusing food or drink	26–76% (4)	13–60% (3)	27% (1)
Altered mental state[c]	26–93% (6)	45–81% (3)	n/a (0)
Stiff neck[a]	13–74% (13)	5–71% (6)	n/a (0)
Impaired consciousness	60–87% (4)	10–72% (2)	n/a (0)
Unconsciousness	4–18% (4)	n/a (0)	n/a (0)
Chills or shivering	n/a (0)	39% (1)	n/a (0)
Photophobia	5–16% (2)	2–31% (5)	n/a (0)
Respiratory symptoms	25–49% (4)	16–23% (2)	n/a (0)
Breathing difficulty[b]	13–34% (4)	11% (1)	n/a (0)
Cold hands or feet	n/a (0)	43% (1)	n/a (0)
Shock	8–16% (2)	27–29% (2)	n/a (0)
Seizures[b]	14–38% (12)	7–17% (3)	n/a (0)
Diarrhoea	21–29% (2)	7–9% (2)	n/a (0)
Abdominal pain or distension	17% (1)	4% (1)	n/a (0)
Leg pain	n/a (0)	11–37% (2)	n/a (0)
Thirst	n/a (0)	8% (1)	n/a (0)
Sore throat, coryza or throat infection	18% (1)	24% (1)	n/a (0)
Ill appearance	n/a (0)	79% (1)	n/a (0)
Capillary refill time >2 seconds	n/a (0)	83% (1)	n/a (0)
Hypotension	n/a (0)	28% (1)	n/a (0)
Abnormal skin colour	n/a (0)	19% (1)	n/a (0)
Bulging fontanelle[d]	13–45% (4)	n/a (0)	n/a (0)
Ear infection or ear, nose and throat infections[e]	18–49% (4)	n/a (0)	n/a (0)
Chest infection	14% (1)	n/a (0)	n/a (0)
Brudzinski's sign	11–66% (2)	n/a (0)	n/a (0)
Kernig's sign	10–53% (3)	n/a (0)	n/a (0)
Abnormal pupils	10% (1)	n/a (0)	n/a (0)
Cranial nerve pair involvement	4% (1)	n/a (0)	n/a (0)
Toxic or moribund state	3–49% (2)	n/a (0)	n/a (0)
Back rigidity	46% (1)	n/a (0)	n/a (0)
Paresis	6% (1)	n/a (0)	n/a (0)
Focal neurological deficit	6–47% (3)	n/a (0)	n/a (0)

n/a: not applicable

[a] Classification of conditions presented in the table reflects the terminology used in the evidence

[b] Some studies appear twice for one symptom or sign if they reported data for subgroups
[c] Includes confusion, delirium and drowsiness. Some studies appear twice if they have reported confusion and delirium separately
[d] The age ranges in the studies were 0–14 years, 0–2 years, 0–12 months and 0–13 weeks
[e] One study reported the number of children and young people with ear nose and throat infections; the other studies reported the number of ear infections only

GDG interpretation of the evidence

The majority of evidence reviewed for the guideline did not distinguish clearly between symptoms and signs of meningococcal septicaemia, meningococcal meningitis and other bacterial causes of meningitis. The data were also limited in that they were obtained from retrospective studies. Prospective studies to identify meningococcal septicaemia and so on in children and young people with fever, for example, would have been more useful for guiding healthcare professionals in the recognition of these conditions. The GDG found no studies which provided frequencies of clinical features in children with bacterial meningitis before admission to hospital. Studies of clinical features noted at or during hospital admission were limited in quality. In particular, none of them allowed the sensitivity or specificity of clinical features to be calculated. The studies were also varied in the type of bacterial meningitis, stage of the illness, type of hospital setting and country. These studies were also likely to be subject to work-up bias in that only children who were clinically suspected to have meningitis (for example because they had neck stiffness) were likely to proceed to have the reference test (lumbar puncture).

The GDG used the evidence presented in table 3.2 as a starting point for formulating recommendations. GDG members then used their clinical judgement and experience to produce a comprehensive overview of symptoms and signs that should lead healthcare professionals to consider bacterial meningitis, meningococcal disease and meningococcal septicaemia. Only one study reported symptoms and signs specifically for meningococcal septicaemia, whereas several studies provided prevalence data for children and young people with 'meningococcal disease', and the GDG used its clinical experience to extrapolate from the meningococcal disease data to meningococcal septicaemia.

The available evidence shows that children and young people with bacterial meningitis are likely to have non-specific features of infection (such as fever, vomiting, irritability and upper respiratory tract symptoms). Many, but not all, children and young people with bacterial meningitis will have neck stiffness or decreased level of consciousness. A minority of children and young people will have seizures or shock. Children under 2 years are more likely to present with irritability, lethargy and decreased level of consciousness, and some will have a bulging fontanelle and neck stiffness. Bacterial and viral causes of meningitis cannot be differentiated reliably based on clinical features alone. However, children with viral meningitis are less likely to have shock, decreased level of consciousness or seizures than are those with bacterial meningitis.

Symptoms and signs that are considered typical of meningeal irritation (headache, neck stiffness or photophobia) occur in a minority of children and young people before hospital admission, but they are more likely to occur in older children and young people.

In the early stages of illness the majority of children and young people experience pain in the extremities, paleness (mottled or pallid appearance, or cyanosis) and cold extremities (despite the presence of fever). In later stages of illness, children and young people may have an altered mental state, hypotension and respiratory symptoms.

Clinical features vary with age. Although fever is a common non-specific symptom it is more often absent in neonates. Babies are less likely to have symptoms and signs of meningism, extremity pain or haemorrhagic rash, whereas older children and young people are more likely to have meningism, confusion, haemorrhagic rash or extremity pain.

The majority of children and young people with meningococcal disease will develop a haemorrhagic rash during their illness, but this may be absent in the pre-hospital phase of the illness, and may initially be blanching or macular in nature.

Although the presence of petechiae in a febrile child or young person can indicate the presence of serious bacterial infection, especially *N. meningitidis*, the majority of children and young people seen with petechial rashes in emergency and primary care settings will not have meningococcal disease. The clinical features in a febrile child or young person with petechiae that are more likely to suggest meningococcal disease are an overall ill appearance, a widespread distribution of petechiae, petechiae that are larger than 2 mm, prolonged capillary refill time and signs of meningeal irritation.

No evidence was identified in relation to the ease with which rashes could be identified on darker skin tones. The GDG discussed this issue and noted that healthcare professionals should check the soles of the feet, the palms of the hands and conjuctivae (the membranes lining the inside of the eyelids and covering the eyeballs) in children and young people with darker skin tones.

Healthcare professionals should be aware of the legal requirement under the Health Protection (Notification) Regulations 2010[*] to notify a proper officer of the local authority urgently on suspicion of meningitis or meningococcal septicaemia. Urgent notifications are to be made orally, usually by telephone, as soon as is reasonably practicable and always within 24 hours. Oral notification should be followed by a written notification to be received by the proper officer within 3 days of the clinical suspicion being formed. The Department of Health has issued guidance on health protection legislation which explains the notification requirements on registered medical practitioners (and, from October 2010, on diagnostic laboratories that test human samples).[†22] The HPA has issued guidance on public health management of meningococcal disease in the UK[15] which covers laboratory investigation of suspected cases, local and national public health surveillance, and public health action after a case to prevent secondary infection, including chemoprophylaxis (using antibiotics and/or vaccines) in close contacts, the wider community and healthcare settings.[‡] Some specific measures specified in the HPA guidance are outlined in section 2.1.

Recommendations

Bacterial meningitis and meningococcal septicaemia in children and young people — symptoms, signs and initial assessment

This guideline assumes that fever in children younger than 5 years will be managed according to 'Feverish illness in children' (NICE clinical guideline 47) until bacterial meningitis or meningococcal septicaemia is suspected.

Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 3.3.

- Be aware that:
  - some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
  - children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia, and the symptoms and signs may become more severe and more specific over time.
- Recognise shock (see table 3.3) and manage urgently in secondary care.

[*] See www.opsi.gov.uk/si/si2010/uksi_20100659_en_1

[†] See www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510

[‡] (see HPA guidance at www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261

Table 3.3. Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Symptom/sign	Bacterial meningitis (meningococcal meningitis and meningitis caused by other bacteria)	Meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia)	Meningococcal septicaemia	Notes
Common non-specific symptoms/signs				
Fever	✓	✓	✓	Not always present, especially in neonates
Vomiting/nausea	✓	✓	✓	
Lethargy	✓	✓	✓	
Irritable/unsettled	✓	✓	✓	
Ill appearance	✓	✓	✓	
Refusing food/drink	✓	✓	✓	
Headache	✓	✓	✓	
Muscle ache/joint pain	✓	✓	✓	
Respiratory symptoms/signs or breathing difficulty	✓	✓	✓	
Less common non-specific symptoms/signs				
Chills/shivering	✓	✓	✓	
Diarrhoea, abdominal pain/distension	✓	✓	NK	
Sore throat/coryza or other ear, nose and throat symptoms/signs	✓	✓	NK	
More specific symptoms/signs				
Non-blanching rash	✓	✓	✓	Be aware that a rash may be less visible in darker skin tones – check soles of feet, palms of hands and conjunctivae
Stiff neck	✓	✓	NK	
Altered mental state	✓	✓	✓	Includes confusion, delirium and drowsiness, and impaired consciousness
Capillary refill time more than 2 seconds	NK	✓	✓	
Unusual skin colour	NK	✓	✓	
Shock	✓	✓	✓	
Hypotension	NK	✓	✓	
Leg pain	NK	✓	✓	
Cold hands/feet	NK	✓	✓	
Back rigidity	✓	✓	NK	
Bulging fontanelle	✓	✓	NK	Only relevant in children aged under 2 years
Photophobia	✓	✓	X	
Kernig's sign	✓	✓	X	
Brudzinski's sign	✓	✓	X	
Unconsciousness	✓	✓	✓	
Toxic/moribund state	✓	✓	✓	
Paresis	✓	✓	X	

Focal neurological deficit including cranial nerve involvement and abnormal pupils	✓	✓	X	
Seizures	✓	✓	X	
Signs of shock • Capillary refill time more than 2 seconds • Unusual skin colour • Tachycardia and/or hypotension • Respiratory symptoms or breathing difficulty • Leg pain • Cold hands/feet • Toxic/moribund state • Altered mental state/decreased conscious level • Poor urine output				
✓ symptom/sign present X symptom/sign not present NK not known if a symptom/sign is present (not reported in the evidence)				

Be alert to the possibility of bacterial meningitis or meningococcal septicaemia when assessing children or young people with acute febrile illness.

Healthcare professionals should be aware that classical signs of meningitis (neck stiffness, bulging fontanelle, high-pitched cry) are often absent in infants with bacterial meningitis.*

Be aware that children and young people with bacterial meningitis commonly present with non-specific symptoms and signs, including fever, vomiting, irritability, and upper respiratory tract symptoms. Some children with bacterial meningitis present with seizures.*

Consider other non-specific features of the child's or young person's presentation, such as:

- the level of parental or carer concern (particularly compared with previous illness in the child or young person or their family),
- how quickly the illness is progressing, **and**
- clinical judgement of the overall severity of the illness.

In children and young people with suspected bacterial meningitis or meningococcal septicaemia, undertake and record physiological observations of heart rate, respiratory rate, oxygen saturations, blood pressure, temperature, perfusion (capillary refill) and neurological assessment (for example the Alert, Voice, Pain, Unresponsive [AVPU] scale) at least hourly.

Healthcare professionals should be trained in the recognition and management of meningococcal disease.

Notify a proper officer of the local authority urgently on suspicion of meningitis or meningococcal septicaemia. This is a legal requirement under the Health Protection (Notification) Regulations 2010.†

Be aware of 'Guidance for Public Health Management of Meningococcal Disease in the UK' (Health Protection Agency Meningococcus Forum, 2006).‡

* This recommendation is from 'Feverish illness in children' (NICE clinical guideline 47). See www.nice.org.uk/guidance/CG47

† See www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health Protection Legislation Guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH_114510

‡ See www.hpa.org.uk

Research recommendations

Bacterial meningitis and meningococcal septicaemia in children and young people — symptoms, signs and initial assessment

What are the symptoms and signs of bacterial meningitis and meningococcal disease in children and young people aged under 16 years that differentiate between these conditions and minor self-limiting infections (including those characterised by fever)?

Why this is important

Research is needed from primary and secondary care settings on the diagnostic accuracy of symptoms and signs suggestive of bacterial meningitis and meningococcal disease in children and young people. The research should focus on identifying individual symptoms and signs, or groups of symptoms and signs that are effective as predictors of bacterial meningitis and meningococcal disease. These symptoms and signs should also differentiate effectively between these conditions and minor self-limiting infections. The research should include consideration of the effectiveness of symptoms and signs of acute feverish illness as predictors of meningococcal disease. Consideration should also be given to the age of the child or young person (in terms of the relevance of particular symptoms and signs) and the clinical setting at presentation. Suitable study designs would include diagnostic accuracy studies as well as observational studies (such as case–control studies), and the research could include a systematic review of studies that have already been published.

4 Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

4.1 Pre-hospital antibiotics for suspected bacterial meningitis and meningococcal disease

Introduction

Children and young people in the UK with bacterial meningitis or meningococcal disease will present to one of several first-contact settings including general practice, out of hours or walk-in centres, emergency departments or NHS Direct, or to paramedics. The priorities for healthcare professionals in these settings are to:

- identify any immediately life-threatening features
- assess the likelihood of serious illness or self-limiting illness, without necessarily diagnosing a particular condition
- determine a source of the illness to direct specific treatment
- make appropriate management decisions based on the results of assessment.[25]

Healthcare professionals will occasionally encounter children and young people with symptoms and signs suggestive of bacterial meningitis or meningococcal disease (see chapter 3). Having identified children and young people with suspected bacterial meningitis or meningococcal disease in the pre-hospital setting, they should be transferred to secondary care urgently. This will often involve contact with the emergency ambulance (999) services to arrange transport and care during transport, and communicating essential clinical information (for example, relevant past medical history, medications and any drug allergies) to hospital-based medical teams, usually by telephone.

Guidance on the administration of parenteral antibiotics to people with suspected meningococcal infection in pre-hospital settings (PL/CMO/99/1)[51] was issued by the Chief Medical Officer (CMO) in 1999*. The guidance emphasised the need for timely recognition of meningococcal infection and urgent transfer to hospital. The guidance stated that

* See www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004235

benzylpenicillin should be carried by GPs in emergency bags (and, presumably, stocked by out of hours services) and administered to patients with suspected meningococcal infection. The guidance also stated that GPs should not be concerned that administering penicillin would delay transfer of the patient to hospital or mask diagnosis. The rationale for this advice was that meningococcal disease usually progresses rapidly and that administering an antibiotic that is active against *N. meningitidis* at the earliest possible opportunity should reduce mortality and morbidity. Conversely, it has been suggested that antibiotic-mediated bacteriolysis might worsen disease initially and that antibiotics might be more safely administered in hospital.[52]

Current guidance from the CMO does not support pre-hospital administration of parenteral penicillin in children with suspected bacterial meningitis in the absence of a non-blanching rash. There are several reasons why it has been customary to administer antibiotics in hospital rather than in the community for suspected bacterial meningitis without a non-blanching rash, including:

- the slower rate of progression of disease compared with septicaemia
- the usual practice of collecting cerebrospinal fluid (CSF) before administering antibiotics; and
- the difficulty in distinguishing bacterial meningitis from other illnesses that do not require antibiotics.

Furthermore, data on use of steroids as adjunctive therapy for bacterial meningitis indicates that the steroids should be administered before or with the first dose of antibiotics, so that administration of antibiotics would have to be delayed until the diagnosis has been made by lumbar puncture in hospital.

Clinical questions

Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome?

Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?

Previous UK guidelines

'Feverish illness in children', NICE clinical guideline 47[25] recommends that children with suspected meningococcal disease be given parenteral antibiotics (benzylpenicillin or a thirdgeneration cephalosporin) at the earliest opportunity.

The SIGN guideline on management of invasive meningococcal disease in children and young people[27] recommends that parenteral antibiotics (benzylpenicillin or cefotaxime) should be given as soon as invasive meningococcal disease is suspected, and this action should not be delayed while investigations are being undertaken.

Studies considered in this section

Studies evaluating the effects of pre-hospital antibiotics in children and young people with suspected bacterial meningitis or meningococcal disease were considered for this section. Studies involving only adults were excluded. All study designs were included. Studies were included only if they were conducted in settings where primary care is available for most children.

Overview of available evidence

No high-quality evidence was found on the effects of pre-hospital antibiotics in children and young people with suspected bacterial meningitis. All the evidence identified related to suspected meningococcal disease and came from six studies, one of which was a systematic review of RCTs [EL=1++], one was a systematic review of observational studies [EL=2+], one was a case–control study [EL=2++], two were retrospective cohort studies [EL=2+ and 2–] and one was a retrospective review of hospital records [EL=3].

Review findings

A systematic review[53] (search date 2007) [EL=1++] assessed the effectiveness and safety of pre-admission antibiotics in people of all ages with suspected meningococcal disease. The search included RCTs and quasi-RCTs, but no RCTs were found that compared preadmission antibiotics with placebo or no treatment.

A systematic review of 14 observational studies[54] [EL=2+] evaluated the effectiveness of preadmission antibiotics in reducing mortality from meningococcal disease in people of all ages. Five of the studies reported data for people who were given only oral antibiotics (that is, no parenteral antibiotics) before admission. In these studies, the oral antibiotics were usually given because of suspected respiratory tract infection, rather than suspected meningococcal disease. As the population of interest in this guideline is children and young people with suspected bacterial meningitis or meningococcal disease, data relating to oral antibiotics are not reported here. Twelve of the studies included in the systematic review (involving a total of 3357 people) included information on preadmission parenteral antibiotics: eight of these studies showed a beneficial effect of giving parenteral antibiotics before admission and four reported adverse effects. Relative risks (RRs) for mortality in these studies ranged from 0.16 (95% CI 0.01 to 2.63) to 2.36 (95% CI 0.25 to 22.54). Only one study reported a statistically significant effect (RR 0.35, 95% CI 0.16 to 0.80). The proportion of people with meningococcal disease who received treatment differed between studies (treatment rates ranged from 15% to 59%, Chi-squared for heterogeneity 11.02, $P = 0.09$, $I^2 = 46\%$) and so studies were considered on an individual basis. The authors of the review could not conclude whether or not antibiotics given before admission had an effect on case fatality rates.

A case–control study conducted in the UK[52] [EL=2++] looked at the use of parenteral penicillin by GPs who had diagnosed meningococcal disease in 26 children who died from the condition and 132 survivors. Administration of parenteral penicillin was associated with increased risk of death (odds ratio [OR] 7.4, 95% CI 1.5 to 37.7) and pre-admission parenteral penicillin was associated with an increased risk of complications, including renal failure, cardiovascular failure, respiratory failure, neurological complications, tissue necrosis requiring excision or amputation (OR 5.0, 95% CI 1.7 to 15.0). Children who received penicillin had more severe disease on admission (median 6.5 versus 4.0, $P = 0.002$). The association between parenteral penicillin and poor outcome may be explained by children who were more severely ill being given penicillin before admission.

A retrospective cohort study conducted in Spain[55] (2009) [EL=2+] examined whether pre-hospital oral antibiotics reduced mortality from invasive meningococcal disease. The study included 848 patients from 31 hospitals, of whom 226 received oral antibiotics before admission. The average age was 10.4 years; children under the age of 1 year were excluded. The mortality rate in those who received pre-hospital antibiotics was 2.7%, compared to 6.9% among those who did not receive antibiotics. The OR for pre-hospital antibiotics was 0.37 (95% CI 0.15 to 0.88) after adjusting for propensity score, time from first symptoms to first dose of antibiotic in hospital and age. After excluding patients whose diagnosis was based solely on clinical suspicions (that is, those for whom there was neither a microbiological culture of *N. meningitidis* from a sterile sample nor a Gram stain compatible with *N. meningitidis*), the OR was 0.4 (95% CI 0.11 to 1.4). The OR for the non-treatment group was 2.7 (95% CI 1.07 to 6.66) after adjusting for propensity score, time from first symptoms to first dose of parenteral antibiotic in hospital and age.

One retrospective cohort study conducted in the UK [56] (1990–1993) [EL=2–] investigated the effects of pre-admission parenteral antibiotics on mortality (data on this outcome were included in the systematic review described above).[54] A further publication from the same study[54] reported long-term sequelae in 46 people with meningococcal disease, of whom 27 had received pre-hospital benzylpenicillin. There was no significant difference in mortality between people given benzylpenicillin before admission to hospital and those who did not receive pre-hospital benzylpenicillin (RR 1.06, 95% CI 0.19 to 5.72). There was no significant difference between the groups in the mean length of hospital stay or in the frequency of sequelae of more than 3 months' duration (seven children were reported to have long-term

sequelae including: partial deafness, oculomotor palsy, seizures, impaired motor skills, arthritis and problems at school). The difference between the groups was reported as non-significant but no *P* value was reported.

A retrospective review of hospital records[57] (1985–2002) [EL=3] examined risk factors associated with mortality in 293 people of all ages with meningococcal disease admitted to a university hospital in Western Norway. There was no significant difference in mortality between people who received pre-admission antibiotics and those who were not treated with antibiotics before admission ($P = 0.34$). The study did not report whether pre-admission antibiotics were given orally or parenterally, but the setting suggests that antibiotics were given parenterally.

Evidence statement

No high-quality evidence was identified in relation to the use of pre-hospital antibiotics for suspected bacterial meningitis. For children and young people with meningococcal disease the available evidence does not allow any conclusion to be drawn about whether or not pre-hospital parenteral antibiotics affect mortality or morbidity.

GDG interpretation of the evidence

The GDG considered that the management of bacterial meningitis and meningococcal septicaemia should be undertaken urgently in the hospital setting because delay in transfer to secondary care is associated with poor outcome. The GDG recommended, therefore, that primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Suspected bacterial meningitis without non-blanching rash

Pre-hospital antibiotics are not currently recommended for children and young people with suspected bacterial meningitis without a non-blanching rash and the GDG found no evidence to direct a change in practice. Such children and young people should be transferred directly to secondary care without giving parenteral antibiotics (unless urgent transfer to hospital is not possible, in which case antibiotics should be given as recommended in section 6.1).

Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia)

Although the GDG found no evidence to direct a change in practice from the advice of the CMO (PL/CMO/99/1)[51] (that is, to give parenteral antibiotics to people with suspected meningococcal disease), their interpretation of the available evidence was that it did not provide strong support for the recommendation. The GDG considered that a strong recommendation to give antibiotics in the community could result in delayed access to secondary care. The GDG's view was that administration of antibiotics in combination with fluid resuscitation was the priority to prevent death in children and young people with meningococcal disease, and that this was currently undertaken almost exclusively in secondary care. For this reason, the consensus view of the GDG was that parenteral antibiotics should be administered as early as practicable in meningococcal disease, but that the priority in clinical management should be immediate access to hospital care.

Benzylpenicillin is the most frequently used antibiotic in primary care and the GDG found no evidence to recommend an alternative. The CMO guidance states that benzylpenicillin should be withheld only in children and young people who have a clear history of anaphylaxis after a previous dose and a history of a rash after penicillin administration is not a contraindication.

Recommendations

Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Suspected bacterial meningitis without non-blanching rash

Transfer children and young people with suspected bacterial meningitis without non-blanching rash directly to secondary care without giving parenteral antibiotics.

If urgent transfer to hospital is not possible (for example, in remote locations or adverse weather conditions), administer antibiotics to children and young people with suspected bacterial meningitis.

Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia)

Give parenteral antibiotics (intramuscular or intravenous benzylpenicillin) at the earliest opportunity, either in primary or secondary care, but do not delay urgent transfer to hospital to give the parenteral antibiotics.

Withhold benzylpenicillin only in children and young people who have a clear history of anaphylaxis after a previous dose; a history of a rash following penicillin is not a contraindication.

Research recommendations

Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

Does the administration of pre-hospital antibiotics improve outcomes in children and young people with suspected meningococcal disease?

Why this is important

The GDG has recommended administration of antibiotics (benzylpenicillin) for children and young people with suspected meningococcal disease in the pre-hospital setting, in accordance with advice issued by the Chief Medical Officer (PL/CMO/99/1). However, no evidence was identified to indicate whether such practice improves outcomes. Research is needed to evaluate the effectiveness of administering antibiotics in the pre-hospital setting. Suitable research designs would include observational studies (e.g. cohort studies or case–control studies) to compare outcomes in children and young people with suspected meningococcal disease according to whether or not they receive antibiotics before admission to hospital. The studies could evaluate the effect of immediate versus delayed administration of antibiotics and comparison of outcomes in children and young people in whom meningococcal disease is confirmed after hospital admission, and those in whom an alternative diagnosis is made.

5 Diagnosis in secondary care

5.1 Non-specific tests for meningococcal disease

Introduction

Meningococcal disease in childhood classically presents with a non-blanching rash in a feverish, ill child, although the rash may occur late in the illness or not at all in children who have meningococcal meningitis without septicaemia. Increased public awareness of meningococcal disease has meant that children may present earlier in the course of disease with fever and a petechial rash, although others may not yet appear unwell. Besides meningococcal disease, there are many other infective causes of petechial rashes in febrile children. Healthcare professionals assessing febrile children with rashes are, therefore, faced with deciding which children have invasive meningococcal disease and require immediate antibiotics and supportive therapy and which do not. Non-specific laboratory investigations are part of the diagnostic work-up of these children.

Clinical question

In children and young people up to 16 years of age with a petechial rash, can non-specific laboratory tests (C-reactive protein, white blood cell count, blood gas) help to confirm or refute the diagnosis of meningococcal disease?

Previous UK guidelines

'Feverish illness in children', NICE clinical guideline 47[25] recommends that a full blood count and C-reactive protein should be performed as part of the initial laboratory investigations in:

- infants younger than 3 months with fever
- children older than 3 months with fever without apparent source with:
  - one or more 'red' features (features suggestive of a high risk of serious illness); or
  - one or more 'amber' features (features suggestive of an intermediate risk of serious illness).

The guideline recommends that the clinician should consider taking a blood gas sample in children with 'red features' as guided by the clinical assessment.

Studies considered in this section

All study designs evaluating the usefulness of white blood count, C-reactive protein (CRP) or blood gas for diagnosing meningococcal disease in children and young people with a petechial rash were considered for this section. Studies assessing the predictive ability of laboratory tests to diagnose invasive bacterial illness were included only if most cases of invasive illness were caused by *N. meningitidis*. Studies that included adults were excluded.

Overview of available evidence

Two prospective cohort studies [EL=2+] were found. One study involved children with petechiae and fever; the other study involved children with a non-blanching rash, 80% of whom had petechiae only. Both studies assessed the diagnostic value of white blood cell count and one study assessed the diagnostic value of CRP. No studies were found evaluating

blood gas as an initial investigation for diagnosing meningococcal disease in children with a petechial rash.

Review findings

One prospective cohort study (USA, 1982–1983) [EL=2+] aimed to determine clinical and laboratory predictors of meningococcal disease in children with fever and petechiae admitted to a children's hospital.[43] Of 190 children aged 3 months to 15 years admitted with fever of more than 38°C and petechiae, 15 (8%) had invasive bacterial illness, 13 of whom had meningococcal disease. A total of 39 children (20.5%) had non-bacteraemic illness (S. pyogenes pharyngitis, urinary tract infection or viral infection). The remaining 136 children (71.5%) had no cause identified for their illness. Results were analysed for the 54 children with a confirmed microbiological diagnosis.

The study found that children with invasive bacterial disease had significantly higher mean peripheral white blood cell (WBC) counts and absolute immature polymorphonuclear neutrophil counts (band forms) than children with non-bacteraemic illness (mean white blood count: 17,600 cells/microlitre with invasive bacterial disease versus 11,600 cells/microlitre with non-bacteraemic illness, $P = 0.005$; peripheral band count: 3,717 with invasive bacterial disease versus 523 with non-bacteraemic illness, $P < 0.001$). The accuracy of initial laboratory tests as indicators of invasive bacterial illness in this subgroup weres: peripheral white blood count more than 15,000 cells/microlitre: sensitivity 67%, specificity 85%, positive likelihood ratio 4.5, negative likelihood ratio 0.39; peripheral absolute band form count more than 500 cells/microlitre: sensitivity 80%, specificity 74%; positive likelihood ratio 3.0, negative likelihood ratio 0.27.

If the peripheral white blood count, the peripheral absolute band form count and cerebrospinal fluid (CSF) white blood count were all normal, the likelihood of invasive bacterial illness was small (negative likelihood ratio of peripheral WBC more than 15,000 cells/microlitre or peripheral absolute band form more than 500 cells/microlitre or pleocytosis more than 7 cells/microlitre: 0.11). The high prevalence of invasive bacterial illness in the analysed subgroup (28%) affects the performance characteristics of the diagnostic tests under evaluation and limits the external validity of the study results to children seen in a secondary care setting.

A prospective cohort study (UK, 1998–1999) [EL=2+] assessed whether clinical features and laboratory investigations could predict meningococcal disease in 233 children admitted to a children's Accident and Emergency Department with a non blanching rash.[44] Fifteen children with an obvious alternative diagnosis were excluded and 218 children younger than 15 years were included in the final analysis. Of the 218 children, 11% (24) had laboratory proven meningococcal disease and 80% (175) presented with petechiae only (defined as new-onset, non-blanching spots in the skin, less than 2 mm in diameter), of whom 4 had meningococcal disease. Forty-three children (20%) presented with both petechiae and purpura (non-blanching spots more than 2 mm in diameter), of whom 20 had meningococcal disease. Children with meningococcal disease were more likely to have an abnormal neutrophil count than children who did not have meningococcal disease (OR 2.7, 95% CI 1.1 to 6.5).

As shown in table 5.1, 38% of children without meningococcal disease also had an abnormal neutrophil count and the diagnostic accuracy of an abnormal neutrophil count or an abnormal white blood cell count was low. No child with a CRP less than 6 mg/litre had meningococcal disease. However, the specificity of a CRP of more than 6 mg/litre for predicting meningococcal disease was low (see table 5.1). A CRP of more than 99 mg/litre had a high specificity but a low sensitivity for predicting meningococcal disease, with less than half of children in the study later diagnosed with meningococcal disease having an initial CRP above 99 mg/litre (see table 5.1).

Table 5.1. Accuracy of white blood cell count, neutrophil count and CRP for diagnosing meningococcal disease.[44]

Variable	Sensitivity	Specificity	Positive likelihood ratio[a]	Negative likelihood ratio[a]
Abnormal white blood cell count	58% (39 to 78)	56% (48 to 63)	1.32	0.75
Abnormal neutrophil count	68% (49 to 88)	62% (55 to 69)	1.79	0.52
CRP >6 mg/litre	100% (96 to 100)	54% (47 to 62)	2.17	0
CRP 6–99 mg/litre[a]	52%	58%	1.26	0.81
CRP >99 mg/litre[a]	47%	96%	11.75	0.55

[a] NCC–WCH analysis

Evidence statement

Evidence about the value of initial blood tests for predicting meningococcal disease in children with a petechial rash is limited by the small number of relevant studies.

There is evidence that children with meningococcal disease presenting to secondary care with a petechial rash are more likely to have a higher white blood cell count, a higher band count and an abnormal neutrophil count compared with children who do not have meningococcal disease. None of the above tests had sufficiently high sensitivity or specificity to accurately predict a diagnosis of meningococcal disease. One study found that a combination of normal peripheral white blood count, absolute band form count and CSF white blood count was associated with a low risk of invasive bacterial illness, including meningococcal disease.

There is evidence from one study that children presenting to secondary care with petechiae and fever with an initial CRP less than 6 mg/litre are unlikely to have meningococcal disease. A high CRP of more than 99 mg/litre can be used to identify children at a high risk of meningococcal disease. A high CRP is, however, poorly sensitive for predicting meningococcal disease and the absence of a high CRP cannot be used to rule out meningococcal disease.

No studies were found evaluating the usefulness of blood gas for diagnosing meningococcal disease in children and young people with a petechial rash.

GDG interpretation of the evidence

Children with invasive meningococcal disease may have a higher white cell count and CRP than those with viral infections and those with non-invasive bacterial infections. However, these tests alone cannot be relied on to predict which children have meningococcal disease. Children early in their illness or with rapidly advancing meningococcal disease may have a normal or low WBC count and a normal CRP.

The finding of a high CRP of more than 99 mg/litre is specific but not sensitive for meningococcal disease in children with fever and a rash. A low CRP does not exclude meningococcal disease.

The GDG concluded that a full blood count and CRP should be performed on children with fever (or history of fever) and a petechial rash and the results combined with a thorough clinical assessment for the signs of septicaemia and meningitis. Abnormal results may support the diagnosis where there is uncertainty but normal results cannot be used to exclude the diagnosis.

No evidence was identified in relation to the diagnostic accuracy of measuring blood gas in children and young people with petechial rash. However, 'Feverish illness in children' (NICE clinical guideline 47)[25] recommends taking a sample of blood gas in children with features suggestive of a high risk of serious illness and this is reflected in the GDG's recommendations.

The GDG highlighted the importance of starting empiric antibiotic treatment (with ceftriaxone) immediately in children with signs of bacterial meningitis or meningococcal septicaemia and this is reflected in recommendations included in this section. The clinical and cost effectiveness evidence relating to the choice of empiric antibiotics is presented in section 6.1.

The GDG noted that although polymerase chain reaction (PCR) is a specific test (see section 5.3 for a discussion of the clinical and cost effectiveness evidence relating to PCR), testing should be carried out using the initial blood sample, and so PCR testing is included in the recommendations in this section.

Recommendations

Diagnosis in secondary care

Perform a very careful examination for signs of meningitis or septicaemia in children and young people presenting with petechial rashes (see table 3.3).

Investigation and management in children and young people with petechial rash

Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):

- petechiae start to spread
- the rash becomes purpuric
- there are signs of bacterial meningitis (see table 3.3)
- there are signs of meningococcal septicaemia (see table 3.3)
- the child or young person appears ill to a healthcare professional.

If a child or young person has an unexplained petechial rash and fever (or history of fever) carry out the following investigations:

- full blood count
- C-reactive protein (CRP)
- coagulation screen
- blood culture
- whole-blood polymerase chain reaction (PCR) for *N. meningitidis*
- blood glucose
- blood gas.

In a child or young person with an unexplained petechial rash and fever (or history of fever) but none of the high-risk clinical manifestations (see table 3.3):

- Treat with intravenous ceftriaxone immediately if the CRP and/or white blood cell count (especially neutrophil count) is raised, as this indicates an increased risk of having meningococcal disease.
- Be aware that while a normal CRP and normal white blood cell count mean meningococcal disease is less likely, they do not rule it out. The CRP may be normal and the white blood cell count normal or low even in severe meningococcal disease.
- Assess clinical progress by monitoring vital signs (respiratory rate, heart rate, blood pressure, conscious level [Glasgow Coma Scale and/or APVU], temperature), capillary refill time, and oxygen saturations. Carry out observations at least hourly over the next 4–6 hours.
- If doubt remains, treat with antibiotics and admit to hospital.

If the child or young person is assessed as being at low risk of meningococcal disease and is discharged after initial observation, advise parents or carers to return to hospital if the child or young person appears ill to them.

Be aware that in children and young people who present with a non-spreading petechial

rash without fever (or history of fever) who do not appear ill to a healthcare professional, meningococcal disease is unlikely, especially if the rash has been present for more than 24 hours. In such cases consider:

- other possible diagnoses
- performing a full blood count and coagulation screen.

5.2 Non-specific tests for bacterial meningitis

Introduction

If meningococcal meningitis presents with features of meningococcal sepsis (a non-blanching rash in a feverish, ill child) then non-specific laboratory blood tests will predominantly reflect inflammation in the bloodstream (see non-specific laboratory tests in children with suspected meningococcal disease in section 5.1). However, if a non-blanching rash does not accompany meningitis, the child will present with symptoms and signs suggesting meningitis. Non-specific laboratory investigations are part of the diagnostic work-up. The definitive test for meningitis is a lumbar puncture with laboratory examination of the CSF. In children with contraindications to lumbar puncture, or in clinical situations where medical staff are reluctant to undertake the procedure and CSF results are not available, the blood test results may then be consulted for evidence to confirm or refute the diagnosis of meningitis. The extent to which blood test results are informative about the presence or absence of bacterial meningitis will assist these decisions.

Clinical question

In children and young people under 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?

Previous UK guidelines

No previous guidelines were identified in relation to this question.

Studies considered in this section

All study designs evaluating blood tests for procalcitonin, C-reactive protein or white blood cell count to discern meningitis from other diseases, or to discern bacterial meningitis from viral/aseptic meningitis, were considered for inclusion in this section. The majority of studies were retrospective and only those conducted in high income countries were included.

Studies of adults and children were included where data were presented separately for child participants. Findings are presented for three age groups: all children, infants and neonates.

Overview of available evidence

Predictive value of individual nonspecific blood tests for the differential diagnosis of bacterial meningitis from other illnesses

Procalcitonin

No studies evaluating procalcitonin were identified.

C-reactive protein

Two US studies were found that investigated the value of blood C-reactive protein (CRP) in aiding differentiation of bacterial meningitis from other illnesses. The first of these was a prospective cohort study[58] [EL=II] which compared blood CRP of children with bacterial meningitis (n=10) with a control group which included children with: aseptic meningitis (n=14); extrameningeal bacterial infection (n=10); other febrile illnesses but presenting with symptoms suggestive of bacterial meningitis (meningeal signs and suggestive history (n=33); or suggestive history alone (n=102); or who were aged under 2 months and undergoing a 'sepsis work-up' (n=23). Significantly more children with bacterial meningitis had a blood CRP level of more than 1.0 mg/decilitre compared with children in the control group (8 out of 75

children with CRP more than 1.0 mg/decilitre versus 2 out of 85 children in control group; P = 0.047). This cutoff of CRP level of more than 1.0 mg/decilitre gave a sensitivity of 80%, specificity 55%, positive predictive value 0.11 and negative predictive value 0.98.

An earlier retrospective cohort study[59] (USA, 1984) [EL=III] compared blood CRP of children with bacterial meningitis (n=21) with a control group which included children with aseptic meningitis (n=8), no meningitis (defined as suspected meningitis but with normal CSF findings) (n=50) and leukaemia (n=40). A serum CRP of more than 1 mg/decilitre was found for 20 out of 21 cases (95%) of children with bacterial meningitis, 1 out of 8 cases (13%) of children with aseptic meningitis, 24 out of 50 cases (48%) with no meningitis and 5 out of 40 cases (13%) with leukaemia. Removing the cases with leukaemia this gives 20 out of 21 cases (95%) with bacterial meningitis versus 25 out of 58 (43%) for controls; P < 0.0001 (Fisher's Exact Test). Again removing cases with leukaemia, this cutoff of serum CRP of more than 1 mg/decilitre gave an overall sensitivity of 95% and an overall specificity of 57% (GDG analysis).

White blood cell count

Two US studies were identified that examined blood WBC counts, as shown in table 5.2.

Table 5.2. Blood white blood cell count – descriptive statistics (infants and children of all ages)[a]

Study and evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood WBC count measure and units	Result	P value
Bonsu, 2003[60] [EL=III]	1992–1999 Hib not reported but organisms isolated included *Escherichia coli* (n=11/22) and Group B streptococcus (n=9/22) Age range: 3–89 days	Median (interquartile range) cells/microlitre	BM=10,200 (4000–15,200) Control=11,200 (8500–14,600)	*P* = 0.26
			Blood WBC count < 5000 cells/microlitre BM=3.2 (2.3–4) Control=4.2 (3.7–4.6)	*P* = 0.005
			Blood WBC count ≥ 5000 cells/microlitre BM=13.3 (9.9–17.1) Control=11.4 (8.8–14.8)	*P* = 0.13
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib: 29/46 Age range: 0–18 years	Median (range) cells/microlitre	Blood WBC counts: BM=10,650 (1900–32,500) AM=10,050 (4000–27,700) EI=15,300 (1500–37,300)	BM versus EI *P* = 0.0013
			Segmented neutrophil counts: BM=4511 (31–25,570) AM=4242 (340–16,905) EI=6796 (352–24,500)	BM versus EI *P* = 0.023
			Blood total neutrophil counts: BM=6970 (714–26,650) AM=4808 (476–20,825) EI=9178 (375–29,400)	BM versus EI *P* = 0.10

[a] AM: aseptic meningitis, BM: bacterial meningitis, EI: extrameningeal bacterial infection, WBC: white blood cell

Of these two US studies, one was a retrospective study[60] (2003) involving 5375 infants aged 3 to 89 days with fever evaluated in the emergency department for serious bacterial infection [EL=III]. Twenty-two children had confirmed bacterial meningitis; the remainder made up a control group (n=5353). No details are given to describe the control group other than that they had a CSF and blood sample sent as part of their clinical evaluation for suspected serious bacterial infection while in the emergency department. Blood WBC count was found to be a poor discriminator of bacterial meningitis from other bacterial illnesses. Results from the study are presented in Table 5.2.

In terms of differential diagnostic accuracy, blood WBC count was not found to be useful (area under the curve for ROC=0.43). For the three cutoff values tested while specificity reached 96% for a threshold of less than 5000 cells/microlitre the sensitivity achieved was only 32%, thus making this cutoff useful for ruling out bacterial meningitis but not as a proof of the disease. At higher thresholds the specificity remained high but sensitivity was not significantly improved (see table 5.3 for details).

Table 5.3. Blood white blood cell count – diagnostic statistics (infants and children of all ages)

Study and evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood white blood cell (WBC) count threshold value	Sensitivity	Specificity	PPV[a]	NPV[a]
Bonsu, 2003[60] [EL=II]	1992–1999 Hib not reported but organisms isolated included *Escherichia coli* (n=11/22) and Group B streptococcus (n=9/22) Age range: 3–89 days	< 5000 cells/microlitre	32%	96%	1.0%	99.7%
		≥10,000 cells/microlitre	50%	38%	0.3%	99.5%
		≥15,000 cells/microlitre	27%	77%	0.5%	99.6%
		≥20,000 cells/microlitre	4.5%	93%	0.3%	99.6%
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib 29/46 Age range 0–18.2 years	>15,000 cells/microlitre	22%	73%	Not calcul-able	Not calcul-able

[a] NPV: negative predictive value; PPV: positive predictive value

An earlier retrospective study[61] described the white blood cell count of children (n=232) undergoing lumbar puncture for suspected meningitis [EL=III]. The study sample comprised: 46 children with bacterial meningitis (median age 11 months, range 0 to 157 months); 132 children with aseptic meningitis (median age 2 months, range 0 to 219 months); and 56 children with extrameningeal infection (median age 6.5 months, range 0 to 79 months). Extrameningeal infections included urinary tract infection (UTI) (n=22), occult bacteraemia (n=13), cellulitis/abscess (n=7), enteritis (n=7), otitis media (n=4), pneumonia (n=2) and septic arthritis (n=1). The values found for WBC counts and neutrophil counts for each study group are detailed in table 5.2. In children without bacteraemia the WBC count was similar in those with bacterial meningitis to those with extrameningeal bacterial infection

(WBC/microlitre: median bacterial meningitis=14,500, extrameningeal bacterial infection=13,800; *P* = 0.57). A WBC count threshold of 1500/microlitre to differentiate between bacterial meningitis and aseptic meningitis or extrameningeal bacterial infection gave a sensitivity of 22% and a specificity of 73%.

Predictive value of individual nonspecific blood tests for differentiating bacterial versus aseptic meningitis

Procalcitonin

Three relevant studies were identified that examined the usefulness of blood procalcitonin assay in differentiating bacterial from aseptic meningitis.

A recent European multicentre study undertook a secondary analysis of retrospective cohort studies from six paediatric emergency or intensive care centres across five European countries[62] [EL=III]. A total of 198 children were included in the analysis (BM=96, aseptic meningitis =102) aged 29 days to 15.9 years (mean 4.8 years). The median level of blood procalcitonin (ng/ml) was significantly higher in cases of bacterial meningitis compared with aseptic meningitis (see table 5.4). Meta-analysis using a pooled diagnostic odds ratio (DOR) showed a significant association between high procalcitonin levels and risk of bacterial meningitis (pooled DOR 139; 95% CI 39-498, I^2=0%).

Table 5.4. Procalcitonin level – descriptive statistics (children of all ages)[a]

Study; evidence level	**Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range**	**Procalcitonin measure; units**	**Result**	***P* value**
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 29 days to 15.9 years	Median (range) nanogram/ml	BM = 21.5 (0.1 to 156.4) AM = 0.3 (0.1 to 22.4)	$P < 10^{-6}$
Dubos, 2006[63] [EL=III]	2000 - 2004 Hib: n=1/21 Age range: 28 days to 16 years	Mean/median (range) nanogram/ml	BM = 20.5/9.1 (0.2 to 107) AM = 0.3/0.2 (0.1 to 4.4)	$P < 10^{-6}$
Gendrel, 2000[64] [EL=III]	1994–1996 Hib: n=6/23 Age range: 3 months to 13 years	Mean (range) nanogram/ml	BM = 60.9 (4.8 to 335) VM = 0.32 (0 to 1.7)	$P < 10^{-4}$

[a] AM: aseptic meningitis; BM: bacterial meningitis; EI: extrameningeal bacterial infection; VM: viral meningitis

The area under the curve (AUC) for the ROC curve for procalcitonin was very high at 0.98 (compared with 0.89 for C-reactive protein, 0.88 for CSF protein and 0.87 for CSF neutrophil count; *P* = 0.001) (see table 5.5 for summary details). Blood procalcitonin was found to be more accurate than C-reactive protein, CSF protein level and CSF neutrophil count in differentiating bacterial from aseptic meningitis.

An earlier retrospective cohort study by the same author[63] (2000–2004) [EL=III] reported similar findings. The study included blood samples from 167 children aged 28 days to 16 years (BM=21, aseptic meningitis=146). Blood procalcitonin was again much higher in bacterial meningitis than in aseptic meningitis. Procalcitonin was found to be the most

accurate test in differentiating bacterial from aseptic meningitis with an ROC AUC of 0.95 (0.95 for C-reactive protein, 0.93 for CSF protein, 0.87 for CSF neutrophil count, 0.81 for CSF WBC count). See tables 5.4 and 5.5 for details.

A third European study[64] [EL=III] (2000) compared blood parameters for differentiating between bacterial meningitis and viral meningitis. The study included 74 children aged 3 months to 13 years (for bacterial meningitis n=23, mean age 3.2 years and for viral meningitis n=51, mean age 2.1 years). The study only reports descriptive statistics for procalcitonin levels: again these are much higher in cases of bacterial meningitis compared with confirmed viral meningitis (bacterial meningitis: mean=60.9 microgram/litre (range 4.8 to 335 microgram/litre) versus viral meningitis: mean=0.32 microgram/litre (0 to 1.7 microgram/litre); $P < 0.0001$).

Table 5.5. Procalcitonin level – diagnostic statistics (children of all ages)

Study; evidence level	Years of data collection; proportion of *Haemophiluinfluenzae* type B (Hib); age range	Procalcitonin threshold value	Sensitivity	Specificity	OR[a] (95% CI)
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	≥0.5 nanogram/ml	99%	83%	434 (95% CI 57 to >1000)
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	≥0.5 nanogram/ml	89%	89%	64 (95% CI 12 to 452)
Gendrel, 2000[64] [EL=III]	1994–1996 Hib: n=6/23 Age range: 3 months to 13 years	Not reported	Not reported	Not reported	Not reported

[a] OR: odds ratio

C-reactive protein

A systematic review with meta-analysis[65] [EL=III] was identified, the aim of which was to evaluate published evidence relating to diagnostic accuracy of CSF and serum C-reactive protein (CRP) tests in the diagnosis of bacterial meningitis. Serum CRP had been measured in 14 of the 35 studies included in the systematic review (see table 5.6 for a summary of diagnostic accuracy data from these studies and the study characteristics). Many of the 35 studies included in the systematic review had fairly small sample sizes (66% included fewer than 100 children and 29% included fewer than 50 children); they had been conducted in different populations (three in the USA, two in Finland, and one each in France, Italy, Spain, Sweden, Poland, South Africa, Thailand, Indonesia and Chile); and they had used different study designs. The two main approaches used in the studies were to recruit either 'patients suspected of having bacterial meningitis, irrespective of final diagnosis' or 'patients with confirmed meningitis'. On the basis of this information and whether recruitment was conducted prospectively, consecutively or selectively, the authors of the systematic review further characterised each study as reporting the 'clinical performance' of a CRP test or not,

with studies that reported clinical performance of the CRP test being defined as prospective studies with patients recruited in clinical setting (see table 5.6).

The included studies were heterogeneous with respect to the cutoff values for CRP used to classify the patients as having bacterial meningitis or viral/aseptic meningitis and with respect to the participants' ages. Seven studies (n=552 participants) included children under 18 years, three included adults and children reported separately (age range 16 to 83 years, n=144 participants), three included a mix of adults and children (age range 1 week to 60 years, n=265 participants) and one study did not reported details of the participants' ages.

The systematic review reported the results of a meta-analysis, but caution should be exercised in interpreting the findings because of the heterogeneity of the included studies with respect to inclusion of low-income countries and dates of data collection. However, in conducting the meta-analysis, no statistically significant inter-study variance was reported by the authors of the systematic review and so the findings from the systematic review are reported here.

Of the 14 studies that examined serum CRP, one was excluded from the analyses because it included only three patients with bacterial meningitis. The total number of patients included in the 13 remaining studies comparing bacterial with aseptic meningitis was 749 (bacterial meningitis n=338, aseptic meningitis n=411). When serum CRP log true-positive fractions were regressed on log false-positive fractions for patients with bacterial and aseptic meningitis, these regression estimates were obtained: intercept 5.0 (95% CI 3.8 to 6.2) with corresponding OR=150 (95% CI 44 to 509); slope –0.17 (P = 0.6). The sensitivity for CRP measurement was 92.4% and the specificity was also 92.4% (standard error 0.068). When the analysis was restricted to the six studies that were classified as estimating 'clinical performance', the regression was intercept 5.0 with corresponding OR=143. The predictive values of serum CRP were reported as being 'almost identical' to those of CSF CRP. The post-test probability of bacterial meningitis given a positive CRP test depends upon the pre-test probability in an assumed clinically relevant range of 0.05 to 0.30. The post-test probability of not having bacterial meningitis given a negative test is high and declines only slightly in that range. At 5% prevalence, PPV=44.8% and NPV=99.7%, whereas at 30% prevalence PPV=86.3% and NPV=97.3%.

A further four studies that were published after the systematic review[65] were identified for inclusion in the guideline review. Two of these studies have already been detailed above (Dubos, 2008[62] and Dubos, 2006[63]). Findings for serum CRP from these studies are presented in table 5.7.

A third recent retrospective study[35] [EL=III] involved 92 children aged 0 to 15 years (mean 5.6 years, median 5.0 years) admitted to a Belgian regional hospital from 1997 to 2005 for observation and with subsequent confirmed diagnosis of viral (n=71) or bacterial (n=21) meningitis. Children with bacterial meningitis were found to have significantly higher level of serum CRP than children with viral meningitis (see table 5.7). A threshold of 2.0 mg was found to have a high sensitivity and a high NPV but a low PPV (see table 5.8).

An earlier retrospective study[66] [EL= III] included 237 children aged 3 months to 15 years, 55 with bacterial meningitis (recruited from 1984 to 1991 into two large Finnish studies) and 182 children with confirmed or presumed viral meningitis (recruited from one Finnish hospital from 1977 to 1992). As in other reported studies, children with bacterial meningitis were found to have significantly higher serum CRP levels than those with viral meningitis (see table 5.7). A CRP threshold of more than 20.0 mg/litre gave high sensitivity and specificity with an NPV of 99%. At a CRP threshold of more than 40.0 mg/litre the specificity and PPV rose to 100%, but this was at the expense of the sensitivity and NPV (see table 5.7).

Table 5.6. Summary of studies providing data on diagnostic accuracy of serum C-reactive protein (CRP) as a predictor of bacterial meningitis (as opposed to viral or aseptic meningitis; based on Gerdes 1998[65])

First author	Year	Country	Meningitis suspected or confirmed	Clinical perform-ance of CRP test evaluated	Age range	CRP cutoff used to define bacterial meningitis (mg/litre)	Number diagnosed as having bacterial meningitis	Number diagnosed as having aseptic meningitis	Number diagnosed as having tuberculous meningitis	Number diagnosed as having other diseases	Sensitivity for bacterial meningitis	Specificity for bacterial meningitis	Specificity for other disease
Peltola	1984	Finland	Confirmed	NR	1 day to 9 years	20	10	12			0.98	0.73	
Clarke	1983	USA	Confirmed	Yes	8 days to 12 years	70	17	18			0.99	0.99	
Benjamin	1984	USA	Suspected	No	1 week to 18 years	10	21	8		50	0.94	0.84	0.56
Vaidia[a]		Thailand	Confirmed	NA	1 month to 14 years		3	24			0.92	0.82	
Roine	1991	Chile	Confirmed	NR	1 month to 12 years	19	60	15			0.95	0.78	
de Beer	1984	South Africa	Confirmed	NR	3 months to 15 years	100	31	28	15		0.90	0.99	0.90
Lembo	1991	USA	Suspected	Yes	Median 6 months	10	10 (n=5 Hib)	14		136	0.78	0.77	0.55
Lizana	1996	Spain	Confirmed	Yes	1–14 years	40	20	60			0.69	0.91	
Lucht	1986	France	Confirmed	Yes	16–72 years	100	24	31			0.99	0.93	
Rizzo	1987	Italy	Confirmed	NR	17–74 years	8	19	10			0.94	0.77	
Pardowski	1995	Poland	Confirmed	NR	19–82 years	40	30	30			0.83	0.99	

First author	Year	Country	Meningitis suspected or confirmed	Clinical perform-ance of CRP test evaluated	Age range	CRP cutoff used to define bacterial meningitis (mg/litre)	Number diagnosed as having bacterial meningitis	Number diagnosed as having aseptic meningitis	Number diagnosed as having tuberculous meningitis	Number diagnosed as having other diseases	Sensitivity for bacterial meningitis	Specificity for bacterial meningitis	Specificity for other disease
Hausson	1993	Sweden	Suspected	Yes	1 week to 60 years	50	60	146		28	0.88	0.90	0.89
Peltola	1982	Finland	Confirmed	Yes	2 weeks to 49 years	19	16	15			0.98	0.92	
Soetiono	1989	Indonesia	Confirmed	NR	NR		20	24			0.89	0.66	

[a] Vaidia excluded from analysis because only three participants had bacterial meningitis
Clinical performance of CRP test evaluated = prospective studies with patients recruited in clinical setting
NR=not reported

Table 5.7. CRP level – descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	C-reactive protein measure; units	Result	*P* value
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	Median (range) mg/litre	BM=136 (4.9–350) AM=14 (0.5–330)	*P* < 10-6
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	Mean/median (range) mg/litre	BM=190/178 (8.5–426) AM=18.6/8 (3–213)	*P* < 10-6
De Cauwer, 2007[35] EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	Mean (SD) mg/litre	BM=13.6 (7.5) VM=1.17 (1.6)	*P* < 10-4
Sormunen, 1999[66] [EL=III]	1977–1992 Hib: n=23/55[b] Age range: 3 months to 15 years	Mean/median (SD/range) mg/litre	BM =16.3/11.1 (21.8/1.4–85.3) VM = 3.8/3.3 (1.8/1.3–9.4)	*P* < 10-4

[a] AM: aseptic meningitis; BM: bacterial meningitis; EI: extrameningeal bacterial infection; VM: viral meningitis
[b] All Gram-negative

Table 5.8. Blood C-reactive protein – diagnostic statistics (children of all ages)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	C-reactive protein threshold value	Sensitivity	Specificity	OR (95% CI) or PPV and NPV[a]
Gerdes, 1998 [65][EL=III]	1982–1996 (year of publication) Hib: not reported Age range: 1 day to 82 years	Findings from meta-analysis	92%	92%	OR=150 (95% CI 44 to 509)
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	≥20 mg/litre	83%	67%	OR=9.9 (95% CI 4.8 to 20.8)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	C-reactive protein threshold value	Sensitivity	Specificity	OR (95% CI) or PPV and NPV[a]
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	≥20 mg/litre	91%	71%	OR=24 (95% CI 5 to 155)
De Cauwer, 2007[35] EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	≥20 mg/litre	95%	83%	PPV=63% NPV= 98%
Sormunen, 1999[66] EL=III]	1977–1992 Hib: n=23/55[b]	>20 mg/litre	96%	93%	PPV=83% NPV=99%
	Age range: 3 months to 15 years	>40 mg/litre	86%	100%	PPV=100% NPV=95%

[a] OR: odds ratio; NPV: negative predictive value; PPV: positive predictive value
[b] All Gram-negative

White blood cell count

Six studies were identified that reported accuracy of blood WBC count for differentiating between bacterial meningitis and aseptic meningitis or viral meningitis. Five of these included studies have already been described in preceding sections.[35;61-63;66] Findings from these studies in relation to blood WBC count are presented in table 5.9. The sixth study[67] investigated blood WBC counts in neonates and is detailed below.

Table 5.9. Blood white blood cell count – descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood WBC count measure; units	Result	*P* value
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	Median (range) cells/microlitre	BM=14,730 (2440–42,000) AM=9,900 (3290–30,000)	$P < 10^{-6}$
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21	Mean/median (range) cells/microlitre	BM=18,495/18,400 (2400–43,200) AM=12,031/10,600	$P = 0.01$

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood WBC count measure; units	Result	*P* value
	Age range 28 days to 16 years		(2000–67,200)	
De Cauwer, 2007[35] [EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	Mean (SD) cells/microlitre	BM=17,157 (10,516) VM=11,470 (4410)	$P = 0.016$
Sormunen, 1999[66] EL=III	1977–1992 Hib: n=23/55[b] Age range: 3 months to 15 years	Mean (SD) cells/microlitre	BM=18,000 (8100) VM=10,600 (4300)	$P < 10^{-4}$
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib: n=29/46 Age range: 0 to 18.25 years	Median (range) cells/microlitre	BM=10,650 (1900–32,500) AM=10,050 (4000–27,700) EI=15,300 (1500–37,300)	Not reported

[a] AM: aseptic meningitis; BM: bacterial meningitis; EI: extrameningeal bacterial infection; VM: viral meningitis; WBC: white blood cell
[b] All Gram-negative

Table 5.10. Blood white blood cell count – diagnostic statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood WBC count threshold	Sensitivity	Specificity	OR (95% CI) or PPV and NPV[b]
Dubos, 2008 [62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	≥15,000/microlitre	48%	78%	OR=3.4 (95% CI 1.7 to 6.6)
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	≥15,000/microlitre	62%	81%	OR=7 (95% CI 3 to 22)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood WBC count threshold	Sensitivity	Specificity	OR (95% CI) or PPV and NPV[b]
De Cauwer, 2007[35] [EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	≥15,000/microlitre	Not reported	Not reported	Not reported
Sormunen, 1999[66] [EL=III]	1977–1992 Hib: n=23/55[c] Age range: 3 months to 15 years	>15,000/microlitre	62%	85%	PPV=58% NPV=87%
		>20,000/microlitre	32%	97%	PPV=79% NPV=82%
		>25,000/microlitre	20%	100%	PPV=100% NPV=80%
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib: n= 29/46 Age range: 0 to 18.25 years	15,000/microlitre (BM versus AM/EI)	22%	73%	Not reported

[a] AM: aseptic meningitis; BM: bacterial meningitis; EI: extrameningeal bacterial infection; WBC: white blood cell
[b] OR: odds ratio; NPV: negative predictive value; PPV: positive predictive value
[c] All Gram-negative

Blood white blood cell count – neonates

One study was identified that looked at blood WBC count in neonates[67] [EL=III]. The study included 34 neonates (aged 28 days or younger) who underwent a complete sepsis evaluation (including lumbar puncture) in a US emergency department from 1982 to 1989, and who had a discharge diagnosis of meningitis (bacterial meningitis=10, aseptic meningitis=24). The total WBC count range was 2600 to 28000 cells/microlitre. No statistically significant differences were found between neonates with bacterial meningitis and aseptic meningitis.

Blood neutrophil count

Four of the previously described studies also included data for the diagnostic accuracy of blood neutrophil count in differentiating bacterial from aseptic or viral meningitis.[35;61-63] Summary statistics for findings from these four studies, all of which were retrospective in design [EL=III], are given in tables 5.10, 5.11 and 5.12.

Table 5.11. Blood neutrophil count – descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood neutrophil count measure; units	Result	*P* value
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9 years	Median (range) cells/microlitre	BM=11,472 (1176-37,800) AM=6417 (1316-23,000)	*P* < 10-6
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	Mean/median (range) cells/microlitre	BM=13,748/14,245 (740–36,290) AM=8403/7300 (1180–51,740)	*P* = 0.06
De Cauwer, 2007[35] [EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	Neutrophils % Mean/median (range/SD)	BM=67.0/68.0 (30–94/19.5) VM=73.9/78.0 (13–91/14.9)	NS
		Absolute neutrophils mean/median (range/SD) cells/microlitre	BM=12,456/9600 (1056–33,652/9308) VM=8667/8100 (1300–22,355/4067)	NS
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib: n=29/46 Age range: 0 to 18.25 years	Segmented neutrophils median (range) cells/microlitre	BM=4511 (31–25,570) AM=4242 (340–16,905) EI=6796 (352–24,500)	BM versus AM NS (by inspection)
		Total neutrophils median cells/microlitre	BM=6970 (714–26,650) AM=4808 (476–20,825) EI=9178 (375–29,400)	BM versus AM Not reported

[a] AM: aseptic meningitis;, BM: bacterial meningitis; EI: extrameningeal bacterial infection; VM: viral meningitis

Table 5.12. Blood neutrophil counts – diagnostic statistics (children of all ages)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood neutrophil count threshold	Sensitivity	Specificity	OR [95% CI] or PPV and NPV[a]
Dubos, 2008[62] [EL=III]	1996–2005 Hib: n=7/96 Age range: 1 month to 15.9	10,000 cells/microlitre	57%	75%	OR=4.1 (95% CI 2.1 to 8.0)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib); age range	Blood neutrophil count threshold	Sensitivity	Specificity	OR [95% CI] or PPV and NPV[a]
	years				
Dubos, 2006[63] [EL=III]	1995–2004 Hib: n=1/21 Age range: 28 days to 16 years	10,000 cells/microlitre	60%	71%	OR=4 (95% CI 1 to 11)
De Cauwer, 2007[35] [EL=III]	1997–2005 Hib: n=1/21 Age range: 0 to 15 years	Not reported	Not reported	Not reported	Not reported
Lembo, 1991[61] [EL=III]	1979–1980 and 1984–1985 Hib: n=29/46 Age range: 0 to 18 years	Not reported	Not reported	Not reported	Not reported

[a] OR: odds ratio; NPV: negative predictive value; PPV: positive predictive value

Evidence summary

Bacterial meningitis versus other infections

No evidence was identified that examined the diagnostic accuracy of procalcitonin for differentiating bacterial meningitis from other infections.

Findings from two small studies showed that at a cutoff of more than 1.0 mg/decilitre, blood C-reactive protein (CRP) levels have moderate to good sensitivity for differentiating bacterial meningitis from other infections but poor specificity.

Findings from two retrospective studies show that blood white blood cell (WBC) counts have poor sensitivity in differentiating bacterial meningitis from other infections. Findings for specificity varied widely.

Bacterial meningitis versus aseptic or viral meningitis

Findings from three retrospective studies showed that blood procalcitonin levels are significantly higher in children with bacterial meningitis compared with those with aseptic meningitis (two studies) or viral meningitis (one study). Findings from two of these studies also report good sensitivity and specificity for the diagnostic accuracy of procalcitonin in differentiating bacterial meningitis from aseptic meningitis.

Findings from four retrospective studies show that blood CRP levels are significantly higher in children with bacterial meningitis compared with aseptic meningitis (two studies) or viral meningitis (two studies). Findings from a meta-analysis involving 13 studies plus four more recent studies show that blood CRP has good sensitivity and moderate to very good specificity at differentiating bacterial meningitis from aseptic meningitis (meta-analysis and two studies) or viral meningitis (two studies).

Four of five retrospective studies that investigated the diagnostic accuracy of blood WBC count reported a significantly higher level in children with bacterial meningitis compared with aseptic meningitis (two studies) or viral meningitis (two studies). All five studies reported poor sensitivity for differentiating bacterial from aseptic or viral meningitis at a threshold of 15000 cells/microlitre or more or 25000 cells/microlitre or more and moderate to good specificities. At a cutoff of more than 25000 cells/microlitre, one study reported a specificity of 100% but a very low sensitivity of 20%.

One small retrospective study found no significant difference in the blood WBC count of neonates with bacterial meningitis compared with those with aseptic meningitis.

Findings from four retrospective studies reported conflicting findings regarding differences between blood neutrophil counts for children with bacterial meningitis compared with aseptic meningitis (three studies) or viral meningitis (one study). Findings from two of these studies show neutrophil count has moderate sensitivity and specificity for differentiating between bacterial and aseptic meningitis.

GDG interpretation of the evidence

CRP, WBC and procalcitonin levels in the bloodstream reflect inflammation in the bloodstream and are not directly informative about inflammation in the cerebrospinal fluid (CSF). Because bacterial infection in the bloodstream often precedes bacterial meningitis, CRP, WBC and procalcitonin levels may be elevated when bacterial meningitis is present.

CRP, procalcitonin and WBC counts have insufficient sensitivity and specificity to differentiate bacterial meningitis from other illnesses.

Raised procalcitonin, CRP and WBC counts and neutrophil count have reasonable specificity (67–93%) for bacterial meningitis in comparison to aseptic meningitis at commonly used cutoffs. Higher thresholds yield higher specificity (up to 100%) at the expense of lowering the sensitivity.

CRP levels of more than 20 mg/litre and procalcitonin of more than 0.5 nanograms/ml have greater than 83% sensitivity for differentiating bacterial meningitis from aseptic meningitis.

Total WBC count and neutrophil count have low sensitivity for differentiating bacterial meningitis from aseptic meningitis.

The evidence review indicates that non-specific laboratory blood tests cannot be used to distinguish bacterial meningitis from other illnesses (other illnesses are defined variously in the reviewed papers and include: febrile illnesses presenting with symptoms suggestive of bacterial meningitis; suspected meningitis but with normal CSF findings; suspected serious bacterial infection; and extrameningeal infections including urinary tract infection, occult bacteraemia, cellulitis/abscess and enteritis).

Where available, high procalcitonin (more than 0.5 nanograms/ml) may be useful to rule in bacterial meningitis (high sensitivity and specificity) but a low procalcitonin is insufficient to rule out the diagnosis. Up to 11% of children will have a low procalcitonin despite having bacterial meningitis.

High CRP (more than 20 mg/litre) may be useful to rule in bacterial meningitis (moderate sensitivity and moderate specificity) but a low CRP is insufficient to rule out the diagnosis. Up to 17% of children will have a CRP less than 20 mg/litre despite bacterial meningitis.

Although total white cell count and neutrophil count have low specificity and sensitivity for bacterial meningitis in comparison with aseptic meningitis, children with a high WBC count (more than 15 cells/microlitre) or neutrophil count (more than 10 neutrophil/microlitre) are three to seven times more likely to have bacterial meningitis.

Although none of the tests allow bacterial meningitis to be ruled out, the GDG felt that they are useful to add to other variables when making the decision about the management of suspected bacterial meningitis.

Recommendations

Investigation and management in children and young people with suspected bacterial meningitis

In children and young people with suspected bacterial meningitis, perform a CRP and white blood cell count:

- If the CRP and/or white blood cell count is raised and there is a non-specifically abnormal cerebrospinal fluid (CSF) (for example consistent with viral meningitis), treat as bacterial meningitis.
- Be aware that a normal CRP and white blood cell count does not rule out bacterial meningitis.
- Regardless of the CRP and white blood cell count, if no CSF is available for examination or if the CSF findings are uninterpretable, manage as if the diagnosis of meningitis is confirmed.

5.3 Polymerase chain reaction tests for bacterial meningitis and meningococcal disease

Introduction

Confirming the diagnosis of bacterial meningitis and meningococcal disease is essential to ensure that the correct antibiotic therapy is used for the correct duration of time and to support decisions about the long-term follow-up of the child. Traditionally, the confirmation of the diagnosis of these diseases has relied on microscopy and culture of blood and cerebrospinal fluid (CSF). With the advent of DNA based diagnostic tests, such as polymerase chain reaction (PCR), it is important to decide which are the most effective and cost-effective diagnostic tests to support management of the child.

Clinical questions

What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal Disease in Children and Young People'[27] recommends that all children with suspected invasive meningococcal disease should have blood taken for meningococcal PCR to confirm the diagnosis. The guideline recommends that if lumbar puncture is performed, CSF should be sent for PCR analysis.

Studies considered in this section

The review included studies of any design assessing the diagnostic value or accuracy of real-time PCR assays that target meningococcal or pneumococcal-specific genes as these types of assay are most widely used in the UK. Laboratory studies that primarily assessed the accuracy of PCR using bacterial isolates and that included only small numbers of clinical samples were excluded from the review. Studies without a well-defined reference standard were excluded.

Overview of available evidence

Three clinical diagnostic studies [one EL=Ib and two EL=II], one retrospective review [EL=III] and one laboratory diagnostic study [EL=III] were found.

Review findings

Blood PCR for suspected meningococcal disease

One prospective study (Australia, 2000–2001) [EL=Ib] compared the diagnostic accuracy of Taqman™ real-time PCR targeting the *N. meningitidis* capsular transfer gene (*ctrA*) with

culture of blood or CSF in 118 children with possible meningococcal septicaemia or meningitis admitted to a tertiary care paediatric hospital.[68] The reference standard for diagnosis of meningococcal disease was a clinical diagnosis reached by consensus of the attending clinician and an infectious diseases physician plus a confirmatory laboratory test in the case of suspected meningococcal meningitis (positive CSF Gram stain, CSF culture or PCR). In total, 24 children were diagnosed with meningococcal disease using the reference standard. The study found that blood PCR was more sensitive than blood culture for diagnosing meningococcal disease. Blood PCR was positive for 21 out of 24 cases (sensitivity 88%, 95% CI 68 to 97) and blood culture was positive for 14 out of 24 cases (sensitivity 58%, 95% CI 37 to 78). Both PCR and culture were 100% specific (95% CI 96 to 100) (see table 5.13).

Of the 24 children with gold standard confirmed meningococcal disease, blood PCR was positive for 8 out of 8 with clinical signs of septicaemia alone, 9 out of 11 with clinical signs of septicaemia and meningitis, and 4 out of 5 children with clinical signs of meningitis alone.

All children with a positive blood culture had positive PCR results. Blood PCR was positive but blood culture negative in 7 out of 24 cases (29%). Blood PCR remained positive for longer than blood cultures after parenteral antibiotics: for a third of patients tested, PCR remained positive up to 72 hours after parenteral antibiotic administration.

One prospective study (UK, 2000–2001) [EL=II] evaluated the diagnostic accuracy of ctrA whole-blood Taqman PCR (WB-Taqman) in 196 children with suspected meningococcal disease admitted to a children's hospital.[69] The reference standard was a clinical diagnosis of meningococcal disease made by the attending physician in the absence of alternative positive microbiological investigations. In total, 98 children were diagnosed with meningococcal disease using the gold standard. The study found that whole-blood PCR performed better than blood culture for confirmation of clinically diagnosed meningococcal disease. Whole-blood PCR was positive for 84 out of 95 clinical cases (sensitivity 88%, 95% CI 81 to 95) and blood culture was positive for 32 out of 98 children (sensitivity 33%, 95% CI 24 to 42). Both techniques were 100% specific (see table 5.13). All children with a positive blood culture had positive PCR results. PCR was positive, but blood culture negative in 52 out of 95 children (55%) with clinically diagnosed meningococcal disease. Of 22 children with clinical signs of meningitis, blood PCR was positive in 16 (sensitivity 78%). The positivity of whole blood PCR in children with clinical signs of meningitis but not septicaemia was not reported. The sensitivity of PCR was not decreased by preadmission antibiotics (PCR sensitivity 93% for 14 children given preadmission antibiotics). The sensitivity of blood culture in children given preadmission antibiotics decreased to 21%.

The study[69] compared the performance of WB-Taqman PCR with that of serum Taqman PCR (S-Taqman) assessed in an earlier cohort study (1997–1999) [EL=II] conducted at the same hospital involving 319 children with suspected meningococcal disease.[70] The earlier study used the same clinical gold standard described above to define meningococcal disease: 166 children were diagnosed with meningococcal disease using the gold standard. Comparative analysis found that case confirmation increased from 47% with S-Taqman[70] to 88% with WB-Taqman, $P < 0.001$.[69] Rates of blood culture positivity were similar for the two studies at $P = 0.8$ (see table 5.13). Both PCR–ELISA and real-time PCR were used in the earlier study, which also used two screening assays, one targeting IS*1106* and one targeting *ctrA*. When all laboratory tests (including blood and CSF culture, PCR and rapid antigen testing) were used for diagnosis, case confirmation increased from 72% (with S-Taqman PCR) in the earlier study to 94% (with WB-Taqman PCR).

CSF PCR for suspected bacterial meningitis (including meningococcal meningitis)

One retrospective review of case notes (Belgium, 2002–2006) [EI=III] compared the performance of duplex CSF real-time PCR with CSF Gram stain and culture in 70 patients admitted to a tertiary care hospital with suspected bacterial meningitis.[71] The PCR assay targeted *ctrA* for *N. meningitidis* and the pneumolysin gene (*ply*) for *S. pneumoniae*. The age of the patients was not recorded. The gold standard for diagnosis of bacterial meningitis was a composite of clinical features of meningitis plus a confirmatory laboratory test (positive CSF Gram stain, positive CSF or blood culture, or positive blood or CSF PCR). Twenty-three

patients were diagnosed with meningococcal meningitis and 14 patients were diagnosed with pneumococcal meningitis using the gold standard.

The study found that CSF PCR was more sensitive than Gram stain or CSF culture for diagnosing meningococcal meningitis and pneumococcal meningitis. For meningococcal meningitis: CSF PCR was positive in 20 out of 23 cases (sensitivity 87%) compared with 6 out of 23 (sensitivity 27%) for CSF Gram stain and 4 out of 23 (sensitivity 17%) for CSF culture (see table 5.13). CSF culture was 100% specific, whereas CSF PCR was 96% specific: the two patients with false positive CSF PCR results had meningococcal septicaemia with probable contamination of CSF by blood. For pneumococcal meningitis, the sensitivity of CSF PCR for detecting *S. pneumoniae* was 100% (14 out of 14 cases) compared with 62% (8 out of 14) for CSF Gram stain and 36% (5 out of 14) for CSF culture. All techniques were 100% specific. CSF PCR was the only positive confirmatory laboratory test in 11 out of 23 patients with meningococcal meningitis and in 5 out of 14 patients with pneumococcal meningitis. Information about prior antibiotic use was not available from the medical notes.

The multiplex real-time Taqman PCR simultaneously targeting *N. meningitidis* (*ctrA*), *Haemophilus influenzae* (*bexA*) and *S. pneumoniae* (*Ply*)[72] detected *N. meningitidis* in 89% of the 36 CSF samples from culture-confirmed cases of meningococcal meningitis [EL= III]. It detected *S. pneumoniae* in 91% of 23 CSF samples from culture-confirmed cases of pneumococcal meningitis. Specificity was not assessed using clinical samples.

Table 5.13. Diagnostic accuracy of real-time polymerase chain reaction (PCR) versus culture in studies with a clinical gold standard[a]

Study	Test details	Samples	Reference standard	PCR sensitivity	PCR specificity	Blood /CSF culture sensitivity	Blood culture specificity
Bryant, 2004 [68]	*ctrA* Taqman PCR	Blood	Consensus clinical diagnosis	88% n=24 cases	100%	58%	100%
Hackett, 2002 [69]	*ctrA* WB-Taqman PCR	Whole blood	Clinical diagnosis in the absence of other positive microbiology	88% n=98 cases	100%	33%	100%
Carrol, 2000 [70]	*ctrA* and IS*1106* S-Taqman and PCR-ELISA	Serum/ plasma	Clinical diagnosis in the absence of other positive microbiology	47% n=166 cases	100%	31%	100%
Van Gastel, 2007 [71]	Duplex Taqman PCR targeting *Neisseria meningitidis ctrA* and *Streptococcus pneumoniae ply*	CSF	Clinical features of meningitis plus positive CSF Gram stain, positive CSF or blood culture, or postive PCR	**Meningococcal meningitis n=23 cases**			
				87%	96%	17%	100%
				Pneumococcal meningitis n=14 cases			
				100%	100%	36%	100%

[a] *ctrA*: *N. meningitidis* capsular transfer; CSF: cerebrospinal fluid

Evidence statement

Blood PCR for suspected meningococcal disease

There is evidence from well conducted clinical studies that real-time PCR of blood samples is more sensitive than blood culture for confirming a clinical diagnosis of meningococcal disease and is highly specific. Whole blood PCR performs significantly better than serum or plasma PCR. In two clinical studies 29% to 55% of children with meningococcal disease had a negative blood culture and a positive blood PCR. The sensitivity of PCR was less affected by antibiotic administration than the sensitivity of blood culture. There is insufficient evidence

from these studies to determine the diagnostic accuracy of whole-blood PCR in children with meningococcal meningitis without septicaemia.

CSF PCR for suspected bacterial meningitis (including meningococcal meningitis)

There is limited evidence about the diagnostic accuracy of CSF real-time PCR.

One small retrospective study found that duplex CSF real-time PCR was more sensitive than Gram stain or CSF culture for diagnosing meningococcal or pneumococcal meningitis in a clinical setting. CSF PCR was highly specific (96% to 100%). One small laboratory study found that CSF multiplex real-time PCR detected *N. meningitidis* in 89% and *S. pneumoniae* in 91% of culture-positive CSF samples.

Cost effectiveness

There is variation in the use of PCR for the diagnosis of meningococcal disease and bacterial meningitis in England and Wales. Therefore, the GDG identified this as an important priority for economic analysis in order to inform guideline recommendations. A summary of this analysis is presented here, with full details given in appendix I.

A model was developed for a population of children presenting to secondary care with a suspicion of meningococcal disease. In this population three diagnostic strategies were compared:

1. routine PCR and blood culture to all
2. blood culture to all followed by PCR only if the blood culture is negative
3. routine 'rapid' PCR and blood culture to all.

The first two strategies were thought by the GDG to represent current practice. At present, the GDG does not consider that the NHS has the necessary infrastructure to offer a rapid PCR strategy and in that sense it can currently be considered only as a hypothetical option. Nevertheless, it was considered useful to include it in the model as it is a strategy for which the technology exists and could plausibly be available in the future.

Antibiotic treatment is generally initiated on admission in those with suspected meningococcal disease or bacterial meningitis. This is a conservative approach to minimise adverse outcomes in actual cases. Therefore, confirmation of the diagnosis may sometimes be used as a basis for discontinuation of treatment and hospital discharge but not to initiate treatment. Therefore, it was not thought that the different diagnostic strategies would lead to differences in outcomes, and consequently the model took the form of a cost-minimisation analysis.

The results for the base-case analysis are shown in table 5.14.

Table 5.14. Base-case costs for alternative diagnostic strategies

Strategy	Cost
1. Routine polymerase chain reaction (PCR) and blood culture to all	£1,412
2. Blood culture to all followed by PCR if blood culture negative	£1,853
3. Routine rapid PCR and blood culture to all	£895

While strategy 2 produces some savings in terms of a reduction in PCR tests ordered, this saving is of a relatively small magnitude because most blood culture results are negative which means that a PCR is then needed to confirm the diagnosis. The model assumes that PCR results would be available three days after admission in strategy 1 compared to five days in cases where PCR was ordered in strategy 2. In strategy 3 the PCR result is available 24 hours after admission. Therefore, the strategies with routine PCR are cheaper overall because the earlier availability of the PCR result facilitates earlier hospital discharge and discontinuation of treatment in some cases which generates a saving which more than offsets the additional PCR costs.

However, there was considerable uncertainty around some of the model parameters particularly with respect to the proportion of patients where an earlier negative PCR result would result in earlier discharge. Therefore, sensitivity analysis was undertaken to explore scenarios in which strategy 2 might be considered cost effective; for example, increasing the proportion of patients who were relatively well and would no longer be suspected of meningococcal disease following a negative blood culture. This subset of patients in the model would be discharged after the negative blood culture, obviating the need to order a PCR in strategy 2. While the sensitivity analysis showed that there were scenarios in which strategy 2 was cheaper, the GDG considered the parameter values to make this happen were outside their plausible ranges.

GDG interpretation of the evidence

PCR testing of blood samples for suspected meningococcal disease

There is high level evidence to support the use of real-time whole blood PCR using ethylenediaminetetraacetic acid (EDTA) for the diagnosis of meningococcal septicaemia in children and young people. There is evidence that PCR remains positive even if taken after antibiotics have been given, when blood culture is likely to be negative. However, a negative PCR test result for *N. meningitidis* does not rule out meningococcal disease. An economic analysis suggested that routine PCR was cheaper than a strategy in which ordering a PCR was conditional on a negative blood culture. As noted above, the GDG felt that a strategy of rapid PCR and blood culture to all was only a hypothetical option as the NHS currently lacks the necessary infrastructure to provide it.

PCR testing of CSF for suspected bacterial meningitis (including meningococcal meningitis)

Although there is no high level evidence to support the use of CSF real-time PCR for the diagnosis of meningococcal or pneumococcal meningitis in children and young people, most of the evidence was gathered in an era before the routine use of such tests. Emerging low level evidence supports the utility of these tests in establishing a diagnosis of bacterial meningitis and identifying the causative organism.

Further evaluation of this test in supporting a diagnosis of meningitis will be necessary. Real-time PCR may help to confirm the diagnosis in those children in whom microscopy and culture of CSF has not shown an organism. Limited evidence suggests that PCR may remain positive for up to 72 hours after antibiotics have been administered. The consensus view of the GDG was that samples retrieved from other blood sciences laboratories may be useful and CSF samples taken up to 96 hours after admission to hospital may give useful results.

Confirmation of the diagnosis helps to determine the appropriate antimicrobial chemotherapy and its duration. Confirmation of the diagnosis of meningococcal disease and bacterial meningitis is also important in assessing the effectiveness of current vaccine policy and will assist the assessment of the need for future vaccines.

Recommendations

Polymerase chain reaction (PCR) tests for bacterial meningitis and meningococcal disease

Perform whole blood real-time PCR testing (ethylenediaminetetraacetic acid [EDTA] sample) for *N. meningitidis* to confirm a diagnosis of meningococcal disease.

The PCR blood sample should be taken as soon as possible because early samples are more likely to be positive.

Use PCR testing of blood samples from other hospital laboratories if available, to avoid repeating the test.

Be aware that a negative blood PCR test result for *N. meningitidis* does not rule out meningococcal disease.

Submit CSF to the laboratory to hold for PCR testing for *N. meningitidis* and *S. pneumoniae*, but only perform the PCR testing if the CSF culture is negative.

Be aware that CSF samples taken up to 96 hours after admission to hospital may give useful results.

5.4 Skin samples and throat swabs for meningococcal disease

Introduction

Diagnostic tools that have been used historically in children and young people with suspected meningococcal disease are microscopy and culture of skin scrapings and nasopharyngeal (throat) swabs. With the advent of real-time PCR testing for *N. meningitidis* it is important to decide whether examination of skin lesions or throat swabs remains useful for confirming the diagnosis of meningococcal disease.

Clinical question

What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?

In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal Disease in Children and Young People' states that in three studies examination of aspirates or scrapings from skin lesions was useful in providing rapid diagnosis of invasive meningococcal disease. The guideline states that, because of the lack of a consistent gold standard and differences in the nature of lesions and techniques, it was not possible to show if examination of skin lesions is more effective in diagnosing invasive meningococcal disease than other tests.[27]

The SIGN guideline found insufficient evidence to form recommendations on the use of throat swabs.

Studies considered in this section

All study designs evaluating the role of laboratory examination of skin lesions and throat swabs in the diagnosis of meningococcal disease were considered for this section. Diagnostic accuracy studies without a defined gold standard were excluded.

Overview of available evidence

Two retrospective studies [EL=III] and one prospective cohort study [EL=III] evaluating the role of laboratory examination of skin lesions were included in the review.

No studies were found evaluating the role of laboratory examination of throat swabs.

Review findings

One retrospective study (1988–1994) [EL=III] evaluated the diagnostic usefulness of Gram stain of films made from petechial scrapings by reviewing data from 52 children admitted to a children's hospital in Ireland with laboratory confirmed meningococcal disease.[73] Meningococcal disease was defined using these laboratory criteria: positive blood culture, positive CSF Gram stain and culture, or positive microscopy of skin scrapings. Petechiae were found in 35 of 52 children, of whom 30 had scrapings taken by the attending clinician. Of these children, 11 had received preadmission antibiotics. Gram-negative diplococci were detected in petechial scrapings from 24 out of 30 children (80%); blood culture was positive in 11 of these 30 children (37%); and CSF microscopy and culture were positive in 6 out of 26 children (23%). Seventeen children had a negative blood culture but positive petechial scraping microscopy (57%). Of the 26 children who had a lumbar puncture and petechial

scrapings, 17 had a negative CSF examination and positive petechial scraping microscopy (65%). In 14 cases, diagnosis of meningococcal disease was based on positive petechial scraping results alone. Previous antibiotic treatment did not seem to affect petechial scraping microscopy results ($P = 0.372$) but was associated with significantly fewer positive blood cultures ($P = 0.04$) and significantly fewer positive CSF Gram stain and cultures ($P < 0.05$).

When all 52 cases of confirmed meningococcal disease were taken into account, Gram stain of petechial scrapings was not significantly more effective than blood culture or CSF examination in detecting meningococcal infection. Blood culture was positive in 19 out of 52 children (37%), CSF Gram stain was positive in 23 out of 48 (48%) and CSF culture was positive in 22 out of 48 (46%).

Positive skin film microscopy was included in the reference standard, which may lead to an overestimation of the diagnostic accuracy of this technique. The specificity of petechial scraping microscopy was not assessed.

A prospective cohort study (2001–2003) [EL=III] conducted at a university hospital in the Netherlands assessed the diagnostic value of skin biopsy of petechiae or purpura in 31 patients with suspected meningococcal disease and skin lesions.[74] Skin biopsy was performed by a dermatologist. Of the cases, 72% were 16 years or younger. Meningococcal infection was defined as: positive culture of blood, CSF or skin biopsy, positive CSF Gram stain, or identification of Gram-negative diplococci in a skin biopsy plus no alternative microbiological diagnosis and response to antibiotics. Of the 31 patients, 25 had confirmed meningococcal infection according to these criteria. An additional 12 skin biopsy specimens from the dermatology department (taken from adult patients with suspected nevus nevocellularis or skin malignancy) were included as negative controls. Of the children, 92% had received antibiotics before skin biopsy. Blood culture was performed before starting intravenous antibiotics.

Gram stain of skin biopsy was positive in 10 out of 25 cases (40%). Gram stain of CSF was positive in 8 out of 14 cases (57%). Comparison of culture results found that a greater proportion of blood or CSF specimens were positive compared with skin biopsy specimens: blood culture was positive in 14 out of 25 cases (56%); CSF culture was positive in 7 out of 14 cases (50%); and skin biopsy culture was positive in 9 out of 25 cases (36%). When results of culture and Gram stain were combined, the proportion of positive results among the different types of specimen was similar: CSF examination was positive in 9 out of 14 cases (64%) and skin biopsy examination was positive in 14 out of 25 cases (56%). In 14 patients the diagnosis was based on positive microbiology from one type of sample: CSF in 7 patients, blood in 4 patients and skin biopsy in 3 patients. There were no false positive results for the 6 clinical controls and the 12 dermatology specimens.

A retrospective study (2000–2006) [EL=III] aimed to determine the diagnostic usefulness of meningococcal real-time PCR performed on biopsy of skin lesions in patients with clinical purpura fulminans (defined as septic shock, extensive purpura and disseminated intravascular coagulation).[75] In total, 34 patients (27 children aged 5 months to 15 years) were admitted with purpura fulminans to the intensive care units of a university hospital in France. Real-time *ctrA* Taqman PCR and culture was performed on biopsy specimens taken from 'necrotic or ecchymotic lesions' or from 'petechial purpura' after cleaning with local antiseptic. Results of skin biopsies from nine patients with purpuric lesions who did not fulfil all the criteria for purpura fulminans were used as negative controls. Blood culture was performed on all 34 patients; 17 patients had serum PCR. Most patients had been given pre-hospital antibiotics. Skin biopsy was carried out within 24 hours of antibiotic administration.

The study found that PCR of skin biopsy was significantly more sensitive than culture of skin biopsy or blood culture for detecting *N. meningitidis* ($P < 0.0001$). Skin biopsy PCR was positive in 34 out of 34 cases (100%) whereas culture of skin biopsy was positive in 5 out of 34 cases (15%). Blood culture was positive in 4 out of 34 cases (12%). Skin biopsy PCR was significantly more sensitive than serum PCR in detecting *N. meningitidis* ($P = 0.023$): skin biopsy PCR was positive in 17 out of 17 cases (100%); serum PCR was positive in 10 out of 17 cases (59%). There were no false positive PCR results for the negative controls.

Evidence statement

One retrospective study found that in children with suspected meningococcal disease and petechiae, Gram stain of petechial scrapings was positive more frequently than blood culture or CSF Gram stain or culture and was the only positive microbiological result in approximately 50% of cases. Prior antibiotic treatment was associated with fewer positive blood and CSF cultures but did not affect the positivity of petechial scraping microscopy.

One prospective study found that microscopy and culture of biopsy specimens taken from petechiae and purpura was as effective as blood culture in detecting meningococcal infection.

One retrospective study found that in patients with purpura fulminans who had received antibiotics, real-time PCR of biopsy specimens taken from ecchymoses or petechiae detected *N. meningitidis* more frequently than culture of skin biopsy or blood culture. Skin biopsy PCR was more sensitive than serum PCR.

Each of these small studies assessed different techniques used on different types of skin lesion. Two studies reported no clinical gold standard with inclusion of the index test in the reference standard. Specificity of skin lesion examination was not adequately addressed. Because of these limitations, the value of skin lesion examination for diagnosing meningococcal disease cannot be reliably assessed from these studies.

No evidence was identified in relation to the effectiveness of throat swabs.

GDG interpretation of the evidence

The laboratory examination of skin scrapings is not widely used in England and Wales as a diagnostic tool in children and young people with suspected meningococcal disease and in the modern NHS it is unlikely to be undertaken in settings other than an intensive treatment unit (ITU). Practice is unlikely to change in the foreseeable future, making it unlikely that skin scrapings will be undertaken to support the diagnosis of meningococcal disease in children.

There is no high-level evidence to support the use of microscopy and culture of skin lesions for the diagnosis of meningococcal disease. Limited evidence (mostly prior to the routine availability of whole-blood real-time PCR) indicates that in children with petechiae in whom meningococcal disease is suspected, particularly those given prior antibiotic treatment, Gram stain of petechial scrapings may help to confirm the diagnosis.

One small study suggests that PCR of skin biopsy specimens in purpura fulminans is more sensitive than PCR of serum. However, the available evidence is not sufficient to recommend routine use of microscopy and culture or PCR of skin scrapings for the diagnosis of meningococcal disease, particularly in the absence of data comparing the usefulness of skin scraping examination with whole-blood PCR.

The whole-blood PCR test in clinical practice has replaced skin scraping examination and the evidence does not support a return to the use of skin scraping for the diagnosis of meningococcal disease.

The GDG is aware that the SIGN Guideline on 'Management of Invasive Meningococcal Disease in Children and Young People'[27] found insufficient evidence on which to base a recommendation about the usefulness of throat swabs for the diagnosis of meningococcal disease. Meningococci are organisms that colonise the human nasopharynx asymptomatically in up to 10% of the population, with higher rates among adolescents and much lower rates in younger children. For this reason it follows that isolation of the organism from a throat swab cannot indicate invasive disease. In view of these observations and the lack of evidence on which to base a recommendation, the GDG came to a consensus that there could be no justification in undertaking throat swabs as a diagnostic test. Diagnosis should be made by isolation/detection of the organism in a normally sterile site (for example blood or CSF).

A review of patients on the Public Health Laboratory Service Meningococcus Reference Unit (MRU) database between 1994 and 1997, where both nasopharyngeal and systemic isolates

were submitted, showed the organisms from both sites were identical in 97% (134 out of 138) of cases. However, in 3% of cases they were different, and a nasopharyngeal isolate in the absence of a systemic isolate does not confirm invasive disease.[15] This suggests that if the diagnosis of meningococcal disease is confirmed by blood PCR, then a meningococcal isolate obtained from the throat is likely to be the cause of the systemic infection (at least in 97% of cases). However, the clinical application of this is limited, and the GDG consensus remained that throat swabs should not be used for diagnosis of meningococcal disease.

Recommendations

Skin samples and throat swabs for meningococcal disease

Do not use any of the following techniques when investigating for possible meningococcal disease: skin scrapings, skin biopsies, petechial or purpuric lesion aspirates (obtained with a needle and syringe), or throat swabs.

5.5 Performing lumbar puncture and interpreting cerebrospinal fluid parameters for suspected bacterial meningitis

Introduction

In cases of suspected meningitis, cerebrospinal fluid (CSF) is routinely obtained by lumbar puncture and examined for the presence of white blood cells (WBCs), red blood cells (RBCs), and protein and glucose concentrations (the latter interpreted as a ratio using a laboratory-determined blood glucose taken at the same time as the CSF). Taken together, these CSF variables can provide a rapid early guide to the probability of the patient having bacterial meningitis, even when bacteria are not detected on CSF Gram staining. Normal ranges for CSF variables vary slightly between laboratories, but approximate values are shown below.

- opening pressure: 10–100 mmH_2O (age under 8 years); 60–200 mmH_2O (over 8 years)
- appearance to the naked eye: clear and colourless
- total protein concentration: 0.15–0.45 g/litre
- glucose concentration: 2.78–4.44 millimole/litre (approximately 60% of the plasma value)
- cell count (per microlitre): 0–5 WBCs (0–20 in neonates), no RBCs (if RBCs are present and the blood WBC count is within the normal range, more than one WBC per 500–1000 CSF RBCs can be expected in a child or young person with meningitis and should not be ignored) [76]

The difficulty in interpreting CSF samples containing red blood cells (traumatic lumbar punctures) is well recognised.[77;78] It has been reported that there is no advantage of adjusting leukocytes and neutrophils in CSF containing blood cells, suggesting that absolute white cell counts should be used rather than adjusted counts.

An increased CSF opening pressure is common, but not invariable, in bacterial meningitis. A CSF opening pressure greater than 250 mmH_2O indicates raised intracranial pressure. CSF containing a high number of WBCs or RBCs (more than 200 WBCs or more than 400 RBCs per microlitre) may appear turbid to the naked eye. Overt turbidity due to the presence of WBCs is usually an indication of bacterial meningitis.

An increased CSF protein concentration may be due to the presence of blood in the CSF, polyneuritis, tumour, injury or any inflammatory or infectious condition of the central nervous system (CNS), including bacterial meningitis. Protein concentrations seen in bacterial meningitis are usually higher than in viral meningitis, and CSF protein levels may be particularly high in TB meningitis. A decreased CSF glucose concentration (CSF plasma to glucose ratio of less than 0.6) may be due to bacterial meningitis, including TB.

An increased WBC count in the CSF is usually an indication of bacterial or viral meningitis, but may also be found in cerebral or spinal abscesses, encephalitis and acute disseminated encephalomyelitis, following seizures, and in some non-infectious disorders (such as acute leukaemia). RBCs in the CSF sample are commonly the result of a traumatic lumbar puncture, but may also indicate bleeding in the CNS.

Differentiation of the CSF WBCs can also be useful. A raised CSF polymorphonuclear (PMN) cell count is usually indicative of bacterial meningitis, whereas a lymphocytic CSF is more often associated with viral meningitis. However, it is important to note that a raised CSF PMN cell count can also occur with viral aetiologies (for example herpes simplex virus or enterovirus meningitis). In addition, lymphocytic CSFs (or a mixture of PMN cells and lymphocytes) are not uncommon in the early stages of bacterial meningitis, especially in cases where oral antibiotics have been given prior to lumbar puncture. Lymphocytes may also be the predominant cell type in TB meningitis.

CSF bacterial culture is routinely performed. However, it should be noted that staining and culture for *Mycobacterium tuberculosis* is only normally performed when specifically requested by the clinician and/or clinical details, including risk factors for TB, are provided. If TB meningitis is suspected on clinical grounds, approximately 5 ml of CSF should be sent for examination to enhance the sensitivity of staining for acid-fast bacilli (which is only rarely positive) and culture. TB PCR should also be considered, and the case should be discussed with a clinical microbiologist and an infectious disease specialist.

Meningococcal PCR testing of CSF (in addition to whole-blood PCR) should also be performed in cases of suspected meningococcal meningitis.

PCR testing for viruses (for example HSV, enteroviruses) should also be considered depending on the clinical presentation and CSF variables. It should be noted that a CSF WBC count in the normal range, or the presence of PMN cells in the CSF, does not exclude viral meningitis.

Clinical question

In children and young people with suspected meningitis, can CSF variables (white blood cell count, glucose, protein) distinguish between bacterial and viral meningitis?

Previous UK guidelines

No previous guidelines were identified in relation to this question.

Studies considered in this section

All study designs evaluating the diagnostic accuracy of tests for CSF white blood cell count, CSF protein or CSF glucose to discern bacterial meningitis from viral or aseptic meningitis were considered for inclusion in this section. The majority of studies were retrospective and only those conducted in high income countries were included. Studies of adults and children were included where data were presented separately for child participants. Findings were presented in three age groups: all children, pre-school children and neonates.Overview of available evidence

CSF white blood cell count

Eleven studies examined the value of CSF WBC count to differentiate between bacterial and aseptic or viral meningitis.[35;62-64;66;79-84] Nine were retrospective studies [EL=III] that generally extracted relevant demographic, clinical and laboratory test data from emergency department admission notes and compared these for children who were subsequently given a confirmed diagnosis of bacterial, viral or aseptic meningitis. Two studies recruited participants and collected data prospectively[80;81] [EL=II]. Seven studies detailed exclusion criteria.[62;63;66;81-84] Nine included children of broad age groups, one study[83] included younger children only (1 month to 3.5 years) and one[84] included neonates.

Bacterial meningitis was compared to viral meningitis in six studies,[35;64;66;81-83] to aseptic meningitis in two studies[62;63] and to more than one non-bacterial type in three others.[79;80;84]

CSF protein

Ten studies examined CSF protein concentration to differentiate between bacterial and aseptic or viral meningitis.[35;62-64;66;79-81;83;84] Eight collected data retrospectively from case notes [EL=III] while two recruited participants and recorded data prospectively[80;81] [EL=II]. Eight included children of broad age groups, one study[83] included infants only (1 month to 3.5 years) and one[84] included neonates.

Bacterial meningitis was compared to viral meningitis in six studies,[35;64;66;81;83] to aseptic meningitis in two studies[62;63] and to more than one non-bacterial type in three others.[79;80;84] Three of the studies described confirmation of the diagnosis of a viral causative agent.[64;81;83]

CSF glucose

Eight studies[35;62;63;66;80;81;83;84] were identified that assessed the diagnostic value of CSF glucose tests to discriminate between bacterial and viral, aseptic and/or nonbacterial meningitis. Five studies included children of all ages, one study included infants[83] and one included neonates.[84] Two of these studies were prospective[80;81] [EL=II and the remainder retrospective.

Bacterial meningitis was compared to viral meningitis in four studies,[35;66;81;83] to aseptic meningitis in two studies[62;63] and to more than one non-bacterial type in two others.[80;84]

Review findings

CSF white blood cell count

Children of all ages

Four studies[35;64;66;82] [EL=II to III] reported that the mean or median[82] CSF while blood cell (WBC) count was significantly higher in bacterial meningitis compared to viral meningitis (see table 5.15). Only two of these four studies[64;82] reported that all samples were systematically tested for viral agents: in the other two studies[35;66] diagnosis was based on a combination of chart review (for example no report of antibiotic therapy, recorded diagnosis of viral meningitis) and a proportion of samples having been tested for viral infection.

Two studies[79;80] [EL=III and EL=II respectively] reported CSF WBC counts for children with bacterial, viral and undetermined meningitis. Although a *P* value was not given in either study, the findings for undetermined meningitis (UM) were of a similar magnitude across the two studies (UM: mean 431 WBCs/ml, SD 772 WBCs/ml and UM: 264 WBCs/ml, SD 204 WBCs/ml respectively). Results for the bacterial and viral groups were consistent across the two studies and with the previously mentioned studies (see table 5.15). Three older studies included children with meningitis where *H. influenzae* was the causative agent in at least 50% of cases (see table 5.15).

Two retrospective studies sought to discriminate between bacterial meningitis and aseptic meningitis[62;63]. The first study, which was a secondary analysis of multicentre data, included 96 cases of bacterial meningitis (from a total n=198). The second study (n=167) included 21 children with bacterial meningitis. Both studies reported that the median CSF WBC count was significantly higher in bacterial meningitis compared to aseptic meningitis (both $P < 10\text{-}6$). However, neither demonstrated that CSF WBC was a strong predictor for distinguishing bacterial from aseptic meningitis. The first study estimated Area Under Curve (AUC) as 0.81 and that a CSF WBC count above the threshold of 200 cells/microlitre was significantly associated with bacterial meningitis (sensitivity 76%, specificity 75%, OR=9, 95% CI 3 to 32, $P < 10^{-5}$). The secondary analysis reported similar findings for the same threshold (sensitivity 79%, specificity 69%, OR=8.3, 95% CI 4.1 to 16.9).

Table 5.15. Cerebrospinal fluid (CSF) white blood cell (WBC) count - descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	CSF WBC count outcome; unit of measurement	Result	*P* value
De Cauwer, 2007[35] [EL=III]	1997–2005 1/22 Hib	Mean (SD); no unit given	BM=5467 (6937) VM=320(718).	$P = 0.01$
Gendrel, 2000[64] [EL=III]	1994–1996 6/23 Hib	Mean (range); cells/ml	BM=4710 (10–17,500) VM=345(10–3200)	$P < 0.01$
Sormunen, 1999[66] [EL=III]	1977–1992 213/325 Hib	Mean (SD); cells/microlitre [6]	BM=4540 (4040) VM=240 (310)	$P < 0.0001$
Baker, 1989[82] [EL=III]	1985–1986 36/54 Hib	Median (range); cells/microlitre	BM=2500 (2–48,180) VM=167 (2–1990)	$P < 0.001$
Chavanet, 2007[79] [EL=III]	1995–2002 Hib not reported but main causes noted as being *S. pneumoniae* (20/36) and *N. meningitidis* 9/36)	Mean (SD); cells/microlitre	BM=2994 (3263) VM=218 (280) UM=431 (772)	
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	Mean (SD); cells/microlitre	BM=2417 (1380) VM=149 (116) UM=264 (204)	
Dubo,s 2006[63] [EL=III]	2000–2004 1/21 Hib	Mean/median/(range); cells/microlitre	BM=3072/1120/(7–10,600) AM=179/85.5/(7–2520)	$P < 10^{-5}$
Dubos, 2008[62] [EL=III]	1998–2005 7/96 Hib	Median (range); WBC count/microlitre	BM=1625 (8–22000) AM=83 (7–1120)	$P < 10^{-6}$

[a] AM: aseptic meningitis; BM: bacterial meningitis; UM: undetermined meningitis; VM: viral meningitis

Three studies[66;81;82] gave estimates of sensitivity, specificity, PPV and NPV for different thresholds of CSF WBC counts to discriminate between bacterial and viral meningitis. One study[80] combined viral and undetermined meningitis groups to compare the bacterial to a non-bacterial meningitis group (see table 5.16). The four studies that presented findings for a threshold of 500 cells/microlitre ranged in size (n=45 to 237), included locally available populations, variously included Gram-negative or both Gram-negative and Gram-positive bacteria, and used different data collection methods. No consistent findings for sensitivity, specificity, PPV and NPV were reported. One study[66] compared three different thresholds but did not find any threshold value of CSF WBC count conferring high sensitivity, specificity and NPV to the test.

Table 5.16. Cerebrospinal fluid (CSF) white blood cell (WBC) count – diagnostic statistics (children of all ages)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	Threshold value	Sensitivity	Specificity	PPV[a]	NPV[a]
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	CSF WBC count threshold >500 cells/microlitre	74%	94%	89%	83%
Baker, 1989[82] [EL=III]	1985–1986 36/54 Hib	CSF WBC count threshold >500 cells/microlitre	83%	78%	83%	Not reported
BenGershom, 1986[81] [EL=II]	Not reported Not reported	CSF WBC count threshold >500 cells/microlitre	88%	72%	68%	90%
Sormunen, 1999[66] [EL=III]	1984–1991 213/325 Hib	CSF WBC count threshold >500 cells/microlitre	78%	89%	69%	93%
Sormunen, 1999[66] [EL=III]	1984–1991 213/325 Hib	CSF WBC count threshold >1000 cells/microlitre	75%	97%	89%	93%
Sormunen, 1999[66] [EL=III]	1984–1991 213/325 Hib	CSF WBC count threshold >2000 cells/microlitre	64%	99%	97%	90%

[a] NPV: negative predictive value; PPV: positive predictive value

Pre-school children

One retrospective study[83] [EL=III] of children aged 1 to 42 months found that the mean CSF WBC count was also significantly higher in bacterial meningitis than in viral meningitis in this younger age group ($P < 0.0001$).

Neonates

A retrospective study of neonates (defined as age under 4 weeks)[84] (n=72 of whom 18 had bacterial meningitis) [EL= III] found that all viral and aseptic meningitis cases had a CSF WBC above a threshold of 22 cells/microlitre, compared to 83% of bacterial meningitis cases. However, this was a small study (bacterial meningitis n=18, viral meningitis n=13 and aseptic meningitis n=41), and neonates who had received antibiotic treatment of assessment were excluded, as were those whose lumbar puncture was 'traumatic' (more than 1000 RBC/mm^3) unless the CSF culture tested positive for bacteria. This could explain why fewer neonates with bacterial meningitis had a CSF WBC more than 22 cells/microlitre.

CSF protein

Children of all ages

Three studies[35;64;66] [EL=III] reported that the mean CSF protein concentration was significantly higher in bacterial meningitis compared to viral meningitis. Two studies[79;80] [EL=III and EL=II, respectively] reported CSF protein concentration for children with bacterial, viral and undetermined meningitis. Although no *P* value was reported, the findings for undetermined meningitis were similar across both studies and results for the bacterial and viral groups were of similar magnitude to those studies where *P* values were reported (see table 5.17).

Table 5.17. Cerebrospinal fluid protein concentration - descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	CSF protein concentration; unit of measurement	Result	*P* value
Grendel, 2000[64] [EL=III]	1994–1996 6/23 Hib	Mean (range); g/litre	BM=2.2 (0.4–4.7) VM=0.57 (0.1–2.7)	*P* < 0.01
Sormunen, 1999[66] [EL=III]	1984–1991 213/325 Hib	Mean (SD); g/litre	BM=1.88 (1.5) VM=0.52 (0.24)	*P* < 0.0001
De Cauwer, 2007[35] [EL=III]	1997–2005 1/22 Hib	Mean (SD); g/litre	BM=1.633 (2.180) VM=0.378 (0.182)	*P* = 0.0003
Chavanet, 2007[79] [EL=III]	1995–2002 Hib not reported but main causes noted as being *S. pneumoniae* (20/36) and *N. meningitidis* 9/36)	Mean (SD); g/litre	BM=2.3 (1.5) VM=0.38 (0.18) UM=0.47 (0.24)	
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	Mean (SD); g/litre	BM=1.74 (0.36) VM=0.74 (0.35) UM=0.46 (0.11)	

[a] BM: bacterial meningitis; UM: undetermined meningitis; VM: viral meningitis

Three studies[35;66;81] estimated the diagnostic accuracy of CSF protein concentration to discriminate between bacterial and viral meningitis providing estimates of sensitivity, specificity, PPV and NPV at different thresholds. One study[80] compared bacterial to 'non-bacterial' meningitis (see table 5.18). The four studies that presented findings for a CSF protein concentration threshold of 100 mg/decilitre ranged in size (n=45 to 237), variously included bacteria which were Gram-positive or Gram-negative or both, and used different data collection methods. The best results for accuracy were reported in a small prospective study[66] (n=45) but were not replicated elsewhere. No consistent findings for sensitivity, specificity, PPV and NPV were reported. One study[66] presented findings for two different thresholds (1.0 g/litre and 1.5 g/litre) but did not find a threshold value of CSF protein concentration conferring high sensitivity and NPV to the test.

Table 5.18. Cerebrospinal fluid (CSF) protein concentration – diagnostic statistics (children of all ages)

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	Threshold value	Sensitivity	Specificity	PPV[a]	NPV[a]
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	CSF (protein) >1.0 g/litre	74%	94%	89%	83%

De Cauwer, 2007[35] [EL=III]	1997–2005 1/22 Hib	CSF (protein) >1.0 g/litre	57%	100%	100%	89%
BenGershom, 1986[81] [EL=II]	Not reported Not reported	CSF (protein) >1.0 g/litre	94%	92%	89%	96%
Sormunen, 1999[66] [EL=III]	1977–1992 213/325 Hib	CSF (protein) >1.0 g/litre	64%	96%	84%	88%
Sormunen, 1999[66] [EL=III]	1977–1992 213/325 Hib	CSF (protein) >1.5 g/litre	50%	99%	96%	85%

[a] NPV: negative predictive value; PPV: positive predictive value

Two retrospective studies [EL=III] evaluated the predictive value of CSF protein concentration to discriminate between bacterial meningitis and aseptic meningitis[62;63]. The first study, which was a secondary analysis of multicentre data, recruited 96 cases of bacterial meningitis (n=198). The second study (n=167) included 21 children with bacterial meningitis. Both studies reported that the median CSF protein concentration was significantly higher in bacterial meningitis compared to aseptic meningitis (both $P < 10^{-6}$). However, neither demonstrated that CSF protein concentration was a strong predictor for distinguishing bacterial from aseptic meningitis. The first analysis reported a lower area under the curve (AUC) estimate of 0.88, lower specificity and a lower OR for the same threshold (sensitivity 88%, specificity 65%, OR=14.2, 95% CI 6.3 to 32.7). The second study estimated the AUC as 0.93 and that a CSF protein concentration above the threshold of 0.5 g/litre was significantly associated with bacterial meningitis (sensitivity 86%, specificity 78%, OR=22, 95% CI 6 to 101, $P < 10^{-8}$; adjusted OR=34, 95% CI 5 to 217, $P < 10^{-3}$; adjustment for blood CRP, CSF WBC and neutrophil count).

Pre-school children

One retrospective study[83] [EL=III] of children aged 1 to 40 months found that the mean CSF protein concentration was significantly higher in bacterial meningitis compared to viral meningitis in this younger age group (bacterial meningitis mean 1.5 g/litre, SD 1.0 g/litre versus viral meningitis 0.4 g/litre, SD 0.2 g/litre, $P < 0.0001$).

Neonates

A retrospective study of neonates[84] [EL=III] (n=72) found that all viral and aseptic meningitis cases had a CSF protein concentration below a threshold of 1.70 g/litre, but only 56% of bacterial meningitis cases had a CSF protein concentration above this level. This threshold conferred high specificity and PPV, but a low sensitivity for identification of bacterial from non-bacterial meningitis (sensitivity 55.6%, specificity 100%, PPV 100%, NPV 87.1%).

CSF glucose

Children of all ages

Two studies [EL=III] compared the mean CSF glucose in children with bacterial meningitis to those with viral meningitis.[35;66] Although the results showed that the mean CSF glucose was higher in viral than in bacterial meningitis in both studies, only one found that this was statistically significant [EL=III]. A third study [EL=II] that included children with viral and aseptic meningitis also reported that those with viral meningitis had a higher mean CSF glucose than those with bacterial meningitis although no *P* value was given (see table 5.19).[80]

Two retrospective studies [EL=III] compared the mean CSF glucose concentrations found in bacterial meningitis and aseptic meningitis[62;63]. Both studies reported that the median CSF glucose concentration was significantly higher in aseptic meningitis than in bacterial meningitis (both $P = 0.01$ and $P < 10^{-6}$, respectively). A third study was a small (n=56)

prospective study[80] [EL=III] including children with viral and aseptic meningitis: this also reported that those with aseptic meningitis had a higher mean CSF glucose than those with bacterial meningitis, although no *P* value was reported.

Table 5.19. Cerebrospinal fluid (CSF) glucose concentration - descriptive statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	CSF glucose concentration; unit of measurement	Result	*P* value
De Cauwer, 2007[35] [EL=III]	1997–2005 1/22 Hib	Mean (SD); millimole/litre	BM=2.46 (1.48) VM=3.37 (0.56)	$P = 0.012$
Sormunen, 1999[66] [EL=III]	1977–1992 213/325 Hib	Mean (SD); millimol/litre	BM=2.9 (1.6) VM=3.3 (0.6)	$P < 0.1$
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	Mean (SD); millimoele/litre	BM=1.54 (0.44) VM=3.08 (0.44) UM=3.47 (0.33)	Not recorded
Dubos, 2006[63] [EL=III]	2000–2004 1/21 Hib	Mean/median/(range); millimole/litre	BM=1.8/1.4/(0.0–4.4) AM=3.0/3.0/(1.3–4.6)	$P = 0.01$
Dubos, 2008[62] [EL=III]	1998–2005 7/96 Hib	Median (range); millimole/litre	BM=1.09 (0.0–6.04) AM=3.17 (0.1–5.65)	$P < 10^{-6}$

[a] AM: aseptic meningitis; BM: bacterial meningitis; UM: undetermined meningitis; VM: viral meningitis

Three studies[35;66;81] gave details of the diagnostic accuracy of CSF glucose concentration in discriminating between bacterial and viral meningitis providing estimates of sensitivity, specificity, PPV and NPV at different thresholds (2.0 millimole/litre, 2.2 millimole/litre and 2.5 millimole/litre). Although optimal specificity was reached in one study at a cutoff value of 2.0 millimole/litre[66], sensitivity was consistently low for this threshold and all others investigated. The best results were found in the study comparing bacterial to 'non-bacterial' meningitis[80] (sensitivity=78%; see table 5.20).

Table 5.20. Cerebrospinal fluid (CSF) glucose concentration - diagnostic statistics (children of all ages)[a]

Study; evidence level	Years of data collection; proportion of *Haemophilus influenzae* type B (Hib)	Threshold value	Sensitivity	Specificity	PPV[b]	NPV[b]
De Cauwer, 2007[35] [EL=III]	1997–2005 1/22 Hib	CSF (glucose) 2.92 millimoles/litre BM versus VM	57%	87%	57%	87%
BenGershom, 1986[81] [EL=II]	Not reported Not reported	CSF (glucose) <2.2 millimole/litre BM versus VM	47%	96%	89%	71%

Sormunen, 1999[66] [EL=III]	1977–1992 213/325 Hib	CSF (glucose) <2.0 millimole/litre BM versus VM	31%	100%	100%	79%
Sormunen, 1999[66] [EL=II]	1977–1992 213/325 Hib	CSF (glucose) <2.5 millimole/litre BM versus VM	35%	96%	79%	79%
Corrall, 1981[80] [EL=II]	1978–1980 12/24 Hib	CSF (glucose) <2.2 millimole/litre BM versus VM/UM	78%	100%	100%	86%

[a] BM: bacterial meningitis; UM: undetermined meningitis; VM: viral meningitis
[b] NPV: negative predictive value; PPV: positive predictive value

Two retrospective studies [EL=III] estimated diagnostic accuracy of CSF glucose concentration to discriminate between bacterial and aseptic meningitis at a 2.5 millimole/litre threshold.[62;63] The first analysis, which included a larger proportion of bacterial meningitis cases, reported slightly better results at the same threshold (sensitivity 67%, specificity 82%, OR=9.3, 95% CI 4.5 to 19.3). The second study estimated that a CSF glucose concentration above the threshold was significantly associated with aseptic meningitis (sensitivity 62%, specificity 78%, OR=6, 95% CI 2 to 17, $P < 10^{-3}$). However, neither demonstrated that CSF protein concentration was a strong predictor for distinguishing bacterial from aseptic meningitis.

Pre-school children

One retrospective study[83] [EL=2-] reported that the mean CSF glucose concentration was significantly higher in viral meningitis than in bacterial meningitis in a younger age group (1 month to 3.5 years) (bacterial meningitis: 1.6 millimole/litre, SD 1.3 millimole/litre versus viral meningitis: 3.2 millimole/litre, SD 0.7 millimole/litre; $P < 0.0001$).

Neonates

One study of neonates [EL=2-] reported estimates of diagnostic accuracy at a CSF glucose threshold of 1.87 millimole/litre.[84] In this study, 11 out of 18 bacterial meningitis cases (61%) had results below this level, as did 7 out of 13 viral meningitis cases (54%) and 7 out of 41 aseptic meningitis cases (17%).. Comparing the results for bacterial meningitis to the combined results for non-bacterial meningitis did not result in clinically meaningful diagnostic accuracy estimates (sensitivity 61 %, specificity 74%, PPV 44%, NPV 85%).

Evidence statement

CSF white blood cell count

There is consistent evidence from eight studies of children of all ages and evidence from one study in pre-school children that CSF white blood cell (WBC) count was significantly higher in bacterial meningitis compared to viral, aseptic and non-bacterial meningitis. Because of the clinical need to reliably discriminate between children with bacterial meningitis and viral meningitis, the diagnostic accuracy of a test should include a high sensitivity. High sensitivity was not found in any study of children at a threshold of 500 cells/microlitre.

Results from a study in neonates suggested that a threshold of 22 cells/microlitre would not have sufficient diagnostic accuracy to discriminate non-bacterial from bacterial meningitis.

CSF protein

CSF protein concentration was consistently reported to be significantly higher in bacterial meningitis compared to viral, aseptic or non-bacterial meningitis in children. No clinically reliable threshold to discriminate between bacterial and viral or aseptic meningitis was determined for CSF protein concentration in children. In neonates, although a threshold was identified under which the CSF protein concentration for all non-bacterial meningitis cases occurred, 44% of bacterial meningitis cases also had these lower results.

CSF glucose

Evidence from two studies of children demonstrated that the mean CSF glucose concentration was significantly higher in aseptic meningitis compared to bacterial meningitis. There were inconsistent findings for the comparison between viral and bacterial meningitis for this age group, although in a study of infants, the mean CSF glucose concentration was significantly higher in viral meningitis than in bacterial meningitis. No clinically reliable threshold to discriminate between bacterial and viral, aseptic and/or nonbacterial meningitis was determined for CSF glucose concentration in children or in neonates.

GDG interpretation of the evidence

Although evidence has been found that there are significant differences in CSF WBC count and protein and glucose concentrations between bacterial and other forms of meningitis, no single variable has been shown to have sufficient diagnostic accuracy to confirm or exclude bacterial meningitis. The GDG is aware of some limited evidence that the presence of polymorphonuclear cells in CSF and the CSF plasma to glucose ratio are independent predictors of bacterial meningitis. In some of the included studies the absence of a positive CSF bacterial culture was used to indicate the absence of bacterial meningitis ('aseptic meningitis'). In these studies, true cases of bacterial meningitis will be defined as 'aseptic meningitis' due to the low sensitivity of CSF bacterial culture.

Given that CSF variables cannot reliably exclude bacterial meningitis, the GDG was of the opinion that CSF WBC counts outside the accepted normal ranges should prompt the initiation of appropriate antibiotic therapy in cases of suspected bacterial meningitis (if antibiotics have not been started prior to the lumbar puncture). While a low CSF to plasma glucose ratio is also an indicator of bacterial meningitis in children aged over 28 days, no evidence was identified to indicate that this variable is commonly abnormal in the presence of a normal CSF WBC count. Recognising the lower sensitivity of the CSF WBC count for bacterial meningitis in neonates, the GDG was also of the opinion that bacterial meningitis should still be considered in neonates in whom the CSF WBC count is within the currently accepted normal range (less than 20 cells/microlitre). Furthermore, the GDG is aware of recent evidence that suggests that the CSF WBC count range in normal neonates is the same as that in older children and adults (less than 5 cells/microlitre) and that mild CSF pleocytosis (which may occur in symptomatic neonates without central nervous system infection) cannot be regarded as a normal finding.[85]

A particular problem is the interpretation of CSF findings in neonates: there is insufficient evidence to guide recommendations for defining the likelihood of bacterial meningitis in this age group. Performance characteristics of meningitis scoring systems based on blood test results and CSF findings have been studied in some populations and similar studies in the UK could improve the diagnosis or exclusion of bacterial meningitis. Studies are, therefore, needed to determine the 'normal' ranges of blood and CSF parameters in children and young people. The studies should include previously healthy children found to have aseptic meningitis as well as those in whom bacterial meningitis is confirmed.

Recommendations relating to the interpretation of CSF parameters (white blood cell count, glucose, protein) are presented in section 5.7.

5.6 Contraindications to lumbar puncture

Introduction

Definitive diagnosis of meningitis requires microscopy, biochemical analysis and PCR analysis of a sample of CSF. Without a CSF sample, the resultant incomplete diagnosis detracts from clinical management. Bacterial meningitis may be clinically suspected but not confirmed, antibiotic use and selection may be inadequate, duration of antibiotic treatment cannot be optimised, development of complications cannot be anticipated and information to parents, prognostication and follow-up may be less well informed. Nevertheless, there are circumstances when a lumbar puncture is contraindicated, because of a risk of complications.

Usually such risk is temporary and lumbar puncture can be deferred rather than abandoned completely.

Clinical question

When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?

When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?

Previous UK guidelines

The 'Feverish Illness in Children' guideline[25] recommends the following:

'Red' group

Children with fever without apparent source presenting to paediatric specialists with one or more 'red' features should have the following investigations performed:

- full blood count
- blood culture
- C-reactive protein
- urine testing for urinary tract infection.

The following investigations should also be considered in children with 'red' features, as guided by the clinical assessment:

- lumbar puncture in children of all ages (if not contraindicated)
- chest X-ray irrespective of body temperature and white blood cell count
- serum electrolytes and blood gas.

'Amber' group

Children with fever without apparent source presenting to paediatric specialists who have one or more 'amber' features should have the following investigations performed unless deemed unnecessary by an experienced paediatrician:

- urine should be collected and tested for urinary tract infection
- blood tests: full blood count, C-reactive protein and blood cultures
- lumbar puncture should be considered for children younger than one year
- chest X-ray in a child with fever greater than 39°C and white blood cell count greater than $20x10^5$/litre."

The SIGN guideline on 'Management of invasive meningococcal disease in children and young people'[27] recommends:*

> 'Lumbar puncture is not recommended in the initial assessment of suspected IMD [invasive meningococcal disease] with features of septicaemia. Lumbar puncture may be considered later if there is a diagnostic uncertainty or unsatisfactory clinical progress, and there are no contraindications.
>
> 'Lumbar puncture should be performed in patients with clinical meningitis without features of septicaemia (purpura) where there are no contraindications.'

The SIGN guideline notes the following contraindications to lumbar puncture:

- cardiorespiratory decompensation
- raised intracranial pressure (signs include: fluctuating or impaired levels of consciousness, focal neurological signs or abnormal posturing, dilated or poorly reactive pupils, relative bradycardia and/or hypertension, papilloedema [although this may not be present initially despite significantly raised ICP]).
- coagulopathy
- purpura/petechial rash.

* See SIGN guideline at www.sign.ac.uk/pdf/sign102.pdf

Studies considered in this section

This systematic review looking at contraindications to lumbar puncture in children with suspected bacterial meningitis and children with suspected meningococcal disease includes five studies, four of which were surveys based on reviews of medical records [EL=3] and one of which was a case–control study of poor quality [EL=2–].

Review findings

A prospective survey conducted in Australia (1991–1992) [EL=3][86] aimed to identify the risks of performing lumbar puncture and poor outcomes associated with not performing lumbar puncture. Of the 218 children admitted to hospital with suspected meningitis, 195 (89.4%) had a lumbar puncture performed immediately. Bacterial meningitis was diagnosed in 18 of these children (31 had viral meningitis). No child developed cerebral herniation following an immediate lumbar puncture. Eleven of the lumbar punctures were defined as traumatic and two children required repeated attempts. In nine of the 18 children with bacterial meningitis the lumbar puncture provided information that was defined by the authors as useful in deciding the appropriate management of the children.

Twenty-three children did not have an immediate lumbar puncture. The main reason for delaying lumbar puncture was severe obtundation, usually with a Glasgow Coma Scale score of 7 or less. Seventeen children had a lumbar puncture later. In seven children the lumbar puncture was delayed due to suspected raised intracranial pressure. A lumbar puncture was performed after a cranial computed tomography (CT) scan showed no abnormalities. Three children in the delayed lumbar puncture group had bacterial meningitis. Six children never had a lumbar puncture performed. Five of this group had bacterial meningitis diagnosed clinically and from blood cultures or urine antigen testing. No adverse outcomes were noted in relation to not having a lumbar puncture performed.

A UK retrospective survey[87] was undertaken in 2000 [EL=3] to describe usual practice at the study hospital and identify the contribution of lumbar puncture to diagnosis and management of care. Medical records were examined of 415 children to identify those with suspected central nervous system (CNS) infections (n=52) or suspected meningococcal septicaemia (n=43). No lumbar puncture was performed in children with contraindications (as defined by the authors). Of the 47 children with suspected CNS infection and no contraindications, 25 (53%) received a lumbar puncture. Contraindications were defined as:

- shock present (tachycardia and poor peripheral perfusion and/or hypotension)
- reduced level of consciousness (Glasgow Coma Score less than 13)
- focal neurological signs present:
  - unequal, dilated or poorly responsive pupils
  - absent 'doll's eye' movements
  - papilloedema
- hypertension and relative bradycardia
- within 30 minutes of a short generalised seizure
- following a prolonged generalised seizure (lasting more than 30 minutes) or tonic seizure
- local superficial infection
- coagulation disorder.

Forty-three children had suspected meningococcal septicaemia without CNS involvement. None of these children had a lumbar puncture performed. No patient in any group died or had sequelae. Sterile CSF cultures allowed 15 of the 25 children who had a lumbar puncture to have antibiotics discontinued compared with three of the 22 children who had no contraindications but did not have a lumbar puncture ($P < 0.001$).

A retrospective survey conducted in Australia (1984–1989) [EL=3] was undertaken to see whether the incidence of cerebral herniation was increased immediately following a lumbar puncture for children with bacterial meningitis.[88] From 445 medical records reviewed, 19 children were identified as having cerebral herniation (a total of 21 episodes; two children had two episodes of herniation). The timing of herniation compared with lumbar puncture was:

- Eight episodes of herniation occurred within 3 hours of lumbar puncture being performed.
- Four episodes occurred between 3 and 12 hours after lumbar puncture.
- Three episodes of herniation occurred between 18.5 and 40.5 hours after lumbar puncture.
- Six episodes of herniation occurred before lumbar puncture or in a child who did not undergo lumbar puncture.

At the time of lumbar puncture three children were unresponsive to pain, three were drowsy but rousable, one had a purpuric rash and clonus of the right ankle, another had neck stiffness, and one had decerebrate posturing and a rash. Outcomes for children who had cerebral herniation were very poor: 14 of the children died, two had no long-term sequelae reported, one had hearing loss and behavioural problems noted on follow-up (timing not noted) and two were discharged with serious neurological impairment.

A UK retrospective case control study (1974–1985) [EL=2–]aimed to identify features of meningitis associated with cerebral herniation and death.[89] The study included 19 children who had been diagnosed with meningitis, who had had a lumbar puncture and who had subsequently died. This group was compared with a matched control group (n=19) of children who had also been diagnosed with meningitis, had had a lumbar puncture and subsequently recovered. The children were matched for: year of admission, gender, age and infecting micro-organism. However, the degree of matching achieved was quite poor with only one child being matched on all four factors and another seven matched on three factors.

Two features of raised intracranial pressure were found to be associated with a significantly increased risk of cerebral herniation: fits on admission (5 out of 17 versus 0 out of 17; RR 7.08, 95% CI 2.2 to 22.1, $P = 0.02$) and Glasgow coma scale score less than 8 (10 out of 17 versus 4 out of 17; RR 4.6, 95% CI 1.06 to 35.8, $P = 0.03$), although due to the small numbers of children involved these findings should be interpreted with caution.

A survey conducted in part prospectively (n=71 children) and in part retrospectively (n=52 children) in Nigeria[90] [EL=3] (1999) sought to determine the frequency and outcomes of possible cerebral herniation in relation to lumbar puncture. The study compared incidence and timing of cerebral herniation in high- and low-risk patients as defined by a weighted scoring system based predominantly on clinical features associated with severe or mild to moderate illness (factors included: unrousable coma (3 points), hypothermia (2 points), convulsions (2 points), shock (1 point), age under 12 months (1 point) and symptoms persisting for more than 3 days (0.5 point).

A lumbar puncture was performed on presentation in 112 children (91%) and deferred in 11. The former group contained 18 children (16%) who were defined as being at high risk compared with seven (64%) of the latter group.

Four groups of children were described among those on whom a lumbar puncture was performed on presentation:

- no herniation pre or post lumbar puncture: 6 out of 18 high risk versus 86 out of 94 low risk (RR 0.4, 95% CI 0.2 to 0.7, $P < 0.0001$)
- herniation pre and post lumbar puncture: 4 out of 18 versus 0 out of 94 ($P = 0.0004$)
- herniation pre lumbar puncture only: 7 out of 18 versus 0 out of 94 ($P < 0.0001$)
- herniation post lumbar puncture only: 1 out of 18 versus 8 out of 94 (RR 0.6, 95% CI 0.1 to 4.9, $P = 1.0$).

Seventeen children who had a lumbar puncture on presentation died, including seven within 24 hours. Eight children who had deferred lumbar puncture died, seven within 24 hours of the procedure.

Evidence statement

There is evidence that cerebral herniation occurs in bacterial meningitis.

There is evidence from two surveys that lumbar puncture is associated with a very low risk of cerebral herniation where it is undertaken on children without impaired level of consciousness or other signs of raised intracranial pressure. Evidence from another two surveys shows that where there are signs of loss of consciousness or other signs of raised intracranial pressure there is an increased risk of cerebral herniation, although there is evidence to suggest that the cerebral herniation noted after lumbar puncture may, in a number of cases, have been developing before the lumbar puncture was performed.

There is no evidence on which to conclude whether or not lumbar puncture causes cerebral herniation in bacterial meningitis.

GDG interpretation of the evidence

When used appropriately, lumbar puncture can provide important clinical information in suspected bacterial meningitis. Results can help to establish the diagnosis and effective management (choice of antibiotics, length of course of antibiotics, follow up arrangements and so on). Its proper use should not be neglected on the basis of over-interpretation of perceived risk.

There was no specific evidence found about the level of platelet count which would contraindicate a lumbar puncture. However, the GDG agreed by consensus that a platelet count below 100 x 10^9/litre was an appropriate cutoff for both neonates and older children and young people. The GDG's view is that a platelet count below 50 x 10^9/litre is not safe in children and young people with disseminated intravascular coagulation and/or shock (but it is acceptable in haematology patients with no other morbidities).

If a lumbar puncture is contraindicated (for example in children and young people with a history of haemophilia), then data from a delayed lumbar puncture may still help to establish a diagnosis or influence management.

The GDG noted that seizures were a serious complication in cases of meningitis and could be particularly difficult to manage in some patients, including those with raised intracranial pressure. Nevertheless, confirmation of diagnosis by lumbar puncture is also important. Seizures are therefore a relative contraindication to lumbar puncture and appropriate management may neutralise that contraindication. The GDG was of the opinion that local or national protocols should be available for the management of seizures associated with bacterial meningitis (see section 6.3).

The GDG noted that a reduced or fluctuating level of consciousness would correspond to a Glasgow Coma Score (or Child's Glasgow Coma Score in the case of children under 4 years) of less than 9 or a drop of 3 or more.

Recommendations relating to contraindications to lumbar puncture are presented in section 5.7.

5.7 Repeat lumbar puncture in neonates

Introduction

Neonatal meningitis differs from bacterial meningitis in older children in various ways. The most common bacteria that cause meningitis in neonates (Group B streptococcus, *L. monocytogenes* and *E. coli*) differ from those in older children, especially in the first week of life. Meningitis that occurs later may also be caused by organisms more commonly acquired in childhood (such as *S. pneumoniae*). Intracranial infection of the neonate is often associated with a poor developmental outcome making it crucial to initiate timely and appropriate treatment. Premature babies are at even greater risk of meningitis caused by a large spectrum of antibiotic-resistant pathogens and associated with a worse outcome than term

babies: however, the sub-population of premature babies who develop meningitis while still in hospital is outside the scope of the guideline.

Historically it is known that, despite apparently adequate courses of antibiotics, neonatal meningitis can relapse or recrudesce. To document CSF sterilisation and thereby increase the chance of successful treatment, many paediatricians have adopted the practice of repeating a lumbar puncture in neonates either early on in treatment or at the end of a course of antibiotics. However, documentation of CSF sterilisation has not been shown to guarantee that the infection will not relapse. This section considers whether repeat lumbar puncture is a useful practice in ensuring treatment success for neonatal bacterial meningitis.

Clinical question

Should lumbar puncture be performed prior to stopping antibiotic treatment in children aged less than 3 months with bacterial meningitis?

Previous UK guidelines

No previous guideline has considered this clinical question in relation to neonates.

Studies considered in this section

Studies were included for consideration in this review if they included term neonates (that is, babies born at 37 weeks' gestation or over, aged 28 days or less). Only studies from high-income countries were included. No limits were placed on study design, thus small case series were also included due to the limited number of eligible studies conducted in this area.

Overview of available evidence

No study was identified that directly addressed the clinical question that was posed. Two retrospective reviews of medical records were identified that were considered to contribute data to help inform the GDG.

Review findings

A retrospective review (USA) [EL=3] of medical records of 128 children with definite or suspected bacterial meningitis between 1992 and 1996 was conducted in order to define the time taken to achieve a sterile CSF after the initiation of antibiotic therapy.[91] Twenty-one infants (median age 21 days, interquartile range [IQR] 9 days, 31 days) had Group B streptococcus meningitis. Following parenteral antibiotic treatment (usually with a third-generation cephalosporin), none of five samples tested within 24 hours was found to be sterile. Of four tested between 24 and 72 hours, three were sterile. All of the six tested after 72 hours were found to be sterile.

In a retrospective review of medical records (1981, USA) [EL=3] clinical and laboratory features of six children with recrudescence and 21 children with relapse were reviewed: nine of the children were neonates.[92] These complications occurred mainly in infants aged less than 2 years and comprised less than 1% of all cases of bacterial meningitis. Neither the initial nor follow-up CSF findings were predictive of recrudescence or relapse. Prolonged or secondary fever was unrelated to these complications. Recrudescence was usually caused by inappropriate therapy whereas relapse after adequate therapy of bacterial meningitis was usually ascribed to persistence of infection in meningeal or parameningeal foci. Relapse did not become manifest until at least 3 days after discontinuation of therapy.

Evidence statement

No evidence was found relating directly to the clinical question.

GDG interpretation of the evidence

Neonates who have persistent or re-emergent fever, deterioration in condition, new clinical findings (especially neurological findings) or persistently abnormal inflammatory markers should have imaging of the CNS and a repeat lumbar puncture as these abnormalities may signify a focus of infection. Positive imaging or a positive lumbar puncture should prompt a

discussion with local microbiology specialists about choice of antibiotics and duration of treatment. Healthcare professionals could consider the use of cranial computed tomography and/or magnetic resonance imaging before repeating lumbar puncture in neonates who have persistent or re-emergent fever, deterioration in clinical condition, new clinical findings (especially neurological findings) or persistently abnormal inflammatory markers.

By consensus, the GDG considers that routine repeat lumbar puncture is not justified in neonates who are on the correct type and dose of antibiotics (based on identification of the causative organism) and are otherwise making a good clinical recovery.

The GDG considered repeat lumbar puncture before stopping antibiotic therapy is not routinely necessary, while acknowledging that some authorities suggest this should be considered. The argument for this is that the CSF white cell count, neutrophil count (or percentage), glucose concentration or protein concentration at the end of therapy may predict those who will relapse or have other complications. However, no published evidence was found to support this.

Recommendations

Performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis

Perform a lumbar puncture as a primary investigation unless this is contraindicated.

Do not allow lumbar puncture to delay the administration of parenteral antibiotics.

CSF examination should include white blood cell count and examination, total protein and glucose concentrations, Gram stain and microbiological culture. A corresponding laboratory-determined blood glucose concentration should be measured.

In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:

- signs suggesting raised intracranial pressure
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - relative bradycardia and hypertension
  - focal neurological signs
  - abnormal posture or posturing
  - unequal, dilated or poorly responsive pupils
  - papilloedema
  - abnormal 'doll's eye' movements
- shock (see table 3.3)
- extensive or spreading purpura
- after convulsions until stabilised
- coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 10^9/litre
  - receiving anticoagulant therapy
- local superficial infection at the lumbar puncture site
- respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

In children and young people with suspected bacterial meningitis, if contraindications to lumbar puncture exist at presentation consider delaying lumbar puncture until there are no longer contraindications. Delayed lumbar puncture is especially worthwhile if there is diagnostic uncertainty or unsatisfactory clinical progress.

CSF white blood cell counts, total protein and glucose concentrations should be made available within 4 hours to support the decision regarding adjunctive steroid therapy.

Start antibiotic treatment for bacterial meningitis if the CSF white blood cell count is abnormal:

- in neonates at least 20 cells/microlitre (be aware that even if fewer than 20 cells/microlitre, bacterial meningitis should still be considered if other symptoms and signs are present – see table 3.3)
- in older children and young people more than 5 cells/microlitre or more than 1 neutrophil/microlitre, regardless of other CSF variables.

In children and young people with suspected bacterial meningitis, consider alternative diagnoses if the child or young person is significantly ill and has CSF variables within the accepted normal ranges.

Consider herpes simplex encephalitis as an alternative diagnosis.

If CSF white cell count is increased and there is a history suggesting a risk of tuberculous meningitis, evaluate for the diagnosis of tuberculous meningitis in line with 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' (NICE clinical guideline 33).

Perform a repeat lumbar puncture in neonates with:

- persistent or re-emergent fever
- deterioration in clinical condition
- new clinical findings (especially neurological findings) or persistently abnormal inflammatory markers.

Do not perform a repeat lumbar puncture in neonates:

- who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery
- before stopping antibiotic therapy if they are clinically well.

Research recommendations

Diagnosis in secondary care

Performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis

What are the normal ranges for blood and CSF parameters in children and young people in the UK?

Why this is important

Bacterial meningitis is a rare disease that is not easily distinguishable clinically from aseptic meningitis. It is, however, important to recognise those children who are most likely to have bacterial meningitis to direct appropriate management of the condition and to avoid inappropriate treatment of aseptic meningitis. Since the introduction of vaccines to protect against Hib, meningococcus serogroup C and pneumococcus, no high-quality studies involving previously healthy children and young people have been conducted in the UK to determine normal ranges for blood test results or CSF findings in bacterial and aseptic meningitis. Such studies are needed to provide reference values to help interpret blood test results and CSF findings in children (especially neonates) and young people with suspected bacterial meningitis.

Does repeat lumbar puncture in neonates with bacterial meningitis alter the prognosis?

Why this is important

Bacterial meningitis in neonates differs from bacterial meningitis in older children in several ways, including the causative organisms and the risk of relapse even after a long course of antibiotics (with the risk being greater in neonates). This has led some healthcare professionals to repeat lumbar puncture before stopping antibiotic treatment to ensure

that the CSF is sterile. The GDG found no evidence from which to evaluate the effectiveness of repeat lumbar puncture for preventing relapse of bacterial meningitis in neonates. A study is required in neonates with documented bacterial meningitis to determine what factors are associated with relapse and whether repeat lumbar puncture alters the prognosis. All neonates included in the study would need to receive a specified antibiotic regimen (tailored to the causative pathogen), involving similar dosages, dosing intervals and duration of treatment. The following data should be collected for each neonate in the study: signs and symptoms, blood test results (inflammatory markers), CSF findings (microbiology and chemistry) and central nervous system imaging. All variables should be measured at the start and end of treatment. Follow up should continue for 1 month after stopping antibiotic treatment, and longer-term follow-up (at 2 years) should also be conducted. Any deterioration in clinical condition should prompt a full clinical assessment, blood analysis, lumbar puncture, and imaging, from which it will be possible to evaluate the risk of relapse according to whether or not repeat lumbar puncture is undertaken.

5.8 Cranial computed tomography for suspected bacterial meningitis

Introduction

Identifying a causative organism in children and young people with suspected bacterial meningitis by examination of cerebrospinal fluid (CSF) obtained by lumbar puncture is essential to ensure optimal management.

Undertaking a lumbar puncture in children with raised intra-cranial pressure may result in cerebral herniation. Cranial computed tomography (CT) scanning prior to lumbar puncture has been advocated for children with a depressed conscious level to help determine the presence or extent of raised intracranial pressure to identify those at risk of cerebral herniation. CT scanning is also used to identify other potential causes of depressed conscious level, such as intracranial mass lesions. However, performing a CT scan might delay treatment in children with suspected meningitis and could be dangerous if undertaken in clinically unstable children. Therefore, it is essential to ensure the appropriate use of CT scanning, together with the accurate interpretation of scan results.

The ability of a CT scan to reliably detect raised intracranial pressure in children with suspected bacterial meningitis was the subject of this evidence review.

Clinical question

In children and young people with suspected or confirmed bacterial meningitis, can a cranial computed tomography (CT) scan reliably demonstrate raised intracranial pressure?

Previous UK guidelines

No previous UK guideline was identified that addressed this clinical question.

Studies considered in this section

All study designs assessing the role of CT scans in diagnosing raised intracranial pressure in children and young people with suspected or confirmed meningitis were considered for this section. Studies involving adults and children were considered for inclusion if outcomes were reported separately for children. Studies involving adults only were not considered.

Overview of available evidence

Three retrospective studies [EL=3] were found.

Review findings

One retrospective study (Sweden, 1994–1997) [EL=3] reported CT scan results of patients admitted to secondary care with bacterial meningitis and raised intracranial pressure (ICP) .[93] Of 53 patients with a diagnosis of bacterial meningitis, 12 (seven patients aged 2 to 16 years) had clinical evidence of increased ICP, confirmed by invasive ICP monitoring (ICP more than 20 mmHg). A cranial CT scan was performed in 10 patients prior to insertion of the ICP monitoring device. Cranial CT showed radiological signs indicating brain swelling in only 5 out of 10 patients (50%).

One retrospective review of medical records (Australia, 1984–1989) [EL=3] aimed to determine if the incidence of cerebral herniation increased immediately after lumbar puncture in children with bacterial meningitis admitted to a paediatric referral centre. The study also assessed whether any children with herniation had normal results on CT scan.[88] Herniation was judged to have occurred if clinical or post-mortem findings were compatible with the diagnosis. CT scans of children with herniation and an equal number of scans from children without herniation were reviewed by a paediatric radiologist. From 445 medical records reviewed, 19 children aged 4 months to 15 years were identified as having cerebral herniation and 14 cranial CT scans were performed. Scans were performed from 1.5 hours before herniation to 18 hours after herniation. Cranial CT scan was normal in 5 out of 14 episodes of herniation (36%). The five normal scans were from four children (one child had two episodes of herniation). Two of the children with normal CT scans died: herniation was confirmed on necropsy.

One retrospective review of medical records (UK, 1986–1989) [EL=3] evaluated the role of cranial CT scan in the detection of raised intracranial pressure in 15 children transferred to a tertiary care centre with bacterial meningitis and clinical signs of raised intracranial pressure.[94] Signs of raised intracranial pressure included: depressed level of consciousness with or without pupillary abnormalities, cranial nerve palsies, hyperventilation, Cheyne Stokes respiration and decorticate or decerebrate posturing. Of the 15 children with suspected raised intracranial pressure, six (40%) had a normal cranial CT scan. Scans of five children (approximately 30%) showed radiological signs of cerebral oedema. ICP measurements and the clinical outcome of children were not reported. The accuracy of CT scan for excluding raised intracranial pressure can therefore not be accurately assessed from these data.

Evidence statement

There is limited evidence from three small retrospective studies that CT scan is an insensitive technique for detection of raised intracranial pressure in children with suspected bacterial meningitis. In two studies, the clinical diagnosis of raised intracranial pressure was mostly presumptive. Studies were conducted in the 1980s and 1990s: no studies using recent CT scanning technology were found.

GDG interpretation of the evidence

Three retrospective studies were found addressing the use of CT scanning in the detection of raised intracranial pressure in children and young people with suspected or confirmed bacterial meningitis.

Although the available evidence was limited and not recent, it indicated that some children with raised intracranial pressure may have a normal CT scan. Due to the reported unreliability of CT scan for detecting raised intracranial pressure in children with suspected bacterial meningitis, the GDG saw no advantage in using CT scanning to aid in the decision regarding the safety of lumbar puncture. The decision to perform a lumbar puncture should be made on clinical grounds (see sections 5.6 and 5.7).

The GDG recognised that children with suspected bacterial meningitis who have a reduced conscious level or focal neurological signs may have alternative diagnoses, for which CT scan detection may be useful.

The GDG stressed that undertaking a CT scan should not delay appropriate treatment and that children should be stabilised clinically prior to transfer for scan.

The GDG note that Advanced Paediatric Life Support (APLS) guidance identifies that in a previously well, unconscious child (Glasgow Coma Scale score less than 9) who is not postictal, clinical signs of raised intracranial pressure may be evident.[95] The GDG also noted that a reduced or fluctuating level of consciousness would correspond to a Glasgow Coma Scale score (or Child's Glasgow Coma Scale score in the case of children under 4 years) of less than 9 or a drop of 3 or more.

Recommendations

Cranial computed tomography in suspected bacterial meningitis

Use clinical assessment and not cranial computed tomography (CT) to decide whether it is safe to perform a lumbar puncture. CT is unreliable for identifying raised intracranial pressure.

If a CT scan has been performed, do not perform a lumbar puncture if the CT scan shows radiological evidence of raised intracranial pressure.

In children and young people with a reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more) or with focal neurological signs, perform a CT scan to detect alternative intracranial pathology.

Do not delay treatment to undertake a CT scan.

Clinically stabilise children and young people before CT scanning.

If performing a CT scan consult an anaesthetist, paediatrician or intensivist.

6 Management in secondary care

6.1 Antibiotics for suspected bacterial meningitis or meningococcal disease

Introduction

The prevalence, causative pathogens, clinical presentation and outcome of bacterial meningitis in children and young people vary with age (see section 2.1 and chapter 3), and these differences will dictate recommendations for empiric and specific antibiotics. As noted in section 2.1, in older children the most frequent bacteria causing meningitis include *N. meningitidis*, *S. pneumoniae* and Hib, whereas in neonates the most common causative organisms are Group B streptococcus, *E. coli* and *L. monocytogenes*. The age at which the transition in pathogens occurs is mainly relevant when considering empiric antibiotic choice and is, therefore, conservatively regarded to be 3 months.

The choice of empiric antibiotics for bacterial meningitis is influenced by the resistance of *H. influenzae* (and to a lesser extent *S. pneumoniae*) to beta-lactam antibiotics. *N. meningitidis* remains sensitive to the penicillins and cephalosporins. In 2004, 11.6% of invasive *H. influenzae* isolates in England and Wales were resistant to ampicillin, 0.6% were resistant to chloramphenicol and 0% were resistant to cefotaxime and rifampicin.[96] In 2007, 3.8% of invasive pneumococci were resistant to penicillin.[97] There is currently a low prevalence of pneumococcal cefotaxime/ceftriaxone resistance in the UK, with only 1.7% of strains reported to have intermediate or high resistance to cefotaxime between 2004 and 2007 (source: Health Protection Agency, London).

Babies who are inpatients at the time of diagnosis of meningitis are specifically excluded from this guideline. These babies are more likely to have been born prematurely and/or to have other underlying problems, and this makes them more susceptible to unusual or antibiotic-resistant pathogens.[98] However, as standard clinical care moves towards earlier discharge from neonatal units, and as persistent colonisation with resistant bacteria is well documented,[98] it is conceivable that premature babies and those with underlying health problems may develop symptoms and signs of meningitis at home rather than on the neonatal unit. The epidemiology of neonatal meningitis therefore requires ongoing surveillance as such changes may have implications for empiric antibiotic therapy.

Another consideration when prescribing empiric antibiotics for infants aged under 3 months is the prevalence of meningitis caused by *L. monocytogenes*, as optimal antibiotic treatment for this pathogen requires a penicillin. Although infection with *L. monocytogenes* is rare (see section 2.1), a strategy of including a penicillin in empiric therapy up to age 8 weeks is, therefore, likely to miss very few cases of *L. monocytogenes* meningitis. If future data are consistent with reports of most cases of *L. monocytogenes* presenting within the first month of life (see section 2.1), the upper age limit for penicillin-based combination therapy may need to be reconsidered. Although ampicillin/amoxicillin is traditionally preferred over penicillin for the treatment of *L. monocytogenes* infection, the minimum inhibitory concentrations are similar for both antibiotics, and either would be effective for empiric treatment. Group B streptococcus is uniformly sensitive to penicillins and cephalosporins. However, ampicillin, gentamicin and cefotaxime resistance among *E. coli* isolates are increasing in England and Wales (61%, 8.5% and 12%, respectively, in 2007).[97]

As noted above, *N. meningitidis* remains sensitive to penicillins and cephalosporins. The clinical presentation of meningococcal septicaemia is often sufficiently distinctive to support a differential diagnosis, but other bacterial pathogens may (rarely) present with a similar rash. The choice of empiric antibiotic needs, therefore, to encompass possible infection with *S. pneumoniae* and Hib.

Clinical questions

What antibiotic regimen (type) should be used to treat children and young people with suspected meningococcal septicaemia in the secondary care setting?

What antibiotic regimen (type) should be used to treat children and young people with suspected meningitis in the secondary care setting?

Previous UK guidelines

'Feverish illness in children', NICE clinical guideline 47,[25] recommends the administration of a third-generation cephalosporin for children with suspected meningitis or suspected meningococcal septicaemia. It also recommends giving an additional antibiotic active against *L. monocytogenes* (such as ampicillin or amoxicillin) to infants younger than 3 months.

The SIGN guideline on management of invasive meningococcal disease in children and young people[27] recommends parenteral cefotaxime for the initial treatment of previously well children older than 3 months with a diagnosis of invasive meningococcal disease. It also recommends parenteral cefotaxime plus an antibiotic active against *L. monocytogenes* for infants younger than 3 months.

Studies considered in this section

A search was conducted for randomised controlled trials (RCTs) and systematic reviews of RCTs evaluating antibiotics used for empiric treatment of suspected bacterial meningitis or meningococcal disease in children and young people. Studies involving adults only were excluded. In line with current prescribing practice and antibiotic-resistance patterns of causative organisms in England and Wales, the search focused on the following antibiotics (or members of similar antibiotic classes).

For suspected bacterial meningitis in children older than 3 months:

- third-generation cephalosporins versus 'conventional antibiotics' (penicillin alone, ampicillin alone, penicillin plus chloramphenicol, ampicillin plus chloramphenicol [with or without gentamicin] and chloramphenicol alone)
- cefotaxime versus ceftriaxone.

For suspected bacterial meningitis in infants younger than 3 months:

- amoxicillin or ampicillin plus cefotaxime or ceftriaxone versus amoxicillin or ampicillin plus gentamicin
- amoxicillin or ampicillin plus cefotaxime or ceftriaxone versus benzylpenicillin plus gentamicin
- amoxicillin or ampicillin plus gentamicin versus benzylpenicillin plus gentamicin
- amoxicillin or ampicillin plus gentamicin versus cefotaxime or ceftriaxone alone.

Because meningitis is often clinically indistinguishable from septicaemia in neonates, empiric treatment for suspected septicaemia in this age group should also cover suspected meningitis. Therefore a search was conducted for RCTs investigating empiric antibiotics for neonatal septicaemia.

For suspected meningococcal disease in children and young people:

- third-generation cephalosporins (including ceftriaxone and cefotaxime) versus benzylpenicillin alone.

Overview of available evidence

Empiric antibiotics for suspected bacterial meningitis

Children older than 3 months

One systematic review and meta-analysis[99] [EL=1+] was found involving children, young people and adults (including some studies in adults only). The GDG conducted a meta-analysis based on a subgroup of studies (excluding studies involving adults only) using data from the systematic review (see appendix H, figures H.1 to H.7). One open-label RCT[100] [EL=1+] was also identified.

Infants younger than 3 months

For suspected bacterial meningitis, no high-quality studies were identified in relation to the empiric antibiotics listed above. Two systematic reviews were identified that evaluated empiric antibiotic treatment of neonatal sepsis: one [EL=1+] assessed empiric antibiotics for early-onset neonatal sepsis;[101] the other [EL=1+] assessed empiric antibiotics for late-onset neonatal sepsis.[102]

Empiric antibiotics for suspected meningococcal disease

No RCTs were identified in relation to any of the antibiotics listed above.

Review findings

Empiric antibiotics for suspected bacterial meningitis

Children older than 3 months

Third-generation cephalosporins versus 'conventional antibiotics' (penicillin alone, ampicillin alone, penicillin plus chloramphenicol, ampicillin plus chloramphenicol plus/minus gentamicin, chloramphenicol alone)

One systematic review and meta-analysis[99] (search date 2007) [EL=1+] comprising 19 RCTs compared the effects of third-generation cephalosporins versus 'conventional' antibiotics for empiric treatment of community acquired bacterial meningitis in 1,496 people of all ages. Of the 19 RCTs identified by the review, 12 studies involved 703 participants younger than 16 years and four studies included adults and children. Three RCTs involving adults only and one RCT that evaluated treatment of confirmed meningococcal disease[103] were excluded from the GDG's meta-analysis. Third-generation cephalosporins included ceftriaxone, cefotaxime and ceftazidime. 'Conventional' antibiotics included regimens with penicillin or ampicillin plus chloramphenicol, ampicillin alone, penicillin alone, chloramphenicol alone, or ampicillin plus chloramphenicol or gentamicin.

The review found no significant difference in mortality between empiric treatment with third-generation cephalosporins and conventional antibiotics (15 RCTs of 1378 people, approximately 90% children; risk difference [(RD] 0%, 95% CI –3% to 3%, *P* = 0.94 [see appendix H, figure H.1]). A subgroup analysis of specific causative organisms found no significant difference in mortality between the intervention groups. Wide CIs for RDs indicated that these subgroup analyses were underpowered to detect clinically important differences (Hib: 9 RCTs, 301 people, RD for mortality 1%, 95% CI –5% to 6%, *P* = 0.82 [see appendix H, figure H.2]; *S. pneumoniae*: 9 RCTs, 92 people, RD for mortality –2%, 95% CI –21% to 18%, *P* = 0.87 [see appendix H, figure H.3]; *N. meningitidis*: 10 RCTs, 390 people, RD for mortality 0%, 95% CI –5% to 5%, *P* = 0.99 [see appendix H, figure H.4]).

Nine studies involving 467 people (adults and children) included information about severe deafness, which was defined as deafness likely to interfere with usual activity. A meta-analysis of these studies found no significant difference between third generation cephalosporins and conventional antibiotics in the proportion of people with deafness (assessed between discharge and approximately 27 months; RD –4%, 95% CI –9% to 1%, *P* = 0.16 [see appendix H, figure H.5]). A meta-analysis of 11 RCTs of 406 people found that cerebrospinal fluid (CSF) culture positivity was significantly decreased at 10–48 hours after starting treatment with

third-generation cephalosporins compared with conventional antibiotics (RD –6%, 95% CI –12% to –1%, *P* = 0.03 [see appendix H, figure H.6]).

Most of the studies in the review were conducted in the 1980s and the review authors noted that methodological quality and/or reporting was uncertain. They also noted that the documented mortality in studies included in the review was low compared with reported mortality in some case series. This raises questions about possible over-representation of less severely ill patients in identified studies and whether these results can be generalised.

Cefotaxime versus ceftriaxone

One four-armed open-label RCT[100] [EL=1–] compared the effects of ceftriaxone (n=50) versus cefotaxime (n=51), ampicillin (n=46) and chloramphenicol (n=53) for the treatment of bacterial meningitis in 200 children aged 3 months to 15 years. The study found no significant difference in mortality between ceftriaxone and cefotaxime (2% with ceftriaxone versus 8% with cefotaxime, no *P* value reported). It found that ceftriaxone sterilised the CSF more rapidly than cefotaxime, ampicillin and chloramphenicol ($P < 0.01$; results for direct comparison of ceftriaxone and cefotaxime were not reported). Diarrhoea was significantly more common with ceftriaxone than with cefotaxime ($P < 0.01$).

Infants younger than 3 months

No high-quality studies were found evaluating empiric antibiotics for the treatment of suspected bacterial meningitis in infants younger than 3 months.

Three of the RCTs identified by the 2007 systematic review[99] compared ceftriaxone or cefotaxime versus ampicillin plus gentamicin for empiric treatment of bacterial meningitis. These RCTs included a small number of neonates but did not report a subgroup analysis of the neonatal population.

Two systematic reviews were found evaluating empiric antibiotics to treat neonatal sepsis: one [EL=1+] assessed empiric antibiotics for early-onset neonatal sepsis[101] and the other [EL=1+] assessed empiric antibiotics for late-onset neonatal sepsis.[102] Between them, the reviews identified two RCTs, both of which included neonates already in neonatal units for morbidities other than suspected sepsis. Neither RCT reported separate data for neonates admitted specifically for suspected bacterial meningitis or septicaemia or meningitis. The review authors concluded that there was inadequate evidence from RCTs in favour of any particular antibiotic regimen to treat early- or late-onset neonatal sepsis.

Empiric antibiotics for suspected meningococcal disease in children and young people

Third-generation cephalosporins (including ceftriaxone and cefotaxime) versus benzylpenicillin alone

No high-quality studies were found comparing third-generation cephalosporins versus benzylpenicillin for empiric treatment of suspected meningococcal disease.

Evidence statement

Secondary care empiric antibiotics for suspected bacterial meningitis

Children older than 3 months

One systematic review found no significant difference in clinical outcomes between third-generation cephalosporins and penicillin/chloramphenicol-based antibiotics in children with suspected bacterial meningitis, including those with suspected meningococcal meningitis. The review found that third-generation cephalosporins sterilised the CSF more quickly than other antibiotics.

There is insufficient evidence to reach a conclusion about whether cefotaxime or ceftriaxone is more effective for empiric treatment of bacterial meningitis in children older than 3 months.

Infants younger than 3 months

No high-quality studies were found comparing antibiotics for the empiric treatment of suspected bacterial meningitis in infants younger than 3 months.

Secondary care empiric antibiotics for suspected meningococcal disease

No high-quality studies were found comparing antibiotics for the empiric treatment of suspected meningococcal disease in children and young people.

Cost effectiveness

The GDG identified the choice of empiric antibiotics as a priority for economic analysis within the guideline. The results of the analysis are summarised here (further details are provided in appendix J).

Where treatment alternatives are equally effective, the most cost-effective option is the cheapest. Therefore, in the absence of any high-level evidence of differences in effectiveness, a cost model was developed to compare benzylpenicillin, cefotaxime and ceftriaxone as antibiotic treatment for children and young people with suspected meningococcal disease or suspected bacterial meningitis in the secondary care setting.

The model results showed that for children weighing up to 50 kg, ceftriaxone was the cheapest option, with the higher drug cost being more than offset by the lower staff costs associated with once-daily dosing. Benzylpenicillin is the most expensive treatment for children weighing 30 kg or less. However, benzylpenicillin becomes relatively more cost effective as children get heavier, because of its lower drug cost, which unlike staffing is a function of weight. For children weighing 37–51 kg the costs of benzylpenicillin and ceftriaxone are very similar. Above 51 kg benzylpenicillin becomes the cheapest antibiotic.

GDG interpretation of the evidence

Secondary care empiric antibiotics for suspected bacterial meningitis

Children older than 3 months

In children older than 3 months with suspected bacterial meningitis, there is no evidence of a difference in clinical outcomes between third-generation cephalosporins and penicillin- and chloramphenicol-based regimens. Therefore, the choice of empiric therapy should be based on the current antibiotic resistance patterns of the most common organisms causing bacterial meningitis in this age group in England and Wales, and on cost effectiveness.

In view of the possibility of penicillin resistance among pneumococcus and Hib the GDG considered that a third-generation cephalosporin should be used as empiric therapy in all cases of suspected bacterial meningitis. It was also noted that the third-generation cephalosporins sterilised the CSF more quickly than other antibiotics.

On the basis of the cost effectiveness data, ceftriaxone is recommended as the first-line agent, chiefly driven by the reduction in staff costs associated with a once-daily dose. There is also the possibility of early discharge from hospital while the child is receiving once-daily dosing. The Medicines and Healthcare products Regulatory Agency (MHRA) advises that ceftriaxone should not be mixed with calcium-containing solutions and should not be given to any patient simultaneously with calcium-containing solutions, even through different infusion lines.[104] Cefotaxime is preferred in this situation.

The possibility of a cephalosporin-resistant pneumococcus causing bacterial meningitis in this age group should also be considered. This would necessitate the empiric use of vancomycin (with or without another agent such as rifampicin) in addition to a third-generation cephalosporin. Currently, there is a low prevalence of cefotaxime and ceftriaxone resistance in the UK and the number of cephalosporin-resistant pneumococcal strains is likely to decline further as a result of the impact of the pneumococcal conjugate vaccine.

Resistance of pneumococcus to penicillin is generally higher in countries other than the UK* and also in children with recent, prolonged or multiple exposure to oral or parenteral antibiotics (within the past 3 months).[105] As a significant proportion of pneumococci with reduced penicillin susceptibility will also be resistant to other antibiotics, the possibility of cephalosporin resistance should be considered in children and young people with a history of recent travel outside the UK or of recent antibiotic exposure.

Infants younger than 3 months

There is no high-quality evidence to support a choice of antibiotics for the empiric treatment of suspected bacterial meningitis in infants younger than 3 months. Therefore, empiric treatment should be based on the antibiotic resistance patterns of the most common organisms causing meningitis in this age group (Group B streptococcus, Gram-negative bacteria, *L. monocytogenes*) and the organisms causing meningitis in other age groups in England and Wales, according to their cost effectiveness.

The GDG considered that the combination of a third-generation cephalosporin and ampicillin or amoxicillin provided adequate cover for the usual organisms causing bacterial meningitis in infants younger than 3 months. However, in some settings known to have high rates of community-acquired, extended-spectrum beta-lactamase-producing Gram-negative organisms (ESBLs), replacement of the cephalosporin with a carbapenem (meropenem) might be considered. The amoxicillin is included to cover *L. monocytogenes* meningitis which, although rare, is associated with high mortality and morbidity. Current epidemiological data indicate that cover for *L. monocytogenes* should be considered up to the age of 2 to 3 months, although nearly all pregnancy-associated cases present in the first month of life (see section 2.1).

The GDG suggests the initial empiric use of cefotaxime, rather than ceftriaxone, in this age group. There are two, largely theoretical, concerns with the use of ceftriaxone. First, *in vivo* and *in vitro* studies have shown that ceftriaxone can displace bilirubin from serum albumin, which may exacerbate hyperbilirubinaemia in infants who are jaundiced, hypoalbuminaemic, acidotic or born prematurely (see the SPC). Second, several neonatal deaths have been associated with calcium–ceftriaxone precipitates; in some cases calcium and ceftriaxone were administered at different times.[104] As infants with meningitis or septicaemia may receive calcium as part of their supportive care, it is prudent to avoid the empiric use of ceftriaxone in this age group. Both of these concerns are most relevant to the youngest and sickest infants with suspected bacterial meningitis. If the healthcare professional is confident that these contraindications do not apply, then empiric use of ceftriaxone rather than cefotaxime may be appropriate for selected infants in this age group. Similarly, as soon as clinical recovery is evident, a switch from empiric cefotaxime to empiric ceftriaxone may be appropriate on the basis of convenience and cost.

The possibility of a cephalosporin-resistant pneumococcus causing bacterial meningitis in this age group should also be considered. This would necessitate the empiric use of vancomycin (with or without another agent such as rifampicin) in addition to a third-generation cephalosporin. As discussed above, cephalosporin resistance should be considered in children with a history of recent travel outside the UK, or recent, prolonged or multiple exposure to antibiotics (for example within the past 3 months).

In addition to bacterial causes of meningitis, the GDG recognised that herpes simplex virus is a rare but important cause of meningoencephalitis that could be confused with the clinical presentation of bacterial meningitis. If this condition is part of the differential diagnosis then appropriate antiviral treatment should be given.

Secondary care empiric antibiotics for suspected meningococcal disease

There was no high-level evidence to support a choice of antibiotics for the treatment of suspected meningococcal disease in children and young people. Therefore, empiric treatment should be based on the current antibiotic resistance patterns of *N. meningitidis* in

* See www.rivm.nl/earss/database/

England and Wales, on the possibility of an alternative aetiological agent (with different antibiotic resistance patterns) and on cost.

Although *N. meningitidis* is usually sensitive to a range of antibiotics in the UK, in view of the possibility of an alternative, more resistant pathogen, the GDG considered that a third-generation cephalosporin should be used as empiric therapy in suspected cases. On the basis of the cost effectiveness analysis, ceftriaxone is recommended as the first line agent chiefly driven by the reduction in staff costs associated with a once-daily dose. There is also the possibility of early discharge from hospital with once daily dosing.

As noted above, the MHRA advises that ceftriaxone should not be mixed with calcium-containing solutions and should not be given to any patient simultaneously with calcium-containing solutions, even through different infusion lines.[104] Cefotaxime is preferred in this situation.

The guideline developers searched for evidence in relation to rifampicin in both the pre-hospital and hospital settings, but no evidence was identified. The GDG consensus was that vancomycin is the recommended drug in the situation where there is a possibility of resistant pneumococci as the paediatric clinical experience is with this drug. Vancomycin is currently included as the drug of choice in textbooks of paediatric infectious disease and in the literature on this subject. The clinical experience with rifampicin in children has mostly been its use in addition to vancomycin where there is cephalosporin resistance.

Recommendations

Management in secondary care

Antibiotics for suspected bacterial meningitis or meningococcal disease

Treat children and young people aged 3 months or older with suspected bacterial meningitis without delay using intravenous ceftriaxone.

Treat children younger than 3 months with suspected bacterial meningitis without delay using intravenous cefotaxime plus either amoxicillin or ampicillin.

Treat suspected meningococcal disease without delay using intravenous ceftriaxone.

Treat children and young people with suspected bacterial meningitis who have recently travelled outside the UK or have had prolonged or multiple exposure to antibiotics (within the past 3 months) with vancomycin in addition to the above antibiotics.

Where ceftriaxone is used, do not administer it at the same time as calcium-containing infusions. Instead, use cefotaxime.*

In children younger than 3 months, ceftriaxone may be used as an alternative to cefotaxime (with or without ampicillin or amoxicillin), but be aware that ceftriaxone should not be used in premature babies or in babies with jaundice, hypoalbuminaemia or acidosis as it may exacerbate hyperbilirubinaemia.

If tuberculous meningitis is part of the differential diagnosis use antibiotic treatment appropriate for tuberculous meningitis in line with 'Tuberculosis' (NICE clinical guideline 33).

If herpes simplex meningoencephalitis is part of the differential diagnosis give appropriate antiviral treatment.

* See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update: Volume 3, Issue 3. Available from www.mhra.gov.uk

Research recommendations

Management in secondary care

Antibiotics for suspected bacterial meningitis or meningococcal disease

In children and young people what are the risk factors for meningitis and septicaemia caused by cephalosporin-resistant strains of pneumococcus?

Why this is important

Although serious invasive disease due to cephalosporin-resistant pneumococci is rare in the UK, the recommended regimen for empiric antibiotic treatment of suspected meningitis and septicaemia in children and young people will not treat cephalosporin-resistant pneumococci adequately. A delay in starting suitable alternative treatment (vancomycin with or without rifampicin) may result in worse outcomes. The ability to identify at presentation those children and young people who are likely to be infected with cephalosporin-resistant strains of pneumococcus would ensure that optimal antibiotic treatment could be started as soon as possible. Additionally, the ability to confidently exclude the possibility of cephalosporin-resistant pneumococci would mean that potentially toxic empiric antibiotic treatment could be avoided. Resistance of pneumococcus to penicillin is generally higher in: countries other than the UK; children who have been exposed to oral or parenteral antibiotics recently (for example, in the previous 3 months), over a prolonged period of time, or on multiple occasions; and children with underlying health problems. The current evidence base is insufficient to determine accurately the risks of cephalosporin-resistant pneumococcal infection according to the duration, number, or type of antibiotic treatment, or the time period over which previous antibiotic exposure or foreign travel is relevant. Large-scale epidemiological studies (for example, cohort studies or case–control studies) are needed to evaluate these risks.

6.2 Treatment for specific infections in confirmed bacterial meningitis

Introduction

In children and young people with suspected bacterial meningitis or meningococcal septicaemia, empiric antibiotic treatment is needed initially (see section 6.1). Once blood culture or cerebrospinal fluid (CSF) samples have been taken, it is usually possible to review the choice of antibiotics after about 48 hours as the results of microbiological culture and sensitivities become available. At this time antibiotics may be changed to those that are most effective against the particular organism identified as causing the illness. It may also be necessary to change to an alternative antibiotic or add in another antibiotic if the antimicrobial sensitivities suggest that the causative organism is fully or partially resistant to the initial antibiotic. The identification of a causative organism may also allow the healthcare professional to decide on the duration of antibiotic treatment (some organisms require longer durations of treatment than others).

For this section, the GDG examined the evidence for deciding which antibiotics are most effective against the meningococcus and the other main causative organisms of bacterial meningitis in children and young people. For each organism, the GDG also attempted to determine the most appropriate duration of treatment to ensure that children and young people received adequate treatment. For pragmatic reasons, the GDG also attempted to make recommendations on the duration of treatment in children and young people with suspected but unconfirmed bacterial meningitis or meningococcal disease.

Clinical questions

What antibiotic regimen should be used to treat confirmed bacterial meningitis or meningococcal septicaemia?

Type of antibiotic

Studies considered for this section

A search was conducted for RCTs and systematic reviews of RCTs evaluating currently used antibiotics for meningococcal disease and meningitis caused by *S. pneumoniae* or Hib in children and young people. For infants younger than 3 months, a search was conducted for RCTs evaluating antibiotics for meningitis caused by Group B streptococcus or *L. monocytogenes*. RCTs involving adults only were excluded from the review. Because of current prescribing practices and antibiotic resistance patterns of causative organisms in England and Wales, the search focused on the following antibiotics.

For meningococcal disease:

- ceftriaxone or cefotaxime
- benzylpenicillin.

For meningitis caused by *S. pneumoniae*:

- ceftriaxone or cefotaxime
- ceftriaxone plus rifampicin
- ceftriaxone plus vancomycin
- chloramphenicol
- fluoroquinolones
- benzylpenicillin
- meropenem.

For meningitis caused by Hib:

- ceftriaxone or cefotaxime

For meningitis caused by Group B streptococcus in infants younger than 3 months:

- ampicillin or amoxicillin with or without an aminoglycoside
- cefotaxime or ceftriaxone
- benzylpenicillin with or without an aminoglycoside.

For meningitis caused by *L. monocytogenes* in infants younger than 3 months:

- ampicillin or amoxicillin with or without an aminoglycoside
- benzylpenicillin with or without an aminoglycoside.

Overview of available evidence

One RCT[103] [EL=1–] was found comparing ceftriaxone and penicillin G for treatment of meningococcal disease. No RCTs were found evaluating antibiotics for treatment of bacterial meningitis caused by organisms other than the meningococcus.

Review findings

Antibiotics for meningococcal disease

No high-quality studies were found that evaluated the antibiotics listed above for the specific treatment of meningococcal disease in children and young people. Only one open-label RCT [EL=1-] was identified.[103] The RCT was conducted in secondary care in Turkey and involved 42 children aged 1 month to 12 years with meningitis or meningococcaemia. Children were randomised to receive either intravenous ceftriaxone (once daily for 4 days) or intravenous penicillin G (six times daily for 5 days). The RCT found no significant difference in mortality between the groups (difference noted as non-significant, no *P* value reported). Necrotic skin lesions were significantly more frequent with penicillin G than with ceftriaxone ($P < 0.05$). Of the 20 children given ceftriaxone, 19 had a positive blood culture for *N. meningitidis*

compared with 13 of 22 given penicillin G, which indicates possible bias in favour of penicillin G.

Antibiotics for meningitis caused by *Streptococcus pneumoniae* and meningitis caused by *Haemophilus influenzae* type b

No RCTs were found that evaluated the above antibiotics for the specific treatment of meningitis caused by *S. pneumoniae* or Hib in children and young people. All identified studies either investigated empiric treatment of bacterial meningitis or compared antibiotics for confirmed bacterial meningitis without performing a pre-specified, organism-specific subgroup analysis.

Antibiotics for meningitis caused by Group B streptococcus or *Listeria monocytogenes* in infants younger than 3 months

No RCTs were found that evaluated the antibiotics listed above for the specific treatment of meningitis caused by Group B streptococcus or *L. monocytogenes* in infants younger than 3 months. All identified studies investigated empiric treatment of bacterial meningitis or compared antibiotics for confirmed bacterial meningitis without performing a pre-specified organism-specific subgroup analysis.

Duration of antibiotic therapy

Previous UK guidelines

The SIGN guideline on management of invasive meningococcal disease in children and young people[27] recommends that the duration of antibiotic therapy for children with invasive meningococcal disease should be 7 days.

Studies considered in this section

A search was conducted for RCTs evaluating the optimal duration of antibiotic therapy for meningococcal disease and meningitis caused by Hib or *S. pneumoniae* in children and young people. For infants younger than 3 months, a search was conducted for RCTs evaluating the optimal duration of antibiotic therapy for meningitis caused by Group B streptococcus, *L. monocytogenes* and Gram-negative bacilli. RCTs involving adults only were excluded from the review. Antibiotics considered for review were as follows.

For meningococcal disease:

- ceftriaxone or cefotaxime
- benzylpenicillin.

For meningitis caused by *S. pneumoniae*:

- ceftriaxone or cefotaxime
- ceftriaxone plus rifampicin
- ceftriaxone plus vancomycin
- chloramphenicol
- fluoroquinolones
- benzylpenicillin
- meropenem.

For meningitis caused by Hib:

- ceftriaxone or cefotaxime.

For meningitis caused by Group B streptococcus in infants younger than 3 months:

- ampicillin or amoxicillin with or without an aminoglycoside
- cefotaxime or ceftriaxone
- benzylpenicillin with or without an aminoglycoside.

For meningitis caused by *L. monocytogenes* in infants younger than 3 months:

- ampicillin or amoxicillin with or without an aminoglycoside
- benzylpenicillin with or without an aminoglycoside.

For meningitis caused by Gram-negative bacilli in infants younger than 3 months:

- cefotaxime or ceftriaxone with or without an aminoglycoside
- meropenem.

Because of a lack of evidence on the duration of treatment with organism-specific antibiotics, RCTs comparing different durations of antibiotic regimens for treatment of bacterial meningitis without organism-specific analysis were included in the review.

Overview of available evidence

No RCTs were found evaluating the optimal duration of currently used antibiotics for meningococcal disease or bacterial meningitis caused by specific organisms. Two studies were included comparing different durations of ceftriaxone treatment for bacterial meningitis without organism-specific analysis.

Review findings

Duration of antibiotic treatment for meningococcal disease

No RCTs were found evaluating the optimal duration of currently used antibiotics for meningococcal disease in children and young people.

Duration of antibiotic treatment for bacterial meningitis

No RCTs were found evaluating the optimal duration of currently used antibiotics for children and young people with meningitis caused by specific organisms. Two studies, one RCT[106] [EL=1+] and one quasi-randomised RCT[107] [EL=1–], compared different durations of ceftriaxone therapy for the treatment of bacterial meningitis caused by various organisms. These studies did not perform an organism-specific analysis for any outcome.

One small, unblinded RCT conducted in India[106] [EL=1+] compared a 7-day course of twice-daily ceftriaxone versus a 10-day course of ceftriaxone. The RCT involved 73 children aged 3 months to 12 years with bacterial meningitis, of whom 38% had a confirmed causative organism, either *H. influenzae*, *S. pneumoniae* or *N. meningitidis*. It found no significant difference between a 7-day course and a 10-day course of ceftriaxone in the clinical response to therapy or in the risk of neurological sequelae at 1 month (*P* values reported as not significant). The RCT found that children given ceftriaxone for 7 days had a shorter hospital stay compared with those given ceftriaxone for 10 days ($P < 0.05$).

One quasi-randomised RCT[107] [EL=1–] compared a 4-day course of ceftriaxone with a 7-day course of ceftriaxone in 102 children aged 3 months or older with bacterial meningitis. All children included in the trial had made a rapid initial recovery, characterised by clinical improvement during the first 4 days of treatment and a negative CSF culture 24 to 36 hours after initiation of treatment. In total, 26 children had *H. influenzae* meningitis, 34 children had meningococcal meningitis and 13 children had pneumococcal meningitis. The RCT found no significant difference between the groups in the proportion of children with fever 5 to 7 days after beginning antibiotics ($P > 0.05$) or in the rate of neurological sequelae ($P = 0.39$) or hearing loss at 1 to 3 months ($P = 0.49$).

Evidence statement

Type of antibiotic

Antibiotics for meningococcal disease

No high-quality studies were found comparing antibiotics currently used to treat meningococcal disease in children and young people.

Antibiotics for Streptococcus pneumoniae meningitis and Haemophilus influenzae type b meningitis

No RCTs were found comparing antibiotics currently used to treat meningitis caused by *S. pneumoniae* or Hib meningitis in children and young people.

Antibiotics for meningitis caused by Group B streptococcus or Listeria monocytogenes in infants younger than 3 months

No RCTs were found comparing antibiotics currently used to treat meningitis caused by Group B streptococcus or *L. monocytogenes* in infants younger than 3 months.

Duration of antibiotic therapy

Duration of antibiotic treatment for meningococcal disease

No RCTs were found evaluating the optimal duration of antibiotic regimens currently used to treat children and young people with meningococcal disease.

Duration of antibiotic treatment for bacterial meningitis

No RCTs were found evaluating the optimal duration of antibiotics to treat children and young people with meningitis caused by specific organisms.

Two small studies found no significant difference in outcomes when children with bacterial meningitis were given a shorter course of ceftriaxone compared with a longer course of ceftriaxone. One RCT found that children given a 7-day course of ceftriaxone had a shorter hospital stay than those given a 10-day course of ceftriaxone. The studies were probably underpowered to detect clinically important differences between the groups.

No RCTs were found that evaluated the optimal duration of antibiotic treatment for bacterial meningitis in infants younger than 3 months.

Cost effectiveness

The GDG identified the choice of antibiotics for confirmed meningococcal disease or confirmed bacterial meningitis as a priority for economic analysis.

In the absence of any high-level evidence of differences in effectiveness, a cost model was used to compare the costs of benzylpenicillin, cefotaxime and ceftriaxone (see appendix J). This suggested that ceftriaxone is the cheapest option for children weighing 37 kg or less. Benzylpenicillin is the most expensive antibiotic for children weighing 30 kg or less. For children weighing 37–51 kg the costs of benzylpenicillin and ceftriaxone are similar. Above 51 kg benzylpenicillin becomes the cheapest antibiotic.

If ceftriaxone facilitates early hospital discharge as a result of once-daily dosing, then the relative cost effectiveness of ceftriaxone is further enhanced as a result of savings associated with the costs of shortening inpatient care.

While there is no good quality evidence to support different antibiotics for confirmed meningococcal disease or confirmed bacterial meningitis on clinical grounds, ceftriaxone is to be preferred on cost grounds. Its requirement for only a single dose means that for a majority of children and young people covered in this guideline the higher costs of the drug are more than offset by reduced staffing costs. If ceftriaxone facilitates early hospital discharge its cost effectiveness relative to alternatives is further enhanced.

GDG interpretation of the evidence

Choice of antibiotics in confirmed meningococcal disease or bacterial meningitis caused by a specific organism

No high-quality studies were found comparing antibiotics currently used to treat meningococcal disease or bacterial meningitis in children and young people. From the reviews of empiric treatment of meningococcal disease and bacterial meningitis it is evident that ceftriaxone provides the most cost-effective treatment for most children and young people. The GDG therefore considered it appropriate to continue (or switch to) ceftriaxone in confirmed disease. This decision should be made after reviewing the results of antibiotic sensitivities and, if the organism is resistant to third-generation cephalosporins, treatment should be changed to an antibiotic to which the organism is sensitive. In children with confirmed *L. monocytogenes* meningitis, ampicillin or amoxicillin should be continued and cefotaxime or ceftriaxone should be replaced with gentamicin.

Penicillin may become the cheapest antibiotic if the child's or young person's weight is above 51 kg. However, the GDG decided not to recommend its use in such children and young people on the grounds that the use of once-daily ceftriaxone is convenient for nursing staff and allows the completion of courses of antibiotics as an outpatient (which would produce further cost savings). The GDG also noted that weights above 51 kg are uncommon in paediatric practice and the guideline would be unnecessarily complicated if penicillin was recommended for this small group of children and young people.

Duration of antibiotic treatment for meningococcal disease

No high-quality studies were found evaluating the optimal duration of antibiotic regimens currently used to treat children and young people with meningococcal disease. The GDG's view is that 7 days is the usual duration of treatment for meningococcal disease in the UK and that 7 days' treatment with antibiotics is also recommended for meningococcal disease in standard UK and USA texts.[108] The GDG could see no reason to change present treatment regimens and recommended that meningococcal disease should be treated with antibiotics for 7 days.

Duration of antibiotic treatment for bacterial meningitis

The GDG is aware that in the UK meningococcal meningitis is usually treated for 7 days, Hib meningitis is usually treated for 10 days and pneumococcal meningitis is usually treated for 10 to 14 days. In infants under the age of 3 months, Group B streptococcal meningitis is usually treated for 14 to 21 days and Gram-negative and *L. monocytogenes* meningitis are usually treated for 21 days. These durations of treatment are also recommended in standard UK and US texts.[108] The GDG noted that two studies have suggested that shorter than standard durations of treatment may result in adequate outcome (the studies were in children older than 3 months). However, there have been no large RCTs of shorter treatment and the GDG considered that the existing studies were underpowered to detect differences in mortality, morbidity or the risk of relapse. The clinical experience of the GDG is that standard durations of treatment are effective with little risk of relapse. The GDG therefore agreed that the duration of treatment for bacterial meningitis should be the same as that most commonly used in the UK at present.

Choice and duration of antibiotics for unconfirmed bacterial meningitis and unconfirmed meningococcal disease

The GDG is aware that many cases of bacterial meningitis and meningococcal disease are not confirmed by microbiological culture. In these cases the decision to continue treatment for suspected disease will be made on clinical grounds and, in the case of meningitis, on the results of CSF microscopy and chemistry (if a lumbar puncture was performed). The GDG considered that for unconfirmed, but clinically suspected, bacterial meningitis, empiric treatment should be continued as appropriate given the age of the child. The duration of treatment should therefore be at least 10 days for children older than 3 months, and 14 days for infants younger than 3 months. These minimum periods reflect the recommended treatment durations for the most likely pathogens in these respective age groups. In children older than 3 months the leading pathogens are *S. pneumoniae* and *N. meningitidis* for which 10 to 14 days and 7 days, respectively, are considered appropriate; a course of 10 days is therefore a reasonable course of therapy to ensure adequate treatment. For infants younger than 3 months Group B streptococcus is the leading pathogen and the recommended course for unconfirmed meningitis is therefore consistent with the minimum course for confirmed Group B streptococcus meningitis. The GDG considered that the choice and duration of antibiotics for unconfirmed, but clinically suspected, meningococcal disease should be the same as for confirmed disease.

Recommendations

Treatment for specific infections in confirmed bacterial meningitis

Children and young people aged 3 months or older

Treat *H. influenzae* type b meningitis with intravenous ceftriaxone for 10 days in total unless directed otherwise by the results of antibiotic sensitivities.

Treat *S. pneumoniae* meningitis with intravenous ceftriaxone for 14 days in total unless directed otherwise by the results of antibiotic sensitivities.

Children younger than 3 months

Treat Group B streptococcal meningitis with intravenous cefotaxime for at least 14 days. If the clinical course is complicated[*] consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Treat bacterial meningitis due to *L. monocytogenes* with intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first 7 days.

Treat bacterial meningitis due to Gram-negative bacilli with intravenous cefotaxime for at least 21 days unless directed otherwise by the results of antibiotic sensitivities. If the clinical course is complicated* consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Treatment of unconfirmed bacterial meningitis

In children and young people aged 3 months or older with unconfirmed, uncomplicated but clinically suspected bacterial meningitis, treat with intravenous ceftriaxone for at least 10 days depending on symptoms and signs and course of the illness.

In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. If the clinical course is complicated,* consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Meningococcal disease

In children and young people with confirmed meningococcal disease, treat with intravenous ceftriaxone for 7 days in total unless directed otherwise by the results of antibiotic sensitivities.

In children and young people with unconfirmed but clinically suspected meningococcal disease, treat with intravenous ceftriaxone for 7 days in total.

6.3 Fluid management in suspected or confirmed bacterial meningitis

Introduction

Maintaining optimal fluid and electrolyte balance is an essential part of managing bacterial meningitis in children and young people. Raised intracranial pressure is a well recognised and life-threatening disorder associated with bacterial meningitis because the normal homeostatic responses to fluid balance status are disrupted. Fluid management in children with meningitis should therefore be based on the need for the brain to be adequately perfused while monitoring for possible development of raised intracranial pressure.

Fluid restriction has traditionally been advocated for children with bacterial meningitis. This practice is based on the rationale that intracranial infection is accompanied by the syndrome

[*] For example, if there is poor response to antibiotic therapy, effusion or abscess, or concomitant intraventricular haemorrhage in a premature baby.

of inappropriate antidiuretic hormone (ADH) secretion (SIADH), in which large amounts of circulating ADH lead to increased water retention by the kidney, decreased plasma osmolality and hyponatraemia. In bacterial meningitis, these fluid and electrolyte disturbances have been linked to cerebral oedema, an increased risk of seizures and adverse neurodevelopmental outcomes.[109;110] The National Patient Safety Agency (NPSA) has issued a patient safety alert that highlighted that some acutely ill children with increased ADH secretion, notably after surgery, may benefit from maintenance fluid being restricted and that the default position in such children should be to restrict fluids because the risks associated with overhydration exceed the risks associated with underhydration.[*, 111] However, the NPSA patient safety alert noted that the NPSA National Reporting and Learning System (NRLS) had received only one incident report at the time of publication (March 2007) and this incident had resulted in no harm, although it was thought likely that incidents had gone unreported in the UK. Furthermore, the risk is particularly associated with the use of hypotonic rehydration fluids which should no longer be available in paediatric treatment areas.

It is now increasingly recognised that children with bacterial meningitis may be underhydrated. In such children, increased ADH secretion may be an appropriate, compensatory response to hypovolaemia, and hyponatraemia and low plasma osmolality may resolve only when sufficient sodium and fluid are given using isotonic solutions.[112] It is, therefore, not clear if fluid restriction is the optimal choice for children with meningitis, and the issue is addressed in this section.

Clinical question

Should fluid volume be restricted in children and young people with suspected or confirmed bacterial meningitis?

Studies considered in this section

RCTs and systematic reviews of RCTs evaluating different fluid volumes used to treat children and young people with bacterial meningitis were considered for this section. Studies involving adults were excluded. The NPSA also provided data on incidents of fluid-induced hyponatraemia in children under 18 years from its NRLS covering the period 2003 to January 2010.

Overview of available evidence

One systematic review[113] [EL=1+] was found which identified three RCTs. A prospective observational study[114] [EL=2+] was also identified (this study reported audit data). NPSA NRLS data on incidents of fluid-induced hyponatraemia in children under 18 years were also considered.

Review findings

The systematic review[113] [EL=1+] evaluated different volumes of fluid for the treatment of bacterial meningitis (search date 2007). The review identified three RCTs that compared the effects of giving full-volume maintenance fluids versus restricted fluid volumes for the initial management of children with acute bacterial meningitis. Two of the three RCTs[115;116] reported clinical outcomes in children (aged 1 month to 12 years) and those results are included here. Maintenance fluid was calculated as 100–110 ml/kg per day for the first 10 kg body weight of the child, 50 ml/kg for the second 10 kg, and 20–25 ml/kg for weight over 20 kg. Initial maintenance fluid was given intravenously as crystalloid solutions for all studies. Restricted fluid volumes consisted of 60–65% of the initial maintenance fluids and were given as milk feeds in one RCT[115] and intravenously as crystalloid solution in the other RCT.[116]

Meta-analysis of the two RCTs[115;116] involving 407 children aged between 1 month and 12 years found no significant difference in mortality between the maintenance and restricted fluid groups (15% with maintenance fluids versus 18% with restricted fluids; RR 0.83, 95% CI 0.54 to 1.30, P = 0.4). In one of these RCTs,[115] which was conducted in Papua New Guinea

[*] NPSA/2007/22; available at http://www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/intravenous-infusions/

(n=357), significantly fewer children who were given maintenance fluids developed spasticity and seizures in the short term compared with children given restricted fluids (spasticity at 14 days: 357 children, RR 0.53, 95% CI 0.29 to 0.98, *P* = 0.04; seizures at 72hrs: 357 children, RR 0.62, 95% CI 0.44 to 0.88, *P* = 0.007). The risk of long-term neurological sequelae assessed at 3 months (including hemiparesis or hemiplegia, and visual and hearing impairment) was significantly lower in the maintenance fluid group than in the restricted fluid group (RR 0.44, 95% CI 0.21 to 0.93, *P* = 0.03). This was the larger of the two RCTs, contributing most of the data for mortality and morbidity, and it was conducted in a setting where some children (25%) were malnourished and presented late for treatment with high mortality rates. The authors of the systematic review[113] noted that inadequate treatment of dehydration could have increased the risk of neurological sequelae in the children receiving restricted fluid in this study. The second RCT[116] was conducted in India (n=50) and specifically excluded children who were malnourished. There were no statistically significant differences in this study between outcomes in children who received maintenance or restricted fluids (children without hyponatraemia: mortality 18% versus 23%, *P* = NS, survival with complications or neurological sequelae, 18% versus 31%, *P* = NS; children with hyponatraemia: mortality 0% versus 27%, *P* = NS, survival with complications or neurological sequelae 36% versus 40%, *P* = NS; exact *P* values not reported).

A prospective observational study[114] [EL=2+] conducted in the UK in 2009 provided audit data for current practice in the management of severe sepsis in children in the UK against a 2002 guideline. The study included 136 children with sepsis (average age 9.8 to 15.1 months). Comparisons were made between children in whom shock reversal occurred and children in whom it did not. Total fluid intake was significantly different between the groups (60 ml/kg versus 80 ml/kg, *P* = 0.004). Children in whom shock was reversed had better outcomes than those in whom shock was not reversed (survival rate 94% versus 75%; *P* = 0.03). Presence of shock after inter-hospital transfer was the only independent predictor of death after admission to the paediatric intensive care unit (OR for death 3.8, 95% CI 1.4 to 10.2, *P* = 0.008).

No high-quality studies were found assessing initial fluid therapy in neonates with suspected or confirmed bacterial meningitis.

The NPSA NRLS database was reviewed for the guideline to identify all incidents of fluid-induced hyponatraemia in children under 18 years in the period 2003 to January 2010. The data provided indicated numbers of deaths and severe incidents plus details of a random selection of 200 moderate-harm, low-harm and no-harm incidents (100 neonates and 100 children). Every incident report in the NRLS that included the term 'hyponatraemia' in children under 18 years was also identified. For neonates, no relevant incidents were identified. For children, there were no relevant incidents involving death or severe harm; three incidents were identified among a random sample of 100 records, all of which reported that no harm had occurred. A further four incidents in children were identified using the free text search for the term 'hyponatraemia'; three of these resulted in no harm and the other was reported as low harm. The conclusion from the NRLS report was that there was no evidence of significant harm resulting from fluid-induced hyponatraemia.

Evidence statement

There is insufficient evidence to determine the optimal volume of fluids for the initial treatment of children with bacterial meningitis in resource-rich settings. Evidence from one RCT indicates that in a setting where children presented late and where mortality was high, restricting fluids may have increased the risk of neurological sequelae. A further RCT involving well-nourished children found no statistically significant differences in mortality or in survival with complications or neurological sequelae. Evidence from an observational study indicates that lower levels of fluid intake may be associated with a lower mortality rate, but no causal relationship was established. Evidence from a recent audit conducted using a prospective observational design suggested that total fluid intake was significantly lower in children in whom reversal of shock occurred, but the study did not establish causality. Evidence provided by the NPSA showed that fluid-induced hyponatraemia in children under 18 years was not associated with significant harm.

GDG interpretation of the evidence

Fluid management in suspected or confirmed bacterial meningitis

In view of the lack of evidence for an optimal fluid volume for management of children with bacterial meningitis and indications that restricted fluids may be harmful, the GDG considered that maintenance fluids should be given to children and young people with bacterial meningitis to maintain adequate hydration.

The GDG also noted that some children with bacterial meningitis may be dehydrated and may need rehydration in addition to maintenance fluids.

Some children with bacterial meningitis may have raised intracranial pressure at presentation (see section 5.6) and be at risk of cerebral oedema, complicating fluid management, but they should still receive adequate fluid volumes to maintain cerebral perfusion. Children with signs of raised intracranial pressure should preferably be managed in consultation with a paediatric intensivist.

A few children with bacterial meningitis will have accompanying shock and may need fluid resuscitation. The clinician should administer fluids judiciously in these children as the risk of hypovolaemia must be weighed against the possible development of cerebral oedema.

The GDG is aware of the risk of hyponatraemia in central nervous system infections and the guidance issued in relation to this in March 2007 by the NPSA.[*,111] The NPSA guidance noted the particular risk associated with use of hypotonic solutions and these were, therefore, removed from paediatric treatment areas as a result of the alert. The NPSA guidance states that isotonic fluids (0.9% saline or 0.9% saline with 5% glucose) should be used when intravenous fluid therapy is required. The GDG agrees with the NPSA view and recommended that in children and young people with bacterial meningitis, isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride with dextrose 5%) should be used for maintenance, whereas in neonates glucose 5% would increase the risk of hypoglycaemia, and so glucose 10% (with added sodium based on daily requirements according to the child's weight, as determined by local protocols) would be more appropriate in this age group.

The NPSA guidance also emphasised that some acutely ill children with increased ADH secretion may benefit from maintenance fluid being restricted. The GDG's view, having considered the lack of evidence of significant harm from not restricting fluids (while noting potential limitations of the NRLS database in that it only contains information about reported incidents) and some evidence of harm resulting from fluid restriction, is that in children and young people with suspected or confirmed bacterial meningitis fluids should not be restricted unless there is evidence of raised intracranial pressure (see section 5.6) or evidence of increased ADH secretion.

Close monitoring of hydration and electrolyte balance is essential. The NPSA guidance includes information about monitoring requirements to detect hyponatraemia, which can develop within a short timescale.

The GDG's view was that if there were signs of raised intracranial pressure or evidence of shock, emergency management for these conditions should be initiated and ongoing fluid management should be discussed with a paediatric intensivist.

Other aspects of management in bacterial meningitis and meningococcal septicaemia

Metabolic disturbances

The GDG noted that, in its members' experience, various biochemical and haematological abnormalities were frequently observed in children with suspected meningococcal septicaemia. The GDG members observed that, in particular, hypoglycaemia, acidosis, hypokalaemia, hypomagnesaemia, hypocalcaemia, anaemia and coagulopathy could compromise the child's or young person's condition. The GDG was of the view that blood

[*] NPSA/2007/22; available at www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/intravenous-infusions/

tests should be undertaken to detect these abnormalities and that correction should be undertaken according to agreed local or national protocols.

Seizures

The GDG noted that seizures were a serious complication in cases of meningitis and could be particularly difficult to manage in some patients including those with raised intracranial pressure. Although seizures are a relative contraindication to lumbar puncture (see section 5.6), appropriate management may neutralise that contraindication. The GDG was of the opinion that local or national protocols should be available for the management of seizures associated with bacterial meningitis or meningococcal septicaemia.

Raised intracranial pressure

The GDG was of the opinion that local or national protocols should be available for the treatment of raised intercranial pressure in children and young people with suspected bacterial meningitis.

Recommendations

Other aspects of management in bacterial meningitis and meningococcal septicaemia

Metabolic disturbances

In children and young people with suspected or confirmed meningococcal septicaemia, anticipate, monitor and correct the following metabolic disturbances using local or national protocols:

- hypoglycaemia
- acidosis
- hypokalaemia
- hypocalcaemia
- hypomagnesaemia
- anaemia
- coagulopathy.

Seizures

Use local or national protocols for management of seizures in children and young people with suspected bacterial meningitis or meningococcal septicaemia.

Raised intracranial pressure

Use local or national protocols to treat raised intracranial pressure.

Fluid management in suspected or confirmed bacterial meningitis

Assess for all of the following:

- signs of shock (see table 3.3)
- raised intracranial pressure
- signs of dehydration.

Refer to 'Diarrhoea and vomiting in children' (NICE clinical guideline 84) for assessment of shock and dehydration.

If present, correct dehydration using enteral fluids or feeds, or intravenous isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with dextrose 5%).

Do not restrict fluids unless there is evidence of:

- raised intracranial pressure, **or**
- increased antidiuretic hormone secretion.*

* See National Patient Safety Agency (2007) Patient Safety Alert 22: Reducing the Risk of Hyponatraemia when Administering Intravenous Infusions to Children. Available from www.nrls.npsa.nhs.uk

Give full-volume maintenance fluids to avoid hypoglycaemia and maintain electrolyte balance.

Use enteral feeds as maintenance fluid if tolerated.

If intravenous maintenance fluid is required, use isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with dextrose 5%). In neonates, use glucose 10% and added sodium chloride for maintenance.

Monitor fluid administration and urine output to ensure adequate hydration and avoid overhydration.

Monitor electrolytes and blood glucose regularly (at least daily while the child or young person is receiving intravenous fluids).

If there are signs of raised intracranial pressure or evidence of shock, initiate emergency management for these conditions and discuss ongoing fluid management with a paediatric intensivist.

6.4 Intravenous fluid resuscitation in meningococcal septicaemia

Introduction

In children with meningococcal disease, early recognition of circulatory failure and aggressive fluid resuscitation to restore intravascular volume is crucial to prevent end-organ damage and death. In addition, inotropic support is frequently necessary to maintain cardiac output and organ perfusion. Studies involving adults[117;201] and a recent study involving children[118] have shown that resuscitation in septic shock is most effective when treatments are directed at achieving specific, time-sensitive haemodynamic goals such as optimising heart rate, blood pressure and capillary perfusion within 60 minutes after initiating therapy. Optimising oxygen delivery as part of this care package by maintaining the central venous oxygen saturation at, or above, 70% has also been associated with improved outcomes in people with septic shock.[117;118;201] As the early recognition of shock and the rational use of vasoactive agents to correct cardiac and vascular dysfunction are integral to the success of resuscitation protocols, the GDG reviewed the evidence for indications for commencing intravenous fluid resuscitation and vasoactive agents in children and young people with meningococcal disease.

Clinical questions

What are the indications for administering intravenous fluids to resuscitate children and young people with suspected meningococcal septicaemia?

What are the clinical indications for giving inotropes in children and young people with suspected or confirmed meningococcal septicaemia?

Previous UK guidelines

Fluids

The 'Feverish illness in children' guideline recommends that children with fever and shock should be given an immediate intravenous fluid bolus of 20 ml/kg, usually 0.9% sodium chloride. Children should be actively monitored and given further fluid boluses as necessary.[25]

The SIGN guideline* recommends that a rapid intravenous infusion of isotonic crystalloid or colloid solution should be given to children with meningococcal sepsis with signs of shock.[27]

* SIGN guideline number 102

Inotropes

The 'Feverish illness in children' guideline recommends that children admitted to hospital with meningococcal disease should be under paediatric care, supervised by a consultant and have their need for inotropes assessed.[25]

The SIGN guideline* on 'Management of Invasive Meningococcal disease in Children and Young People' recommends that children with fluid resistant shock should be treated early with inotropes. Intubation and mechanical ventilation should be considered for these children.[27]

Studies considered for this section

Fluids

Studies of all designs evaluating intravenous fluid administration in children with suspected or confirmed meningococcal septicaemia were considered for this section. Because of a lack of evidence, studies involving children and young people with sepsis, septic shock or shock associated with infection were reviewed for extrapolation.

Inotropes

Studies of all designs evaluating administration of the following inotropes in children with suspected or confirmed meningococcal septicaemia were considered for this section: dopamine, dobutamine, adrenaline, noradrenaline and vasopressin. Because of a lack of evidence, studies involving children and young people with sepsis, septic shock or shock associated with infection were reviewed for extrapolation.

Overview of available evidence

No studies were found that directly addressed the clinical indications for fluid resuscitation or for commencing inotropes in children and young people with suspected or confirmed meningococcal septicaemia or in children with sepsis or septic shock.

One case–control study of children with meningococcal disease [EL=2++] and one retrospective study of children with septic shock [EL=2–] were included to provide data for extrapolation to inform the GDG discussion.

Review findings

One case–control study[119] [EL=2++] aimed to determine whether suboptimal management in hospital contributed to poor outcome in children admitted with meningococcal disease (England, Wales and Northern Ireland, 1997–1999). In the study 143 children under 17 years who died from meningococcal disease (cases) were matched by age with 355 survivors (controls) from the same region of the UK. A panel of paediatricians reviewed hospital records to compare the hospital care received by survivors and non-survivors during the first 24 hours of admission. The panel used pre-defined optimal management protocols for meningococcal disease as a standard of care to judge the quality of hospital treatment. Optimal resuscitation for children with meningococcal disease complicated by cardiovascular failure was pre-defined as: 40 ml/kg of fluid in the first hour given in aliquots of 20 ml/kg, followed by mechanical ventilation and administration of peripheral inotropes (dopamine or dobutamine) if shock persisted. In the event of a poor response to volume resuscitation and peripheral inotropes the protocol recommended starting an adrenaline infusion.

Multivariate analysis found that failure to administer adequate inotropes in the first 24 hours was associated with a 23.7-fold increase in the odds of mortality (OR 23.7, 95% CI 2.6 to 213, $P = 0.005$) in children with meningococcal disease and cardiovascular failure. Not being under the care of a paediatric team was associated with a 66-fold increase in the odds of dying ($P = 0.005$) and failure of supervision by a consultant was associated with a 19.5-fold increase ($P = 0.015$). Giving too little fluid in the first 24 hours was significantly associated with death in univariate analysis (OR 2.5, 95% CI 1.4 to 4.7, $P = 0.004$).

* SIGN guideline number 102

A retrospective cohort study[120] (1993–2001) [EL=2–] reviewed the effects of early shock reversal on the outcome of 91 infants and children with septic shock transferred from local hospitals to one children's hospital in the USA. Information about each patient's care and clinical condition at the local hospital was obtained from a database used by the children's hospital's transport team. Shock reversal (defined by return of normal systolic blood pressure and capillary refill time to less than 3 seconds) was successfully achieved in 24 out of 91 children (26%) by the time of arrival of the transport team (median time: 75 minutes). Successful shock reversal in this time period was associated with an approximately 9 fold increase in the odds of survival compared with children with persistent shock (survival: 96% for early shock reversal versus 63% for persistent shock state; OR 9.49, 95% CI 1.07 to 83.89, $P < 0.001$). Shock reversal was achieved by compliance with a protocol that included early and aggressive fluid administration, commencing dopamine for fluid-refractory shock, epinephrine for dopamine-resistant cold shock and norepinephrine for warm shock during the first hour of resuscitation.

A prospective observational study[114] [EL=2+] conducted in the UK in 2009 provided audit data for current practice in the management of severe sepsis in children in the UK against a 2002 guideline. The study included 136 children with sepsis (average age 9.8 to 15.1 months). Comparisons were made between children in whom shock reversal occurred and children in whom it did not. Total fluid intake was significantly different between the groups (60 ml/kg versus 80 ml/kg, $P = 0.004$). Children in whom shock was reversed had better outcomes than those in whom shock was not reversed (survival rate 94% versus 75%, $P = 0.03$). Presence of shock after inter-hospital transfer was the only independent predictor of death after admission to the paediatric intensive care unit (OR for death 3.8, 95% CI 1.4 to 10.2, $P = 0.008$).

Evidence statement

No studies were found that directly addressed the clinical indications for fluid resuscitation or for commencing inotropes in children and young people with meningococcal septicaemia.

One study found that insufficient intravenous fluid and inotrope administration in the first 24 hours was associated with a higher risk of mortality in children with meningococcal disease and circulatory failure.

One study with poor methodology found that early reversal of shock using intravenous fluids and inotropes was associated with lower mortality in children with sepsis.

GDG interpretation of the evidence

There was no available evidence directly addressing the clinical indications for starting intravenous fluid resuscitation or vasoactive drug therapy in children and young people with meningococcal septicaemia.

Intravenous fluid resuscitation

Many children with meningococcal septicaemia have circulatory failure with haemodynamic dysfunction. There is, however, evidence to indicate that children with meningococcal disease or septic shock have worse outcomes if circulatory failure is not adequately treated. The GDG therefore considered that fluid resuscitation should be started immediately in these children.

Vasoactive drug therapy

The GDG's view was that if there were signs of raised intracranial pressure or evidence of shock, emergency management for these conditions should be initiated and ongoing fluid management should be discussed with a paediatric intensivist.

There is no evidence to support the use of one inotrope over another in children or young people with meningococcal septicaemia. However, evidence from adult studies[117;201] and one recent study in children[118] support the concept that vasoactive agents, which enhance oxygen delivery, may improve outcome in septic shock.

The GDG's view was that if shock remains intractable, despite fluid resuscitation (more than 40 ml/kg) and increasing requirements for intravenous (IV) adrenaline and/or IV

noradrenaline, potential reasons (such as persistent acidosis, incorrect dilution or extravasation) should be considered and further management options should be discussed with a paediatric intensivist.

The GDG was of the opinion that local or national protocols should be available for the administration of vasoactive agents in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

Recommendations relating to starting resuscitation fluids and vasoactive agents for meningococcal disease are presented at the end of section 6.5.

6.5 Type and volume of intravenous fluids for meningococcal septicaemia

Introduction

In children with meningococcal septicaemia and signs of shock, early and aggressive intravenous fluid resuscitation is the accepted standard of care. Inadequate fluid resuscitation is associated with early deterioration in organ perfusion and higher morbidity and mortality.[119] The UK Advanced Paediatric Life Support protocol recommends the initial use of 0.9% sodium chloride or 4.5% human albumin followed by boluses of albumin for resuscitating children with septic shock, proposing that crystalloids leak quickly out of the intravascular compartment.[95] However, a systematic review published in 1998 assessing the effects of human albumin administration in critically ill adults suggested that human albumin might increase mortality in this population group compared with crystalloids,[121] raising concerns about the widespread use of colloids for fluid resuscitation. Although the review did not include RCTs of children with sepsis and did not provide information to guide management of meningococcal septicaemia, its publication led to a change from using human albumin to crystalloids for resuscitation in many centres. There is still uncertainty about the optimal type of fluid to resuscitate children with septic shock. In practice, both isotonic crystalloid solutions (0.9% sodium chloride, lactated Ringer's solution) and colloid solutions (such as 4.5% human albumin) are used.

Clinical question

What type of intravenous fluid should be used to resuscitate children and young people with suspected meningococcal septicaemia?

Previous UK guidelines

The 'Feverish illness in children' guideline recommends that children with fever and shock should be given an immediate intravenous fluid bolus of 20 ml/kg, usually 0.9% sodium chloride. Children should be actively monitored and given further fluid boluses as necessary.[25]

The SIGN guideline on 'Management of Invasive Meningococcal disease in Children and Young People' recommends that children with meningococcal sepsis with signs of shock should be given a rapid intravenous infusion of isotonic crystalloid or colloid solution. The guideline recommends that a total of 60 ml/kg should be administered as three boluses of 20 ml/kg, with assessment after each bolus.[27]

Studies considered in this section

RCTs comparing colloid and crystalloid solutions for resuscitation of children and young people with meningococcal septicaemia were considered for this section. Because of a lack of evidence, the search was broadened to include RCTs involving children and young people with sepsis, septic shock or shock associated with infection. RCTs involving adults with sepsis or septic shock that compared the effects on mortality of resuscitation with colloid and crystalloid solutions were also considered for extrapolation.

Overview of available evidence

No RCTs were found evaluating different types of intravenous fluid for resuscitation of children and young people with meningococcal septicaemia.

Six RCTs were reviewed for extrapolation. Five RCTs compared the use of crystalloid and colloid solutions for resuscitation of children: one RCT involved children with septic shock [EL=1+], one RCT involved children with malaria [EL=1+], and two RCTs involved children with dengue shock syndrome [EL=1+ and EL=1++]. One RCT compared the effects of crystalloid versus colloid solutions in a subgroup of critically ill adults with severe sepsis [EL=1++].

Review findings

One RCT conducted in India[122] [EL=1+] evaluated the effectiveness of crystalloid solution (0.9% saline) and colloid solution (polymer from degraded gelatin in saline [Haemaccel™]) in restoring circulating volume in 60 children aged 1 month to 12 years with septic shock. Fluid was administered in boluses of 20 ml/kg every 10 to 20 minutes until blood pressure or central venous pressure returned to normal. The RCT found no significant difference in mortality between the groups (29% with crystalloid versus 31% with colloid, $P > 0.1$). The median volume of fluid needed for initial resuscitation was significantly higher in the crystalloid group compared with the colloid group (50 ml/kg (range 20–108 ml/kg) with saline versus 30 ml/kg (range 20–70 ml/kg) with gelatin, $P = 0.018$). There was no significant difference in the time taken for resuscitation between the groups ($P = 0.41$).

One phase II RCT conducted in Kenya[123] [EL=1+] compared the safety and efficacy of crystalloid solution (0.9% saline) versus colloid solution (4.5% human albumin) for volume expansion in 150 children with severe malaria and a metabolic acidosis (base deficit more than 8 millimole/litre). Fluid was given as an intravenous bolus of 20 or 40 ml/kg over 1 hour. The RCT found that in 49 children with severe acidosis (base deficit more than 15 millimole/litre), the secondary outcome of mortality was lower in children given 4.5% human albumin than in children given 0.9% saline (9% with human albumin versus 31% with saline). The difference was not statistically significant ($P = 0.06$). Most deaths occurred in children admitted with coma. Hypotension and other signs of shock were not criteria for entry to the trial.

Two RCTs conducted in Vietnam examined the effects of different types of resuscitation fluid in children with dengue shock syndrome. Dengue shock syndrome was defined as dengue haemorrhagic fever plus either low pulse pressure (less than 20 mmHg) or unrecordable blood pressure, plus clinical signs of circulatory insufficiency such as cold extremities and thready pulse.

The first RCT[124] [EL=1+], involving 50 children aged 5 to 15 years, compared two crystalloid solutions (0.9% saline and Ringer's lactate) and two colloid solutions (Dextran 70 and Gelafundin 35000 [3% gelatin]) for initial resuscitation of children with dengue shock syndrome. Fluids were given intravenously as 20 ml/kg over one hour, followed by 10 ml/kg over the following hour. There were no deaths. The RCT found no significant difference among the fluids in the duration of shock ($P = 0.36$ across four groups).

The second RCT[125] [EL=1++] compared a crystalloid solution (Ringer's lactate) versus two colloid solutions (6% dextran 70 and 6% hydroxyethyl starch 200/0.5) for the initial resuscitation of 383 children with moderately severe dengue shock syndrome (pulse pressure more than 10 mmHg and less than or equal to 20 mmHg). Resuscitation fluid was given as an intravenous bolus of 15 ml/kg over 1 hour followed by 10 ml/kg over the second hour. Further colloid was given if there was no improvement in cardiovascular status after initial fluid resuscitation. The RCT found that, for moderately severe dengue shock, the proportion of children requiring rescue colloid therapy was similar for colloids and crystalloid (comparison of Ringer's lactate versus either colloid solution: RR 1.08, 95% CI 0.78 to 1.47, $P = 0.65$). There was no significant difference among the groups in the risk of adverse effects such as clinical fluid overload or coagulopathy (reported as not significant, P values not reported). Significantly more children given dextran had allergictype reactions after infusion

(transient high fevers and rigors) compared with the other fluids ($P < 0.001$ for three-way comparison). One child given hydroxyethyl starch died of profound shock and gastrointestinal bleeding.

One large multicentre RCT[126] [EL=1++] compared the effects of colloid solution (4% human albumin) versus crystalloid solution (0.9% saline) on 28-day, all-cause mortality in 7000 critically ill adults admitted to intensive care units (ICUs) in Australia and New Zealand. The allocated study intervention was used for all fluid resuscitation in the ICU to maintain or increase intravascular volume. Patients had a range of morbidities requiring medical and surgical treatment. A subgroup analysis of 1218 patients with severe sepsis found no significant difference in mortality between 4% human albumin and 0.9% saline (31% with 4% human albumin versus 35% with 0.9% saline; RR 0.87, 95% CI 0.74 to 1.02, $P = 0.088$). The study was noted to be underpowered to detect small differences in mortality in the pre-defined subgroups. Co-morbidities and causative organisms in the patients with sepsis were not reported.

Evidence statement

No high-quality studies were found evaluating different types of intravenous fluid for resuscitation of children and young people with meningococcal septicaemia.

In children with septic shock, one RCT found that a greater volume of crystalloid solution (0.9% saline) was needed to restore circulating volume compared with colloid solution (Haemaccel™). It found no significant difference in mortality between crystalloid and colloid.

In children with severe malaria plus severe acidosis, one RCT found that fluid resuscitation with colloid solution (4.5% human albumin) was associated with a non-significant reduction in mortality compared with crystalloid solution (0.9% saline).

Evidence from RCTs involving children with dengue shock syndrome found no significant difference in the duration of shock or the need for further fluid boluses between initial resuscitation with different crystalloid and synthetic colloid solutions. One study found that significantly more children given synthetic colloid solutions had allergic type reactions compared with children given crystalloid solutions.

In critically ill adults, one large RCT found no significant difference in 28-day mortality between fluid resuscitation with colloid solution (4% human albumin) and crystalloid solution (0.9% saline) in a subgroup of patients with severe sepsis.

Cost effectiveness

In the absence of evidence evaluating different types of intravenous fluid for children and young people with meningococcal septicaemia, the GDG considered it important to consider the cost effectiveness in framing its recommendation. A 'what-if' analysis was undertaken to ascertain the circumstances in which the more expensive colloid solution would be cost effective (see appendix K). A cost comparison suggested that colloid solution was markedly more expensive (£34) than crystalloid solution (£0.51). In the absence of evidence of greater effectiveness with colloid solution, crystalloid solution was considered to be cost effective.

GDG interpretation of the evidence

The GDG concluded that there is insufficient evidence to decide whether crystalloid or colloid solutions have greater effectiveness for volume resuscitation in children and young people with meningococcal septicaemia.

Initial bolus

The Resuscitation Council (UK) 2005 guidelines for Paediatric Advanced Life Support state that there are no clear advantages in using colloid in the initial stages of resuscitation for hypovolaemia post cardiac arrest. The guidelines recommend the use of isotonic saline solutions and the avoidance of dextrose-based solutions as the latter are redistributed rapidly from the intravascular space and cause hyponatraemia and hyperglycaemia, which may worsen neurological outcome after cardiac arrest.[127]

The Advanced Paediatric Life Support (APLS) Protocol recommends an initial bolus of crystalloid or colloid followed by further boluses of colloid for resuscitation of children with septic shock.[95] There is currently no evidence that colloid is superior to crystalloid for initial resuscitation and the GDG considered other factors to inform its recommendations:

- The colloid solution that was used most widely for resuscitation of children was 4.5% human albumin until concerns were raised about its safety and efficacy.[121] Although the evidence is not universally applicable to paediatric sepsis, and a subsequent publication by the same group raised no concerns about the safety of albumin,[128] 4.5% human albumin is no longer routinely available on resuscitation trolleys or in some accident and emergency departments.
- As 4.5% human albumin is a blood product, its use in children may be less acceptable than crystalloid without evidence of superior efficacy.
- The crystalloid solution that is now used most widely for volume resuscitation in children is 0.9% sodium chloride. It is readily available and is considerably cheaper than 4.5% human albumin or other colloid solutions.
- Many children will require only one bolus of fluid and minimising exposure to expensive, blood-derived products by limiting use of 4.5% human albumin to those requiring ongoing resuscitation (see below) was considered good practice.

In view of the lack of evidence for greater effectiveness of human albumin, its cost and problems with its availability, the GDG concluded that 0.9% sodium chloride should be given as an initial bolus for fluid resuscitation in children with meningococcal septicaemia and signs of shock.

Second and subsequent boluses

The GDG noted the lack of evidence to direct the choice of fluid for resuscitation after the initial bolus. Although the GDG recognised that the same issues discussed for the initial bolus also applied to subsequent boluses, it was of the view that for ongoing resuscitation of children there were important additional considerations:

- Expert opinion of those GDG members involved in resuscitation of children, including paediatric intensivists, was strongly in favour of using 4.5% human albumin for subsequent boluses.
- There is a greater likelihood that 4.5% human albumin could be made available to the resuscitation setting after the initial fluid bolus.
- The preference for using human albumin for ongoing resuscitation is driven by concerns also noted in the APLS guidance that, when compared with colloids, crystalloid fluids:
  - diffuse more readily into the interstitial space
  - may be associated with peripheral oedema
  - where capillary leak exists, allow more water to enter the interstitial space, because of lower osmotic pressure
  - need 2 to 3 times the volume of colloids to expand the vascular space, and
  - have been reported to be associated with lower mortality (however, this is unproven for shock in childhood conditions).[129]

The GDG acknowledged the body of expert opinion and published guidance in support of the use of colloid solutions (considered to mean 4.5% human albumin solutions) for the ongoing management of shock in children after the first bolus, and recognised that there was an absence of evidence to direct a change in current management protocols used by paediatric intensivists. At the same time, the GDG acknowledged that some experts and guidelines considered that 0.9% sodium chloride should be used in this setting.

The GDG therefore agreed that, after the initial bolus, further fluid management should be with either 0.9% sodium chloride or 4.5% human albumin.

Other colloids are not recommended owing to the possibility of adverse or allergic reactions.

Hartmann's solution (sodium lactate) should not be used for resuscitation as it may produce lactic acidosis in seriously ill patients with poor tissue perfusion.[130]

The GDG is aware of concerns about interactions between calcium-containing solutions and ceftriaxone, and noted recent MHRA advice* that ceftriaxone should not be given to any patient simultaneously with calcium-containing infusions.[104] The guideline developers therefore recommend that calcium-containing resuscitation fluid should not be used if ceftriaxone is given (instead use cefotaxime; see section 6.1).

The GDG noted that children with meningococcal septicaemia often require more than 40 ml/kg of fluid for initial resuscitation. Such children will probably require mechanical ventilation and inotropic support.

Recommendations

Intravenous fluid resuscitation in meningococcal septicaemia

In children and young people with suspected or confirmed meningococcal septicaemia:

- If there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards.
- If the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes.
- If the signs of shock still persist after the first 40 ml/kg:
  - immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
  - start treatment with vasoactive drugs
  - be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume
  - consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes.
- Discuss further management with a paediatric intensivist.

Vasoactive therapy for shock in meningococcal septicaemia

If shock persists despite fluid resuscitation (more than 40 ml/kg) and treatment with either intravenous adrenaline or intravenous noradrenaline, or both, consider potential reasons (such as persistent acidosis, incorrect dilution, extravasation) and discuss further management options with a paediatric intensivist.

Use local or national protocols for the administration of vasoactive agents in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

* Update to latest MHRA guidance www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON059804

Research recommendations

Intravenous fluid resuscitation in meningococcal septicaemia

How effective is albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock?

Why this is important

There are theoretical reasons why albumin solution may be more effective than crystalloid solution in children and young people with septic shock. However, no clinical studies have evaluated the effectiveness of albumin solution in children and young people with meningococcal disease. Concerns about the safety of colloids such as albumin solution led to a widespread change in clinical practice in the 1990s to using crystalloid solutions, despite a lack of evidence of equivalent effectiveness. Although albumin solution is considerably more expensive than crystalloid solution, a small additional benefit of albumin over crystalloid (one death prevented in more than 14,000 treated cases) would make the use of albumin solution cost effective. Randomised controlled trials are therefore needed to compare the effectiveness of albumin and crystalloid solutions in children and young people with septic shock.

6.6 Respiratory support in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia

Introduction

A seriously ill infant or child should have a structured and sequential clinical assessment of his or her airway, breathing and circulation, with appropriate interventional management at each stage.

With the potential for raised intracranial pressure and seizure activity in infants and children with bacterial meningitis, together with the extensive fluid resuscitation often required in those with meningococcal septicaemia (see section 6.5), the risk of respiratory compromise in these individuals is often increased.

The GDG reviewed the evidence to provide guidance on timely tracheal intubation and mechanical ventilation for an optimal outcome in children with bacterial meningitis or meningococcal disease.

Clinical question

In children and young people with suspected or confirmed meningococcal septicaemia, what are the clinical indications for intubation and mechanical ventilation?

In children and young people with suspected or confirmed bacterial meningitis, what are the clinical indications for intubation and mechanical ventilation?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal Disease in Children and Young People' recommends that children with progressive meningococcal disease should be intubated and mechanically ventilated if there is increased work of breathing, hypoventilation or low level of consciousness, or if the child is moribund.[27]

Studies considered in this section

All study designs evaluating the indications for tracheal intubation in children and young people with suspected or confirmed meningococcal septicaemia or meningitis were considered for this section. Owing to a lack of evidence, a search was conducted for all study

designs assessing the indications for tracheal intubation in people of all ages with sepsis, septicaemia or septic shock.

Overview of available evidence

No studies were found evaluating the indications for tracheal intubation in children and young people with meningococcal septicaemia or bacterial meningitis. No studies were identified in children or adults with sepsis, septicaemia, septic shock or other types of meningitis that could be used for extrapolation.

GDG interpretation of the evidence

No evidence was found addressing the indications for tracheal intubation in children and young people with meningococcal septicaemia or bacterial meningitis. Therefore, the expert opinion of the GDG, Paediatric Advanced Life Support guidelines and guidelines on the management of septic shock that have influenced current clinical practice in the UK[131-134] were considered to reach a consensus recommendation.

Reactive tracheal intubation and mechanical ventilation is accepted best practice for children:

- with respiratory failure
- with coma
- who are moribund, and
- for whom there is a need to control intractable seizures.

Children with meningococcal septicaemia may deteriorate rapidly. The GDG therefore strongly recommends that the clinician should anticipate clinical deterioration in such children and prioritise airway management and pre-emptive tracheal intubation and mechanical ventilation before overt signs of respiratory failure have developed.

The GDG supported the clinical practice of a group of paediatric specialists who recommend that, owing to the risk of pulmonary oedema, children who have received 40 ml/kg of resuscitation fluid with continuing signs of shock should be pre-emptively intubated. Tracheal intubation and mechanical ventilation in these circumstances protects the airway, reduces the risk of pulmonary oedema, facilitates adequate oxygenation and ventilation, and reduces the work of breathing and oxygen consumption.[135]

In a child with ongoing shock or raised intracranial pressure, tracheal intubation should also be considered to assist with invasive procedures that facilitate the ongoing management and monitoring of the child, such as central and arterial line insertions.

The GDG agreed that there should be a low threshold for tracheal intubation and mechanical ventilation of infants and children prior to their transfer to another hospital (for example for intensive care treatment) in view of the potential risk of deterioration en route.

The GDG considered that critically ill children should be intubated only by healthcare professionals with expertise in paediatric airway management. These include experienced anaesthetists, paediatric intensivists or paediatric emergency physicians who have maintained their clinical skills. The GDG stressed the need to seek suitable help immediately when children first present to the hospital, so that expertise with paediatric airway management is obtained as soon as possible.

The GDG is aware that there may be issues related to translating from the non-intubated sick child or young person to an intubated child or young person. The GDG's discussions and recommendations highlighted the need for healthcare professionals to be aware that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are very ill and at risk of deterioration during intubation (further hypotension, pulmonary oedema and aspiration). These children and young people should be nil by mouth from admission to hospital: fluid boluses, vasoactive drugs and access to a healthcare professional experienced in the management of critically ill children should available before intubation (see sections 6.3, 6.4 and 6.5).

The GDG was of the view that self-ventilating children and young people in the emergency setting should receive oxygen therapy according to standard protocols during initial

assessment to counteract the hypoxaemia that is frequently present in septicaemia and to improve cerebral oxygenation in the presence of raised intercranial pressure associated with meningitis.

The GDG was of the opinion that local or national protocols should be available for intubation in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

Recommendations

Respiratory support in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia

In self-ventilating children and young people with signs of respiratory distress, administer 15-litre face mask oxygen via a reservoir rebreathing mask.

If there is a threatened loss of airway patency, implement airway-opening manoeuvres, and start bag–valve mask ventilation in preparation for tracheal intubation.

A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

Be aware that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are very ill and at grave risk of sudden deterioration during intubation. Anticipate aspiration, pulmonary oedema or worsening shock during intubation. Ensure that they are nil by mouth from admission to hospital and that the following are available before intubation:

- facilities to administer fluid boluses
- appropriate vasoactive drugs
- access to a healthcare professional experienced in the management of critically ill children.

Undertake tracheal intubation and mechanical ventilation for the following indications:

- threatened (for example, loss of gag reflex), or actual loss of airway patency
- the need for any form of assisted ventilation, for example bag–mask ventilation
- clinical observation of increasing work of breathing
- hypoventilation or apnoea
- features of respiratory failure, including:
  - irregular respiration (for example, Cheyne–Stokes breathing)
  - hypoxia (PaO_2 less than 13 kPa or 97.5 mmHg) or decreased oxygen saturations in air
  - hypercapnia ($PaCO_2$ greater than 6 kPa or 45 mmHg)
- continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- signs of raised intracranial pressure
- impaired mental status:
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - moribund state
- control of intractable seizures
- need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit or another hospital.

Use local or national protocols for intubation.

6.7 Corticosteroids for bacterial meningitis

Introduction

Bacterial meningitis is accompanied by marked inflammation in the subarachnoid space and corticosteroids given with antibiotics can reduce this inflammation. In clinical practice, benefit

has been reported particularly in children with Hib meningitis but, with changing epidemiology and the decline in particular in Hib cases following routine immunisation, the place of adjunctive corticosteroid therapy for bacterial meningitis is uncertain. The GDG conducted a meta-analysis of RCTs of adjunctive corticosteroid therapy in the treatment of acute bacterial meningitis in children.

Clinical question

Should corticosteroids be used in the treatment of children and young people with suspected or confirmed bacterial meningitis?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal disease in Children and Young People' recommends that parenteral dexamethasone should be given to children with bacterial meningitis of unknown origin or with meningococcal meningitis for 4 days. The guideline recommends commencing dexamethasone with, or within 24 hours of, the first dose of antibiotic.

Studies considered in this section

RCTs and systematic reviews of RCTs evaluating corticosteroid use in children and young people with suspected or confirmed bacterial meningitis were considered for this section. Studies involving adults were excluded from the review.

Overview of available evidence

Two systematic reviews were found: the first[136] [EL=1++] investigated the effects of adjunctive corticosteroids in people of all ages with acute bacterial meningitis and the second[137] [EL=1+] assessed the effects of adjunctive dexamethasone in childhood bacterial meningitis. The first review reported a separate analysis of children treated in low-income settings and high-income settings for some outcomes. The GDG expanded the meta-analysis of high-income studies using data from the 'all-income' analyses in the first review[136]. An analysis of hearing loss in children with pneumococcal meningitis from high-income settings was performed using data extracted from the second review.[137] Data from studies involving children from low-income settings were extracted from the first review[136] and from one subsequent RCT[138] [EL=1+]. One quasi-randomised RCT[139] [EL=1–] was found investigating the effect of dexamethasone in neonates.

Review findings

The first systematic review[136] [EL=1++] (search date 2006) comprised 20 RCTs, of which 15 involved 2074 children younger than 16 years. In 14 of 15 studies involving children, intravenous dexamethasone was given at doses ranging from 0.4 to 1.5 mg/kg/day for 2 to 4 days. In the remaining study, intravenous methylprednisolone was given for 3 days. The control group (controls) in 10 of the 11 RCTs were given placebo: in one study the control group did not receive placebo. The review assessed the effects of corticosteroids on mortality, severe hearing loss and neurological sequelae. Severe hearing loss was defined as bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. Neurological sequelae included focal neurological deficits, epilepsy (not present before meningitis), severe ataxia and severe memory or concentration disturbance.

Data from studies conducted in high-income settings

Of the 1037 children in the analysis, approximately 61% had meningitis caused by Hib, approximately 16.5% had pneumococcal meningitis and approximately 14% had meningococcal meningitis.

Mortality

A meta-analysis of studies involving children with bacterial meningitis from high income settings performed by the first review[136] found that corticosteroids plus antibiotics had no beneficial effect on mortality compared with controls (P = 0.45; see table 6.2). Because of low

event rates, organism-specific subgroup analyses for mortality were underpowered and are not reported further (see appendix H, figure H.8).

Severe hearing loss

The first review[136] found that corticosteroids significantly reduced the risk of severe hearing loss compared with controls for meningitis caused by any bacterium ($P < 0.0001$; see table 6.2). This benefit was evident for children with Hib meningitis ($P = 0.001$; see table 6.2 and appendix H, figure H.9). For meningitis caused by bacteria other than Hib, fewer children given corticosteroids developed severe hearing loss compared with controls, but the difference was not statistically significant ($P = 0.07$; see table 6.2 and appendix H, figure H.10).[140,136] For meningitis caused by *S. pneumoniae*, a meta-analysis found no significant difference in the risk of severe hearing loss between dexamethasone and controls ($P = 0.75$; see table 6.2 and appendix H, figure H.11).[137]

Neurological sequelae

The first review found no significant difference between corticosteroids and controls in the proportion of children with short-term neurological sequelae ($P = 0.29$; see table 6.2).[136] Further meta-analysis found that corticosteroids were associated with a significant reduction in the proportion of children with long-term neurological sequelae compared with controls ($P = 0.04$; see table 6.2 and appendix H, figure H.12).[136]

Timing of corticosteroids

The GDG review found that when corticosteroids were given before or with the first dose of antibiotic (early administration), the risk of long-term neurological sequelae was reduced compared with controls (four RCTs, 328 children; RR 0.48, 95% CI 0.25 to 0.92, $P = 0.03$), but this benefit was not seen in studies in which corticosteroids were administered after the first dose of antibiotic (late administration) (four RCTs, 379 children; RR 0.81, 95% CI 0.42 to 1.57, $P = 0.53$)[136] (see appendix H, figure H.13). Corticosteroids were associated with a reduced risk of severe hearing loss whether administered early or late in children with bacterial meningitis (early administration: four RCTs, 325 children; RR 0.36, 95% CI 0.15 to 0.87, $P = 0.02$ versus late administration: five RCTs, 501 children; RR 0.29, 95% CI 0.14 to 0.63, $P = 0.002$)[136] (see appendix H, figure H.14). Different timing of administration did not alter the effect of corticosteroids on mortality, short-term neurological sequelae or severe hearing loss in children with pneumococcal meningitis[136;141] (see appendix H, figures H.15, H.16 and H.17, respectively). However, owing to the small number of included studies, the analyses were underpowered to detect significant differences between the groups.

Adverse events

The GDG review found that adjunctive corticosteroids were not associated with a significantly increased risk of adverse effects, including gastrointestinal bleeding, herpes zoster or herpes simplex infection, fungal infection or secondary fever ($P = 0.98$; see table 6.2 and appendix H, figure H.18).[136]

Data from studies conducted in low-income settings

The first review[136] reported a subgroup analysis of four RCTs conducted in low-income countries involving 1037 children. Approximately 25% of children had Hib meningitis and 32% had pneumococcal meningitis. The review found no significant difference between adjunctive corticosteroids and controls (placebo or no corticosteroids) in the risk of mortality, severe hearing loss or short-term neurological sequelae (see table 6.2)[136]. A large study conducted in Malawi, involving 596 children, contributed most of the events in these analyses.[142] Many of the children in this study were anaemic and malnourished, 34% were HIV positive and 36% of participants had received antibiotic therapy prior to admission.

Another RCT[138] [EL=1+] compared the effects of adjunctive intravenous dexamethasone (0.15 mg/kg 6 hourly for 48 hours), oral glycerol, a combination of both interventions and placebo on mortality, profound hearing loss and severe neurological sequelae (including blindness, quadriplegia, hydrocephalus or severe psychomotor retardation). The RCT involved 654 children aged 2 months to 16 years with bacterial meningitis (six centres in Latin America).

The RCT found no significant difference in mortality (OR 0.82, 95% CI 0.45 to 1.49, *P* = 0.509) or in the risk of profound hearing loss (OR 0.79, 95% CI 0.33 to 1.91, *P* = 0.604) between dexamethasone alone and placebo. It found that fewer children given dexamethasone alone developed severe neurological sequelae compared with placebo but the difference did not reach statistical significance (OR 0.48, 95% CI 0.21 to 1.07, *P* = 0.072). Two of the six centres in the study did not include a placebo arm and therefore inclusion of these results in the analysis may have compromised the benefit of randomisation. Similar to the low-income studies in the first review,[136] many of the children in the study were anaemic, presented late and had been given preadmission oral antibiotics.

All of the studies identified in the systematic review for this guideline (from both high- and low-income settings) analysed data from children with either bacteriologically confirmed bacterial meningitis or probable bacterial meningitis diagnosed on the basis of typical CSF cytology and biochemistry. Therefore, the outcome of children in whom corticosteroids were initially administered on clinical grounds, but then withdrawn because bacterial meningitis was excluded after investigation, was not assessed.

Corticosteroids for meningitis in infants younger than 3 months

Although some of the RCTs identified by the two systematic reviews[136;137] included infants younger than 3 months, no study performed a subgroup analysis of this age group.

One quasi-randomised RCT conducted in Jordan[139] [EL=1–] investigated the effect of dexamethasone on mortality, neurological sequelae and hearing loss in 52 full-term newborn infants with bacterial meningitis. Neonates admitted with suspected bacterial meningitis were given dexamethasone plus antibiotics or antibiotics alone. Dexamethasone (0.15 mg/kg 6 hourly) was given before the first dose of antibiotics and continued for a total of 4 days. The study found no significant difference in mortality between the groups after 1 week (*P* = 0.87). It found similar proportions of children with mild to moderate neurological, developmental abnormality or hearing loss at 2 year follow-up (*P* values not reported). In total, 44% of neonates in the study had meningitis caused by *Klebsiella pneumoniae*, 5% had Group B streptococcus meningitis and 7% had *E. coli* meningitis. The spectrum of causative pathogens in the study suggests that the results probably can not be generalised to all newborns with meningitis in England and Wales.

Evidence statement

High-income settings

All bacterial pathogens

In children with bacterial meningitis, evidence from 11 RCTs conducted in high-income countries showed no significant difference in mortality with corticosteroids plus antibiotics compared with antibiotics alone. A meta-analysis of five RCTs showed no significant difference in the risk of short-term neurological sequelae with adjunctive corticosteroid therapy compared with antibiotics alone. Because of low numbers of events, these meta-analyses were probably underpowered to detect clinically important differences between the groups.

One meta-analysis of ten RCTs showed that treatment with corticosteroids plus antibiotics reduced the risk of severe hearing loss compared with antibiotics alone. A meta-analysis of eight RCTs showed that corticosteroids plus antibiotics reduced the risk of long-term neurological sequelae compared with antibiotics alone.

Haemophilus influenzae type b (Hib) meningitis

In children with Hib meningitis in high income settings, there is insufficient evidence to determine whether treatment with corticosteroids plus antibiotics alters the risk of mortality compared with antibiotics alone.

Evidence from eight RCTs showed that corticosteroids plus antibiotics reduced the risk of severe hearing loss compared with antibiotics alone.

***Streptococcus pneumoniae* meningitis**

In children with pneumococcal meningitis in high-income settings, there is insufficient evidence to determine whether treatment with corticosteroids plus antibiotics alters the risk of mortality compared with antibiotics alone.

Evidence from nine RCTs showed no significant difference in the risk of severe hearing loss with corticosteroids plus antibiotics compared with antibiotics alone. There is insufficient evidence to determine whether the timing of corticosteroid administration relative to the first dose of antibiotics alters the risk of severe hearing loss in children with pneumococcal meningitis.

Non-Hib meningitis

In children with meningitis caused by bacteria other than Hib, evidence from nine RCTs showed a trend towards reduction in the risk of severe hearing loss with corticosteroids plus antibiotics compared with antibiotics alone.

Timing of corticosteroids relative to antibiotics

Evidence from two small meta-analyses showed that, compared with antibiotics alone, corticosteroids given before or with the first dose of antibiotics to treat children with bacterial meningitis (termed 'early administration') significantly reduced the risk of long-term neurological sequelae whereas corticosteroids given after the first dose of antibiotics ('late administration') did not reduce the risk of long-term neurological sequelae. Corticosteroids were associated with a reduced risk in severe hearing loss whether administered early or late in children with bacterial meningitis. There is insufficient evidence to determine whether the timing of corticosteroid administration relative to the first dose of antibiotics alters the risk of mortality or short-term neurological sequelae.

Low-income settings

Evidence from RCTs conducted in low-income settings found no significant difference in the risk of mortality, severe hearing loss or short-term neurological sequelae between adjunctive corticosteroids compared with controls (placebo or no corticosteroids).

Corticosteroids for meningitis in infants younger than 3 months

No high-quality studies were found evaluating adjunctive corticosteroids to treat meningitis in infants younger than 3 months or in neonates.

Table 6.1. Corticosteroids for bacterial meningitis (van de Beek et al, 2007 review)[136]

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
Bademosi (1979)	n= 52	10–59 years	27 male 25 female	Not specified	Pneumococcal (n=52)	Not specified	Bacteriologically proven pneumococcal meningitis. Consecutive patients admitted to medical wards with bacteriologically proven pneumococcal meningitis. All participants had meningitis, but it is not clear how the diagnoses were made (for example at admission or later)
Belsey (1969)	n= 102	0–17 years	Not specified	Pressure: normal up to 150 mmHOH Protein: normal up to 75 mg/100ml Glucose: up to 45 mg/100ml Glutamic oxalacetic transaminase: up to 23 units (None of these were explicitly linked to inclusion criteria)	• Il. influenzae (n=41) • Unknown (n=19) • Pneumococcal (n=11) • Meningococci (n=11) • Unknown (n=19)	• Meningitis due to Gram-negative enteric bacteria, staphylococci, streptococci and mycobacteria. • Recent exposure to measles, varicella or herpes. • Previous neurological procedures. • Presumptive meningococcemia with shock rather than meningitis. • Already receiving steroids for another reason at admission.	Purulent meningitis. All participants had purulent meningitis. Lumbar puncture was performed at admission, along with blood cultures and blood counts. It is not stated whether these were used to diagnose meningitis or not.
Bennett (1963)	n= 329	Not specified. Included 135 children under 16 years and 194 adults from 16 to	195 male 134 female	Not specified or linked to inclusion criteria. Inclusion: any patient with a life threatening infection	• *Diplococcus pneumoniae* (n=56, including 2 with endocarditis) • Unknown (n=10) • *Neisseria meningitidis* (n=9) • *Mycobacterium tuberculosis* (n=6) • *Streptococcus haemolyticus*	Not specified	Study could not be found to establish details.

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
		over 75 years.			group a (n=1) • Aseptic (n=1) • *Escherichia coli* (n=1) • *Proteus mirabilis* (n=1)		
Bhaumik (1998)	n=30	12–75 years	26 male 4 female	WBC count >100/mm^3 with at least 60% polymorphs Sugar of less than half simultaneous blood sugar (These were inclusion criteria, alongside increased protein in CSF)	• No isolates (n=15) • *S. pneumoniae* (n=9) • *N. meningitidis* (n=6)	Suspicion of brain abscess, intracranial empyema or treated outside study setting with antibiotics for more than 3 days.	• Acute pyogenic meningitis. • Consecutive patients with acute pyogenic meningitis. • 15 had clinical picture suggestive of bacterial meningitis with CSF white blood cell count greater than 100/mm3 with at least 60% polymorphs, increased protein in CSF and CSF sugar of less than half of simultaneous blood sugar level. • 15 had clinical picture suggestive of bacterial meningitis and identification of organism in CSF by Gram staining or culture. • Participants were randomised into treatment groups, and it is not clear if this was done before or after diagnosis.
Ciana (1995)	n= 73	2–72 months	Not specified (reported not to be significantly different between groups)	Leucocytes >100/mm^3 Glucose <2 millimole/litre (Both used to establish diagnosis)	• *S. pneumoniae* (n=25) • No isolate (n=19) • *H. influenzae* type b (n=12) • *N. meningitis* (n=11) • *Escherichia coli* (n= 3)	• Encephalitis, congenital heart disease and bacterial endocarditis. • Persistent inflammatory CSF signs with repeated negative cultures.	• CSF based diagnosis of bacterial meningitis. • All participants had bacterial meningitis. • Diagnosis established when significant inflammatory changes were detected upon CSF examination (leucocytes >100/mm^3 and glucose <2 millimole/litre).

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
deLemos (1969)	n=117	>1 month (no upper age limit specified)	Not specified, but reported to be comparable between groups	Details were obtained, but thresholds were not specified.	• *Il. influenzae* (n=69) • *N. meningococcus* (n=16) • *Pneumococcus* (n=13) • Other (n=3)	Not specified	• CSF diagnosis of acute bacterial meningitis by lumbar puncture. • All participants had bacterial meningitis.
Girgis (1989)	n=278	3 months – 60 years	278 male 151 female	Details were obtained, but thresholds were not specified.	• *Neisseria meningitidis* (n=267) • *Streptococcus pneumoniae* (n=106) • *Haemophilus influenzae* (n=56)	Not specified	Signs and symptoms of acute bacterial meningitis. But any participants with sterile CSF and blood cultures and where no organism could be seen on Gram stained films of their CSF were excluded from the final analysis.
Kanra (1995)	n=56	2–16 years	Not specified	Details were used to establish diagnosis, but thresholds were not specified.	Pneuomococcal meningitis (n=56)	• Treatment with orally or parenterally administered antibiotics before the first dose of dexamethasone. • Known hypersensitivity to drugs used in the study, congenital or acquired abnormality of the central nervous system, recurrent meningitis, posttraumatic meningitis or underlying neurologic abnormality.	Children admitted with pneumococcal meningitis (basis of diagnosis is not specified, such as clinical signs/symptoms or blood culture). But all CSF specimens were examined to establish the diagnosis before treatment (although the study does not specify if anyone was excluded as a result of the CSF findings).
Kilpi (1995)	n=122	3 months – 15 years	59 male 63 female	Leukocyte count at least 1000 x 10^6/litre (Used as inclusion criteria along with positive CSF culture or positive blood culture in patients	• *H. influenzae* type b (n=65) • *Neisseria meningitidis* (n=41) • *Streptococcus pneumoniae* (n=12) • Group B streptococcus (n=2) • *Staphylococcus aureus* (n=1)	• Meningococcal meningitis receiving penicillin instead of ceftriaxone. • Bacterial meningitis caused by *Listeria monocytogenes* resistant to ceftriaxone. • Septic arthritis treated with amoxiciliin and cefradine before diagnosis of	Suspected or confirmed bacterial meningitis. Diagnoses based on positive CSF culture, or if the total CSF leukocyte count was at least 1000 x 10^6/litre and the blood culture was positive in patients with characteristic

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
				with characteristic symptoms and signs)	• *Escherichia coli* (n=1)	bacterial meningitis. • Not given drugs as instructed in study. • Treated with mannitol on first day of study.	symptoms and signs of bacterial meningitis. (study does not state how many children with suspected bacterial meningitis did not meet the diagnosis criteria, and whether they were excluded or not).
King (1994)	n=101	1 month – 18 years	45 male 56 female	White blood cell count >1000 x 10^6/litre or White blood cell count between 100 and 1000 x 10^6/litre with neutropenia or sepsis. (Inclusion criteria alongside clinical diagnosis, bacteria seen on Gram stain, recovery of bacteria or the presence of bacterial antigens. Participants were also included if assumed to have bacterial meningitis but were too unstable for lumbar puncture)	• *Haemophilus influenzae* type b (n=57) • *Neisseria meningitidis* (n=18) • *Streptococcus pneumoniae* (n=13) • Group B streptococcus (n=1) • No isolate (n=12)	• History of antecedent hearing or neurological disorder • Previous episode of meningitis, congenital or acquired immunodeficiency syndromes or presence of a ventricular shunt. • Current use of steroids or a contraindication to use of steroids. • Received first dose of intravenous antibiotic 24 hours or more previously.	Suspected bacterial meningitis. Diagnosis was made on clinical grounds by the admitting paediatrician. Lumbar puncture was performed to confirm the diagnosis. It is not stated whether patients whose lumbar puncture did not confirm bacterial meningitis were excluded or not, but 65% of children in one group and 70% in the other group are reported to have had laboratory confirmed bacteremia.
Lebel (1988) (two studies)	n=98 n=102	2 months – 16 years	45 male 53 female 60 male 42 female	Details used to establish inclusion, but thresholds not specified.	• *H. influenzae* (n=75, n=79) • *S. pneumoniae* (n=9, n=8) • *N. meningitis* (n=8, n=9) • No isolates (n=5, n=4) • Group B *streptococcus* (n=1, n=2)	• Aseptic meningitis, gastrointestinal bleeding, recurrent meningitis associated with leakage of CSF, tuberculous meningitis. • History of hypersensitivity to beta-lactam antibiotics.	Suspected or proved bacterial meningitis. Blood cultures were obtained on admission and a diagnosis was established before antimicrobial therapy started, but it is not clear

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
						• Acquired or congenital abnormality of central nervous system, prosthetic device such as shunt or known hepatic or renal impairment. • Received more than one intravenous dose of antibiotics beforehand.	whether exclusions were made based on the results. Across the four groups, 81%, 78%, 74% and 78% had bacteremia on admission, although nine children were not tested on admission (it is not clear why they were not tested).
Lebel (1989)	n=60	3 months – 16 years	37 male 23 female	Details used to establish inclusion, but thresholds not specified.	• *Haemophilus influenzae* type B (n=45) • *Streptococcus pneumoniae* (n=9) • *Neisseria meningitidis* (n=4) • No isolate (n=0)	Known hypersensitivity to beta-lactam antibiotics, congenital or acquired abnormality of central nervous system, or prosthetic device of central nervous system.	Suspected or proven bacterial meningitis. All patients had examinations and cultures of CSF at diagnosis. No patients had CSF or clinical findings compatible with the diagnosis of aseptic meningitis.
Molyneux (2002)	n=598	2 months – 13 years	337 male 261 female	100 white cells (mostly granulocytes) (reviewer comment: the paper did not specify the context of the white cells, for example 100 white cells per mm^3) (Used as definition of meningitis, or positive Gram stain, or grew bacteria in culture)	• *S. pneumoniae* (n=238) • *H. influenzae* (n=170) • No growth on culture (n=78) • *N. meningititis* (n=67) • *Salmonella spp* (n=29) • Other (n=16)	Received a broad spectrum of antibiotics up to 24 hours before admission.	Bacterial meningitis based on CSF at admission, positive Gram stain or bacterial culture. Children were initially enrolled on the basis of a clinical diagnosis – when the history and physical findings were suggestive of meningitis and a lumbar puncture showed hazy or cloudy cerebrospinal fluid. If the cerebrospinal report was incompatible with a diagnosis of bacterial meningitis, the child was removed from the study.
Odio (1991)	n=101	6 weeks – 13 years	59 male 42 female	Details used to establish inclusion,	• *H. influenzae* type b (n=79) • *Streptococcus pneumoniae*	• Congenital or acquired abnormality of central	Culture proved bacterial meningitis or evidence of

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
				but thresholds not specified.	(n=8) • Unknown (n=8) • *Neisseria meningitidis* (n=2) • *Escherichia coli* (n=2) • Group B streptococcus (n=1) • Salmonella group D (n=1)	nervous system, prosthetic device in central nervous system, previous episodes of bacterial meningitis, underlying neurological abnormality. • History of hypersensitivity to beta-lactam antibiotics, previous parental antibiotic therapy, aseptic meningitis.	severe meningeal inflammation and findings characteristic of bacterial infection in CSF. Patients with aseptic meningitis were excluded. Eight patients had an unknown causal agent.
Qazi (1996)	N=89	2 months – 12 years	54 male 35 female	Leucocytes >1000 x 10^6cells/litre (predominantly polymorphonuclear) Protein >1 g/litre Glucose <1.66 millimole/litre (or 50% of serum glucose) (At least two of these for inclusion, or bacteria on Gram stain, or positive CSF latex agglutination test)	• No organism isolated (n=49) • *Haemophilus influenzae* (n=20) • *Neisseria meningitidis* (n=8) • *Streptococcus pneumoniae* (n=6) • *Salmonella spp* (n=2) • *Pseudomonas aeruginosa* (n=1) • *Streptococcus agalactiae* (n=1) • *Staphylococcus aureus* (n=1) • *Klebsiella pneumoniae* (n=1)	• Underlying renal disease, hepatic disease, prior central nervous system diseases. • Tuberculous meningitis or obvious viral infection or aseptic meningitis.	Presenting with bacterial meningitis. Children suspected of having meningitis had a lumbar puncture, set of blood cultures, and so on. Preliminary diagnosis of bacterial meningitis was based on criteria already outlined in threshold column. It is not clear whether children that did not meet the criteria for bacterial meningitis were excluded from the study. No organism was isolated in 49 of the participants included in the final analysis.
Schaad (1993)	n=115	3 months – 16 years	69 male 46 female	Reactive protein: normal is 0–20 mg/litre Other details used to establish inclusion, but thresholds not specified.	• *H. influenzae* (n=67) • *N. meningitidis* (n=28) • *S. pneumoniae* (n=11) • No isolate (n=9)	Not specified.	Suspected or confirmed bacterial meningitis. Diagnosis was based on CSF. It is not clear if patients who did not have a confirmed diagnosis from CSF were excluded or not. 67% of participants included

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
							in the final analysis had bacteraemia, although eight children were not tested (it is not reported why they were not tested).
Thomas (1999)	n=60	18-79 years	34 male 26 female	Details used to establish inclusion, but thresholds not specified. Inclusion criteria: fever over 38°C, cloudy CSF, or elevated white blood cell count with more than 50% polymorphonuclear cells	• *S. pneuomniae* (n=31) • *N. meningitidis* (n=18) • Unknown (n=8) • *Streptococcus bovis* (n=1) • *H. influenzae* (n=1) • *Listeria monocytogenes* (n=1)	• Received more than one dose of parental beta-lactam antibiotic or any other adequate treatment for more than 3 hours. • Septic shock, acute post surgical or post traumatic meningitis, brain abscess. • History of hypersensitivity to betalactam antibiotics or to corticosteroids or organ transplantation.	Clinical signs of presumed primary bacterial meningitis (see threshold column for inclusion criteria). It is not clear whether diagnoses were later confirmed, although the causal agents were reported in most cases (see causal agent column). 10% of one group and 16% of the other group had unknown causal agents.
Wald (1995)	n=143	8 weeks – 12 years	79 male 64 female	White blood cell count at least 10 cells/microlitre with a predominance of polymorphonuclear leukocytes (Inclusion criteria, or any white blood cell count and a Gram stain or latex particle agglutination test positive for a potential bacteria pathogen)	• *H. influenzae* type b (n=83) • *S. pneumoniae* (n=33) • *N. meningitis* (n=24) • *Aseptic meningitis* (n=15) • *Streptococcus pyogenes* (n=1) • *H. influenzae* type a (n=1) • Nontypeable *H. influenzae* (n=1)	• Congenital or acquired abnormality of central nervous system (including prosthetic device), pre-existing hearing loss, congenital or acquired immunodeficiency or underlying renal or hepatic impairment. • Hypersensitivity to beta-lactam antimicrobials, administration of corticosteroids before enrolment, receipt of more than one dose of intravenous antibiotic before enrolment, or lack of receipt of study drug within 4 hours of first dose of intravenously	Suspected bacterial meningitis. Bacterial meningitis was suspected if CSF met criteria outlined in thresholds column. 72% of one group and 70% of the other group of children had bacteremia on admission.

Study	Number of participants	Age range	Male/ female	Threshold for CSF measures	Types of bacterial meningitis (numbers)	Exclusions	Characteristics of included participants
						administered antibiotic. • Those who received oral antimicrobial therapy in the 3 days before date of admission were permitted to enter the study but were excluded at 48 hours if CSF culture was sterile and antigen detection tests were negative, as the meningitis could not be classified as either bacterial or aseptic.	
de Gans (2002)	n=301	17 years and older (upper age range not specified)	169 male 132 female	Leukocyte count >1000/mm^3 (Used for inclusion, or cloudy CSF or bacteria on Gram's staining)	• *Streptococcus pneumoniae* (n=108) • *Neisseria meningitidis* (n=97) • Negative bacteria culture (n=65, including 2 where CSF culture not performed) • Other bacteria (n=29)	• Hypersensitivity to beta-lactam antibiotics or corticosteroids, pregnant, cerebrospinal shunt, or oral or parenteral antibiotics in previous 48 hours. • History of active tuberculosis or fungal infection, or recent history of head trauma, neurosurgery or peptic ulcer disease. • Enrolment on another trial.	Suspected meningitis in combination with any of the previously outlined criteria in threshold column. (It is not clear whether 'suspected meningitis' therefore refers to signs/symptoms) 23% of study group and 21% of control group had a negative bacterial culture.

Table 6.2. Data from studies conducted in high-income settings

Organisms	Details of meta-analysis	Number of RCTs[a]; number of children	RR[a]	95% CI	*P* value
Mortality					
All organisms	van de Beek et al, 2007[136]	11 RCTs, 1037 children	1.40	0.59 to 3.33	0.45
Severe hearing loss					
All organisms	van de Beek et al, 2007[136]	10 RCTs, 910 children	0.32	0.18 to 0.57	<0.0001[b]
Haemophilus influenzae type b	GDG meta-analysis of children only: data extracted from all patients van de Beek et al[136]	8 RCTs, 493 children	0.29	0.14 to 0.61	0.001[b] (Forest plot: figure H.9)[c]
Bacteria other than *Haemophilus influenzae* type b	GDG analysis using data from Kanra et al [140] and van de Beek et al, 2007[136]	9 RCTs, 333 children	0.48	0.22 to 1.05	0.07 (Forest plot: figure H.10)[c]
Streptococcus pneumoniae	GDG analysis using data from McIntyre et al, 1997[137]	9 RCTs, 147 children	0.90	0.45 to 1.77	0.75 (Forest plot: figure H.11)[c]
Short-term neurological sequelae					
All organisms	van de Beek et al, 2007[136]	5 RCTs, 354 children	0.76	0.45 to 1.27	0.29
Long-term neurological sequelae					
All organisms	GDG meta-analysis of children only: data extracted from all patients van de Beek et al, 2007[136]	8 RCTs, 707 children	0.62	0.39 to 0.98	0.04[b] (Forest plot: figure H.12)[c]
Adverse effects					
All organisms	GDG analysis of children only: data extracted from all patients van de Beek et al, 2007[136]	10 RCTs, 919 children	1.00	0.67 to 1.48	0.98 (Forest plot: figure H18)[c]

[a] RCT: randomised controlled trial; RR: relative risk
[b] Significant *P* value
[c] See Appendix H

Table 6.3. Data from studies conducted in low-income settings

Organisms	Details of meta-analysis	Population	RR	95% CI	*P* value
Mortality					
All organisms	van de Beek et al[136]	4 RCTs, 1037 children	0.96	0.78 to 1.18	0.69
Severe hearing loss					
All organisms	Data from van de Beek[136] and Qazi et al[143]	3 RCTs, 473 children	1.03	0.66 to 1.62	0.88
Short term neurological sequelae					
All organisms	van de Beek et al[136]	2 RCTs, 482 children	1.08	0.82 to 1.44	0.60

GDG interpretation of the evidence

After considering the results of studies of the use of adjunctive corticosteroids in meningitis occurring in high- and low-income settings, the GDG concluded that substantial differences in the populations precluded combining the data to inform best practice in the UK. Therefore to inform its recommendations, the GDG focused on results from studies conducted in high-income settings.

In children with bacterial meningitis from high-income settings, there is no evidence from meta-analyses that corticosteroids reduce mortality or short-term neurological sequelae. There is evidence that adjunctive corticosteroids reduce the risk of severe hearing loss and long-term neurological sequelae following bacterial meningitis. Cases of Hib meningitis predominated in these meta-analyses and, in a subgroup analysis of children with Hib meningitis, benefit for severe hearing loss from adjunctive corticosteroids remained apparent. There is no evidence that corticosteroids reduce the risk of severe hearing loss in children specifically with pneumococcal meningitis, but the small sample size means that this subgroup analysis was underpowered to detect such an effect. A subgroup analysis of children with non-Hib meningitis (including cases caused by pneumococcus and meningococcus) revealed a trend to benefit for severe hearing loss with adjunctive corticosteroids. There was no evidence of an increased risk of harmful effects in children with bacterial meningitis given corticosteroids in the steroid trials.

Data from analysis of meningitis cases in adults, in whom Hib infection is rare, supports the conclusion that adjunctive corticosteroids confer benefit. The 2007 systematic review[136] found that adjunctive corticosteroids reduced overall mortality in adults receiving corticosteroids compared with controls regardless of bacterial aetiology, as well as in cases specifically of pneumococcal meningitis (data extracted from all patient analysis).[136] The risk of short-term neurological sequelae in adults was also reduced with adjunctive corticosteroids.[136]

The GDG recognised that the benefit of steroids in Hib meningitis in children is widely accepted and that, since the pathology in other types of bacterial meningitis is similar, these benefits are likely to extrapolate to pneumococcal and meningococcal cases. The GDG then considered whether it was possible to identify those children with bacterial meningitis for whom steroids could be recommended.

The steroid trials had different entry criteria and are difficult to translate directly to current clinical practice. A particular problem is the reporting of the data only in the cases of proven bacterial meningitis in some of the studies and the absence of reporting of detailed entry criteria in others. Some of the studies that have examined the potential benefits of corticosteroids in meningitis used a substantially raised CSF white cell count (more than 1000/microlitre) or positive Gram stain as an entry criterion. The average CSF white cell count reported in studies of steroids in bacterial meningitis (including those that do not report the WBC count as an entry criterion) is greater than 1000/microlitre, and often substantially greater. The GDG was of the view that the available evidence is limited to the groups of children who met entry criteria for these studies or were actually included in the studies. Studies that have used CSF white cell count (see section 5.5) to predict bacterial meningitis consistently found that the majority of cases were aseptic with higher specificity reported with a CSF white cell count cutoff more than 1000/microlitre. Similarly, a CSF protein concentration more than 1 g/litre had a high specificity for bacterial meningitis. Therefore, broader use of steroids for all children with pleocytic CSF carries the risk of exposing a large group of children to steroids for whom there is no evidence of benefit.

Furthermore, the reduction in bacterial meningitis as a result of immunisation means that the aetiology of most cases of meningitis will be viral. Indeed, with the introduction of effective vaccines to prevent bacterial meningitis caused by Hib, serogroup C meningococcus and some serotypes of pneumococcus, the epidemiology of meningitis in children in England and Wales has changed substantially and continues to do so. The marked decline in cases of Hib meningitis in particular has meant that the benefit of adjunctive corticosteroids is far less certain, but the GDG concluded that the trend to benefit in non-Hib cases should still support their use in those who have strong evidence of bacterial meningitis. However, there

are no studies that provide data to allow distinction between bacterial and aseptic meningitis in a highly vaccinated population and to determine or justify 'strong evidence'. Indeed, there were very few cases of aseptic meningitis included in any of the steroids trials.

One study in the USA[144] found very low rates of bacterial meningitis (3.7%) in a cohort of over 3000 children with a pleocytic CSF. Only 15% of those with a WBC count over 500 had bacterial meningitis and 28% among those with CSF WBC count over 1000 (Lise Nigrovic, personal communication). This study excluded those who had been pre-treated with antibiotics (544 cases) and those who were considered critically ill (but well enough to have a lumbar puncture; 218 cases), and the proportions with bacterial meningitis may have been higher. However, there were still relatively few cases of bacterial meningitis among those who were excluded with little impact on overall disease rates (Lise Nigrovic, personal communication) and the conclusion stands that most children with pleocytic CSF have aseptic meningitis. Children with aseptic meningitis were not included as a specific study group in any of the steroid trials and there are no effectiveness or adequate safety data for steroid use in aseptic meningitis.

Therefore, the importance of establishing a microbiological diagnosis in cases of meningitis is emphasised to minimise the administration of corticosteroids to children with aseptic meningitis (in whom there is a lack of evidence about the benefit or harm of corticosteroids) or cases of tuberculous meningitis (where giving corticosteroids in the absence of anti-tuberculosis treatment may cause harm). Accordingly, the recommendation for corticosteroid therapy is closely tied to a recommendation for lumbar puncture in all cases of suspected meningitis where this procedure can be undertaken safely.

There is a lack of data from RCTs to support decisively the contention that the timing of steroid administration is critical to its beneficial effect. A meta-analysis of studies of children from high-income settings showed a reduction in severe hearing loss whether steroids were given early (before or with the first dose of antibiotic) or up to 12 hours later (the latest time in most studies). For long-term neurological sequelae, the benefit seen for steroids given before or with the first dose of antibiotic is no longer evident when steroids are administered after the first dose. Accordingly, the GDG recommends administration of adjunctive corticosteroid before or with the first dose of antibiotic. In exceptional cases where this has not been achieved, administration of steroids should not be considered beyond 12 hours.

The GDG concluded that steroids should be used where there is strong evidence of bacterial meningitis to reduce the risk of hearing loss, but should not be used where the evidence is weak. The GDG was also of the view that those given steroids should match the population included in the steroid trials as closely as possible. Use of steroids when the CSF WBC count was more than 1000 cells/microlitre would target at least 50% of cases of bacterial meningitis and was considered a logical step given the benefits documented in such cases in the steroid trials. An additional number could reasonably be included by use of steroids where the Gram stain was positive confirming the diagnosis of bacterial meningitis or the CSF protein was more than 1 g/litre. The GDG did not support the use of steroids for other groups of children who had not been adequately studied in trials and for whom there was a very high (90%) chance of aseptic meningitis. The GDG considered use of other variables (for example C-reactive protein, other CSF parameters) to inform the decision to treat but noted that none of these were consistently used specifically to identify the populations who had been studied in the steroid trials.

The dosage recommended by the GDG (0.15 mg/kg up to a maximum dose of 10 mg four times daily for 4 days,) corresponds to the dosage of 0.6 mg/kg/day used in eight of the 13 studies included in the first systematic review[136] that reported results for children and young people under 16 years. The dosage recommended by the GDG has also been used in UK clinical practice for several years.

The GDG was concerned that TB meningitis might be overlooked and that there was a risk in giving steroids without anti-tuberculous therapy. The GDG considered that 'Tuberculosis', NICE clinical guideline 33,[11] should be followed if TB was on the differential diagnosis.

Corticosteroids for meningitis in infants younger than 3 months

There are no high-quality studies of children aged under 3 months to support the use of adjunctive corticosteroids for bacterial meningitis in this age group. As the bacteria commonly responsible for meningitis in these patients differ from those found in older children, the GDG does not recommend the use of steroids in the treatment of bacterial meningitis in infants younger than 3 months.

Recommendations

Corticosteroids

Bacterial meningitis

Do not use corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis.

Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[*] for suspected or confirmed bacterial meningitis as soon as possible if lumbar puncture reveals any of the following:

- frankly purulent CSF
- CSF white blood cell count greater than 1000/microlitre
- raised CSF white blood cell count with protein concentration greater than 1 g/litre
- bacteria on Gram stain.

If tuberculous meningitis is in the differential diagnosis, refer to 'Tuberculosis' (NICE clinical guideline 33) before administering steroids, because steroids may be harmful if given without antituberculous therapy.

If dexamethasone was not given before or with the first dose of antibiotics, but was indicated, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics.

After the first dose of dexamethasone discuss the decision to continue dexamethasone with a senior paediatrician.

Research recommendations

Corticosteroids

Bacterial meningitis

What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis?

Why this is important

Neonatal bacterial meningitis is associated with high morbidity, despite the availability of antibiotics that are highly effective against the leading causes of bacterial meningitis in this age group. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms. Corticosteroids are effective as an adjunct to antibiotic treatment in older children with meningitis caused by Hib, and in adults with bacterial meningitis. However, there is insufficient evidence to support a recommendation for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the spectrum of organisms causing infection in neonates is different, and the impact on the developing

[*] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice. The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Dexamethasone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

brain of the causative organisms during inflammation may not be the same. A large-scale randomised controlled trial is therefore needed to compare the effectiveness of antibiotic treatment plus corticosteroids with antibiotic treatment alone in neonates with suspected or confirmed bacterial meningitis.

6.8 Corticosteroids for meningococcal septicaemia

Introduction

Severe sepsis is associated with marked hormonal and metabolic responses including the increased release of adrenocorticotropic hormone (ACTH) from the pituitary gland, which functions to stimulate the production of corticosteroids (glucocorticoids and mineralocorticoids) by the adrenal glands. The physiological role of the stress response is to maintain normal tone of blood vessels, increase cardiac output and blood pressure, and modulate the inflammatory response. Glucocorticoids inhibit the production of various proinflammatory cytokines, prostaglandins and other proinflammatory mediators, while stimulating the production of anti-inflammatory cytokines.

The anti-inflammatory and cardiovascular stabilising properties of corticosteroids provided a rationale for their use in people with sepsis and septic shock. However, after several large clinical trials indicated that high dose corticosteroids showed either no benefit or the potential to cause excess mortality in people with septic shock, the routine use of corticosteroids as adjunctive therapy for septic shock was abandoned.

Recently, the debate about the use of corticosteroids in sepsis has been revived by results of studies examining the relationship between adrenal function and sepsis. It has been shown that many adults with septic shock have adrenal dysfunction, and that transient adrenal insufficiency, which is found in 50–80% of people with sepsis, may be associated with an adverse outcome.[145] In children with meningococcal disease, low serum cortisol levels, together with high ACTH levels, have been associated with higher mortality.[146]

These biological insights and the results of recent trials in adults have led to recommendations from the Surviving Sepsis Campaign[131] that low dose corticosteroids should be considered for adults with septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors.

Clinical question

Should corticosteroids be used in the treatment of children and young people with suspected or confirmed meningococcal septicaemia?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal Disease in Children and Young People' recommends that corticosteroids should not be given to children with meningococcal septicaemia. The guideline notes that a trial of hydrocortisone should be considered in the small subgroup of children with meningococcal septic shock and signs of absolute adrenal insufficiency (inotrope-resistant shock, hypoglycaemia and hyponatraemia).

Studies considered in this section

RCTs and systematic reviews of RCTs evaluating the effects of corticosteroids in children and young people with suspected or confirmed meningococcal septicaemia were considered for this section. Because of a lack of evidence, all study designs of children and young people with sepsis, septicaemia or septic shock were included. RCTs and systematic reviews of RCTs involving adults with sepsis, septicaemia or septic shock were also considered for extrapolation.

Overview of available evidence

No studies were found assessing corticosteroid use in children and young people with meningococcal septicaemia. Five studies examined the effects of corticosteroids in people

with sepsis or septic shock: one RCT [EL=1+] involved children only, one systematic review involved mostly adults [EL=1++] and two RCTs [EL=1++] and one meta-analysis [EL=1+] recruited adults only. Two RCTs in adults with septic shock [EL=1++] examined whether the outcome of treatment with corticosteroids was dependent on adrenal function.

Review findings

One RCT[147] [EL=1+] assessed the effects of dexamethasone on sepsis in 72 African children aged 1 month to 16 years. Children admitted with sepsis syndrome or septic shock caused by Gram-negative and Gram-positive organisms were randomised to receive intravenous dexamethasone (0.6 mg/kg/day) or placebo for 48 hours. Dexamethasone was administered 5 to 10 minutes before the first dose of antibiotic. The RCT found no significant difference between dexamethasone and placebo in survival to discharge (83% with dexamethasone versus 89% with placebo, $P = 0.73$). There was no significant difference in the proportion of children with shock reversal at 48 hours after treatment ($P = 0.29$). About half of the children in the study were malnourished and most presented to hospital late in the course of illness.

One systematic review and meta-analysis[148] (search date 2003) [EL=1++] evaluated the effect of systemic corticosteroids on mortality in people of all ages with severe sepsis and septic shock. The review included 16 trials (RCTs and quasi RCTs) involving 2063 people, of whom 207 (10%) were children. One RCT involved children only and is also reported separately above.[147] Another study enrolled adults and children but reported adult data only. Systemic corticosteroids included hydrocortisone, methylprednisolone, betamethasone or dexamethasone. Overall, the review found no significant difference in 28-day, all-cause mortality between corticosteroids and controls (15 RCTs, 2022 people, mortality: 34% with corticosteroids versus 33% with controls; RR 0.92, 95% CI 0.75 to 1.14, $P = 0.46$). Significant heterogeneity in the results prompted the authors to perform a subgroup analysis of different dosage regimens of systemic corticosteroids (long course: at least 5 days of low-dose [300 mg/day or less] hydrocortisone or equivalent; and short course: less than 5 days treatment with more than 300 mg hydrocortisone).

The review found no benefit for mortality in people given short course, high-dose corticosteroids (eight RCTs, 1115 people; mortality: 32% with corticosteroids versus 30% with controls; RR 0.97, 95% CI 0.72 to 1.31, $P = 0.84$). Meta-analysis of five RCTs involving 465 adults, most of whom had vasopressor-dependant septic shock, found that long course, low-dose corticosteroids significantly reduced 28-day mortality compared with controls (mortality: 45% with corticosteroids versus 56% with controls; RR 0.80, 95% CI 0.67 to 0.95, $P = 0.01$). The review found that corticosteroid therapy was not associated with a significantly increased risk of adverse effects compared with controls (gastroduodenal bleeding: RR 1.16, 95% CI 0.82 to 1.65, $P = 0.40$; superinfection: RR 0.93, 95% CI 0.73 to 1.18, $P = 0.54$).

Two RCTs[149;150] [EL=1++] published subsequent to the systematic review[148] also assessed the effects of long course, low-dose hydrocortisone (200 to 300 mg/day) in adults with vasopressor-dependent septic shock. One large multicentre RCT (CORTICUS trial)[149] involving 499 adults with septic shock of less than 72 hours duration found no significant difference in 28-day mortality between corticosteroids and placebo in all patients (overall mortality: 34% with hydrocortisone versus 32% with placebo; RR 1.09, 95% CI 0.84 to 1.41, $P = 0.51$). The RCT found that hydrocortisone administration was associated with an increased risk of new episodes of sepsis or septic shock compared with placebo (OR 1.37, 95% CI 1.05 to 1.79). The other RCT[150] found that in 41 adults with early hyperdynamic septic shock (cardiac index 3.5 litre/min/m^2 or more and onset of shock within 24 hours of recruitment), intravenous low-dose hydrocortisone significantly shortened the time to shock reversal compared with placebo (median time: 53 hours with corticosteroids versus 120 hours with placebo, $P < 0.02$). The study found no significant difference in 28-day mortality between corticosteroids and placebo (39% with hydrocortisone versus 48% with placebo, $P = 0.6$), but was not powered to investigate this outcome.

One meta-analysis[151] [EL=1+] conducted in 1995 aimed to evaluate clinical evidence and treatment effects of steroids in sepsis and septic shock. Ten RCTs with a total of 1329 patients with sepsis or septic shock were included, with the number of patients from any trial ranging from 31 to 382. The mean age range was 50 to 65 years, and the proportion of men ranged

from 55% to 97%. Each study compared steroids to no steroids, with positive effects and adverse events as outcomes. The global pooled effect was −0.2% (CI −9.2 to 8.8) in favour of corticosteroids. Only one of the ten studies (172 patients) had a significant result in favour of corticosteroids, and when this was removed, an effect of 4.8% in favour of controls was found.

The pooled effect for mortality rates was −1.7% (six studies, 696 participants; CI −11.0 to 7.6), for gastrointestinal bleeding was 2.3% (five studies, 696 patients; CI −0.7 to 5.4), for secondary infection was 0.4% (seven studies, 1066 patients; CI −4.4 to 5.2) and for hypoglycaemia was 0.2% (four studies, 529 participants; CI −4.0 to 4.4). Studies that used a dose of less than 20 g hydrocortisone during the first 24 hours (five studies, 530 patients) had a pooled effect of −1.9% (CI −20.0 to 16.2) whereas studies with a higher dose (five5 studies, 799 patients) had a pooled effect of 3.6% (CI −2.5 to 9.8).

Corticosteroid therapy and adrenal function

One RCT[152] [EL=1++] identified by the 2004 systematic review[148;153] found that in adults with septic shock and relative adrenal insufficiency (defined by poor response to a corticotropin test), a short course of intravenous low-dose hydrocortisone plus oral fludrocortisone significantly reduced 28-day mortality compared with placebo (mortality: 53% with corticosteroids versus 63% with placebo; adjusted OR 0.54, 95% CI 0.31 to 0.97, $P = 0.04$). There was no significant difference in mortality between corticosteroids and placebo in all patients (mortality: 55% with corticosteroids versus 61% with placebo; adjusted OR 0.65, 95% CI 0.39 to 1.07, $P = 0.09$) or in people with a normal response to corticotropin (mortality: 61% with corticosteroids versus 53% with placebo; adjusted OR 0.97, 95% CI 0.32 to 2.99, $P = 0.96$).

The CORTICUS trial[149] found that the effects of corticosteroids in adults with septic shock were not dependent on adrenal function (mortality in non-responders to corticotropin: 39% with corticosteroids versus 36% with placebo; RR 1.09, 95% CI 0.77 to 1.52, $P = 0.69$; mortality in responders to corticotropin: 29% with corticosteroids versus 29% with placebo; RR 1.00, 95% CI 0.68 to 1.49, $P = 1.00$).

Evidence statement

There is no available evidence on the effects of corticosteroids in children and young people with meningococcal septicaemia.

There is insufficient high-quality evidence to reach a conclusion about the effects of corticosteroids in children and young people with sepsis or septic shock.

Evidence from a large meta-analysis of 15 studies involving mainly adults indicates that corticosteroids do not reduce mortality in people with severe sepsis and septic shock. The definition of septic shock, the duration and severity of shock, and the corticosteroid regimens differed among the studies.

When vasopressor-dependent septic shock in adults is considered, evidence from eight RCTs showed that high-dose corticosteroids were not beneficial in reducing mortality compared with controls, whereas a meta-analysis of five RCTs showed that low-dose corticosteroids significantly reduced 28-day mortality compared with controls. Subsequent evidence from two RCTs found no significant difference in 28-day mortality between long course, low-dose corticosteroids and placebo, with one RCT reporting an increased risk of new episodes of sepsis with corticosteroids compared with placebo.

Two RCTs that assessed whether the effects of corticosteroids were altered by differences in adrenal function in adults with septic shock found conflicting results.

GDG interpretation of the evidence

In view of the lack of evidence about the effects of corticosteroids in children and young people with septicaemia, results from studies in adults were considered. These studies showed that high-dose corticosteroids were not beneficial in the management of severe sepsis and septic shock and that high (treatment) doses could be unsafe.

Studies of low-dose corticosteroids in adults with septic shock showed conflicting results.

The GDG recognised that there is a subgroup of children with meningococcal septicaemia who have vasopressor-unresponsive shock and who may have adrenal insufficiency. Use of corticosteroids in this population has not been studied. However, the GDG considered that this subgroup of children may benefit from replacement doses of corticosteroids. The GDG's view was that low (physiological) doses would be safe in this group. The dosage recommended by the GDG was based on adult studies,[148] which demonstrated the effectiveness of doses of 200 mg to 300 mg daily, corresponding to a dosage of 0.25 mg/m^2 (with body surface area as the denominator) four times daily. This dosage is also recommended in the British National Formulary for Children (BNFc).[154]

Recommendations

Meningococcal septicaemia

Do not treat with high-dose corticosteroids (defined as dexamethasone 0.6 mg/kg/day or an equivalent dose of other corticosteroids).

In children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 0.25 mg/m^2 four times daily)* should be used only when directed by a paediatric intensivist.

Research recommendations

Meningococcal septicaemia

How effective is steroid replacement treatment in children and young people with vasopressor-unresponsive shock caused by septicaemia, including meningococcal septicaemia?

Why this is important

Well-conducted but relatively small randomised controlled trials involving adults only suggest that low-dose corticosteroid replacement treatment may ameliorate haemodynamic failure and inflammatory dysregulation associated with severe sepsis. Such treatment may also improve outcomes following septic shock. Severe sepsis in children and young people differs from that in adults, in that multiple-organ dysfunction is less common in children and young people, and mortality is lower. A randomised controlled trial involving children and young people is needed to evaluate the effectiveness of corticosteroid replacement treatment. Studies involving adults only suggest that those with normal adrenal function have worse outcomes if they receive steroids than those with adrenal dysfunction, and so the proposed trial should consider whether testing for adrenal dysfunction before starting steroid replacement treatment improves outcomes.

6.9 Adjunctive therapies

Introduction

Despite effective immunisation against serogroup C meningococcus, meningococcal septicaemia and meningitis remain important causes of morbidity and mortality in children and young adults. Early recognition of disease, antibiotics, prompt treatment of shock and raised intracranial pressure and supportive intensive care are the mainstays of treatment for

* The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice. The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Hydrocortisone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

meningococcal septicaemia. However, because of the continued high mortality associated with this disease, attempts to improve outcome have focused on the development of adjunctive treatments that may modulate the inflammatory process.[155-157]

Improvements in understanding of the pathophysiology of sepsis have allowed the development of new therapies that aim to interrupt or limit the detrimental physiological changes that accompany severe sepsis and septic shock. In meningococcal septicaemia, most of these derangements are triggered by the presence of endotoxin in the bloodstream. In addition, endotoxin-mediated inflammation leads to severe endothelial cell dysfunction and abnormal clotting.

Activated protein C

The sole adjunctive therapy for severe sepsis with high quality evidence to support a survival advantage is activated protein C (aPC). This is a natural anticoagulant that inactivates clotting factors Va and VIIIa. aPC is generated by interaction of a thrombin–protein C complex with thrombomodulin and the protein C receptor on the surface of the endothelial cell, and its function is dependent on circulating protein S. In sepsis, including meningococcal septicaemia, protein S and protein C levels are reduced, thrombomodulin expression is downregulated on endothelial cells, and endothelial protein C receptor expression is reduced. The net effect is deficiency of aPC.

The efficacy and safety of recombinant human aPC in adults with severe sepsis have been shown in a large multi-centre, placebo-controlled trial in which aPC was associated with a reduction in mortality from 30.8% in the placebo group to 24.7% in the intervention group.[157]

However, the incidence of serious bleeding was higher in people treated with aPC. A subsequent study in adults at lower risk of death showed no benefit and a higher risk of severe bleeding in those treated with aPC compared with placebo.[155]

Bactericidal permeability-increasing protein

Endotoxin is one of the most important bacterial components that contribute to the inflammatory process in meningococcal septicaemia. Levels of circulating endotoxin directly correlate with the severity of meningococcal disease, and with elaboration and release of inflammatory mediators. Circulating endotoxin is bound and neutralised by neutrophil granule proteins, including the bactericidal permeability-increasing protein (BPI). A recombinant form of BPI consisting of 21 amino acids of the N-terminal fragment of naturally occurring BPI (rBPI21) has been shown to function synergistically with antimicrobials in the killing of many bacteria, and to bind and neutralise endotoxin. This recombinant protein has been the subject of studies in children with severe meningococcal septicaemia.[156;158]

Clinical question

What is the effect of experimental therapies in children and young people with suspected or confirmed meningococcal septicaemia?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal Disease in Children and Young People' recommends that activated protein C should not be used for the treatment of children with meningococcal sepsis.[27]

Studies considered in this section

RCTs evaluating the effects of activated protein C and bactericidal permeability-increasing protein in children and young people with suspected or confirmed meningococcal septicaemia were considered for this section. Where evidence in children with meningococcal septicaemia was lacking, RCTs of children and young people with septicaemia were reviewed. Studies involving adults were not considered for review.

Overview of available evidence

One RCT of activated protein C involving children with severe sepsis [EL=1+], and one RCT of bactericidal permeability-increasing protein involving children with meningococcal septicaemia [EL=1+] were reviewed.

Review findings

Activated protein C

One phase III multicentre and multinational RCT[159] [EL=1+] evaluated the safety and efficacy of recombinant activated protein C (aPC) in 477 children and young people aged between 38 weeks' corrected age and 17 years with severe sepsis. In total, 11% of children had meningococcal septicaemia. Patients were randomised to receive aPC (intravenous infusion of 24 micrograms/kg/hour) for 96 hours or placebo. Because of the lower mortality rate of sepsis in children, the study was not powered to show a benefit in mortality but measured time to complete organ failure resolution as a primary endpoint and surrogate for mortality.

The RCT found no significant difference between placebo and aPC in the time taken for resolution of organ failure (P = 0.72). It found no significant difference between placebo and aPC in mortality at 28 days (17.2% with aPC versus 17.5% with placebo; RR 1.06, 95% CI 0.66 to 1.46, P = 0.93). A post-hoc subgroup analysis found a trend towards reduced mortality in children with disseminated intravascular coagulopathy (14% with aPC versus 22% with placebo, P = 0.05). An analysis of study–drug related adverse events found a significantly increased risk of serious study–drug related bleeding events in children given aPC compared with placebo over 28 days (P = 0.04). More children given aPC had central nervous system (CNS) bleeding events over both follow-up periods. Overall, there was no significant difference between the groups in serious bleeding events during the 6-day drug-infusion period (P = 0.83) or over the 28-day study period (P = 0.97). It was unclear how study–drug related bleeding events were distinguished from other serious bleeding events. A subgroup analysis found that children younger than 60 days had a significantly increased risk of serious adverse events (P = 0.03). The trial was suspended for futility at the second planned interim analysis.

Bactericidal permeability-increasing protein

One double-blind phase III RCT conducted in the UK and the United States[158] [EL=1+] assessed the effects of recombinant bactericidal permeability-increasing protein (rBPI) in 393 children and young people with severe systemic meningococcal disease. Patients aged from 12 weeks to 18 years were randomised to receive rBPI21 (2 mg/kg over 30 minutes followed by 2 mg/kg over 24 hours) or placebo (human albumin solution). The study found no significant difference between placebo and rBPI21 in mortality at 60 days (OR 1.31, 95% CI 0.62 to 2.74, P = 0.48). As 18% of children died before completing the rBPI21 infusion, an analysis of children who survived to complete rBPI21 infusion was performed. The RCT found a lower mortality in the rBPI21 treated group (2%) compared with the placebo group (6%) but the difference was not statistically significant (P = 0.07). Fewer children given rBPI21 had multiple severe amputations compared with placebo. This difference did not reach statistical significance (OR 2.47, 95% CI 0.94 to 6.51, P = 0.067). The RCT found that rBPI21 significantly increased the proportion of children with a functional outcome at 60 days similar to that before illness (OR 1.75, 95% CI 1.08 to 2.82, P = 0.019). Because the trial was underpowered to detect significant differences in the primary endpoint of mortality at 60 days, a composite endpoint that included data on morbidity was introduced. However, the authors acknowledged that the composite endpoint was methodologically flawed and these data are not included in the guideline appraisal.

Evidence statement

Activated protein C

No RCTs have been conducted assessing the effects of activated protein C in children with meningococcal septicaemia. There is insufficient evidence to assess the efficacy of activated

protein C in children and young people with severe sepsis, and the limited available evidence raises concerns about safety, particularly in infants younger than 60 days.

Bactericidal permeability-increasing protein

There is insufficient evidence to assess the effects of recombinant bactericidal permeability-increasing protein in children and young people with meningococcal septicaemia.

GDG interpretation of the evidence

The lack of a beneficial effect noted in the single study of activated protein C in children and the concerns raised over risk of bleeding in young infants indicate that activated protein C should not be used in meningococcal septicaemia.

There is insufficient evidence to recommend the use of recombinant bactericidal permeability-increasing protein in children and young people with meningococcal septicaemia and the GDG considered that further investigation of this therapy is required.

Recommendations

Adjunctive therapies

Do not use activated protein C or recombinant bacterial permeability-increasing protein in children and young people with meningococcal septicaemia.

Research recommendations

Adjunctive therapies

Does early intervention with anti-endotoxin treatments such as recombinant bactericidal permeability-increasing protein improve outcomes in children and young people with severe meningococcal septicaemia?

Why this is important

Disease progression in meningococcal septicaemia is rapid and so anti-endotoxin treatment is likely to be effective only if it is given early in the course of disease. A multi-centre randomised controlled trial involving children and young people with severe sepsis reported that the mean time of delivery of recombinant bactericidal permeability-increasing protein rBPI21 was 5.9 hours after receiving initial antibiotic treatment. The results of the trial suggest that rBPI21 might be more effective if given earlier in the course of the disease, such as when meningococcal septicaemia is first diagnosed and treated in the emergency department, or within 2 hours of giving intravenous antibiotics. A further randomised controlled trial is needed to evaluate the effectiveness of such practice in children and young people with severe meningococcal septicaemia.

6.10 Monitoring for deterioration for meningococcal disease

Introduction

Many scoring systems have been developed specifically for assessment of children with meningococcal disease, although not all scores have been scientifically derived or validated. The severity scoring systems are based on a number of clinical features and investigation results, which together generate a score; the higher the score, the higher the risk of mortality (or morbidity) in children. These scoring systems are generally used after a diagnosis of meningococcal disease has been made or strongly suspected to identify children at high risk and select them for further treatment or higher level care (such as paediatric intensive care). Scores that are based on clinical features of meningococcal disease can be generated early in

the course of the disease and can theoretically influence clinical management. Severity scores that incorporate results of laboratory investigations have the advantage of using more specific indicators of inflammation, but the time delay in obtaining results from the laboratory makes them less useful in a rapidly evolving clinical scenario.

The PN product (the product of platelet and neutrophil counts) can discriminate between survivors and non-survivors of meningococcal disease, but needs further validation.[160] It is not a recognised severity scoring system and therefore was not considered in this review.

Other scoring systems used for general clinical management of ill children or the identification of children who may have meningococcal disease or meningitis are not included in this review.

Clinical question

In children and young people with suspected or confirmed meningococcal disease, does the use of severity scoring systems affect outcomes or management?

Previous UK guidelines

The SIGN guideline on 'Management of Invasive Meningococcal disease in Children and Young People' recommends that children with invasive meningococcal disease should have sequential documentation of the Glasgow meningococcal septicaemia prognostic score (GMSPS) and that any deterioration should be discussed with intensive care.[27]

Studies considered in this section

All study designs evaluating the role of severity scoring systems in children and young people with suspected or confirmed meningococcal disease were considered for this section. Studies of adults only were excluded. Studies describing the initial development of a score, retrospective studies in which investigator blinding to outcome was not reported and studies that included less than 40 participants were excluded from the review. Studies conducted solely in tertiary care were excluded from the review.

Overview of available evidence

No studies were found that addressed whether using severity scoring systems altered the management or the outcome of children and young people with meningococcal disease.

Two cohort studies [EL=II and EL=III] were identified evaluating the accuracy of different scoring systems in predicting mortality in secondary care.

Review findings

One prospective cohort study[161] [EL=II] compared the performance characteristics of the GMSPS with nine other severity scores (Stokland, Stiehm and Damrosch, Ansari, Niklasson, Leclerc, Kahn and Blum, Lewis, Istanbul and Bjark) and with laboratory markers of severe disease. The study involved 278 children younger than 16 years admitted to six hospitals in the UK with confirmed (73%) or suspected meningococcal disease (1988–1990 and 1992–1994). The GMSPS was recorded on admission and repeated if the child's condition deteriorated. If a GMSPS of 8 or more was recorded, transfer to paediatric intensive care unit (PICU) was suggested. These patients comprised approximately 30% of the total with meningococcal disease. Overall mortality in the study was 9.4%.

The study found that a GMSPS of 8 or more had a sensitivity of 100%, a specificity of 75%, a positive likelihood ratio of 4.2 and a positive predictive value for mortality of 29%. The GMSPS correlated significantly with laboratory markers of severity, including endotoxin and cytokine levels ($P < 0.0001$). Of the nine other severity scores, the Lewis, Istanbul and Ansari scores had sensitivities of 100%, with positive likelihood ratios ranging from 2.4 to 6.7 (see table 6.4). The GMSPS was noted to be the only score that could be derived using clinical criteria alone.

Table 6.4. Performance characteristics of scores predicting mortality in secondary care[161]

Score threshold	Lewis ≥2	Istanbul ≥5	GMSPS ≥8	Ansari ≥3
AUC	0.95	0.95	0.96	0.93
Se (%)	100	100	100	100
Sp (%)	85	83	76	58
PPV (%)	39	36	29	21
NPV (%)	100	100	100	100
+ve LR	6.7	5.9	4.2	2.4

AUC: area under the receiver-operating characteristic curve; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio

One combined prospective and retrospective study[162] [EL=III] compared the prognostic accuracy of eight meningococcal-specific scoring systems (GMSPS, MenOPP bedside clinical [MOC] score of Gedde Dahl, Stiehm, Niklasson, Leclerc, Garlund, Tesoro and Tüysüz scores). The study involved 125 children younger than 17 years admitted to a university hospital in the Netherlands with culture-proven meningococcal disease (1986–1994). Mortality was 21%.

The study found that the overall discriminative ability of the GMSPS was significantly better than eight scores (area under the ROC curve [AUC] for competitor scores ranged from 0.74 to 0.83; comparisons with GMSPS: $P < 0.01$ to $P = 0.03$). The ability of the GMSPS to discriminate between survivors and non-survivors was better than the MOC score but for this comparison the difference was not statistically significant (AUC 0.925 for GMSPS versus 0.87 for MOC score; $P = 0.19$; no CIs reported). When the base deficit was omitted from the GMSPS, the AUC remained high (AUC=0.92). The external validity of the study was limited by its restriction to one hospital site and by the exclusion of children with unproven meningococcal disease.

Evidence statement

No studies were found examining whether using severity scoring systems altered the management or the outcome of children and young people with meningococcal disease.

Two studies conducted in secondary care showed that several meningococcal-specific severity scores, including the GMSPS, had good performance characteristics for predicting death from meningococcal disease.

GDG interpretation of the evidence

There is no evidence to show that severity scoring systems alter the outcome of children and young people with meningococcal disease.

The GDG agreed that scoring systems (most often, and best, GMSPS) may be clinically useful for severity assessment in meningococcal disease as part of local management arrangements and in conjunction with discussion about transfer to tertiary PICU care.

Severity scoring systems can be used in secondary or tertiary care to stratify children with meningococcal disease for purposes of research. Children who have a higher risk of mortality can then be entered into trials of new management or treatment. In secondary care, the GMSPS can be used for this purpose

In severe meningococcal disease the priority is to manage airway, breathing and circulation, regardless of mortality or severity predictors from GMSPS or other scoring systems.

The GDG considers that there is insufficient evidence to recommend change of current clinical practice around use of severity scoring systems in meningococcal disease. The GDG

highlighted in their recommendations the importance of monitoring for deterioration in children and young people with meningococcal disease.

Recommendations

Monitoring for deterioration for meningococcal disease

Monitor children and young people closely after admission to hospital for signs of deterioration (monitor respiration, pulse, blood pressure, oxygen saturation and Glasgow Coma Scale score).

Be aware that children and young people with meningococcal disease can deteriorate rapidly, regardless of the results of any initial assessment of severity.

Research recommendations

Monitoring for deterioration for meningococcal disease

Are severity scoring systems useful for directing clinical management of suspected or confirmed meningococcal disease in children and young people?

Why this is important

Scoring systems are used widely in clinical research to classify the severity of suspected or confirmed meningococcal disease in children and young people. They are also used in clinical practice in some areas of the UK. Such systems can be applied relatively easily at presentation, and sequentially thereafter. If severity scoring systems can be used to identify changes in clinical condition that would direct clinical management to improve outcomes they could have widespread applicability in clinical practice. Studies are, therefore, needed to evaluate the usefulness of severity scoring systems for meningococcal disease in children and young people. The outcomes evaluated in the studies should include mortality and morbidity; they could also include satisfaction with care among children and young people, their parents or carers and other family members.

6.11 Retrieval and transfer to tertiary care

Introduction

The majority of children with suspected or confirmed meningococcal disease are initially treated at their local district general hospital. Due to the potential for clinical instability and the need for escalation in treatment, these children often require transfer to a regional paediatric intensive care unit (PICU) for ongoing management. Aggressive early treatment of meningococcal disease can reduce mortality; however, this relies on prompt recognition and treatment and appropriate ongoing intensive care management. Initial resuscitation and stabilisation will take place in the hospital where the child presents, but some children will require transfer to a regional PICU. These children require a secure airway, mechanical ventilation, central venous and arterial access for drug therapy and cardiovascular monitoring. Due to the potential instability of these children and the significant interventions required, specialist paediatric retrieval teams have been established in the UK over recent years[163;164] with the aim of optimising the outcome of critically ill children who require transfer to a regional PICU.

The GDG reviewed the evidence to provide guidance on the use of specialist paediatric transport teams to improve the outcome of children with meningococcal disease.

Clinical question

Do specialist transport teams improve outcomes and/or reduce adverse incidents during the transfer of children with meningococcal disease?

Previous UK guidelines

No previous guidelines were identified in relation to this question.

Studies considered in this section

All study designs evaluating specialist paediatric transport teams were considered for inclusion in this section.

Studies of children with meningococcal disease were included or studies of children with critical illness where the majority of the sample had meningococcal disease.

Overview of available evidence

Two studies were included in the review, both of which were conducted in the UK (London) and were descriptive studies [EL=3]. No comparative studies were identified which evaluated the outcomes of a specialist paediatric transfer team.

A prospective descriptive study[163] [EL=3] was conducted to evaluate morbidity and severity of illness during inter-hospital transfer of critically ill children by a specialised paediatric retrieval team. The study involved 51 critically ill children (24 [47%] with meningococcal disease) transferred to a paediatric unit. The retrieval team consisted of a paediatric intensivist (senior registrar or consultant) and an experienced intensive care nurse. Two children had preventable deterioration during transport (including one child with meningococcal shock who developed hypo-glycaemia). On admission and before retrieval the severity of illness (PRISM) score decreased in 28 children and was unchanged in 23 (median 1.0, range 0 to 24; $P < 0.001$). During stabilisation and transfer the PRISM score decreased in 34 children, was unchanged in 11 and increased in 6 (median 3.0, range −6 to 17; $P < 0.001$). Interventions undertaken by the specialist retrieval team included:

- endotracheal intubations/reintubation 57% (n=29)
- establishing central venous access 87% (n=32)
- establishing arterial access 63% (n=32)
- colloid therapy 70% (n=28)
- vasoactive therapy 27% (n=6).

A retrospective case series[164] [EL=3] with historical comparison between years of data collection was conducted to investigate the effect on patient outcome of a new PICU specialising in meningococcal disease and a specialist transport service delivering mobile intensive care. Findings were based on data collected for children admitted between June 1992 and December 1997 with confirmed diagnosis of meningococcal disease or with clinical features of meningococcal disease and no confirmed alternative diagnosis (n=331). Septicaemia was the principal diagnosis in 281 cases. The case fatality rate compared with the PRISM predicted fatality rate by year was reported as shown in Table 6.5.

Table 6.5. Observed and predicted fatality rates from meningococcal disease

Year	Observed fatality rate % (n)	PRISM predicted fatality rate % (n)
1992/3	22% (10)	32% (14)
1994	13% (5)	32% (12)
1995	11% (8)	25% (18)
1996	10% (8)	26% (21)
1997	2% (2)	34% (34)

Logistic regression analysis controlling for disease severity (PRISM score), age and sex showed the overall reduction in odds of risk of death 1992 to 1997 as 59% (OR for yearly

trend 0.41, 95% CI 0.27 to 0.62). The findings from the study were complicated by two trials of treatments for meningococcal disease running during the study period. The effects of these trials are controlled for statistically in the analysis using a logistic regression model. There was no significant reduction in the rate of complications following meningococcal disease (amputations/skin grafting: 1992 to 1995 was 5.8% versus 1996 to 1997 5.5%; neurological abnormality: 1992 to 1995 was 9.7% versus 1996 to 1997 7.3%). This is an evaluative description of the impact of a multifactorial intervention including the paediatric specialist transport service and a PICU specialising in the care of children with meningococcal disease. From these data it is not possible to conclude which of these components has the greater impact on outcomes.

Evidence summary

No studies were found which compared outcomes from a specialist paediatric transfer team with an alternative transfer method.

Findings from a UK descriptive study showed that a specialist paediatric transfer team can effectively stabilise and safely transfer critically ill children. A second UK descriptive study showed a decrease in mortality over time following establishment of a specialist paediatric transfer team and a PICU specialising in care of children with meningococcal disease.

GDG interpretation of the evidence

There is limited evidence specifically focusing on the transfer of children with meningococcal disease. Evidence suggests that the transfer of critically ill children from a district general hospital to a tertiary referral centre by a specialist paediatric retrieval team provides safe transfer for all critically ill children, including those with meningococcal disease.

The GDG recognised that the evidence was limited and studies included were from one UK city. Regional PICUs across the UK have, over recent years, established retrieval services to provide specialist transfer for all critically ill children from district general hospitals to PICUs. Personnel involved in these teams include medical and nursing staff with specialist knowledge and skills in caring for critically ill children.

Although the use of specialist retrieval teams to transfer children with meningococcal children from district general hospitals to PICUs has contributed to an improved outcome for these children, the GDG recognised that this improvement has been multifactorial. Improved media publicity, improved district general hospital recognition, management and liaison with regional PICUs as well as specialist retrieval teams and the expansion of PICUs across the UK have assisted in this improvement.

Recommendations

Retrieval and transfer to tertiary care

Children and young people who need resuscitation should be discussed with a paediatric intensivist as soon as possible.

Transfer of children and young people to tertiary care should be undertaken by an experienced paediatric intensive care retrieval team comprising medical and nursing staff.

7 Long-term management

Introduction

Following bacterial meningitis and meningococcal disease, there is a wide and varied range of potential long-term sequelae. Although the majority of children and young people recover completely, some are left with disabilities and more subtle problems that can have profound effects on their lives and the lives of their families.

The incidence, type and severity of sequelae is influenced by the infecting organism, the age of the child and the severity of the acute illness, but it can nevertheless be difficult to predict which children will develop sequelae. The potential impact of the illness is further complicated by the fact that some sequelae may not become apparent until months or years after the acute illness.

It is important for clinicians planning discharge of children after bacterial meningitis or meningococcal disease to understand typical patterns of recovery, potential sequelae and specific recommendations for follow-up assessment and treatment, particularly for assessments and treatments that are time-critical. This is also important for GPs who may need to refer children who later develop sequelae back into specialist care. Parents and young people need to understand these issues so that they are empowered to seek care and support as needs arise.

7.1 Long-term effects of bacterial meningitis

Clinical question

What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?

Previous UK guidelines

No previous UK guideline was identified that addressed this clinical question. However, 'Cochlear implants for children and adults with severe to profound deafness' (NICE TA 166)[26] is relevant to this section in that it addresses cochlear implants for severe to profound deafness in children and adults, and this can include children and young people who have had bacterial meningitis.

Studies considered for this review

Papers published since 1995 were considered for inclusion in this review. Studies of children or those involving predominantly children or where children were identified as a separate sub-group were included. The specific outcomes of interest were: visual impairment, hearing loss, psychosocial and/or behavioural problems, mobility and/or ambulation, post-traumatic stress disorder, educational achievement, speech, cognition, pain, quality of life, hydrocephalus, epilepsy and cerebral palsy.

Overview of available evidence

Four studies looked at data from a large cohort of children in England and Wales who had meningitis in the first year of life. One of these[165] [EL=2+] aimed to compare the sequelae at

5 years of children who had had bacterial meningitis with matched controls. Three studies looked at data from a large cohort of Dutch children. These three studies[166-168] [EL=2+] aimed to determine the occurrence of educational, behavioural and general health problems. An additional 11 cohort studies[169-179] [EL=2+] and five case series[180-184] [EL=3] looked at various long-term outcomes of bacterial meningitis.

Review findings

Four studies were conducted on a cohort of children in England and Wales. The first cohort study[165] [EL=2+] from England and Wales aimed to compare the sequelae at 5 years of children who had had meningitis in their first year of life with matched controls. The study had participation from parents and GPs of 1485 meningitis survivors and 1391 controls matched for age and sex from the same GP list. *H. influenzae* (26%), *N. meningitidis* (25%) and *S. pneumoniae* (9%) made up the majority of cases. *E. coli* and Group B streptococcus were present in 4% and 6% of cases respectively. GPs completed a questionnaire on developmental problems and seizure disorders. Parents completed a questionnaire on the child's health, development and learning.

There was a significant relative risk (RR) for: learning difficulties (RR 7.0; , 95% CI 4.1 to 11.8), neuromotor disabilities (RR 8.6; 95% CI 4.9 to 15.2), seizure disorders (RR 2.7; 95% CI 1.9 to 3.9), hearing problems (RR 1.9; 95% CI 1.6 to 2.2), sensorineural hearing loss (RR 22.8; 95% CI 7.22 to 72.1), ocular or visual disorders (RR 3.4; 95% CI 2.6 to 4.6), speech and/or language problems (RR 3.5; 95% CI 2.8 to 4.6) and behavioural problems (RR 3.6; 95% CI 2.6 to 4.9). Cerebral palsy was reported in 79 of the 1485 meningitis survivors (5.3%) compared to 2 of the 1391 matched controls (0.1%), but it was not reported whether this was significant.

Children with Group B streptococcus showed the highest proportion of disability, with 31% of children developing a severe or moderate disability and 51% developing no disability. In cases of *S. pneumoniae* and *E. coli*, 24% developed a severe or moderate disability, although half of the children showed no disability. In cases of *H. influenzae*, 11% developed a moderate or severe disability, with 57% not developing a disability. In cases of *N. meningitidis*, 9% of children developed a severe or moderate disability and 61% did not develop a disability. The rate of severe or moderate disability in other Gram-positive bacteria cases was 48%, with 35% showing no disability. The authors of the study noted that the data used was from 1985–1987, before the Hib vaccine was routinely used.

The second cohort study[185] [EL=2+] based on the same population aimed to assess how meningitis in the first year of life affects teenage behaviour. This study used 739 cases and 480 controls matched for age and sex from the same GP lists from throughout England and Wales. The mean age was 13.3 years (SD 0.4 years). The incidence of each strain of meningitis was not specified. A postal questionnaire was used, with questions on emotional symptoms, conduct problems, hyperactivity, peer problems and prosocial behaviour, as well as the impact of the child's behaviour on the family or classroom. The meningitis group was split into complicated meningitis (one of more of the following: meningitis diagnosed prior to age 28 days, birth weight less than 2 kg, coma, convulsions, hydrocephalus, a temperature above 40^{o}C, ventriculitis or relapse) or uncomplicated meningitis.

Comparing meningitis to controls, there was a significant relative risk for an abnormal score on total deviance in both complicated and uncomplicated meningitis from parents (RR 2.18; 95% CI 1.77 to 2.68; and RR 1.79; 95% CI 1.44 to 2.22 respectively) and teachers (RR 1.62; 95% CI 1.27 to 2.08; and RR 1.45; 95% CI 1.13 to 1.86). There was also a significant relative risk for an abnormal score on impact (a measure of the child's burden on parents or teachers) in both complicated and uncomplicated meningitis from parents (RR 3.48; 95% CI 2.56 to 4.73; and RR 2.46; 95% CI 1.78 to 3.39 respectively) and from teachers (RR 1.59; 95% CI 1.25 to 2.03; and RR 1.44; 95% CI 1.13 to 1.84 respectively). There was also a significant decrease in relative risk in all meningitis survivors compared to controls for a normal score in social skills from parents (RR 0.82; 95% CI 0.73 to 0.91) and teachers (RR 0.88; 95% CI 0.80 to 0.98). The authors noted, however, that there were several pieces of data missing, including 129 controls' teacher ratings for total deviance, and 139 controls' teacher ratings for impact. The authors noted that this study was conducted prior to the Hib vaccine.

The third cohort study[186] [EL=2+] based on the same population aimed to assess whether meningitis in the first year of life adversely affects academic achievement at age 16. This study used 460 cases and 288 controls matched for age and sex from the same GP list from across England and Wales. The prevalence of each strain of meningitis was not specified.

Pupils were asked to list all the GCSE examinations they had taken, with grades. One hundred and seventeen survivors (25.4%) and 19 controls (4.1%) achieved no passes at GCSE, 105 survivors (22.8%) and 41 controls (14.2%) achieved between one and four passes, 198 survivors (43.0%) and 189 controls (65.6%) achieved between five and ten passes, and 40 survivors (8.7%) and 39 controls (13.5%) achieved more than ten passes at GCSE. There was a significant difference in the mean number of GCSE passes between the two groups in comprehensive schools (5.05, SD 4.1; versus 6.88, SD 3.5; $P < 0.0001$), but this difference was not significant in independent or grammar schools. However, the greatest differences between survivors and controls were among those who passed fewer than five GCSEs (in comprehensive schools, 36 versus 11) and these were not represented in independent or grammar schools, where only one survivor and no controls achieved less than five GCSEs. The authors noted that this study was conducted prior to the introduction of the Hib vaccine.

The fourth study[5] [EL=2+] aimed to determine the prevalence of serious sequelae among a national cohort of children aged 5 years who had had neonatal meningitis. At follow-up 166 children in the cohort had completed questionnaires. The study also used 109 GP controls matched for sex and age and 191 hospital controls matched for gestational age, birth weight, sex and age. The mean age at follow-up was 63.4 months in survivors, 69.3 months in GP controls and 63.4 months in hospital controls. No disability was found in 51% of survivors, 71% of GP controls and 63% of hospital controls. Mild disability was found in 26% of survivors, 27% of GP controls and 30% of hospital controls. Moderate disability was found in 18% of survivors, 2% of GP controls and 5% of hospital controls. At follow-up 5% of survivors and hospital controls but no GP controls had a severe disability.

There was a statistically significant difference between survivors and GP controls for a severe or moderate disability (OR 16.4, 95% CI 4.1 to 142.7, $P < 0.0001$) and hospital controls (OR 3.9, 95% CI 2.0 to 8.1, $P < 0.0001$). A Statement of Special Educational Needs was significantly more common among survivors than either GP controls (OR 4.9, 95% CI 1.1 to 45.4, $P < 0.05$) or hospital controls (OR 3.4, 95% CI 1.1 to 12.4, $P < 0.05$). Behaviour problems were found in 38% of survivors, 27% of hospital controls and 17% of GP controls. Sensorineural hearing loss was found in 3% of survivors, no GP controls and 1% of hospital controls while conductive hearing loss was reported in 13% of survivors, 8% of GP controls and 7% of hospital controls. Cerebral palsy was reported in 15 survivors (9%) compared to 5 hospital controls (3%) ($P < 0.01$, OR 3.7, 95% CI 1.2 to 13.3) and no GP controls. Hydrocephalus was present in 14 survivors (8%) and 5 hospital controls (3%) ($P < 0.002$, OR 8.7, 95% CI 1.9 to 79.7) and no GP controls. No children were blind. Four survivors (2%), three3 hospital controls (2%) and no GP controls had epilepsy (*P* values not reported). Forty-one cases of meningitis were caused by Group B streptococcus, of which 39% had no disability, 27% had a mild disability, 29% had moderate disability and 5% had a severe disability. E coli and other Gram-negative bacteria were responsible for 20 cases, 50% of which had no disability, 20% had mild disability, 25% had moderate disability and 5% had severe disability.

Three studies were conducted on a Dutch cohort. The first cohort study[166] [EL=2+] aimed to determine the occurrence of educational, behavioural and general health problems in Dutch school age survivors of bacterial meningitis. The study looked at 680 survivors of bacterial meningitis and 304 controls (235 siblings, 64 close friends, 5 of unknown relationship). There was a significant difference between the median age of the survivors and of the controls (survivors: 8.5 years, ranging from 4.3 to 13.6 years versus controls: 9.1 years, ranging from 3.2-14.9 years; $P < 0.01$). Hearing problems were reported by parents and further details regarding the type or severity of problems were not provided, but there was a significant difference in the number of survivors and controls reported to have hearing problems (7% versus 1%, $P < 0.001$). Perfect health was also reported by parents, with 47% of survivors and 70% of controls being reported as such ($P < 0.001$).

There was a significant difference between survivors and controls on a score for behavioural problems (FS-II score, 84.6 versus 89.9, $P < 0.001$ adjusted for gender and age). This score did not differ significantly with age at the onset of bacterial meningitis (1 month or younger at onset: 84.1 versus older than 1 month at onset: 84.6; $P > 0.5$ adjusted for age and gender). In terms of school achievement, there was a significant difference in the number of survivors and controls who would be repeating their kindergarten year (55 out of 111 survivors [50%] versus 9 out of 25 controls [36%]; $P < 0.001$). There was an odds ratio of 2.5 comparing the number having to repeat a year at school for survivors and controls (16% versus 8%). Comparing *S. pneumoniae* survivors to *N. meningitidis* survivors resulted in an OR of 0.7 (12% versus 18%). There was an odds ratio of 5.6 (adjusted for age and gender) between survivors and controls for deficient school achievement (20% survivors versus 5% controls). The odds ratio for deficient school achievement between *S. pneumoniae* survivors and *N. meningitidis* survivors was 1.3 (22% versus 19% respectively). The odds ratio for concentration problems between groups was 5.7 (22% of survivors versus 5% of controls) and for *S. pneumoniae* compared to *N. meningitidis* survivors it was 1.3 (23% versus 21%). The odds ratio for hyperactive behaviour was lower at 1.8 (29% of survivors versus 17% of controls) and between *S. pneumoniae* and *N. meningitidis* survivors it was 1.1 (31% versus 29%). An odds ratio of 2.4 was reported for mobility (1% versus 0.3%), 5.9 for cognition (27% versus 6%) and 3.9 for pain (14% versus 5%).

The second cohort study[167] [EL=2+] aimed to establish the incidence of sensorineural hearing loss in children who had survived non-Hib bacterial meningitis. Cases of meningitis caused by Hib (n=117) or rare pathogens (n=4) and those secondary to immunodeficiency state (n= 84) were excluded. The study included 395 children who had hearing evaluated as part of the routine follow-up of meningitis, out of a larger cohort of 628. The mean age at infection was 2.4 years and at follow-up it was 11.7 years. Hearing loss was detected within 6 months of meningitis in all but two children. Forty-three survivors (11%) had hearing loss, with five children (1%) receiving cochlear implants.

There was a significant difference in the number of children with hearing loss between different causative agents (n=628, $P < 0.001$), although only 395 of these children (63%) had their hearing evaluated. *S. pneumoniae* accounted for 49% of the children with hearing loss, but only 14% of the children without hearing loss. *N. meningitidis* was responsible for 47% of the hearing loss cases and 81% of cases with no hearing loss. *Escherichia coli* caused 5% of the hearing loss cases and 1% of those without hearing loss. Neither Group B streptococcus nor *L. monocytogenes* caused any cases of hearing loss, and only 3% and 1% of the cases with no hearing loss respectively.

The third cohort study[168] [EL=2+] aimed to describe health-related quality of life of survivors of meningitis. The study included 182 non-Hib meningitis survivors along with 353 controls representative of the Dutch school-age population. The mean age at infection was 2.4 years (range 0.1 to 9.5 years) and follow-up was 5 to 10 years after meningitis. Only those without severe sequelae were included. *N meningitidis* caused 78% of the cases and *Streptococcus pneumoniae* a further 16%. Group B streptococcus was responsible for 3%, *Escherichia coli* for 2% and *L. monocytogenes* for 1%.

There was no significant difference between survivors and controls on scores of: emotional/behavioural functioning (96.7 versus 97.9, effect size = 0.10, $P = 0.17$, no CIs reported in this study), general behaviour (76.3 versus 78.5, effect size = 0.11, $P = 0.09$), impact on parental or carer emotions (82.8 versus 86.3, effect size = 0.15, $P = 0.02$) or impact on parental or carer's free time (94 versus 94, effect size = 0, $P = 0.98$), or on an overall score of health-related quality of life (0.93 versus 0.92, effect size = −0.03, $P = 0.34$). There was also no significant difference on scores of mobility (1 versus 1, $P = 0.14$) and the difference in scores for cognition was borderline in terms of significance (0.96 versus 0.97, $P = 0.05$). Although a statistically significant difference between survivors and controls was reported for pain scores, the data reported in the publication did not provide enough significant figures to determine the direction of effect (0.99 versus 0.99, $P = 0.02$). The outcomes reported in this study may not be representative of those in all survivors of bacterial meningitis, as the study did not include survivors with severe sequelae at discharge from hospital.

A cohort study[169] [EL=2+] conducted in England aimed to estimated the overall long-term health-related quality of life implications of meningitis in childhood. This study only looked at children with pneumococcal meningitis and was conducted in two areas of England. The study included 70 children aged 5 years and over who had had pneumococcal meningitis, 61 sibling controls and 5 neighbourhood controls of similar age and same sex. Children over the age of 11 completed the Health Utilities Index Mark 3 (HUI-3) for measuring health related to quality of life. Parents of children under 11 completed the questionnaire for them.

Significant differences in mean scores were found for hearing (0.930 versus 0.996, *P* = 0.005) and an overall score (0.774 versus 0.866, *P* = 0.019). No significant differences were found in mean scores for: vision (0.981 versus 0.992, *P* = 0.434), speech (0.976 versus 0.995, *P* = 0.248), ambulation (0.986 versus 1.000, *P* = 0.333), dexterity (1.000 versus 1.000, *P* = 1.000), emotion (0.915 versus 0.942, *P* = 0.297), cognition (0.871 versus 0.916, *P* = 0.167) or pain (0.952 versus 0.972, *P* = 0.203). Univariate analyses were conducted for each attribute with no correction for multiple comparisons (for example Bonferroni correction) and so the significance levels reported may overestimate the true effects. Also, the significance of the overall score probably reflects the effect of hearing.

A prospective cohort study[170] [EL=2+] conducted in Australia aimed to investigate long-term neurobehavioural outcomes from childhood bacterial meningitis. The study involved 130 cases and 130 controls at a 7-year follow-up, and 109 cases and 96 controls at a 12-year follow-up. The cases were children aged 3 months to 14 years with bacterial meningitis and the controls were matched from the classroom of each case child or taken from another school in the same region. The large majority of the children had Hib (78%). *Staphylococcus pnuemoniae* (11%) and *N. meningitidis* (5.5%) were the second and third most prevalent types of meningitis. The Wechsler Intelligence Scales-III, Full Scale Intellectual Quotient (IQ) and the Wide Range Achievement Test-3 were used to assess ability. There were significant differences between the groups in: verbal comprehension (95.0 versus 99.4, *P* = 0.009), perceptual organisation (99.4 versus 103.6, *P* = 0.029), reading ability (99.0 versus 104.3, *P* = 0.007) and spelling (95.4 versus 101.3, *P* = 0.002). There were no significant differences in full scale IQ (97.2 versus 101.6, *P* = 0.10), freedom from distractibility (97.7 versus 99.7, *P* = 0.323) or arithmetic (95.0 versus 97.4, *P* = 0.146). The age at which children developed meningitis was not a significant predictor of long-term, health-related quality of life, although meningitis before age 12 months was significantly related to poorer performance on tasks requiring language and executive skills.

A retrospective cohort study[171] [EL=2+] conducted in The Netherlands aimed to evaluate the neurological outcome of meningitis in children. It studied 103 children aged 1 month to 15 years with bacterial meningitis who presented at a hospital in The Netherlands. *N. meningitidis* (50%), *S. pneumoniae* (10%) and *H. influenzae* type B (33%) made up the majority of cases, with no pathogen identified in the remaining 8%. Clinical records were used to establish neurological and audiological sequelae. The median follow-up time was 6.7 months. Two (2%) children had died. Of 13 children who had their persistent neurological sequelae assessed during follow--up, seven individuals had neurological sequelae consisting of: five cases of mental retardation, three cases of persistent palsy of the abducens nerve, three cases of locomotion deficits and one case of epilepsy. Of the 83 children whose hearing function was assessed at follow-up, seven individuals suffered hearing loss, with one child becoming deaf and six suffering from mild hearing loss.

A cohort study[172] [EL=2+] conducted in The Netherlands aimed to examine behaviour problems, personality, self-perceived confidence and academic deficits in children who recovered from meningitis without obvious medical sequelae. The study involved 674 children with non-Hib bacterial meningitis. *N. meningitidis* (80%) and *S. pneumoniae* (14%) made up the majority of cases. The mean age at onset of meningitis was 2.4 years, and the mean age at follow-up was 10 years. Parents completed part of the Child Behaviour Checklist and the Personality Questionnaire for Children. Children completed a Dutch adaptation of the Self-Perception Profile for Children and the Academic Achievement Test. There was a moderate deviation from normal in the total behavioural problem score (n=61, deviation=0.52, *P* < 0.001). The estimated percentage of children with behaviour problems after surviving bacterial meningitis was 9%. Two hundred and fifty-eight children (38%)

showed a deficit in writing to dictation, 159 (24%) showed a deficit in reading aloud, 116 (17%) showed a deficit in copying sentences and 222 (33%) showed a deficit in written arithmetic. Of the children, 184 (27%) showed a deviation on at least two of these four academic deficit tasks.

A retrospective cohort study[173] [EL=2+] conducted in Australia aimed to demonstrate whether one causative agent of meningitis is more likely to cause profound hearing loss and labyrinthitis ossificans Data were obtained from the Notifiable Diseases Database System of the New South Wales Health Department, the Australian National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases and the Sydney Cochlear Implant Centre. A total of 1568 recorded cases of meningitis were found. Of all confirmed cases of meningitis, 80 (5.1%) were later cochlear implant patients. A causative agent (*N. meningitidis*, *S. pneumoniae* or Hib) could be confirmed from medical records for 35 cases of cochlear implants.

N. meningitidis caused 56.9% of the cases of meningitis and 11.4% of cases of cochlear implants (incidence of cochlear implants in survivors of *N. meningitidis* = 0.4%). *S. pneumoniae* caused 41.1% of cases of meningitis and 85.7% of cases of cochlear implants (incidence of cochlear implants in survivors of *S. pneumoniae* = 4.6%). Hib caused 1.9% of cases of meningitis and 2.9% of cases of cochlear implants (incidence of implants in survivors of Hib = 3.2%). In people who received cochlear implants, *N. meningitidis* was the causative agent of meningitis in 5.7% of people who had moderate or severe ossification of the cochlear, *S. pneumoniae* was the causative agent in 38.6% of people who had moderate or severe ossification of the cochlear and Hib was the causative agent in 15.7% of people who had moderate or severe ossification of the cochlear. However, there was no statistically significant difference between the incidence of ossification in the three types of meningitis (P = 0.45) or in the degree of ossification (*S. pneumoniae* versus *N. meningitidis,* P = 0.17; *S. pneumoniae* versus Hib, P = 0.66). The mean age at time of deafness was 2 years 9 months.

A prospective cohort study[174] [EL=2+] conducted in Australia aimed to determine the outcomes of bacterial meningitis in school-age survivors. The study included 158 survivors, with 130 completing follow-up (this resulted in 131 cases as one child had meningitis twice). Grade, sex and classroom matched controls were used. Ages ranged from 3 months to 14 years, with the median age at admission being 1 year 5 months. Hib was responsible for 100 (76%) of the 131 cases, *S. pneumoniae* for 18 (14%) and *N. meningitidis* for 6 (5%).

A significant difference in the number of survivors and controls with a full scale IQ under 70 was found (11 versus 0, P < 0.001). Although the significance was not reported, a difference was also found between groups for severe to profound deafness (3 versus 0). There were also differences between groups regarding the number of children with no problems (95 survivors versus 116 controls), one minor problem (such as IQ 70–80, mild to moderate deafness; 16 survivors versus 14 controls) and more than one minor problem or at least one major problem (such as IQ less than 70, blindness, severe to profound deafness; 20 survivors versus 0 controls). Although significance was not reported, there was a difference between survivors and controls in the incidence of: spasticity (2% versus 0%), blindness (1% versus 0%), epilepsy (5% versus 0%) and VP shunt (2% versus 0%).

A retrospective cohort study[175] [EL=2+] conducted in Canada aimed to build predictive models of severe adverse outcomes of bacterial meningitis. One hundred and one cases of bacterial meningitis were reported, with a mean age at diagnosis of 10.8 days and all cases being diagnosed within the first 28 days of life. Premature babies (gestational age less than 35 weeks) were excluded due to risk of pre-existing neurological complications. Outcome information was available for all survivors to age 1 year, and the latest outcome information was 4 years. Group B streptococcus was the causative agent in nearly half of the cases (n=50, 49.5%). *Escherichia coli* was responsible for 25 cases (24.8%), *S. pneumoniae* for 5 (5%) and Hib for 3 (3%). Development delay was reported in ten cases (9.9%) and hearing loss in one (1%). Cerebral palsy was found in one survivor (1%), hemiparesis in three (3%) and blindness in two (2%). Three (3%) also had seizure disorder. There was no significant difference in age between those with a good outcome and those with an adverse outcome (11.2 days versus 9.1 days, P = 0.314).

A cohort study[176] [EL=2+] conducted in Australia aimed to determine whether the intellectual and cognitive impairments observed at 7 years after bacterial meningitis persist into adolescence. The original cohort involved 166 children, of which 130 (82%) were available at the first follow-up (mean 6.7 years since meningitis) and 109 (66%) at second follow-up (mean 11.5 years since meningitis). At first follow-up 130 grade and sex matched controls were used, and 96 (74%) were re-evaluated at second follow-up. Ages ranged from 3 months to 14 years, with the mean age at first follow-up being 8.4 years.

At the second follow-up, 29% of survivors and 11% controls had at least one minor impairment (such as IQ 70–80, educational deficit; OR 3.2, 95% CI 1.5 to 6.7) and 23% of survivors and 5% of controls had at least one major impairment (such as IQ less than 70, severe–profound deafness more than 70 dB) or more than one minor impairment (OR 5.4, 95% CI 2.0 to 14.3). Four percent of survivors and no controls had an IQ less than 70, and 5% of survivors and 3% of controls had an IQ between 70 and 80 (OR 3.2, 95% CI 1.5 to 6.7). Educational deficits were seen in 10% of survivors and 3% of controls (OR 3.5, 95% CI 1.0 to 15.9) and 7% of survivors and no controls were deaf (at 25–69 dB). One survivor (1%) and no controls were blind, while two survivors (2%) and no controls had VP shunt. While 23% of survivors and 7% of controls had behaviour problems (OR 3.8, 95% CI 1.6 to 9.8), 62% of survivors and 89% of controls had no problems at the two year follow-up (OR= 0.2, 95% CI 0.1 to 0.4). Overall, meningitis subjects were at substantially greater risk of an adverse outcome than controls (OR 4.7, 95% CI 2.2 to 10.0)

A cohort study[177] [EL=2+] aimed to quantify long-term impairment after neonatal meningitis. The study included 111 survivors of neonatal meningitis, 113 hospital controls matched for sex, age and birth weight and 49 GP controls born at term and matched for birth date and sexy. The mean age was 9.4 years. Children were excluded if their meningitis was caused by organisms other than Group B streptococcus, Gram-negative bacteria or *L. monocytogenes*. Group B streptococcus accounted for the majority of the cases (n=49, 44%), of which 63.3% of the survivors had a normal outcome, 14.3% had a mild outcome, 8.1% moderate and 14.3% had a severe outcome. E coli affected 42 children, with 64.2% having a normal outcome, 21.4% mild, 9.6% moderate and 4.8% severe. *L. monocytogenes* was responsible for 13 cases, with 76.9% having a normal outcome, 15.4% mild, 0% moderate and 7.7% severe. Gram-negative bacteria caused seven cases, with 30% having a normal outcome, 14% mild, 28% moderate and 28% severe.

Survivors had a significantly lower IQ than hospital controls (88.8 versus 99.4, $P < 0.001$) and GP controls (88.8 versus 99.6, $P < 0.002$). There was no significant difference between GP and hospital controls. There was a significant difference on scores of mobility between survivors and hospital controls (movement assessment battery for children [mABC] score for survivors 7.1 versus hospital controls 5.0; $P = 0.001$) and between survivors and GP controls (mABC score: survivors 7.1 versus GP controls 4.0; $P = 0.003$). A normal overall outcome was found in 63.1% of survivors, 86.7% of hospital controls and 84% of GP controls. A mild overall outcome was found in 17.1% of survivors, 11.5% of hospital controls and 16% of GP controls. A moderate overall outcome was reported in 9% of survivors, 1.8% of hospital controls and no GP controls. 10.8% of survivors had a severe overall outcome, whereas no hospital or GP controls did. Severe hearing loss in this study was reported at more than 60 dB.

A retrospective cohort study[178] [EL=2+] conducted in Sweden aimed to investigate whether children with bacterial meningitis without obvious neurological sequelae at discharge from hospital have sequelae several years later. The study included 304 survivors with sibling controls. Controls were excluded if they had neurological impairment. Median age at follow-up was 9.6 years for survivors and 11 years for controls. H. influenzae was responsible for 85% of the cases, *S. pneumoniae* for 9% and *N. meningitidis* for 6%. There was a significant difference between survivors and controls for hearing impairment as reported by parents (20% versus 2%, $P < 0.001$) but no significant difference for inattention (4% versus 2%, $P = 0.21$) or for hyperactivity-impulsiveness (4% versus 1%, $P = 0.092$). There was no significant difference between survivors and controls for dizziness (3% versus 1%, $P = 0.27$), impaired vision (15% versus 16%, $P = 0.90$) or speech difficulties (7% versus 5%, $P = 0.60$). There were, however, significant differences between survivors and controls for balance

impairment (6% versus 1%, $P < 0.001$) and in the number of individual symptoms of inattention ($P < 0.05$) and hyperactivity-impulsiveness ($P < 0.01$) reported.

A cohort study[179] [EL=2+] aimed to investigate whether otitis media with effusion (OME) is the mechanism of reversible hearing loss after meningitis. The study included 124 children with meningitis, along with 124 age and sex matched controls. Ninety-two of the cases (74%) were meningococcal meningitis. Five survivors (4%) had conductive hearing loss (auditory brainstem responses threshold of more than 30dB HL) at discharge. Three survivors regained their hearing after 9 months. There were no reports of acute otitis media in survivors or controls.

A case series[184] [EL=3] conducted in the US aimed to describe the incidence of acute-phase neurologic complications in a sample of 126 children with Hib meningitis. The mean age at testing was 9.7 years (range 6 to 14 years). Only children who had had a single episode of Hib meningitis and were between the ages of 6 and 14 years at the time of testing were included. Data was collected from medical records, with some information provided by parents. The mean duration since hospitalisation was 8.2 years (range 1 to 13 years). At follow-up, three children (2%) had seizures, 15 (12%) had hearing loss, two (2%) had hemiparesis and 7% had low IQ. Eighteen percent of survivors had deficits in reading, 19% in spelling and 20% in arithmetic. Fifteen percent of survivors had repeated a grade at school, while 22% had a behaviour problem at school. Twenty-three percent had a behaviour problem at home.

A case series[180] [EL=3] conducted in Canada aimed to establish the proportion of children who develop sensorineural hearing loss after bacterial meningitis. The study included 79 children with a confirmed causative agent of bacterial meningitis. The majority of these children (n=58, 73.4%) were aged less than 2 years. The causative agent in 29 (36.7%) of the 79 cases was *S. pneumoniae*. *N. meningitidis* was responsible for 13 cases (16.5%), and Group B streptococcus for 12 (15.2%). *H. influenzae* caused 11 cases (13.9%) and *E. coli* caused 7 (8.9%). Sixty-eight of the 79 children had an audiological assessment; at a mean of 13.2 days after admission (±7.25 days) for those assessed as inpatients (n=42, 61.7%) and 74.3 days (±13.8 days) after discharge for those assessed as outpatients (n=26, 38.3%). Some degree of hearing loss was seen in 22 (32.3%) of the 68 children. Permanent sensorineural hearing loss was reported in 11 (64.7%) of the 17 children who were followed up, which is 16.1% of the children who underwent an audiological assessment. A statistically significant association between *S. pneumoniae* meningitis and sensorineural hearing loss was found ($P < 0.001$) with no significant results for the other pathogens.

A case series[183] [EL=3] conducted in Australia aimed to gain information on the outcome of pneumococcal meningitis to target vaccination strategies. The study included 94 cases of meningitis (93 children). The age of survivors ranged from 1 day to 16.5 years, with a median of 12.4 months. Three survivors who had meningitis as neonates were included in the study and 67 (71.3%) of the children were under 2 years at the onset of meningitis. All children had microbiologically confirmed pneumococcal meningitis. Medical records were obtained 12 to 140 months after the diagnosis of meningitis. There were eight meningitis related deaths and one unrelated death, leaving 85 survivors at follow-up.

Sixty-one survivors (72%) had no apparent sequelae, 16 (19%) had severe sequelae and 8 (9%) had less severe sequelae. Seventeen survivors (20%) had some degree of hearing loss. There was no significant relationship between age at diagnosis and the risk of sensorineural hearing loss ($P = 0.43$). Four survivors (5%) had hemiparesis and 6 (7%) had quadriparesis. Seizure disorder was present in 12 survivors (14%), and 4 (5%) had visual deficits.

A case series[182] [EL=3] aimed to evaluate the outcome of invasive pneumococcal disease in children. Sixty-one children with pneumococcal meningitis were included in the analysis. Ages ranged from 1 month to 16 years, with the majority of children aged between 2 and 11 months. At least one neurological sequela was found in 16 children (26%), with 8 of these (13%) having multiple neurological deficits. Sensorineural hearing impairment was reported in 7 of the 51 children (14%) who had an auditory assessment. Six survivors (10%) had cerebral palsy.

A case series[181] [EL=3] conducted in Greece aimed to assess the long-term effects of pneumococcal meningitis. The study included 63 children, of whom 47 completed follow-up and hospital records were used to establish sequelae in the other 16. Ages ranged from 1 month to 14 years (mean 2.6 years) and 55% of the children were aged less than 1 year, with 70% being male. A diagnosis was established with a CSF culture of *S. pneumoniae*. Follow-up took place 4 to 23 years after discharge and children who died before follow-up were excluded from the analysis. No complications were found in 33 survivors (70%). Fourteen (30%) had at least one defect, with 8 (17%) having a combination of complications. Mental retardation was found in nine survivors (19%) and behavioural problems with marginal IQ in one (2%). Sensorineural hearing loss was present in eight (17%) children, of which four cases were profound or severe and four were moderate or mild. Seizure disorder was reported in 15% of survivors and motor defect in 11%. Two percent of children had behaviour problems with marginal IQ and 2% had visual impairment.

Evidence statement

Bacterial meningitis appears to have a significant relative risk for health, development, deviancy and burden on parents and/or teachers. Significant differences were found between meningitis survivors and controls forhearing loss, quality of life, educational achievement, mobility, behaviour, pain, hydrocephalus, speech and cerebral palsy. Differences were also found between survivors and controls for spasticity, visual impairment, epilepsy, VP shunts and cognition, although these differences were not reported as being significant. Seizures were reported in some survivors, but the incidence was not compared to controls.

The studies included in the review looked at data from a large cohort of bacterial meningitis sufferers in England and Wales, another large cohort in the Netherlands, as well as smaller cohorts and hospital records from the UK, The Netherlands, Australia, Canada, Greece, Sweden and the USA.

Where data by pathogen was available, Group B streptococcus appears to have the worst outcomes, with an average of 29% of survivors developing moderate or severe disabilities. An average of 22% of *S. pneumoniae* survivors developed moderate or severe disabilities and 4.7% required cochlear implants. An average of 19% of *E. coli* sufferers developed moderate or severe disabilities. Nine percent of *N. meningitidis* survivors developed severe or moderate disabilities and 0.4% required cochlear implants. *H. influenzae* appeared to have the least damaging long-term effects, with only 1% of survivors developing severe or moderate disabilities and 3.2% requiring cochlear implants. See table 7.1 for a summary.

Table 7.1. Summary of moderate or severe disability and cochlear implants by causative agent

Organism	Survivors with moderate or severe disability	Incidence of cochlear implant in survivors
Group B streptococcus	29% (3 studies, 22–34%)	-
Streptococcus pneumoniae	22% (2 studies, 19–24%)	4.7%
Escherichia coli	19% (2 studies, 14–24%)	-
Neisseria meningitidis	9%	0.4%
Haemophilus influenzae	1%	3.2%

The GDG interpretation of the evidence and recommendations are presented at the end of section 7.2.

7.2 Long-term effects of meningococcal disease

Clinical question

What proportion of children and young people with meningococcal septicaemia develop physical and psychological morbidity?

Previous UK guidelines

The SIGN guideline on the 'Management of Invasive Meningococcal Disease in Children and Young People (2008)'[27] made the following recommendations regarding long-term complications:

'All children who have had a diagnosis of meningitis should have their hearing tested to allow any therapies required to be started as early as possible.

'Children and families or carers of children who have survived invasive meningococcal disease should be made aware of potential long-term complications of the disease.

'When assessing the follow-up needs of children with meningococcal disease healthcare professionals should consider the following potential morbidities:

- hearing loss
- neurological complications
- psychiatric, psychosocial and behavioural problems
- bone and joint complications, with awareness that these may not be apparent for many years after illness
- post necrotic scarring with possible requirements for amputations and skin grafting. Long-term follow-up may be needed for children for scar revision, surgical repair of deformities, leg length discrepancy, angular deformities and poorly fitting prosthesis
- renal impairment, particularly in those who required renal replacement therapy during their acute illness.

'All children who have had meningococcal sepsis or meningitis should have a follow-up appointment and be carefully assessed for evidence of any immediate or potential long-term complications.

'An individual care plan should be developed for each patient on leaving hospital.

'Healthcare professionals involved in the follow-up of children with meningococcal disease need to be aware of the potential for post-traumatic stress disorder in both the children and their families and carers.'

'Cochlear implants for children and adults with severe to profound deafness' (NICE TA 166)[26] is relevant to this section in that it addresses cochlear implants for severe to profound deafness in children and adults, and this can include children and young people who have had meningococcal disease.

Studies considered for this section

Papers published since 1994 were considered for inclusion in this review. Studies of children or those involving predominantly children or where children were identified as a separate sub-group undertaken in high income countries (Western Europe, North America, Australia and New Zealand) were included. The specific outcomes of interest were: visual impairment, hearing loss, psychosocial/behavioural problems, mobility/ambulation, post-traumatic stress disorder, educational achievement, speech, cognition, pain, quality of life, hydrocephalus, epilepsy and cerebral palsy.

Overview of available evidence

One systematic review published in 2008 was identified for inclusion in this review.[27] The review comprised 22 studies, mainly case series and single cohorts from both high income and low income countries. Data between the years 1985 and 2002 were collected. The findings from high income countries (n=9) were extracted for the current review. An additional six studies were also included: one descriptive survey [EL=3], one prospective cohort study [EL=2+], three retrospective cohort studies [EL=2+] and a case series [EL=3].

Review findings

The review findings will be presented for each of the major morbidities considered and the data synthesised where possible to give an approximation of the proportion of children who develop each of the sequelae discussed.

Hearing loss

A systematic review[27] [EL=3] comprising 22 studies included eight studies conducted in high income countries (1108 children surviving meningococcal disease) which reported hearing loss as an outcome. The timing of follow-up ranged from 'more than 12 weeks following hospital discharge' to 12 years post discharge, although this is not reported clearly in all studies. Measures of hearing loss also differ between studies (for example auditory brainstem response, play audiometry) and are not always fully described. Findings from these studies reported the rates of moderate to severe hearing loss as being between 1.9% and 15% (these figures both derived from Canadian studies).

A multicentre prospective survey[187] [EL=3] (n=159 episodes of systemic meningococcal infections) carried out in the USA between 2001 and 2005 identified 14 cases of hearing loss (six unilateral, eight bilateral) in the 146 surviving children, an incidence of 9.6%. The timing of follow-up and measure of hearing loss used are not described.

The overall incidence of hearing loss based on all seven studies is 4% (57 out of 1369).

Orthopaedic complications including amputations

The same systematic review detailed above[27] [EL=3] included four studies conducted in high-income countries that reported orthopaedic sequelae following meningococcal disease (total 1159 children). A case series described 'skeletal, vascular or cutaneous sequelae' together, reporting an incidence of 40 out of 122 (33%). The study reported amputations and cutaneous lesions requiring skin grafting and noted the need for longer term follow-up of children requiring limb surgery in order to detect cases of growth arrest. Time to presentation of growth arrest was noted as being 2 to 9 years following discharge from hospital (median 4 years). A Canadian study included in the review reported 13 out of 340 children requiring amputation. A further five orthopaedic sequelae were also described (three children with permanent knee damage from septic arthritis, one with an ankylosing finger and one with reduced bone growth causing asymmetry of the legs). Two other studies only reported children requiring amputation with incidences of 1 out of 407 and 7 out of 151. The severity of amputations was only reported for one study where 4 out of 13 amputations involved loss of part or all of at least one limb.

Four additional studies were identified that reported orthopaedic complications. A prospective survey conducted in the USA 2001-2005[187] [EL=3] identified 2 out of 146 children requiring amputation (one all four limbs, one toes only).

A prospective cohort study[188] [EL=2+] (Netherlands, data collection 2001–2005) described an incidence of two amputations out of 47 (fingers) and one child with lower limb shortening with associated genu varum deformity.

A cohort study also conducted in the Netherlands (data collected 2005–2006 for children who were admitted with meningococcal disease 1988-2001)[189] reported 5 out of 65 children undergoing amputation [EL=2+]. One child was found to have lower limb length discrepancy and one child had varus deformity of the right ankle.

A case series [EL=3][190] conducted in the Netherlands reported 8% of 120 children had amputation of extremities due to irreversible necrosis of tissue, and 6% had limb length discrepancy.

The overall incidence of children requiring amputation across all studies was 3% (40 out of 1415). The severity of amputations varied greatly between individuals, with most involving digits rather than limbs. The incidence of orthopaedic complications other than amputation was 3% (15 out of 587).

Skin complications including scarring

Four studies included in the systematic review[27] [EL=3] reported outcomes relating to skin complications and scarring. One of these studies reported cutaneous outcomes together with vascular and skeletal outcomes and is reported in the sub-section above. Two additional included studies report incidence of scarring as 32 out of 471 children (Canada, data

collection 1990–1994) and 16 out of 407 (Eire, data collection 1995–2000). One study, of poorer quality, reported the need for skin grafting in 8 out of 150 children.

In addition to the systematic review, four studies were identified that reported cutaneous sequelae. The incidence of scarring (ranging from mild to severe) was reported as:

- 33 out of 65 children, with scarring most commonly found on limbs[191] [EL=3] (Netherlands, data collection 1988–2001)
- 14 out of 146 children, 4 of whom required skin grafting[187] [EL=3] (multicentre study, 2006)
- 26 out of 47 children[188] [EL=2+] (Netherlands, data collection 2001–2005)
- 58 out of 120 children, with scarring most commonly found on legs[190] (Netherlands, 2009).

The overall incidence of skin damage or scarring across all studies was 13% children (187 out of 1406).

Psychosocial complications

Three studies included in the systematic review[27] [EL=3] report psychosocial complications (total number of children involved =777). A retrospective cohort study included a self-completion quality of life (QoL) questionnaire (n=231 completed questionnaires). Twenty-three percent of respondents noted a reduction in QoL (presumably this is comparative to life before the illness) with problems including reduced energy, increased anxiety, reduction in leisure activities and a reduced ability to work. A case–control study followed up participants (n=115 cases and 115 controls) 8 to 12 years after their illness and administered a battery of tests of neurological function, coordination, cognition and behaviour to assess neurodevelopmental status.

Participants in the control group scored higher in all four tests. Measures of motor function, cognitive ability and behaviour all showed significant detriments following meningococcal disease. Three cases versus one control were found to have attention deficit hyperactivity disorder (ADHD), with a further eight cases versus no controls with possible ADHD. Nine cases versus three controls were identified as having special educational needs, with an additional 29 cases versus 14 controls being assessed for suspected learning difficulties. One cohort study reported the incidence of neurological developmental delay as 18 out of 407 children. No further details are given.

Three additional studies also described psychosocial consequences following meningococcal disease.

A prospective cohort study[188] [EL=2+] compared parental ratings of children's QoL following meningococcal disease with a population-based reference group. The study included 47 children who had suffered meningococcal septic shock (MSS) and been cared for in a paediatric intensive care unit (parental response rate 89%) and a reference group of 353 children aged 5 to 13 years and 175 women aged 26 to 35 years as comparator for mothers. For cases the median follow-up interval was 14 months, median age at time of follow-up 4.8 years (range 1 to 17 years).

Eight of the 12 domains on the infant and toddler QoL questionnaires showed no significant difference between the cases and controls. For four domains children who had survived MSS scored significantly lower than the reference group, those domains being: physical abilities, general health perceptions, parental or carer impact – emotional, and change in health. Parental ratings for children aged 4 to 17 years showed no difference compared with the reference group for 12 of 14 domains. The two domains where a significant difference was seen were general health perceptions and physical summary. For both age groups the general health perception score was very low compared with the reference group, indicating that parents perceived their child's current health status as poor and were concerned about future health as well. Specific ongoing psychosocial problems reported by parents were: behavioural/emotional problems (n=6), fatigue (n=2), sleep disturbances (n=1) and stuttering (n=1). The overall number of children still receiving follow-up for psychosocial problems was 10 out of 47 (21%).

A cohort study[191] [EL=3] compared the self-esteem of children who had survived MSS with a same age, same sex normative reference group. Self-esteem was measured using recognised and tested scales (although some reported measures of reliability are moderate rather than good). The questionnaire was administered to two age groups: children aged 8 to 11 years (n=29 completed questionnaires) and adolescents aged 12 to 17 years (n=36 completed questionnaires) at least 4 years after discharge from hospital. Children aged 8 to 11 years who had survived MSS scored very similarly to those in the reference group. More differences were seen in the adolescent groups. On six of the seven domains on the self-esteem questionnaire male (n=16) or female (n=20) adolescents who had survived MSS scored significantly ($P < 0.05$) lower than the same sex reference group (males n=601; females n=785). These domains were: scholastic competence (males), social acceptance (males and females), athletic competence (males), physical appearance (males), close friendship (males and females) and global self-worth (males and females). Severity of illness, age at time of illness and age at time of follow-up did not seem to be significant predictors of long-term self-esteem scores.

A second cohort study conducted in the Netherlands (2005–2006; children admitted to PICU 1988–2001)[189] [EL=2+] compared the behavioural and emotional problems of children surviving MSS (n=89, age 6 to 17 years) with data from normative reference groups (n=1538). Behavioural, emotional and post-traumatic stress problems were assessed using standard, tested scales administered to children (n=45 completed questionnaires; response rate 74%; age 11 to 17 years) and to parents and teachers of children aged 6 to 17 years surviving meningococcal septic shock (n=89 parents, response rate 85%; n=61 teachers, response rate 58%). The sample of children completing a questionnaire themselves represented a sub-sample of the main study group. Overall, scores obtained for emotional, behavioural and post-traumatic stress scales were similar for the children following PICU admission for MSS compared with the reference group. Only one significant difference was noted: mothers of children who had suffered MSS reported more somatic complaints in the children compared to the reference group. Severity of illness (recorded using the PRISM score) was not found to be significantly associated with later behavioural, emotional or post-traumatic stress problems. Parents of children who were younger at the time of illness were found to report significantly more emotional, behavioural and post-traumatic stress problems in their children than parents of older children.

Neurological sequelae

The systematic review[27] [EL=3] included four studies which reported neurological sequelae following meningococcal disease. A cohort study (data collection 1980–1990) followed up children 1 year after discharge and found 6 out of 29 had neurological problems (three seizures, three ataxia). A case–control study identified 4 out of 139 children as having severe neurological complications including microcephaly, spastic quadriplegia, epilepsy and blindness. Significantly more cases than controls performed poorly on measures of coordination, cognition and behaviour (see section above on psychological/behavioural sequelae). Two further studies report incidence as 8 out of 151 children having seizures and 2 out of 51 with neurological sequelae; no other details are given.

A prospective cohort study[188] [EL=2+] looking primarily at QoL in children surviving meningococcal disease also reported neurological sequelae. These were reported for 3 out of 47 children and comprised: motor skills problems (n=1), pes equinus (n=1) and Raynaud phenomenon at amputated finger (n=1).

The prospective survey conducted in the USA[187] [EL=3] reported an incidence of children having seizures as 9 out of 146, ataxia as 4 out of 146 and hemiplegia as 3 out of 146, giving a total incidence of neurological sequelae of 11% (16 out of 146). The timing of these sequelae in relation to discharge from hospital is not clear.

The overall incidence of neurological sequelae reported in the included studies was 7% (19 out of 278).

Pain

Only one study was identified that reported specifically on pain as an outcome. A prospective cohort study[188] [EL=2+] (Netherlands, data collection 2001–2005) described an incidence of 10 out of 47 children experiencing chronic pain (lower limbs, n=7; headache, n=3). Pain was the most frequent chronic symptom. However, in a comparative section of the study, the incidence of pain was found not to be significantly different from the reference class for either age group assessed (children aged 0 to 3 years were compared with a reference group of 410 children aged 3 months to 3 years, while children aged 4 to 17 years were compared with a reference group of 353 schoolchildren aged 5 to 13 years).

Evidence statement

There is evidence from a number of descriptive and comparative studies that show the proportion of children who have developed long-term sequelae following meningococcal disease. The approximate percentages derived from these studies are shown in table 7.2

Table 7.2. Summary of long-term effects of meningococcal septicaemia

Morbidity	Incidence
Hearing loss	4% (7 studies)
Orthopaedic complications	Amputations: 3% (7 studies) Orthopaedic complications other than amputation: 3% (4 studies)
Skin complications including scarring	13% (8 studies)
Neurological sequelae	7% (6 studies)
Pain	21% (1 small study)

For psychosocial outcomes there is evidence from three studies that quality of life is reduced following meningococcal disease, although the degree of this reduction is uncertain and does not appear large. Findings from one case–control study showed self-esteem to be lower in adolescents following meningococcal disease than for those in a reference group. Findings from one cohort study showed poorer neurodevelopmental status in children following meningococcal disease compared with controls which was associated with an increase in ADHD and special educational needs, although the numbers involved are small. In contrast another cohort study found no difference in emotional, behavioural or post-traumatic stress problems in children following meningococcal disease compared with a reference group.

GDG interpretation of the evidence

The GDG members were aware from their own experience and considerable evidence from the literature that significant morbidity was associated with some cases of meningococcal disease. Children and young people who had meningococcal disease with shock were especially likely to have orthopaedic or skin problems in addition to psychological problems. Those who had meningitis were more likely to have hearing loss and other neurological problems (including pain) and behavioural difficulties. The GDG was of the view that this information should be provided to parents at discharge and at follow-up during convalescence in order to empower families to seek appropriate help and to cope with the child's or young person's new disabilities or other needs.

The National Deaf Children's Society (NDCS) Quality Standards in Paediatric Audiology, Vol IV[192] states that hearing should be tested as soon as possible before discharge but within 4 weeks of fitness to test. The GDG's view was that children and young people who are found to have severe or profound deafness should be offered an urgent assessment for cochlear implants. The assessment should be conducted as soon as the child or young person is fit to undergo testing because ossification of the cochlear can occur very rapidly and a delay in assessment may mean that cochlear implants will not be possible. After discharge an appointment with a paediatrician should be arranged to provide information and coordinate the necessary services for the child (for example, assessment for cochlear implants, referral to

psychological or orthopaedic services). In making their recommendations, the GDG highlighted children and young people who experience disability as a result of having bacterial meningitis or meningococcal septicaemia as a priority for receiving follow-up care and support to minimise health inequalities associated with their disabilities. Guidance on cochlear implantation for severe to profound deafness in children (and adults) is provided in 'Cochlear implants for children and adults with severe to profound deafness' (NICE TA 166).[26]

Recommendations

Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

Before discharging children and young people from hospital:

- consider their requirements for follow-up, taking into account potential sensory, neurological, psychosocial, orthopaedic, cutaneous and renal morbidities, **and**
- discuss potential long-term effects of their condition and likely patterns of recovery with the child or young person and their parents or carers, and provide them with opportunities to discuss issues and ask questions.

Offer children and young people and their parents or carers:

- information about and access to further care immediately after discharge, **and**
- contact details of patient support organisations including meningitis charities that can offer support, befriending, in-depth information, advocacy, counselling, and written information to signpost families to further help, **and**
- advice on accessing future care.

Offer a formal audiological assessment as soon as possible, preferably before discharge, within 4 weeks of being fit to test.

Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' [NICE technology appraisal 166]).

Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate services. The following morbidities should be specifically considered:

- hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)
- orthopaedic complications (damage to bones and joints)
- skin complications (including scarring from necrosis)
- psychosocial problems
- neurological and developmental problems
- renal failure.

Inform the child's or young person's GP, health visitor and school nurse (for school-age children and young people) about their bacterial meningitis or meningococcal septicaemia.

Healthcare professionals with responsibility for monitoring the child's or young person's health should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects of bacterial meningitis and meningococcal septicaemia.

Research recommendations

Long-term management

Does routine follow-up reduce the incidence of psychosocial stress and long-term morbidity in children and young people who have had bacterial meningitis or meningococcal septicaemia and their families?

Why this is important

Access to follow-up therapies (such as occupational therapy) and other services for children and young people who have had bacterial meningitis or meningococcal septicaemia is recommended. Qualitative research is needed to evaluate the effectiveness of this practice. The research should seek to elicit views and experiences of the children and young people themselves and the impact on their parents or carers and other family members.

7.3 Immune testing

Introduction

A number of inherited defects of the immune system have been reported in certain patients with meningococcal disease. The best known of these are deficiencies of the complement system, which is a collection of immune molecules that are involved in the killing of encapsulated organisms such as the meningococcus. A range of defects of the complement system have been described in survivors of meningococcal disease, and people with certain types of complement deficiency are prone to recurrent meningococcal disease or other serious bacterial illnesses.[193] People with complement deficiencies may also be at risk of infection with unusual serogroups of meningococcus.[194] Defects of other components of the immune system, such as deficiencies of immunoglobulins and mannan-binding lectin (an activator of complement), have also been described in patients with meningococcal disease.[195;196]

The benefits of identifying immune deficiencies in survivors of meningococcal disease include lowering the threshold for diagnosing future infections in these individuals and identifying family members who may be at risk of meningococcal or other infections. People with identified immune deficiencies can also be protected at least partially from further infections by immunisation or long-term prophylactic antibiotics. For these reasons, some authorities have suggested that all survivors of meningococcal disease should be screened for complement deficiency.[197] However, before any recommendations can be made on screening it is first important to identify the prevalence of immune deficiencies in children with meningococcal disease.[198]

Clinical question

What is the prevalence of primary immunodeficiency in children and young people with meningococcal disease?

Previous UK guidelines

No previous UK guideline was identified that addressed this clinical question.

Studies considered in this section

All study designs determining the prevalence of the following primary immune deficiencies in children and young people diagnosed with meningococcal disease were considered for this section: deficiencies of components of the classical, alternative and terminal complement pathways; deficiencies of the mannan-binding lectin protein; and deficiencies of total immunoglobulin, immunoglobulin G or immunoglobulin G subclasses. Studies conducted in the UK, Europe, Northern America and Australasia were considered for the review. Studies of people of all ages were included only if prevalence was reported separately for a subgroup of children.

Overview of available evidence

Six studies determining the prevalence of complement deficiency in survivors of meningococcal disease caused by any serogroup were included in the review [EL=3]. Four of the studies involved children only and two involved people of all ages, but reported prevalence data separately for subgroups of children. Two studies were found assessing the prevalence of complement deficiency in survivors of infection with uncommon meningococcal serogroups [EL=3]. Two of the included studies also investigated the prevalence of total immunoglobulin and immunoglobulin G (IgG) subclass deficiency. No studies were found investigating the prevalence of deficiency of mannan-binding lectin in children and young people with meningococcal disease.

Review findings

One study conducted in the UK[199] (1996–1999) [EL=3] screened 297 children aged 2 months to 16 years for complement deficiencies after recovery from meningococcal disease. The EL reflects the design of the study in the hierarchy of evidence, however it was conducted very well and the results are very relevant to the question. The study found a deficiency of C2 in one child aged 4 years who had recovered from serogroup B meningococcal infection (prevalence 0.3%). The child had a history of previous systemic pneumococcal disease. In this hospital-based study 212 children with confirmed meningococcal disease had complement assessed. Of the 297 children with confirmed disease, 203 had group B, 138 had group C, 11 were non-groupable and 1 had W135. However, it was not reported which of these children had complement taken. Moreover, as well as the child aged 4 years with a history of pneumococcal disease, it was noted that three other children had a relevant medical history: two children had recovered from pneumonia and one had recovered from a urinary tract infection.

A study conducted in The Netherlands[200] (1991–1993) [EL=3] involved 29 children aged 9 months to 14.4 years admitted to a PICU with fulminant meningococcal septic shock. It found properdin deficiency in one boy aged 7 years infected with meningococcus serogroup Y but found no complement deficiencies in the remaining 28 surviving children. There was no history of recurrent meningococcal infection. This study reported the serogroups of 25 of the 29 children: 20 serogroup B, 5 serogroup C and the child with serogroup Y: 4 children did not have serogrouping performed.

A study conducted in a hospital in Switzerland[201] (1988–1995) [EL=3] found no evidence of complement deficiency in 35 children younger than 16 years who had recovered from meningococcal meningitis. Serogroups were not reported. Familial occurrence or recurrence of meningitis was reported in three children, but other bacterial meningitis were included in the study and the recurrence rate in children with meningococcal meningitis was not reported.

A multicentre study conducted in Denmark[202] (1983–1985) [EL=3] found no evidence of complement deficiency in 23 children aged 3 months to 16 years (out of a study group of 47 people) admitted to hospital with meningococcal disease. Serogroups were reported in 35 of the total cases with meningococcal disease: 13 patients had serogroup B, 4 had serogroup C, none had serogroup X, 1 had serogroup Y and serogroups for 17 were not determined. There was no history of recurrent disease in patients with meningococcal disease.

A population-based retrospective survey conducted in Italy[203] (1985–1989) [EL=3] aimed to determine the prevalence of complement deficiencies and other immune abnormalities associated with meningococcal disease. From national notification records 520 survivors of meningococcal disease were identified, of whom 65 people (12.5%) were available for investigation and 59 were enrolled in the study. Thirty-four participants (58%) were younger than 14 years at the time of infection. In total, 10 out of 59 people (17%) had deficiencies of terminal complement pathway components, of whom three were younger than 14 years (prevalence in children younger than 14 years was 9%). All people with complement deficiency had been infected with meningococcal serogroup C compared with 61% of people without complement deficiency ($P \leq 0.05$). Fifty percent of people with complement deficiency had a history of recurrent meningococcal infection. The number of complement

sufficient people with a history of recurrent infection is inconsistently reported in the study (2% or 10%). There was no evidence of total immunoglobulin or IgG subclass deficiency. The low participation rate (12.5%) and the high rate of recurrent disease in an unselected series of patients — inconsistently reported in the study as 10% or 17% — suggest the possibility of selection bias. This would result in a study population that may not be representative of the general population with meningococcal disease.

There were other caveats with this study: the total recurrence rate seems high for an unselected series, although the figures are inconsistent. The study initially reports that 6 out of 59 participants (10%) had a history of recurrent disease. Later it states that 10 out of 59 (17%) had recurrent disease: 5 with complement deficiencies and 5 without. The uptake is worryingly low (12.5%). The authors scrutinised the study population and reported that it was representative of the entire population in terms of: age range (1–60 years), sex, geographical spread and distribution of meningococcal serogroups (serogroup A 10%, serogroup B 22% and serogroup C 68%). Serogroup C was the most prevalent strain causing 79% of meningococcal disease in Italy from 1985 to 1989. Twelve percent had severe disease; severe disease defined as 'meningococcaemia sometimes accompanied by DIC (disseminated intravascular coagulation), arthritis or encephalitis'.

A population-based retrospective survey conducted in The Netherlands[194] (1959–1992) [EL=3] estimated the prevalence of complement deficiency in survivors of meningococcal disease caused by any serogroup. Patients with meningococcal disease were identified from National Reference laboratory records (n=7732). One hundred and seventy-six survivors were selected for the study based on age and infecting meningococcal serogroup; 62 (35%) were younger than 5 years at the time of disease. The study found a primary complement deficiency in three people, one younger than 5 years at the time of disease (prevalence of complement deficiency in children younger than 5 years: 1.6%). This child had survived infection with meningococcal serogroup A or C (exactly which serogroup was not reported) and had a deficiency of a terminal complement pathway component. The study did not report the rate of complement deficiency in children aged between 5 and 16 years.

People with a history of serogroup B infection were underrepresented in the study population (45%) compared with the frequency of serogroup B infection in the general population (71%). This suggests that, because of the limitations of selected sampling, the study population may not be representative of the general population with meningococcal disease. This study selected patients by serogroup, so the distribution of serogroups was not representative.

Meningococcal disease caused by uncommon serogroups

One survey[194] (1959–1992) [EL=3] determined the prevalence of complement deficiency in people who had disease caused by uncommon serogroups: X, Y, Z, W135, 29E or nongroupable meningococcus. Of 97 people included in the study, 16 (16.5%) were aged between 5 and 15 years and 30 (31%) were younger than 5 years at the time of meningococcal infection. In total, 32 out of 97 people (33%) had a complement deficiency. Of the 46 children younger than 15 years, 9 (19.5%) had a complement deficiency: 8 were aged between 5 and 15 years and 1 child younger than 5 years. Complement deficiencies included properdin deficiency, C3 deficiency and deficiencies of the terminal complement pathway components. Some people with deficiencies of C3 and the terminal complement pathway components had a history of recurrent meningococcal disease. There was no history of recurrent meningococcal disease in properdin-deficient individuals. In this study the serogroup distribution (based on 97 people of all ages, mostly unselected sample) was:

- W 135: 54 people (56%): 16/54 (30%) with complement deficiency
- X: 9 people (9%) of whom 3 (33%) with complement deficiency
- Y: 23 people (24%) of whom 11 (48%) had complement deficiency
- Z: 1 person (1%) — no one had complement deficiency
- 29E: 2 people (2%) — no one had complement deficiency
- non-groupable; 8 people (8 %) of whom 2 (25%) had complement deficiency.

Serogroup was not reported by age.

A population-based retrospective survey conducted in Germany[204] (1966–1992) [EL=3] estimated the prevalence of complement and immunoglobulin deficiency in 30 survivors of infection with uncommon meningococcal serogroups (X, Y, Z, W135, 29E), of whom 15 were younger than 10 years at the time of infection. The study included a matched control group comprised of 30 survivors of infection with meningococcal serogroup B. In total, 8 out of 30 people (27%) infected with either serogroup W135 or Y had a deficiency of a terminal complement pathway component (C7 or C8). All people in the control group were complement sufficient ($P < 0.01$). One person with complement deficiency was younger than 10 years (prevalence: 7%). The study did not report the rate of complement deficiency in children aged between 10 and 16 years. It did not report recurrent disease. There was no evidence of total IgG or IgG subclass deficiency. Uncommon serogroups in the study group were reported as:

- W135: 13 patients (43.3%)
- Y: 11 patients (36.6%)
- X: 4 patients (13.3%)
- 29E: 1 patient (3.3%)
- Z: 1 patient (3.3%)

Five out of 11 patients (17%) infected with serogroup Y had complement deficiency and three patients (10%) infected with serogroup W135 had complement deficiency.

No relevant studies of the prevalence of deficiency of mannan-binding lectin in children with meningococcal disease were identified.

Evidence statement

There is evidence from three studies involving a total of 355 children that the estimated prevalence of complement deficiency in children and young people younger than 16 years with meningococcal disease is approximately 0.3%.

One study using selected sampling found complement deficiency in 1.6% of children younger than 5 years with meningococcal disease. Complement deficiencies included C2 deficiency and deficiencies of terminal complement pathway components.

One small study conducted in tertiary care found that one of 29 children admitted to tertiary care with meningococcal septic shock had complement deficiency. The small sample size provides insufficient evidence to reach a conclusion about the prevalence of complement deficiency in severely ill children with meningococcal disease.

There is limited evidence from two small studies that the prevalence of complement deficiency in children infected with unusual meningococcal serogroups is higher, ranging from 7% in one study of children younger than 10 years to 19.5% in a second small study of children younger than 15 years. In the second study, 90% of children with complement deficiency were older than 5 years. Complement deficiencies included properdin deficiency, C3 deficiency and deficiencies of the terminal complement pathway components.

Two studies found no evidence that total immunoglobulin deficiency or immunoglobulin G subclass deficiency is associated with meningococcal disease in children and young people.

No relevant studies were found evaluating the prevalence of deficiency of mannan-binding lectin in children and young people with meningococcal disease.

Cost effectiveness

The GDG identified testing for complement deficiency as a priority for economic analysis within the guideline. The evaluation compared:

i. a strategy of selective testing in children who have had meningitis caused by meningococcus serogroups other than B, or who have had previous serious bacterial infections (including meningococcal disease) versus no testing

ii. selective testing versus routine testing of all children with meningococcal disease.

There is a lack of evidence on the degree of protection that would be afforded by treatment, using immunisation or long-term antibiotic prophylaxis, in those identified with immune deficiency. Therefore, the evaluation took the form of a threshold analysis exploring the scenarios when each strategy could be considered cost effective. A summary of this analysis is presented below. Full details of the evaluation are given in appendix L.

The rationale for selective testing is that there exists a clearly identified sub-group with a higher pre-test probability of complement deficiency. If selective testing is not cost effective relative to no testing then routine testing will not be cost effective. If selective testing is cost effective relative to no testing the decision between selective and routine testing hinges on whether the additional cases identified by routine testing can be achieved at an acceptable cost, which we take to be £20,000 per quality adjusted life year (QALY) in this case.

In addition to uncertainty about any treatment effect size there is also uncertainty with respect to the savings and the QALY gain (which is a weighted average based on the incidence of all sequelae including death) from an averted meningitis case. While there is published data on the cost and QALY implications of averted disease[205;206], children who are susceptible to repeat infection often have milder disease[207;208]. Therefore, this analysis shows the threshold for cost effectiveness for both testing strategies, varying the gain from an averted case between 0 and 10 QALYs and the relative risk reduction with treatment between 0% and 100%. The analysis was undertaken using a lower bound estimate of the saving from an averted case of meningococcal disease (based on the treatment cost of an acute episode) and a higher saving of £10,000 per averted case. It was assumed that the prevalence of complement deficiency was 0.3% amongst all children with meningococcal disease, but 1% in the subgroup who accounted for 10% of all cases. The results are illustrated in figures 7.1 to 7.4.

Scenario 1: Saving per averted case = £3,179

Figure 7.1. Threshold cost effectiveness for selective testing

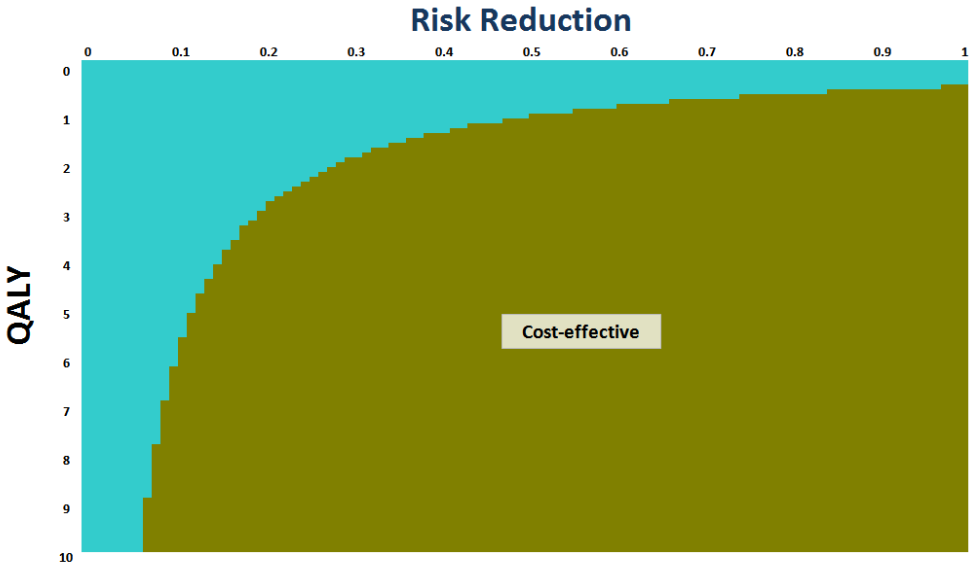
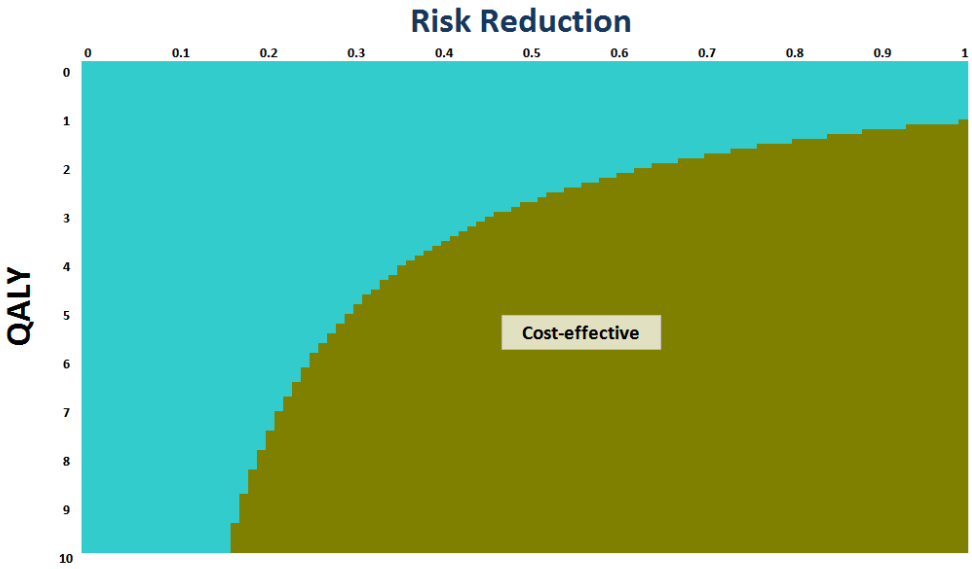


Figure 7.2. Threshold cost effectiveness for routine testing



Scenario 2: Saving per averted case = £10,000

Figure 7.3. Threshold cost effectiveness for selective testing

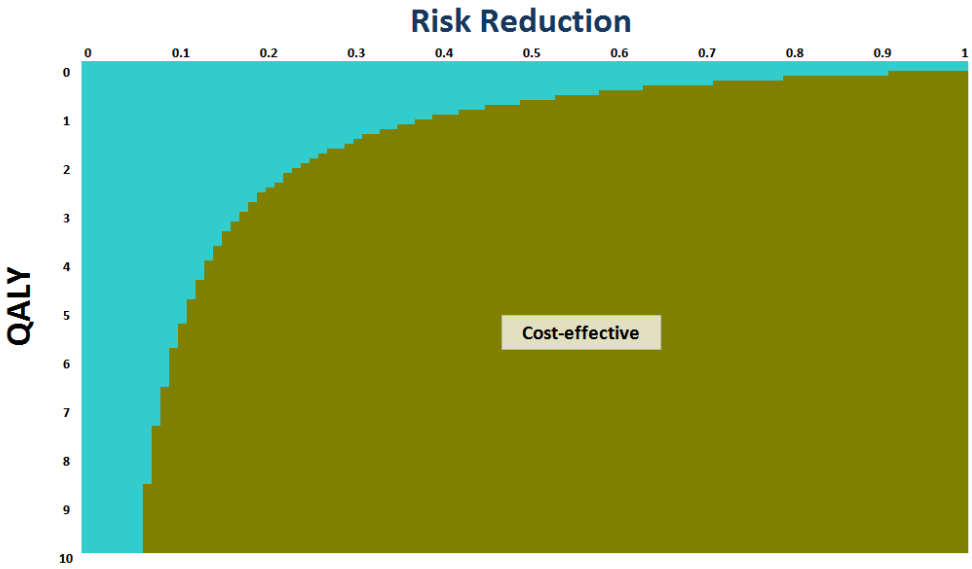
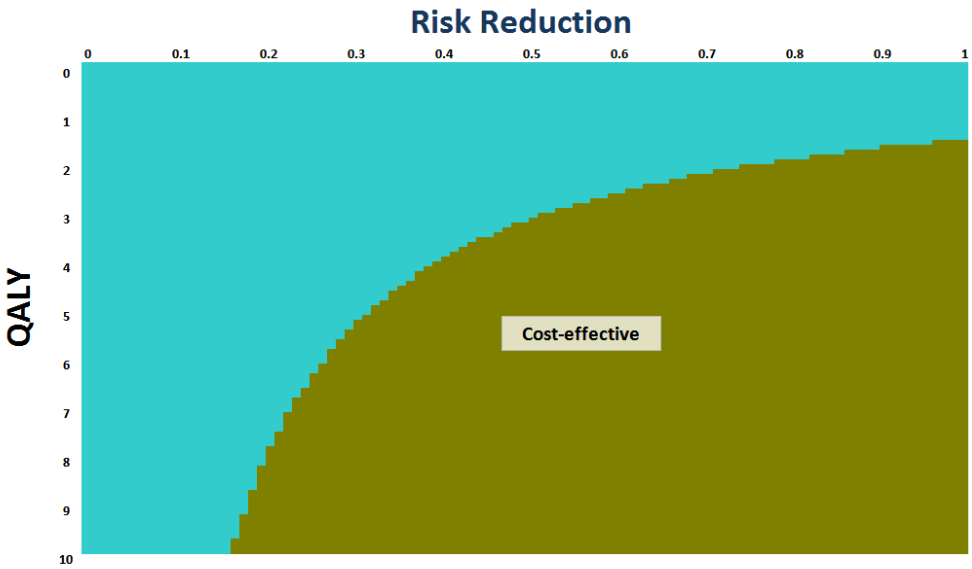


Figure 7.4. Threshold cost effectiveness for routine testing



The regions shaded green indicate treatment cost effectiveness and QALY gains per averted case combinations under two alternative scenarios for the cost saving associated with an averted case of meningococcal disease. The frontier between the green and blue shaded area gives the cost effectiveness threshold (that is, the treatment efficacy needed for a given QALY gain per averted case and vice versa).

In both cost-saving scenarios, the results show that the thresholds are markedly less for the selective testing strategy. So, for example, using the conservative estimate about the cost saving per averted case, the QALY gain that would be needed if treatment gave complete protection against subsequent infection would be 0.4 QALYs per averted case. Or, if treatment reduced the risk of subsequent infection by 50%, the minimum QALY gain per averted case for cost effectiveness would be 1.0. Conversely, the minimum QALY gain necessary for routine testing to be cost effective relative to selective testing at treatment efficacy of 50% would be 4.2 QALYs. Given that disease tends to be milder in this group of patients, such a QALY gain cannot be necessarily considered likely.

As figure 7.3 shows, the impact of a higher cost saving on the selective testing strategy is to substantially reduce the thresholds for cost effectiveness. With treatment reducing the risk of infection by 50% the QALY gain threshold for cost effectiveness falls to 0.7. The higher cost saving also reduces the thresholds for the cost effectiveness of routine testing relative to selective testing with the equivalent QALY threshold being 3.8.

GDG interpretation of the evidence

On considering the evidence regarding complement deficiency, the GDG concluded that one study[199] was most relevant to the UK child population despite the study design being low in the hierarchy of evidence. In this study of nearly 300 children it was found that only one child in an unselected series of children with meningococcal disease had a complement deficiency. The affected child had serogroup B meningococcal disease and a previous history of serious bacterial infection. At the time the most prevalent serogroups causing meningococcal disease were serogroups B and C. The other studies included in the review did not report any cases of complement deficiency in children with serogroup B meningococcal disease (although not all studies gave data on serogroups). The review showed that complement deficiency was considerably more common in children who had meningococcal disease caused by rare serogroups, particularly serogroup Y. An economic analysis suggested that the

cost effectiveness thresholds for testing for complement deficiency in a subgroup (that is, serogroup Y) were substantially lower than those for a strategy which tested all children with meningococcal disease. The evidence was not sufficiently robust to derive point estimates for the incremental cost effectiveness of either strategy. However, only modest treatment efficacy and QALY gains were shown to be necessary for cost effectiveness by a threshold analysis in the subgroup strategy, even with conservative assumptions about the cost savings from an averted case of meningococcal disease. Furthermore, the overall cost impact of such a strategy would be very small. It should be noted, however, that this analysis suggested that the results were very sensitive to test specificity and that a specificity of 98% or more was required for cost effectiveness with the base–case assumptions of cost and treatment efficacy noted above. While the threshold analysis did not show that routine testing is not cost effective, the higher QALY and treatment efficacy thresholds necessary make it far less likely, especially given that subsequent disease is generally milder in patients with complement deficiency.[207;208] The GDG therefore considered that testing for complement deficiency could not be justified in children with meningococcal disease cause by the serogroup B meningococcus unless there was a history of previous serious bacterial infection, but it was justified in children who had meningococcal disease caused by the historically rare serogroups (A, X, Y, W135, Z, 29E and non-groupable).

The situation with disease caused by the serogroup C meningococcus is less clear. While most studies did not find any cases of complement deficiency in children with disease caused by this serogroup, one (possibly selective) study did find a number of cases of complement deficiency in children with disease caused by the serogroup C meningococcus. The GDG was aware that cases of serogroup C meningococcal disease are now rare in the UK as a result of universal immunisation against this serogroup. In 2007/2008 there were only 29 cases of disease caused by the serogroup C meningococcus in England and Wales.[209] It is, therefore, reasonable to include serogroup C meningococcal disease in the category of rare serogroups that would justify testing for complement deficiency. Moreover, there is good evidence from the laboratory evaluation of the immune response to MenC vaccine in the UK that the combination of antibody and complement correlates with protection against serogroup C meningococcal disease[198] providing theoretical grounds to suspect that complement deficiency could result in vaccination failure. The GDG therefore considered that it may be worthwhile testing for complement deficiency in children who have had serogroup C meningococcal disease.

Many cases of meningococcal disease are not confirmed by microbiological culture or polymerase chain reaction (PCR) tests. According to current epidemiology, the great majority of these cases are likely to be caused by the serogroup B meningococcus. The GDG therefore considered that testing for complement deficiency could not be justified in cases of unconfirmed meningococcal disease.

The GDG also considered the role of possible immune deficiency in instances where there have been more than one case of meningococcal disease in a family. This raises the possibility of immune deficiency because most deficiency syndromes, including complement deficiency, are inherited and it is possible that earlier cases in the family may not have been screened for immune deficiency. Although no evidence was found, the GDG made a pragmatic decision that it would be appropriate to test cases where there had been previous cases in the immediate family (that is, parents and siblings). This decision would not apply to cases where there had been more than one family member affected during an outbreak because this would almost certainly represent simple person-to-person transmission rather than an underlying susceptibility to meningococcal disease.

Regarding other forms of immunodeficiency, the GDG found no evidence that deficiencies of immunoglobulins or mannan-binding lectin are prevalent in survivors of meningococcal disease. The GDG concluded that testing for deficiencies of these components of the immune system could not be recommended, except in children and young people who have a history that is highly suggestive of an immunodeficiency. The GDG's consensus view was that a history of serious, persistent, unusual or recurrent infections would be highly suggestive of an immunodeficiency.

Recommendations

Immune testing

Test children and young people for complement deficiency if they have had either:

- more than one episode of meningococcal disease, **or**
- one episode of meningococcal disease caused by serogroups other than B (for example, A, C, Y, W135, X, 29E), **or**
- meningococcal disease caused by any serogroup and a history of other recurrent or serious bacterial infections.

Children and young people with recurrent episodes of meningococcal disease should be assessed by a specialist in infectious disease or immunology.

Do not test children and young people for complement deficiency who have had either:

- a single episode of meningococcal disease caused by serogroup B meningococcus, **or**
- unconfirmed meningococcal disease.

Discuss appropriate testing for complement deficiency with local immunology laboratory staff.

If a child or young person who has had meningococcal disease has a family history of meningococcal disease or complement deficiency, test the child or young person for complement deficiency.

If a child or young person who has had meningococcal disease is found to have complement deficiency, test their parents and siblings for complement deficiency.

Refer children and young people with complement deficiency to a healthcare professional with expertise in the management of the condition.

Do not test children and young people for immunoglobulin deficiency if they have had meningococcal disease, unless they have a history suggestive of an immunodeficiency (that is, a history of serious, persistent, unusual, or recurrent infections).

8 References, glossary and abbreviations

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Abbreviations

ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
AM	aseptic meningitis
aPC	activated protein C
APLS	advanced paediatric life support
AUC	area under the curve
AVPU	alert, voice, pain unresponsive
bexA	*Haemophilus influenzae* or *Bacillus influenzae*
BM	bacterial meningitis
BNF	British National Formulary
BNFC	British National Formulary for Children
BPI	bacterial permeability increasing protein
Chi^2	Chi-square distribution
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMO	chief medical officer
CNS	central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	cranial computed tomography
ctrA	*N. meningitidis capsular transfer*
D	day
dB HL	decibel of hearing loss
df	degrees of freedom
DOR	diagnostic odds ratio
EBSCO	Elton B. Stephens Company
EDTA	ethylenediaminetetraacetic
EI	extrameningeal bacterial infection
EL	evidence level
g	gramme
GCSE	General Certificate of Secondary Education
GDG	Guideline Development Group
GMSPS	Glasgow meningococcal septicaemia prognostic score
GP	general practitioner
h	hour
Hib	*Haemophilus influenzae* type b
HPA	Health Protection Agency
HRG	Healthcare Resource Group
HSV	herpes simplex virus
HUI-3	Health Utilities Index Mark 3
ICER	incremental cost-effectiveness ratio
ICP	intercranial pressure
ICU	intensive care unit
IMD	invasive meningococcal disease
IQ	intelligence quotient
IQR	interquartile range
IV	intravenous
kg	kilogramme
kPa	kiloPascal

LR	likelihood ratio
m	month
mABC	movement assessment battery for children
menC	meningococcal C
mg	milligramme
MHRA	Medicines and Healthcare products Regulatory Agency
ml	millilitre
mm	millimetre
mmHg	millimetre of mercury
mmH_2O	millimetre of water
mmol	millimole
MOC	MenOPP bedside clinical
MSS	meningococcal septic shock
n	number
NDCS	National Deaf Children's Society
ng	nanogrammes
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NK	not known
NPSA	National Patient Safety Agency
NPV	negative predictive value
ns	not significant
OME	otitis media with effusion
ONS	Office for National Statistics
OR	odds ratio
$PaCO_2$	pressure of carbon dioxide
PaO_2	pressure of oxygen
PCR	polymerase chain reaction
PICU	paediatric intensive care unit
Ply	*Streptococcus pneumonia*
py	pneumolysin gene
PMN	polymorphonuclear
PPV	positive predictive value
PRISM	Pediatric Risk of Mortality
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
QoL	quality of life
RBC	red blood cell
RCPCH	Royal College of Paediatrics and Child Health
RCT	randomised controlled trial
rBP121	recombinant bactericidal permeability-increasing protein
RR	relative risk
SD	standard deviation
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIGN	Scottish Intercollegiate Guidelines Network
se	sensitivity
sp	specificity
SPC	summary of product characteristics
SpO_2	oxygen saturation
TA	technology appraisal
TB	tuberculosis

UK	United Kingdom
UM	undetermined meningitis
USA	United States of America
UTI	urinary tract infection
+ve	positive
-ve	negative
VM	viral meningitis
WBC	white blood cell
WMD	weighted mean difference
WTP	willingness to pay
y	year

Glossary of terms

Adjunctive therapy	The use of one medication to improve response or help decrease some of the side effects of another medication.
Antidiuretic hormone (ADH)	Also known as vasopressin, a hormone secreted by the posterior pituitary gland which helps the body conserve the right amount of water. ADH prevents the production of dilute urine (and so is antidiuretic).
Antigen	Any substance that may be specifically bound by any antibody molecule.
Apnoea	A temporary stopping or interruption to breathing.
Bacterial meningitis	Bacterial infection of the meninges.
Band form	An immature polymorphonuclear leukocyte (neutrophil).
Bolus	A volume of fluid given quickly.
Brudzinski's sign	With the patient supine, the physician places one hand behind the patient's head and places the other hand on the patient's chest. The physician then raises the patient's head (with the hand behind the head) while the hand on the chest restrains the patient and prevents them from rising. Flexion of the patient's lower extremities (hips and knees) constitutes a positive sign.
Capillary refill time (CRT)	A test performed on physical examination in which the skin is pressed until blanched by the clinician's finger and the time taken for the skin to return to its previous colour is measured. CRT can be measured peripherally (on the extremities) or centrally (on the chest wall). A prolonged CRT may be a sign of circulatory insufficiency (such as shock) or dehydration.
Cerebral oedema	Swelling of the brain.
Cerebrospinal fluid (CSF)	The watery fluid that surrounds the brain and spinal cord. Samples of CSF can be obtained by lumbar puncture.
Circulatory failure	The inability of the cardiovascular system to adequately supply oxygenated blood to the tissues. This can be caused by shock.
Coagulopathy	A condition affecting the blood's ability to form a clot.
Cold shock	Cold shock is shock in children with sepsis associated with vasoconstriction in the skin and peripheries.
Colloid solution (including synthetic colloids)	Colloid solutions contain substances of high molecular weight that do not readily migrate across capillary walls. By increasing osmotic pressure within the bloodstream, colloids draw fluid in from other compartments to increase the vascular volume. Plasma and plasma substitutes are known as colloids and they contain large molecules that do not readily leave the intravascular space where they exert osmotic pressure to maintain circulatory volume. Examples are albumin, hetastarch, dextran and gelofusine. Albumin provides about 80% of the plasma colloid osmotic pressure in healthy adults. Albumin for therapeutic uses is prepared from donor plasma. Normal human serum albumin is available as 4–5% or 15–25% solutions: 5%

	albumin solution is osmotically and oncotically equivalent to plasma whereas 25% albumin solution is hyperoncotic. The major clinical use of albumin is as a volume expander in the treatment of shock caused by blood or plasma loss. Plasma substitutes (dextrans, gelatine and the etherified starches) are macromolecular substances which are metabolised slowly. They may be used at the outset to expand and maintain blood volume in shock.
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Complement system	A series of enzymes present in the blood that, when activated, produces widespread inflammatory effects and directly destroys micro-organisms.
Conjugate vaccine	A vaccine in which two different antigens are joined together (conjugated) to improve the immune response. Typically, this means conjugating a polysaccharide antigen to a protein antigen to improve the antibody response to the polysaccharide antigen, for example as with the recent pneumococcal polysaccharide–protein conjugate vaccine.
Corticotropin test	The short corticotropin stimulation test is widely used to assess adrenocortical function in critically ill patients.
C-reactive protein (CRP)	A plasma protein that circulates in increased amounts during inflammation and after tissue damage. Measurement of CRP in blood samples is widely used as a marker of infection or inflammation.
Crystalloid solution	Intravenous fluids made up of water with various dissolved salts and sugars.
Cytokine	A member of a large family of proteins that are important for immunity and inflammation and that act on the effector cells of the immune system.
Dengue haemorrhagic fever	A severe manifestation of infection with the tropical mosquito-borne Dengue virus, characterised by haemorrhagic lesions of the skin, reduced platelet count and leakage of the fluid part of blood into the tissues.
Doll's eye movements	When the head is moved from side to side, the eyes remain fixed in midposition, instead of the normal response of moving laterally toward the side opposite to the direction the head is turned.
Ecchymoses	An ecchymosis is a non-blanching area of skin caused by loss of blood from a blood vessel. In simple terms it appears like a bruise. It implies a larger size than a petechial spots and has a more diffuse border than purpuric spots. It can be caused by a bruise (which implies trauma), but can also be caused by a bleeding problem. Ecchymoses can similarly occur in mucous membranes, for example in the mouth.
Empiric antibiotic	Antibiotic that treats a wide spectrum of microorganisms. Empiric antibiotics are used before the specific organism is known. Once this is known, a more specific antibiotic can be given.

Encapsulated bacteria	Bacteria surrounded by a sugar (polysaccharide) coat, for example the bacteria causing meningitis that are discussed in this guideline.
Endothelial cell	Endothelial cells are thin flat cells which line the inside of all blood vessels from the heart to the capillaries. They have structural and metabolic roles.
Endotoxin	These are chemicals that are released by bacteria and can cause some of the damaging effects of infections. The endotoxins of some bacteria can cause cells to break down, which can, in the most severe cases, cause shock from septicaemia. Endotoxins can also interfere with the body's response to fighting infections.
End-tidal capnography	A device that allows non-invasive measurement of exhaled carbon dioxide.
Epidemiology (for instance of bacterial meningitis)	The branch of medical science dealing with the transmission and control of disease.
External validity	The degree to which the results of a study hold true in non-study situations, such as in routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Extravasation	The leakage of intravenous drugs from the vein into the surrounding tissue.
Focal neurological deficit	A finding on physical examination of a deficiency or impairment of the nervous system that is restricted to a particular part of the body or a particular activity. A focal neurological deficit is caused by a lesion in a particular area of the central nervous system. Examples include weakness of a limb or cranial nerve palsy. These signs suggest that a given disease process is focal rather than diffuse.
Fontanelle	A membrane-covered gap or soft spot between the skull bones on the top of an infant's skull near the front. A bulging fontanelle can be a sign of meningitis.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also generalisability of study results to non-study patients or populations.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Herd immunity	The development of immunity for all of the community (or 'herd'), including for unvaccinated individuals, that occurs when a sufficient number of other individuals in the community have been vaccinated.
Hyperdynamic shock	'Warm shock' hypotension, vasodilation, normal or increased cardiac output.
Hyponatraemia	An electrolyte disturbance in which the sodium concentration in the plasma is too low (below 135 micromole/litre).

Ill appearance	An ill-looking child is an overall impression the assessing healthcare professional can make when presented with a child or young person. This impression is formed not only from objective measurements but also from subjective feelings about how the child looks and reacts. If a healthcare professional's subjective instinct is to describe the child as 'ill-looking' then the child is most likely at high risk of serious illness. Healthcare professionals should be confident to follow their impressions of a child's wellbeing.
Inotrope	A medication used to strengthen the cardiac muscular contractions and improve blood circulation.
Intraosseous infusion	Injection of fluid directly into the bone marrow.
Isotonic fluid	Solution that has the same salt concentration as the normal cells of the body and the blood.
Kernig's sign	Extension of the knees is attempted: the inability to extend the knees beyond 135 degrees without causing pain constitutes a positive test for Kernig's sign.
Leucocyte count	The number of white blood cells per unit volume in venous blood. A differential leucocyte count measures the relative numbers of the different types of white cell.
Lumbar puncture	A procedure in which cerebrospinal fluid is obtained by inserting a hollow needle into the space between vertebrae in the lumbar region of the spine. The procedure is used to diagnose meningitis and encephalitis.
Mannan binding lectin	Mannose binding lectin (MBL), also named mannose- or mannan-binding protein (MBP), is an important factor in innate immunity.
Meningism	Stiffness of the neck associated with backwards extension of the cervical spine.
Meningitis	Inflammation of the meninges, the membranes that lie between the surface of the brain and the inside of the skull. Meningitis is usually caused by infection with bacteria or viruses. Bacterial meningitis is a serious condition associated with appreciable mortality and significant neurological complications.
Meningococcal disease	Any of a number of infections caused by the bacterium *Neisseria meningitidis* (also known as meningococcus). In young children meningococcal disease usually manifests as septicaemia, meningitis or a combination of the two. Meningococcal septicaemia is the leading infectious cause of death in childhood in the UK.
Meningococcal septicaemia	Systemic meningococcal infection (with or without circulatory failure) without clinical meningitis. This is a serious medical condition in which there is rapid multiplication of bacteria in the bloodstream and in which bacterial toxins are present in the blood. Septicaemia is usually fatal unless treated promptly with parenteral antibiotics.
Meningoencephalitis	Meningitis plus encephalitis: inflammation of the meninges and the brain.

Microbial resistance	The ability of microorganisms to withstand an antibiotic to which they were once sensitive.
Microbial sensitivity	The susceptibility of microorganisms to antibiotics.
Minimum inhibitory concentration	The minimum inhibitory concentration is the lowest concentration of an antimicrobial agent that will inhibit the visible growth of a microorganism after overnight incubation in the laboratory. They are important measures in diagnostic laboratories as they show whether the organism in question is resistant to an antimicrobial agent.
Moribund	A condition where the individual is close to death.
Neonate	A newly born baby aged less than 28 days.
Neutrophils	A type of white blood cell, also called polymorphonuclear leucoytes.
Paediatric intensivist	A specialist in paediatric intensive care medicine.
Parenteral antibiotic	An antibiotic given by a route other than by mouth, usually by intravenous or intramuscular injection.
PCR Elisa	A capture assay for nucleic acids that mimic enzyme linked immunosorbant assays. In this assay, PCR products hybridized to an immobilized capture probe.
Petechiae	These are small pinprick-sized (less than 2 mm diameter) and pinprick-appearing purple spots. They are non-blanching.
Plasma osmolality	The number of osmoles per solvent.
Pleocytosis (pleocytic CSF)	An abnormal increase in the number of cells in the cerebrospinal fluid.
PN product	The product of platelet and neutrophil counts.
Polymerase chain reaction (PCR)	Polymerase chain reaction is a method of creating copies of specific fragments of DNA. The PCR rapidly amplifies a single DNA molecule into many DNA molecules so that further tests can be carried out.
Postictal	Refers to the altered state of consciousness that occurs following the cessation of a generalised seizure.
Procalcitonin	A precursor of the hormone calcitonin that is released into the bloodstream in response to infection or inflammation. Procalcitonin can be measured in blood samples and it is currently under development as a potential test for the detection of serious infections.
Protein C	Protein C is a major physiological anticoagulant. It is a vitamin K-dependent serine protease enzyme that is activated by thrombin into activated protein C (APC). The activated form (with protein S and phospholipid as a cofactor) degrades Factor Va and Factor VIIIa.
Protein S	Protein S is a vitamin K-dependent plasma glycoprotein synthesized in the endothelium. In the circulation, Protein S exists in two forms.
Pulse pressure	The pulse pressure is the difference in pressure between the highest blood pressure (systolic) and lowest blood pressure (diastolic) in one cardiac cycle. It represents the

	force the heart generates each time it beats.
Purpura	These are medium sized (2 mm or more diameter) purple spots. They may sometimes be slightly raised above the rest of the skin surface. They are non-blanching.
Raised intracranial pressure	When pressure exceeds 18 cm H_20 with associated signs such as headache and vomiting. Signs suggesting raised intracranial pressure are: • a full or bulging fontanelle • relative bradycardia and hypertension • focal neurological signs • abnormal posture or posturing • unequal, dilated or poorly responsive pupils • papilloedema • abnormal 'doll's eye' movements.
Rapid antigen testing	Rapid antigen testing looks for an antigen that is specific to the organism in question. These tests have problems with specificity (the proportion of negative test results which are correctly identified as being negative) and sensitivity (the proportion of positive test results which are correctly identified as being positive).
Real-time PCR	Real-time PCR is a laboratory technique that amplifies and measures the quantity of DNA produced.
Recombinant	Produced by genetic engineering.
Serogroup	One way of classifying a group of closely-related organisms based on a characteristic shared antigen. A serogroup may contain a number of serotypes.
Serotype	One way of classifying a group of closely-related organisms based on a characteristic shared antigen.
Shock	Condition in which the circulatory system fails such that the blood pressure is too low to provide adequate blood supply to the tissues.
Sign	A finding on physical examination of a patient that provides the clinician with an objective indication of a particular diagnosis or disorder (see also Symptom).
Subarachnoid space	The space between the two inner membranes of the meninges — the pia and arachnoid mater — which contains the cerebrospinal fluid. The meninges is a system of three membranes that surround the central nervous system: the inner pia mater, the arachnoid mater and the outer dura mater.
Symptom	A patient's report of an abnormal feeling or sensation that provides the clinician with a subjective indication of a particular diagnosis or disorder (see also Sign).
Thrombin	Thrombin (activated Factor II [IIa]) is a coagulation protein that has many effects in the coagulation cascade. It is a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalysing many other coagulation-related reactions.
Thrombomodulin	Thrombomodulin is a cell surface-expressed glycoprotein, predominantly synthesised by vascular endothelial cells. It is a cofactor in the thrombin-induced activation of protein

	C in the anticoagulant pathway by forming a 1:1 stoichiometric complex with thrombin.
Tonic seizure	A seizure in which the limbs become stiff but do not jerk. A typical seizure usually lasts less than 20 seconds. Consciousness is usually preserved. If the person is standing when the seizure starts, he or she often will fall.
Vasopressin	A hormone that is produced in the neuronal cells of the hypothalamic nuclei and stored in the pituitary gland. It is used as a potent vasopressor in septic shock as it causes smooth muscle contraction.
Vasopressor	An agent that produces vasoconstriction and a rise in blood pressure (usually understood as increased arterial pressure).
Warm shock	Warm shock is a type of shock in children with sepsis characterised by high cardiac output and low peripheral vascular resistance.

Health economics terms

Cost–consequence analysis	A form of economic evaluation where the costs and consequences of two or more interventions are compared, and the consequences are reported separately from costs.
Cost-effectiveness analysis	A form of economic evaluation in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-minimisation analysis	A form of economic evaluation that compares the costs of alternative interventions that have equal effects.
'Cost of illness' study	A study that measures the economic burden of a disease or diseases and estimates the maximum amount that could potentially be saved or gained if a disease was eradicated.
Cost–utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life years (QALYs).
Decision(-analytic) model (and/or technique)	A model of how decisions are or should be made. This could be one of several models or techniques used to help people to make better decisions (for example, when considering the trade-off between costs, benefits and harms of diagnostic tests or interventions).
Decision tree	A method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or cost effectiveness of different actions can then be compared.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future.

	Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominate (in cost-effectiveness analysis)	A term used in health economics when a treatment option is both more clinically effective and less costly than an alternative option. This treatment is said to 'dominate' the less effective and more costly option.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and their consequences.
Equity	Fair distribution of resources or benefits.
Health-related quality of life	A combination of a person's physical, mental and social wellbeing; not merely the absence of disease.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.
Markov modelling	A decision-analytic technique that characterises the prognosis of a cohort of patients by assigning them to a fixed number of health states and then models transitions among health states.
Model input	Information required for economic modelling. For clinical guidelines, this may include information about prognosis, adverse effects, quality of life, resource use or costs.
Net benefit estimate	An estimate of the amount of money remaining after all payments made are subtracted from all payments received. This is a source of information used in the economic evidence profile for a clinical guideline.
One-way sensitivity analysis (univariate analysis)	Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Probabilistic sensitivity analysis	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example Monte Carlo simulation).
Quality adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations.

Appendix A

Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

1.1 Short title

Bacterial meningitis and meningococcal septicaemia in children

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Women's and Children's Health to develop a clinical guideline on meningitis and meningococcal disease in children and young people for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Meningitis is a condition characterised by an inflammation of the pia and arachnoid mater, the two inner meninges (or coverings) of the brain and the spinal cord. The term is usually restricted to inflammation that results from infective agents. Bacterial septicaemia is the spread of bacteria through the blood stream, which may be associated with changes to circulation and a lowered blood pressure. Both conditions can be caused by several different bacteria.

b) Meningitis is mostly caused by bacteria. It can also be caused by viruses, and rarely by fungi, but this guideline will cover only bacterial meningitis. The principle causative organisms in children and babies older than 3 months include *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus). *Haemophilus influenzae* type b is now rare since the introduction of vaccination. In babies younger than 3 months, *Group B Streptococcus, Escherichia coli* and *Listeria monocytogenes* are most common causative organisms. Infections are typically acquired by person-to-person droplet transmission. Meningococcal infections account for the majority of cases of meningitis in the UK and Republic of Ireland.

c) Meningococcal disease is caused by *N. meningitidis*, and includes two predominant patterns of illness: meningitis and septicaemia (meningococcaemia or meningococcal septicaemia), although a proportion of cases show features of both. Meningococcal infections can also affect other organs, including lungs (pneumonia), joints (bacterial arthropathy) and eyes (conjunctivitis). The organism is carried in the nose by up to 40% of the population (incidence is highest in teenagers and there is almost no carriage in early childhood) and is usually asymptomatic. However, in a small minority of those who encounter the organism for the first time, meningitis, septicaemia or both can occur.

d) Between 1999 and 2005, total reported cases of meningococcal disease fell from 2967 to 1300 in England and Wales, and cases of meningococcal meningitis dropped from 1145 to 579. This fall was partly a result of the introduction of the meningitis C vaccine and partly a natural dip in the incidence of the disease. The total number of cases of all other infective meningitis over the same time period fell from 860 to 807 cases. In 2004 the annual incidence of meningococcal disease was 4.0 100,000 people in England and 3.9 per 100,000 in Wales, based on enhanced surveillance data.

e) Children younger than 9 years are the most at risk of contracting bacterial meningitis and meningococcal septicaemia. The age based incidences of meningococcal disease and bacterial meningitis in England and Wales in 2005 were 31.3 per 100,000 and 4.8 per 100,000 in the age groups 0–4 and 5–9 years respectively. Meningococcal disease is the most common infectious cause of death in children aged between 1 and 5 years.

f) Patients with meningitis or meningococcal septicaemia present to primary care as well as to emergency departments. All patients with meningitis are managed in hospital.

g) Typical presentations of meningitis vary depending on age. Common features in children and young people include fever, vomiting, headache, neck pain, photophobia, confusion, drowsiness and fits. Young babies may present with irritability and refusal to feed. Children and young people with septicaemia present with fever, vomiting, cold hands and feet, shivering, pale or mottled skin, fast breathing, rash, confusion and drowsiness. The rash associated with meningococcal disease ranges from a non-specific macular rash to the characteristic purpuric (raised, non-
blanching, bluish purple) rash. This purpuric rash is mostly seen with septicaemia but is not always present initially.

h) Meningitis and meningococcal disease carry a significant risk of mortality and serious long term morbidity. Up to 20% of the children who contract severe meningococcal septicaemia die, usually within 24 hours of the first symptoms appearing. Complications of infection with *N. meningitidis* include neurological damage, loss of hearing, acute renal failure and clotting abnormalities. Critical decrease in blood supply to the limbs may result in

loss of fingertips and skin. Long term complications include residual headaches, memory disturbances, epilepsy, learning difficulties and other neurological sequelae including deafness, blindness and cerebral palsy.

i) There has been a reduction in the incidence of meningitis over the years as a result of vaccines and improved awareness. This has affected some disease causing organisms more than others. However there continues to be variation in areas such as initial assessment and initiation of treatment, disease severity assessment and prevention of secondary cases. The absence of a consistent approach in the management of meningitis and meningococcal disease is reflected in considerable variation in the quality of care between settings.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see ‘Further information’). ‘The guideline development process: an overview for stakeholders, the public and the NHS’ describes how organisations can become involved in the development of a guideline. ‘The guidelines manual’ provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) All children and young people from birth up to their 16th birthday who have or are suspected to have bacterial meningitis or meningococcal septicaemia.

4.1.2 Groups that will not be covered

a) Children and young people with known immunodeficiency.

b) Children and young people with brain tumours, existing hydrocephalus or intracranial shunts.

c) Neonates already receiving care in neonatal units.

4.2 Healthcare setting

a) Management in primary and secondary care.

4.3 Clinical management

a) Diagnosis of bacterial meningitis and meningococcal septicaemia:

• symptoms and signs

• identification of levels of risk based on probabilities of combinations of signs and symptoms

• differentiating between meningococcal septicaemia and other causes of non-blanching rash.

b) Management of suspected bacterial meningitis and meningococcal septicaemia in primary care and in the pre-hospital setting.

c) Management of bacterial meningitis and meningococcal septicaemia in secondary care:

• choice of antibiotics

• fluid resuscitation – type of fluid and timing of administration

• timing and role of intubation and the decision to initiate it

• corticosteroids for the treatment of meningitis

• use of scoring systems such as Glasgow Meningococcal Septicaemia Prognostic Score in diagnosis and management

• role of recombinant Bpi (bacterial permeability increasing protein) and activated protein C.

d) Retrieval and transfer to secondary and tertiary care.

e) Choice and timing of investigations:

• blood tests

• aspirates and swabs

• lumbar puncture

• radiology – computed tomography

• immunological testing.

f) Information that should be given to parents and carers:

• at the time of initial presentation.

• after diagnosis

• regarding short- and long-term effects, including significant psychological and physical morbidities.

g) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the summary of product characteristics to inform their decisions for individual patients.

h) The Guideline Development Group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

i) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.4 Status

4.4.1 Scope

This is the final scope.

4.4.2 Guideline

The development of the guideline recommendations will begin in February 2008.

4.4.3 Related NICE guidance

Feverish illness in children: assessment and initial management in children younger than 5 years. NICE clinical guideline 47 (2007). Available from www.nice.org.uk/CG047
Intrapartum care: Care of healthy women and their babies during childbirth. NICE clinical guideline 55 (2007). Available from www.nice.org.uk/CG055
The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 20 (2004). Available from www.nice.org.uk/CG020

5 Further information

Information on the guideline development process is provided in:

• 'The guideline development process: an overview for stakeholders, the public and the NHS'

• 'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix B

Declarations of interest

This appendix includes all interests declared on or before 21 June 2010.

GDG member	Interest
Angela Cloke	No interests declared
Linda Glennie	*Personal pecuniary interests:* Conference expenses and/or lecture fees from GlaxoSmithKline, Lilly, Wyeth and Xoma; advisor to Novartis *Non-personal pecuniary interests:* Meningitis Research Foundation receives funding from Baxter, Brahms and Beximco Pharmaceuticals, Dorset Orthopaedic, GlaxoSmithKline, Lilly, Novartis, Sanofi Pasteur, Wyeth/Pfizer and Xoma for organising conferences and providing educational materials/services
Caroline Haines	No interests declared
Paul Heath	*Personal pecuniary interests:* Conference expenses from Sanofi Pasteur *Non-personal pecuniary interests:* St George's, University of London receives funding from GlaxoSmithKline, Novartis and Wyeth for research into meningitis vaccines
J Simon Kroll	*Personal pecuniary interests:* Consultancy for GlaxoSmithKline, Novartis and Sanofi Pasteur (as member of Paediatric Vaccines Advisory Boards); conference expenses from GlaxoSmithKline and Wyeth *Non-personal pecuniary interests:* Department receives funding from Baxter and Sanofi Pasteur for research into vaccines to prevent meningococcal disease and from Wyeth for educational activities
Ian Maconochie	No interests declared
Sheila McQueen	No interests declared
Philip Monk	No interests declared
Simon Nadel	No interests declared
Nelly Ninis	No interests declared
Andrew Pollard	*Non-personal pecuniary interests:* University Department receives funding from GlaxoSmithKline Vaccines, Novartis Vaccines, Sanofi Pasteur MSD and Wyeth Vaccines for research into meningococcal, Hib or pneumococcal and payment from these manufacturers for advisory work, sponsorship for scientific/educational meetings and travel expenses; principal investigator on meningitis vaccine research projects funded by Meningitis Research Foundation, the Wellcome Trust and Meningitis UK
Martin Richardson	No interests declared
Matthew Thompson	*Non-personal pecuniary interests:* Principal investigator on a project funded by the Meningitis Research Foundation

GDG member	Interest
Alistair Thomson	*Personal pecuniary interests:* Conference expenses from Mead Johnson *Non-personal pecuniary interests:* Adviser to Meningitis Trust; principal investigator on a research project investigating the role of microcirculation in pathophysiology of meningococcal disease funded by the Meningitis Research Foundation

NCC-WCH staff	Interest
Shannon Amoils	No interests declared
Jay Banerjee	No interests declared
Paula Broughton-Palmer	No interests declared
Shona Burman-Roy	No interests declared
Andrew Clegg	No interests declared
Ella Fields	No interests declared
Rupert Franklin	No interests declared
Paul Jacklin	No interests declared
Rosalind Lai	No interests declared
Moira Mugglestone	No interests declared
M Stephen Murphy	No interests declared
Maria Peila	No interests declared
Julia Saperia	No interests declared
Roz Ullman	No interests declared
Cristina Visintin	No interests declared
Danielle Worster	No interests declared

External advisors	Interest
James Stuart	No interests declared
David Turner	*Personal pecuniary interests:* Member of data and safety monitoring board sponsored by Choice Pharma for a clinical trial of a novel agent for treatment of severe sepsis in adults (not directly related to meningitis or meningococcal infection)

Appendix C

Registered stakeholder organisations

The list of registered stakeholder organisations is available on the NICE website: www.nice.org.uk/guidance/index.jsp?action=download&o=34295

Appendix D

Clinical questions

In children and young people under 16 years of age, what symptoms and signs or combinations of symptoms and signs are predictive of bacterial meningitis?

In children and young people under 16 years of age, what symptoms and signs or combinations of symptoms and signs are predictive of meningococcal septicaemia?

Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome?

Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?

In children and young people up to 16 years of age with a petechial rash, can non-specific laboratory tests (C-reactive protein, white blood cell count, blood gas) help to confirm or refute the diagnosis of meningococcal disease?

In children and young people under 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?

What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?

What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?

In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs?

In children and young people with suspected meningitis, can CSF variables (white blood cell count, glucose, protein) distinguish between bacterial and viral meningitis?

When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?

When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?

Should lumbar puncture be performed prior to stopping antibiotic treatment in children less than 3 months of age with bacterial meningitis?

In children and young people with suspected or confirmed bacterial meningitis, can a cranial computed tomography (CT) scan reliably demonstrate raised intracranial pressure?

What antibiotic regimen (type) should be used to treat children and young people with suspected meningococcal septicaemia in the secondary care setting?

What antibiotic regimen (type) should be used to treat children and young people with suspected meningitis in the secondary care setting?

What antibiotic regimen should be used to treat confirmed bacterial meningitis or meningococcal septicaemia?

What are the indications for administering intravenous fluids to resuscitate children and young people with suspected meningococcal septicaemia?

What are the clinical indications for giving inotropes in children and young people with suspected/confirmed meningococcal septicaemia?

What type of intravenous fluid should be used to resuscitate children and young people with suspected meningococcal septicaemia?

Should fluid volume be restricted in children and young people with suspected/confirmed bacterial meningitis?

In children and young people with suspected or confirmed meningococcal septicaemia, what are the clinical indications for intubation and mechanical ventilation?

In children and young people with suspected or confirmed bacterial meningitis, what are the clinical indications for intubation and mechanical ventilation?

Should corticosteroids be used in the treatment of children and young people with suspected/confirmed bacterial meningitis?

What is the effect of experimental therapies in children and young people with suspected/confirmed meningococcal septicaemia?

Should corticosteroids be used in the treatment of children and young people with suspected/confirmed meningococcal septicaemia?

What is the effect on outcomes of using scoring systems in children and young people with suspected/confirmed meningococcal disease?

Do specialist transport teams improve outcomes and/or reduce adverse incidents during the transfer of children with meningococcal disease?

What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?

What proportion of children and young people with meningococcal septicaemia develop physical and psychological morbidity?

What is the prevalence of primary immunodeficiency in children and young people with meningococcal disease?

Appendix E

Search strategies

The search strategies are presented in a separate file.

Appendix F

Excluded studies

The excluded studies are listed in a separate file.

Appendix G

Included studies evidence tables

The evidence tables for included studies are listed in a separate file.

Appendix H

Meta-analyses (Forest plots) conducted as part of guideline development

H.1 Empiric antibiotics

Figure H.1. Mortality from all organisms

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	0	10	0	7	1.2%	0.00 [-0.21, 0.21]
Barson 1985	0	27	0	23	3.6%	0.00 [-0.08, 0.08]
Bryan 1985	4	18	3	18	2.6%	0.06 [-0.20, 0.31]
Congeni 1984	2	22	1	23	3.3%	0.05 [-0.10, 0.19]
Delrio 1983	0	39	0	39	5.7%	0.00 [-0.05, 0.05]
Girgis 1988	7	50	10	50	7.3%	-0.06 [-0.21, 0.09]
Haffejee 1988	2	16	3	15	2.3%	-0.08 [-0.33, 0.18]
Jacobs 1985	0	23	1	27	3.6%	-0.04 [-0.14, 0.06]
Nathan 2005	14	247	12	256	36.7%	0.01 [-0.03, 0.05]
Odio 1986	3	42	3	43	6.2%	0.00 [-0.11, 0.11]
Peltola 1989	5	101	4	99	14.6%	0.01 [-0.05, 0.07]
Rodriguez 1985	12	61	8	39	6.9%	-0.01 [-0.17, 0.15]
Sharma 1996	0	11	0	12	1.7%	0.00 [-0.15, 0.15]
Steele 1983	0	15	0	15	2.2%	0.00 [-0.12, 0.12]
Wells 1984	0	12	1	18	2.1%	-0.06 [-0.22, 0.10]
Total (95% CI)		**694**		**684**	**100.0%**	**-0.00 [-0.03, 0.03]**
Total events	49		46			

Heterogeneity: Chi² = 2.91, df = 14 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)

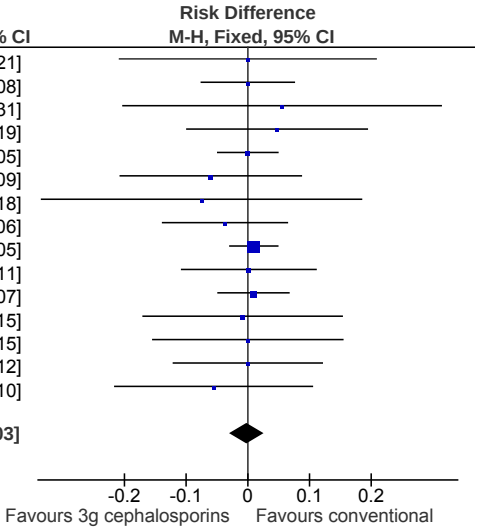


Figure H.2. Mortality from *Haemophilus influenzae* type B (Hib)

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bryan 1985	2	7	2	9	5.3%	0.06 [-0.37, 0.49]
Congeni 1984	0	14	0	16	10.1%	0.00 [-0.12, 0.12]
Delrio 1983	0	6	0	9	4.9%	0.00 [-0.23, 0.23]
Jacobs 1985	0	14	1	15	9.8%	-0.07 [-0.24, 0.10]
Odio 1986	2	33	2	39	24.2%	0.01 [-0.10, 0.12]
Peltola 1989	1	36	0	31	22.6%	0.03 [-0.05, 0.10]
Rodriguez 1985	2	27	1	15	13.1%	0.01 [-0.15, 0.17]
Sharma 1996	0	7	0	8	5.1%	0.00 [-0.22, 0.22]
Steele 1983	0	6	0	9	4.9%	0.00 [-0.23, 0.23]
Total (95% CI)		**150**		**151**	**100.0%**	**0.01 [-0.05, 0.06]**
Total events	7		6			

Heterogeneity: Chi² = 1.10, df = 8 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

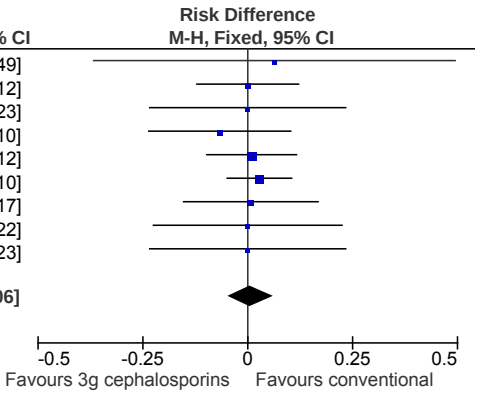


Figure H.3. Mortality from *Streptococcus pneumoniae*

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bryan 1985	1	2	1	3	5.8%	0.17 [-0.71, 1.04]
Congeni 1984	1	3	1	3	7.3%	0.00 [-0.75, 0.75]
Girgis 1988	3	13	4	13	31.5%	-0.08 [-0.42, 0.26]
Jacobs 1985	0	5	0	3	9.1%	0.00 [-0.39, 0.39]
Odio 1986	1	9	1	4	13.4%	-0.14 [-0.61, 0.33]
Peltola 1989	0	6	0	1	4.2%	0.00 [-0.63, 0.63]
Rodriguez 1985	6	12	2	5	17.1%	0.10 [-0.41, 0.61]
Sharma 1996	0	1	0	1	2.4%	0.00 [-0.85, 0.85]
Steele 1983	0	5	0	3	9.1%	0.00 [-0.39, 0.39]
Total (95% CI)		**56**		**36**	**100.0%**	**-0.02 [-0.21, 0.18]**
Total events	12		9			

Heterogeneity: Chi² = 0.77, df = 8 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

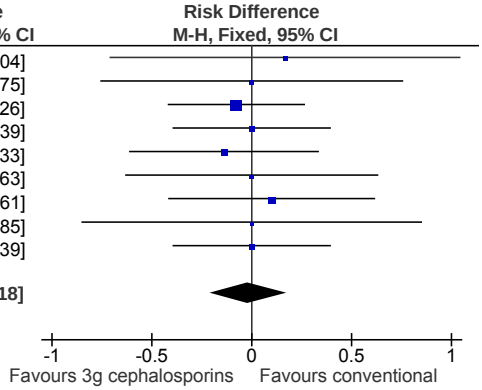


Figure H.4. Mortality from *Neisseria meningitidis*

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Barson 1985	0	2	0	1	0.7%	0.00 [-0.73, 0.73]
Bryan 1985	0	1	0	2	0.7%	0.00 [-0.73, 0.73]
Congeni 1984	0	3	0	1	0.8%	0.00 [-0.68, 0.68]
Girgis 1988	0	11	0	10	5.5%	0.00 [-0.17, 0.17]
Jacobs 1985	0	3	0	5	2.0%	0.00 [-0.39, 0.39]
Nathan 2005	6	160	5	148	80.1%	0.00 [-0.04, 0.05]
Peltola 1989	0	1	0	1	0.5%	0.00 [-0.85, 0.85]
Rodriguez 1985	0	11	1	6	4.0%	-0.17 [-0.49, 0.16]
Sharma 1996	0	3	0	3	1.6%	0.00 [-0.46, 0.46]
Steele 1983	1	6	1	12	4.2%	0.08 [-0.25, 0.42]
Total (95% CI)		**201**		**189**	**100.0%**	**-0.00 [-0.05, 0.05]**
Total events	7		7			

Heterogeneity: Chi² = 1.28, df = 9 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

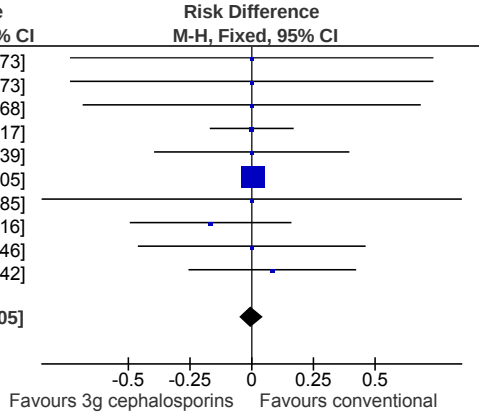


Figure H.5. Effect of third-generation cephalosporins on deafness with all organisms

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	2	10	1	7	3.6%	0.06 [-0.30, 0.42]
Barson 1985	3	21	5	15	7.5%	-0.19 [-0.47, 0.09]
Bryan 1985	2	14	3	18	6.8%	-0.02 [-0.28, 0.23]
Delrio 1983	8	27	14	30	12.3%	-0.17 [-0.42, 0.08]
Haffejee 1988	0	14	0	12	5.6%	0.00 [-0.14, 0.14]
Jacobs 1985	1	23	2	26	10.5%	-0.03 [-0.17, 0.10]
Peltola 1989	4	96	4	95	41.2%	-0.00 [-0.06, 0.06]
Steele 1983	1	15	1	15	6.5%	0.00 [-0.18, 0.18]
Wells 1984	0	12	0	17	6.1%	0.00 [-0.13, 0.13]
Total (95% CI)		**232**		**235**	**100.0%**	**-0.04 [-0.09, 0.01]**
Total events	21		30			

Heterogeneity: Chi² = 5.04, df = 8 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

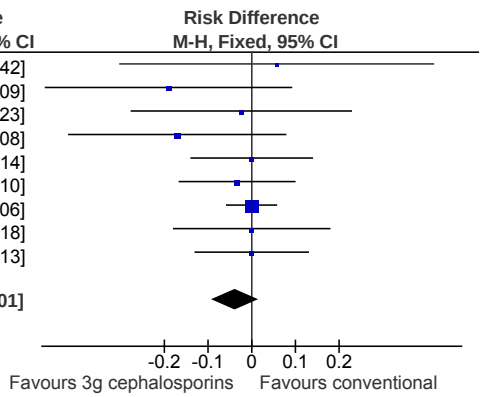


Figure H.6. Effect of cephalosporins in all culture-positive children

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	0	10	0	7	4.1%	0.00 [-0.21, 0.21]
Barson 1985	8	24	8	20	10.8%	-0.07 [-0.35, 0.22]
Bryan 1985	2	16	2	17	8.2%	0.01 [-0.22, 0.23]
Congeni 1984	0	21	4	21	10.4%	-0.19 [-0.37, -0.01]
Delrio 1983	1	19	1	20	9.7%	0.00 [-0.14, 0.14]
Girgis 1988	0	14	0	14	7.0%	0.00 [-0.13, 0.13]
Haffejee 1988	3	16	3	13	7.1%	-0.04 [-0.34, 0.26]
Jacobs 1985	0	23	0	15	9.0%	0.00 [-0.10, 0.10]
Odio 1986	0	42	7	43	21.1%	-0.16 [-0.28, -0.05]
Steele 1983	0	15	0	15	7.5%	0.00 [-0.12, 0.12]
Wells 1984	0	12	0	9	5.1%	0.00 [-0.17, 0.17]
Total (95% CI)		**212**		**194**	**100.0%**	**-0.06 [-0.12, -0.01]**
Total events	14		25			

Heterogeneity: Chi² = 10.41, df = 10 (P = 0.41); I² = 4%
Test for overall effect: Z = 2.14 (P = 0.03)

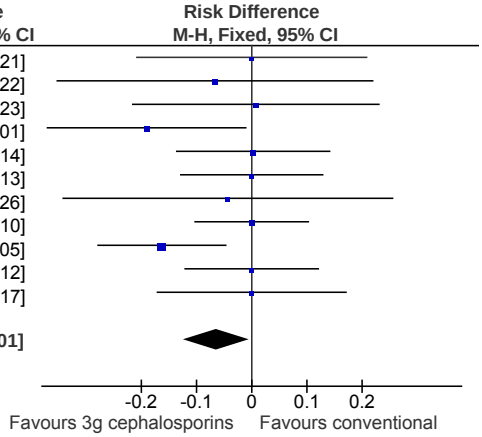
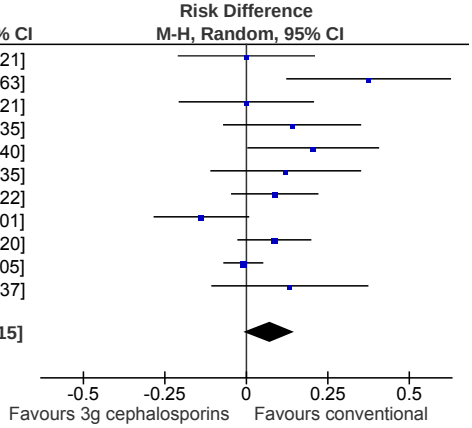


Figure H.7. Diarrhoea following use of cephalosporins

Study or Subgroup	3 g cephalosporins Events	Total	Conventional Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Aronoff 1984	0	10	0	7	7.6%	0.00 [-0.21, 0.21]
Barson 1985	16	27	5	23	6.1%	0.38 [0.12, 0.63]
Bryan 1985	2	18	2	18	7.7%	0.00 [-0.21, 0.21]
Congeni 1984	5	22	2	23	7.5%	0.14 [-0.07, 0.35]
Delrio 1983	16	39	8	39	7.9%	0.21 [0.01, 0.40]
Haffejee 1988	3	16	1	15	6.8%	0.12 [-0.11, 0.35]
Jacobs 1985	2	23	0	27	11.3%	0.09 [-0.04, 0.22]
Odio 1986	3	42	9	43	10.6%	-0.14 [-0.28, 0.01]
Peltola 1989	25	101	16	99	12.5%	0.09 [-0.03, 0.20]
Rodriguez 1985	1	61	1	39	15.4%	-0.01 [-0.07, 0.05]
Steele 1983	3	15	1	15	6.5%	0.13 [-0.11, 0.37]
Total (95% CI)		**374**		**348**	**100.0%**	**0.07 [-0.01, 0.15]**
Total events	76		45			

Heterogeneity: Tau² = 0.01; Chi² = 26.29, df = 10 (P = 0.003); I² = 62%
Test for overall effect: Z = 1.80 (P = 0.07)



H.2 Corticosteroids

Figure H.8. Mortality from specific organisms

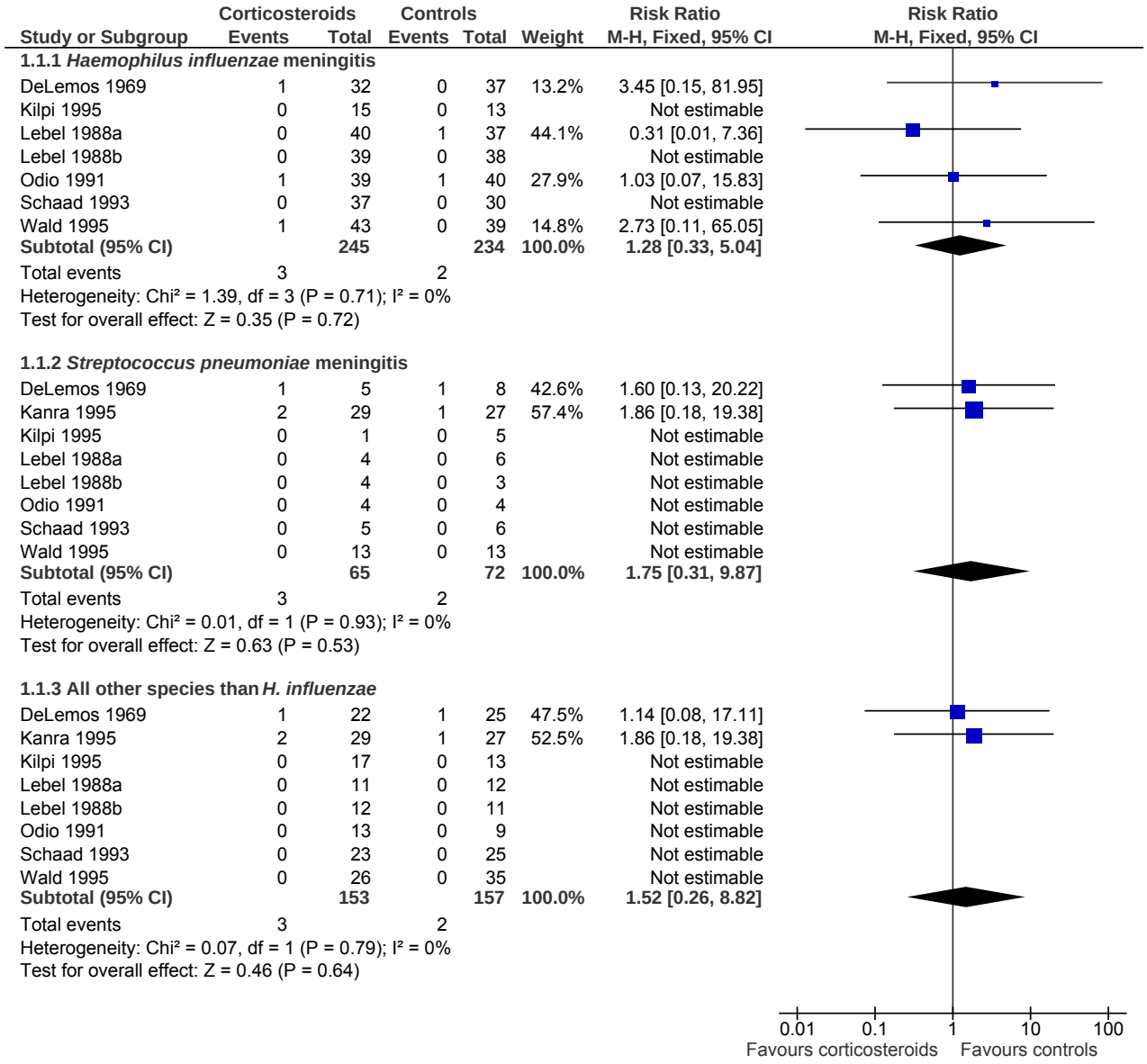


Figure H.9. Severe hearing loss from *Haemophilus influenzae* type B (Hib)

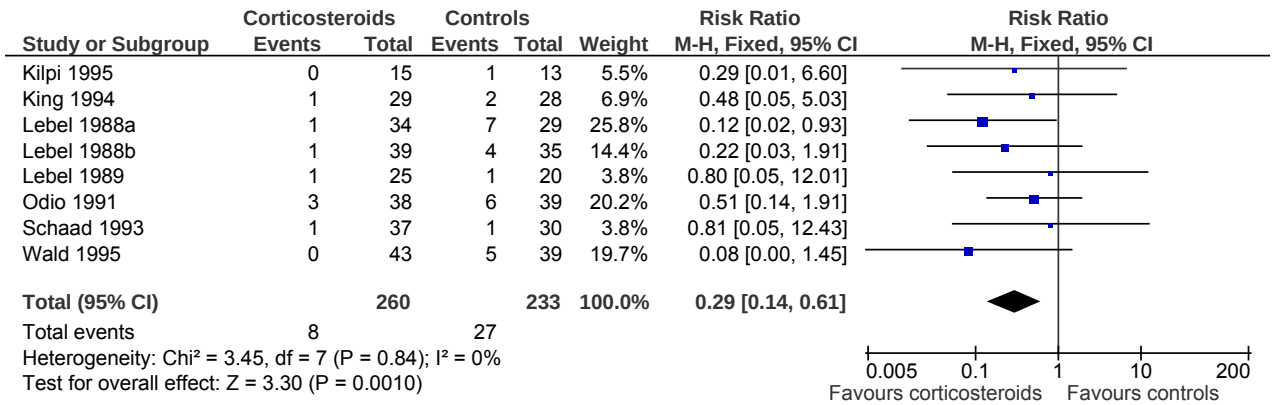


Figure H.10. Severe hearing loss from species other than *Haemophilus influenzae* type B (Hib)

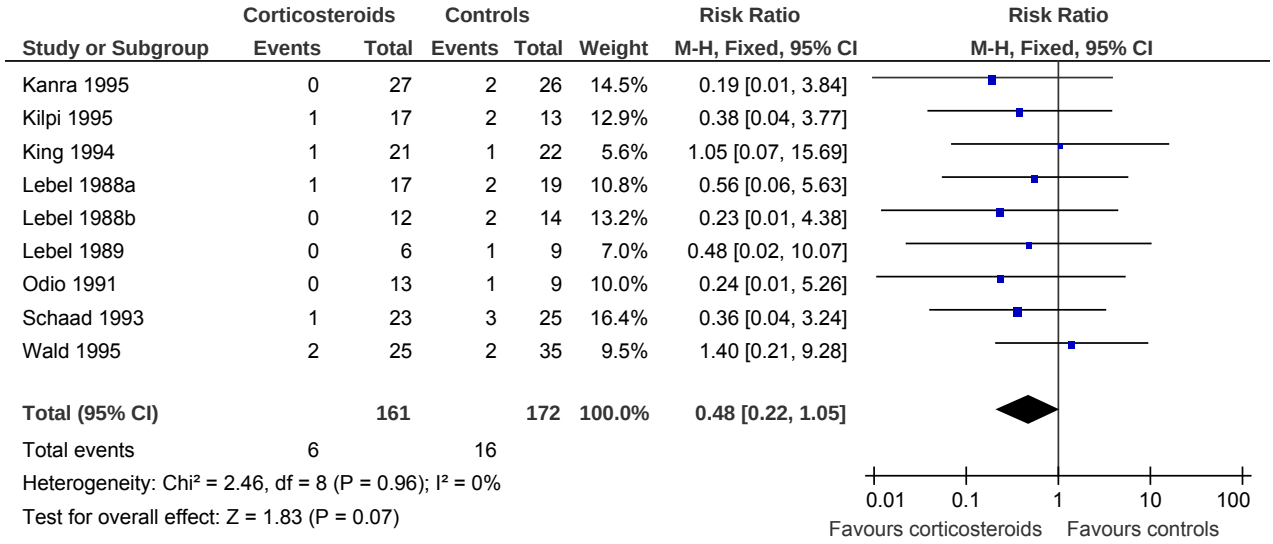


Figure H.11. Severe hearing loss from *Streptococcus pneumoniae*

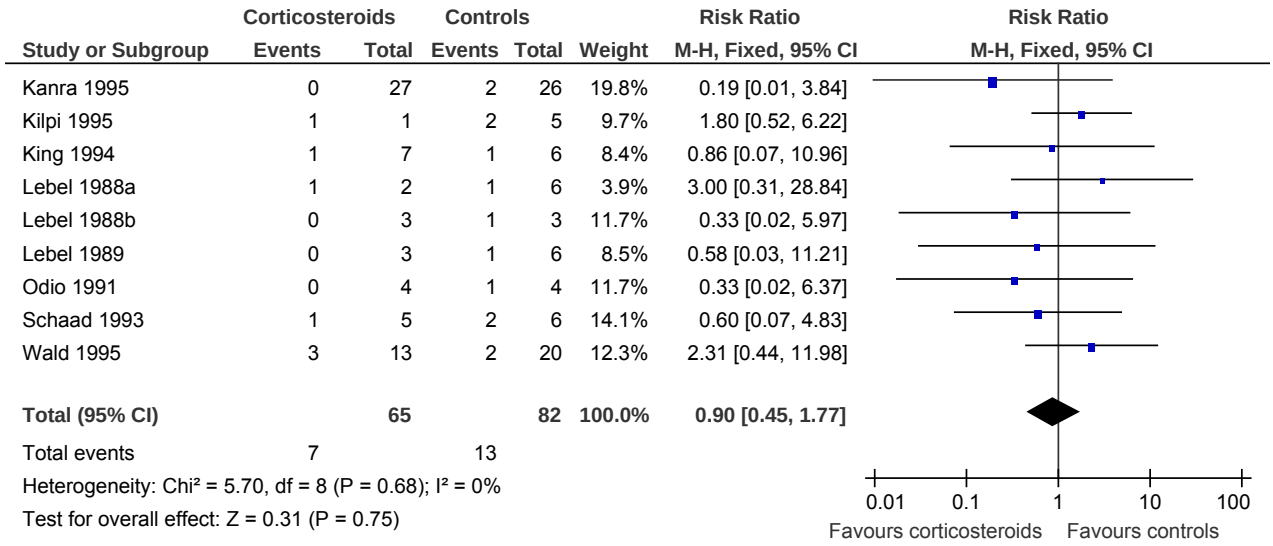


Figure H.12. Long-term neurological sequelae from all organisms

Study or Subgroup	Corticosteroids Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kanra 1995	2	29	1	27	2.5%	1.86 [0.18, 19.38]
Kilpi 1995	2	32	2	26	5.3%	0.81 [0.12, 5.38]
King 1994	5	37	3	44	6.6%	1.98 [0.51, 7.75]
Lebel 1988a	3	38	3	34	7.6%	0.89 [0.19, 4.14]
Lebel 1988b	2	43	6	41	14.7%	0.32 [0.07, 1.49]
Odio 1991	5	51	15	48	37.1%	0.31 [0.12, 0.80]
Schaad 1993	3	60	5	55	12.5%	0.55 [0.14, 2.19]
Wald 1995	4	68	6	74	13.8%	0.73 [0.21, 2.46]
Total (95% CI)		**358**		**349**	**100.0%**	**0.62 [0.39, 0.98]**
Total events	26		41			

Heterogeneity: Chi² = 6.80, df = 7 (P = 0.45); I² = 0%

Test for overall effect: Z = 2.03 (P = 0.04)

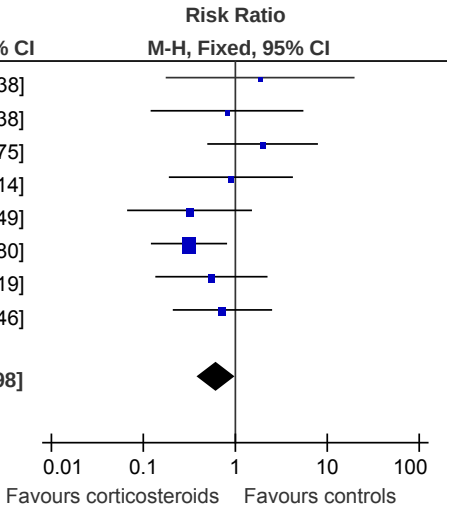


Figure H.13. Effect of timing of steroids on long-term neurological sequelae

Study or Subgroup	Corticosteroids Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Corticosteroids given before or with first dose of antibiotics						
Kanra 1995	2	29	1	27	4.3%	1.86 [0.18, 19.38]
Kilpi 1995	2	32	2	26	9.2%	0.81 [0.12, 5.38]
Odio 1991	5	51	15	48	64.6%	0.31 [0.12, 0.80]
Schaad 1993	3	60	5	55	21.8%	0.55 [0.14, 2.19]
Subtotal (95% CI)		**172**		**156**	**100.0%**	**0.48 [0.25, 0.92]**
Total events	12		23			

Heterogeneity: Chi² = 2.42, df = 3 (P = 0.49); I² = 0%

Test for overall effect: Z = 2.19 (P = 0.03)

12.1.2 Corticosteroids given after first dose of antibiotics						
King 1994	5	37	3	44	15.4%	1.98 [0.51, 7.75]
Lebel 1988a	3	38	3	34	17.8%	0.89 [0.19, 4.14]
Lebel 1988b	2	43	6	41	34.5%	0.32 [0.07, 1.49]
Wald 1995	4	68	6	74	32.3%	0.73 [0.21, 2.46]
Subtotal (95% CI)		**186**		**193**	**100.0%**	**0.81 [0.42, 1.57]**
Total events	14		18			

Heterogeneity: Chi² = 3.12, df = 3 (P = 0.37); I² = 4%

Test for overall effect: Z = 0.63 (P = 0.53)

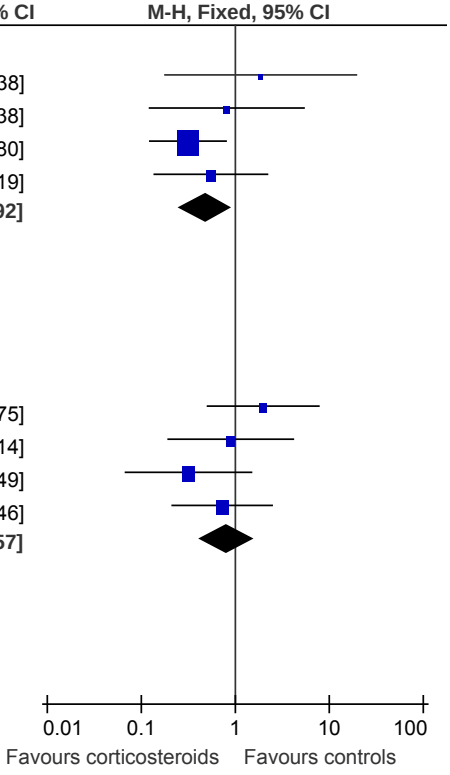


Figure H.14. Effect of timing of steroids on severe hearing loss

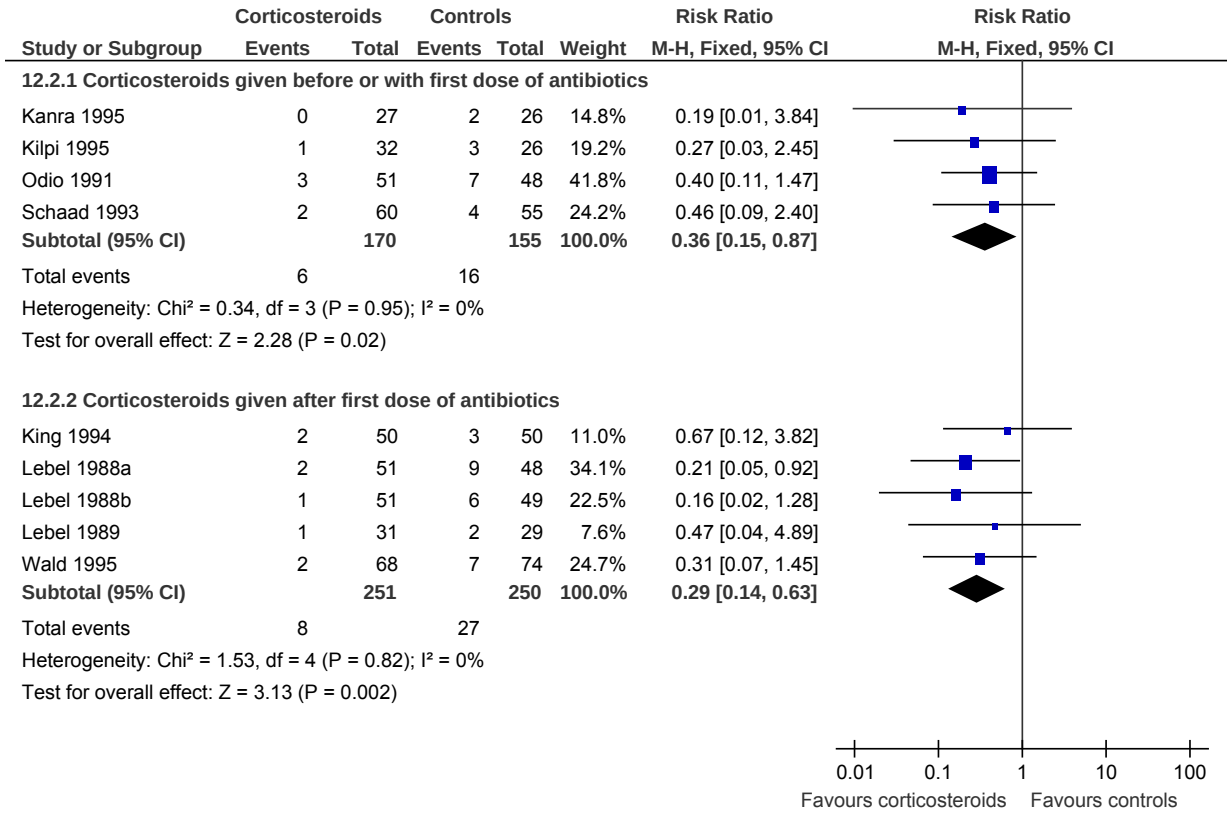


Figure H.15. Effect of timing of steroids on mortality

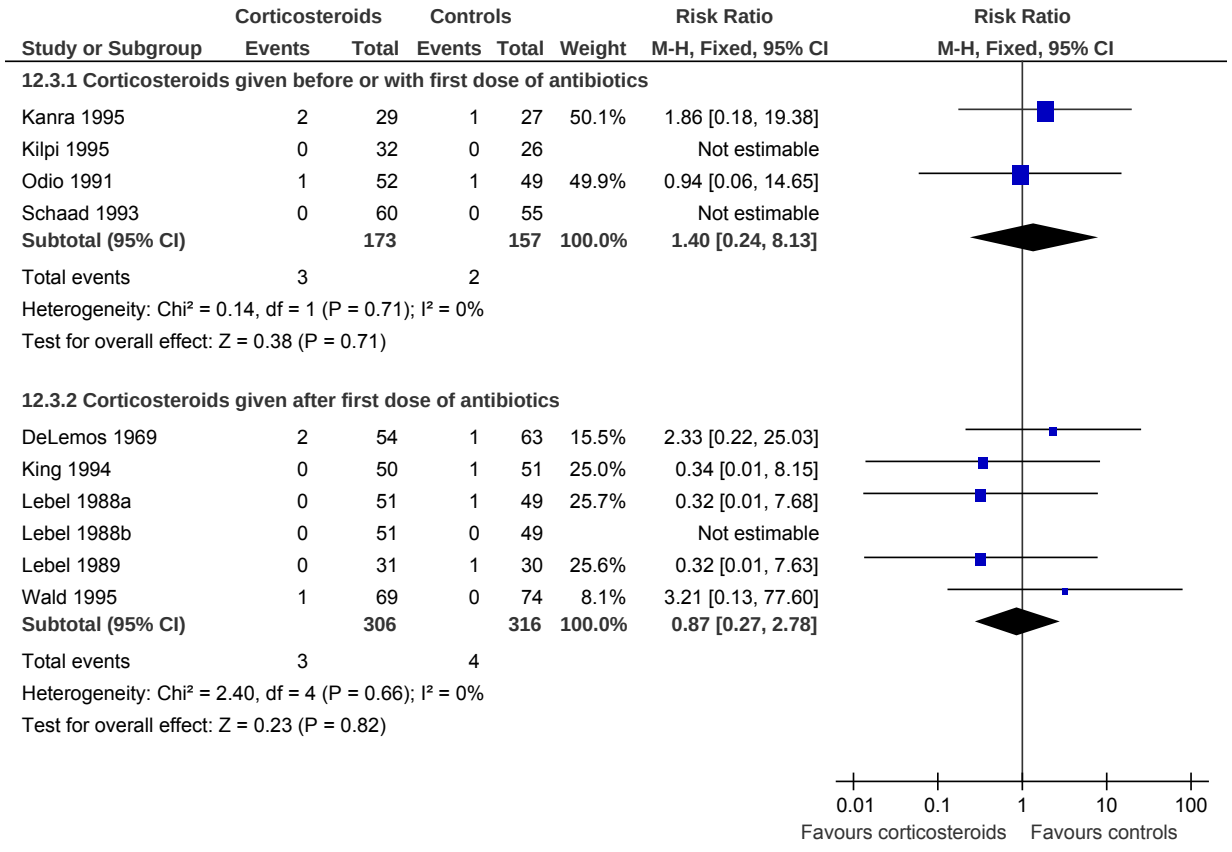


Figure H.16. Effect of timing of steroids on short-term neurological sequelae

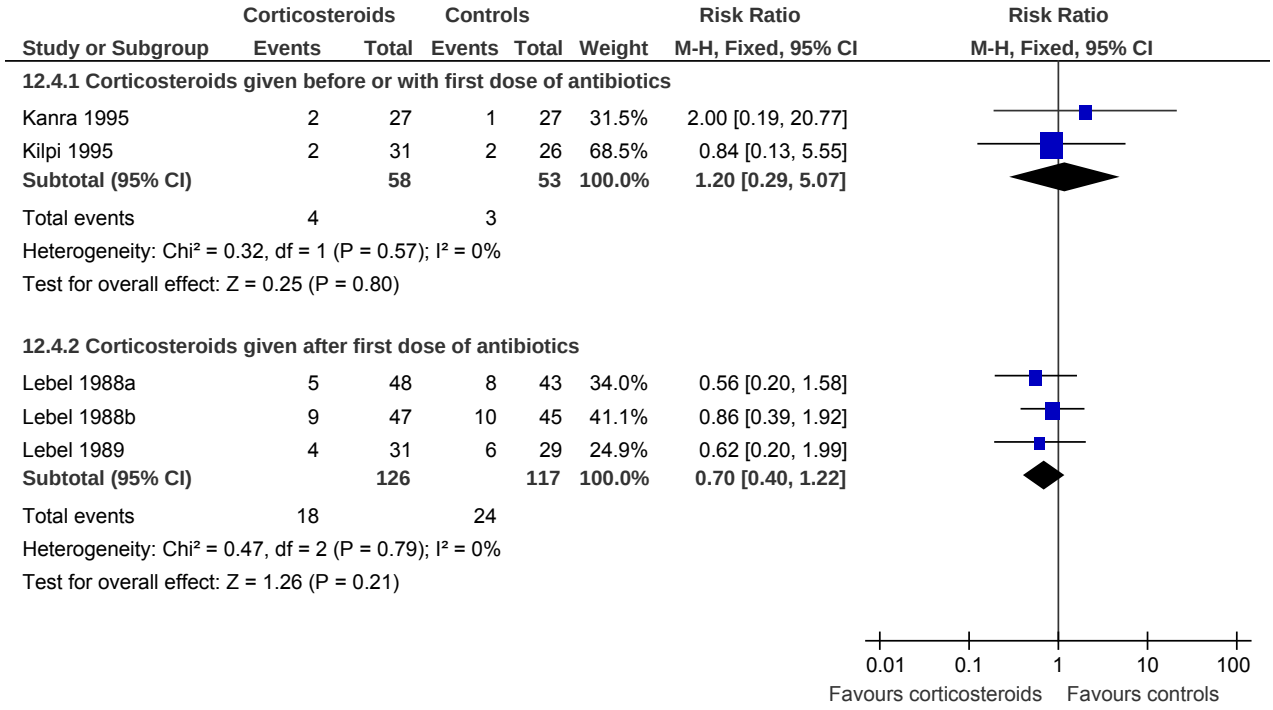


Figure H.17. Effect of timing of steroids on severe hearing loss from *Streptococcus pneumoniae*

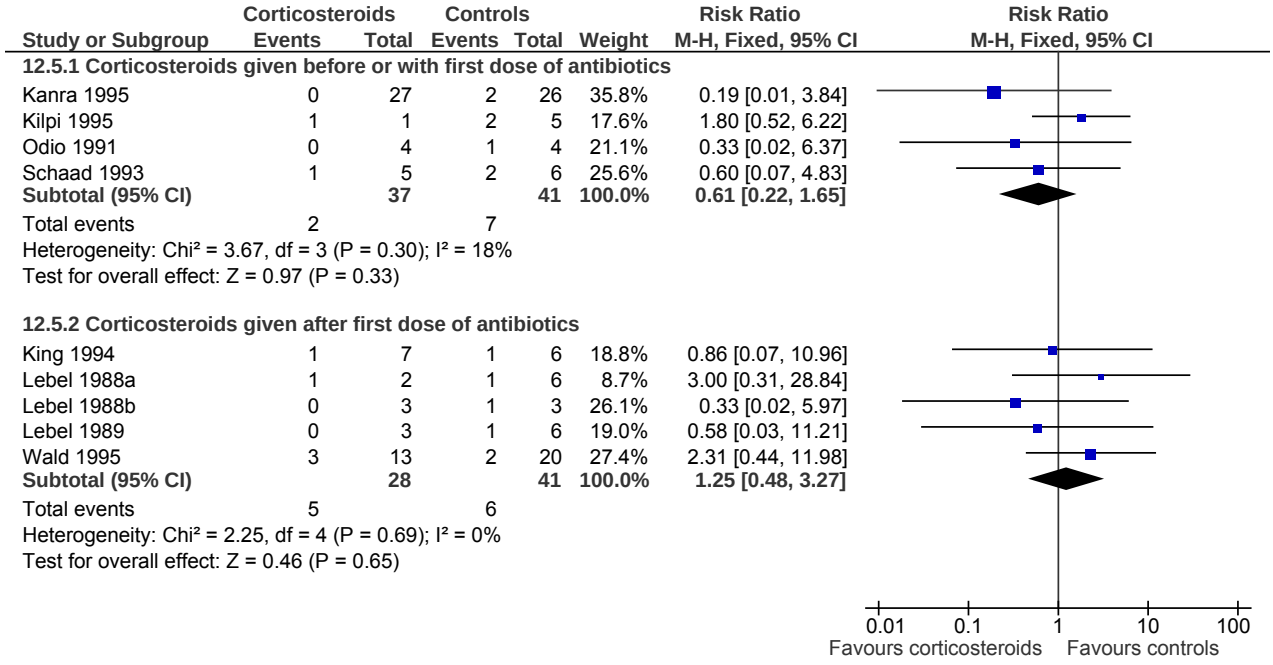
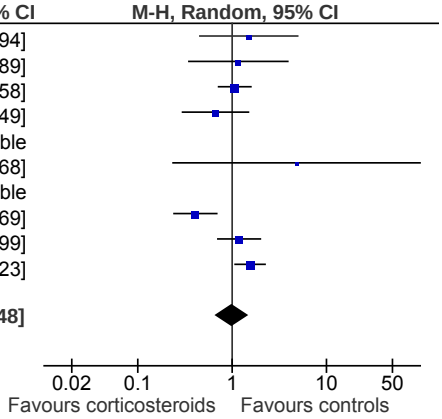


Figure H.18. Adverse effects following administration of corticosteroids

Study or Subgroup	Corticosteroids Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Belsey 1969	6	43	4	43	7.5%	1.50 [0.46, 4.94]
Kanra 1995	5	29	4	27	7.4%	1.16 [0.35, 3.89]
Kilpi 1995	21	32	16	26	18.9%	1.07 [0.72, 1.58]
King 1994	8	50	12	50	11.9%	0.67 [0.30, 1.49]
Lebel 1988a	0	51	0	49		Not estimable
Lebel 1988b	2	51	0	49	1.6%	4.81 [0.24, 97.68]
Lebel 1989	0	31	0	29		Not estimable
Odio 1991	13	52	30	49	16.6%	0.41 [0.24, 0.69]
Schaad 1993	22	60	17	55	16.7%	1.19 [0.71, 1.99]
Wald 1995	39	69	27	74	19.5%	1.55 [1.08, 2.23]
Total (95% CI)		**468**		**451**	**100.0%**	**1.00 [0.67, 1.48]**
Total events	116		110			

Heterogeneity: Tau² = 0.17; Chi² = 19.87, df = 7 (P = 0.006); I² = 65%
Test for overall effect: Z = 0.02 (P = 0.98)



Appendix I

Cost effectiveness of polymerase chain reaction for diagnosis in suspected meningococcal disease

I.1 Introduction

The recently published SIGN guideline on the 'Management of Invasive Meningococcal Disease in Children' recommends that all children with suspected invasive meningococcal disease should have blood taken for meningococcal polymerase chain reaction (PCR) to confirm the diagnosis.[27] However, while this may reflect the practice of some units in England and Wales, there is variation with other units only offering PCR in the event of a negative blood culture result.

While there is evidence from clinical studies showing that blood PCR has a greater diagnostic accuracy than blood culture, this does not automatically mean that routine PCR for all patients would represent an optimal use of scarce resources. Therefore, we compare the cost effectiveness of three diagnostic strategies in children presenting in secondary care with a suspicion of meningococcal disease:

1. routine PCR* and blood culture to all
2. blood culture followed by a PCR only if the blood culture is negative
3. routine 'rapid' PCR and blood culture for all

Strategies 1 and 2 are intended to reflect current practice in England and Wales. Strategy 3 has been included because it reflects an option that is technically feasible. However, the infrastructure does not currently exist to support such a strategy and is unlikely to exist within the next few years.

Children who present with a suspicion of meningococcal disease in secondary care will be started on antibiotic therapy immediately and the results of the diagnostic tests are less important than symptom severity in directing treatment. Most children would continue treatment for 7 days unless there was a confirmed negative diagnosis. The low sensitivity of blood culture means that a negative culture will rarely be used as a basis for discontinuation of therapy, which is why a PCR is usually required in order to confirm a diagnosis There is no expectation that these diagnostic strategies would have a clinically significant bearing on patient outcomes and therefore our economic assessment takes the form of a cost minimisation analysis. While routine PCR for all children may increase the diagnostic costs, the earlier availability of confirmed negative results may produce some offsetting savings by facilitating early discontinuation of treatment and hospital discharge.

I.2 Method

This analysis is undertaken from the perspective of the NHS and personal social services which is in accordance with NICE guidelines methodology.† The model was developed in Tree Age Pro 2007® using a Markov decision analytic approach to reflect the importance of the temporal aspect in the analysis. The Markov modelling approach involves a transition between different health states over time. The model is split into cycles of equal duration and at the end of each cycle a transition to another health state is possible unless the state is said to be 'absorbing'.‡ In this analysis we model outcomes over a period of 7 days to reflect the normal course of

* Targeting ctrA gene

† See www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

‡ Death is an example of an 'absorbing state' from which the patient cannot transfer in subsequent model cycles

antibiotic treatment for a child presenting in secondary care with a suspicion of meningococcal disease. A cycle duration of 4 hours was chosen, as most mortality occurs within 4 hours of initial presentation to secondary care. Furthermore, most of the cases in which a diagnosis of meningococcal disease can be ruled out on clinical grounds (that is, because of an alternative diagnosis) would become apparent within that 4 hour window. The model is run for 42 cycles in total.

A schematic of the model is shown in figures I.1 to I.4 alongside a description of the strategies. The Markov model notation is described briefly below.

Model notation

Decision node: the branch entering the decision node represents the population in which a decision between competing alternative strategies has to be made. The branches emanating from this node represent the alternative strategies that are available and are being compared in the analysis.

This indicates a truncated tree. Sometimes it is useful for presentational reasons not to show the complete decision tree.

This denotes the start of the Markov process.

Chance node: the branches emanating from a chance node give alternative patient pathways with implications for costs, outcomes and, in a Markov model, transition to other states. Probabilities are assigned to each branch emanating from a chance node.

Terminal node: in a Markov model these denote the transition to the various health states at the end of a cycle.

The Markov states

There are five Markov states:

- suspicion
- treat
- possible no disease
- discharged
- dead.

Suspicion

This is the initial state and all patients start in this state. However, all patients move out of this state at the end of the first cycle. This transition at the end of the first cycle does not necessarily mean that meningococcal disease is no longer suspected but rather that the initial patient cohort has been divided into subgroups. Patients are started on antibiotic treatment in this state.

Treat

Patients in this state receive the full 7-day course of antibiotic treatment.

Possible no disease

Testing has most value for patients in this state. Their objective condition is that they do not have meningococcal disease but that is not known to clinicians until they have a confirmed negative PCR. Most of these patients remain in this state until the PCR result becomes available, although a proportion of 'well' patients may be discharged with a negative blood culture. Other patients are discharged when the PCR (negative) becomes available

Discharged

Patients in this state are discharged from hospital and antibiotic treatment is discontinued

Dead

Meningococcal disease has a high mortality rate and a proportion of the initial cohort are assumed to have died during the first 4 hours after hospital admission with a suspicion of meningococcal disease

I.3 Diagnostic strategies with model schematics

Figure I.1: The diagnostic strategies

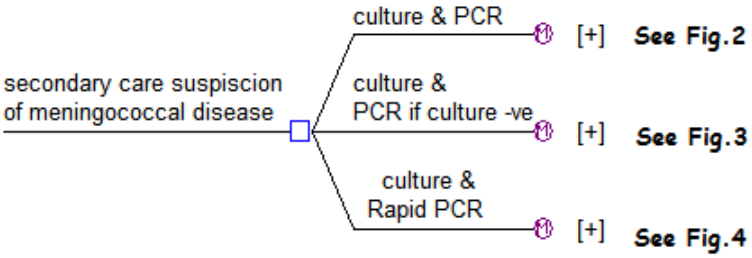
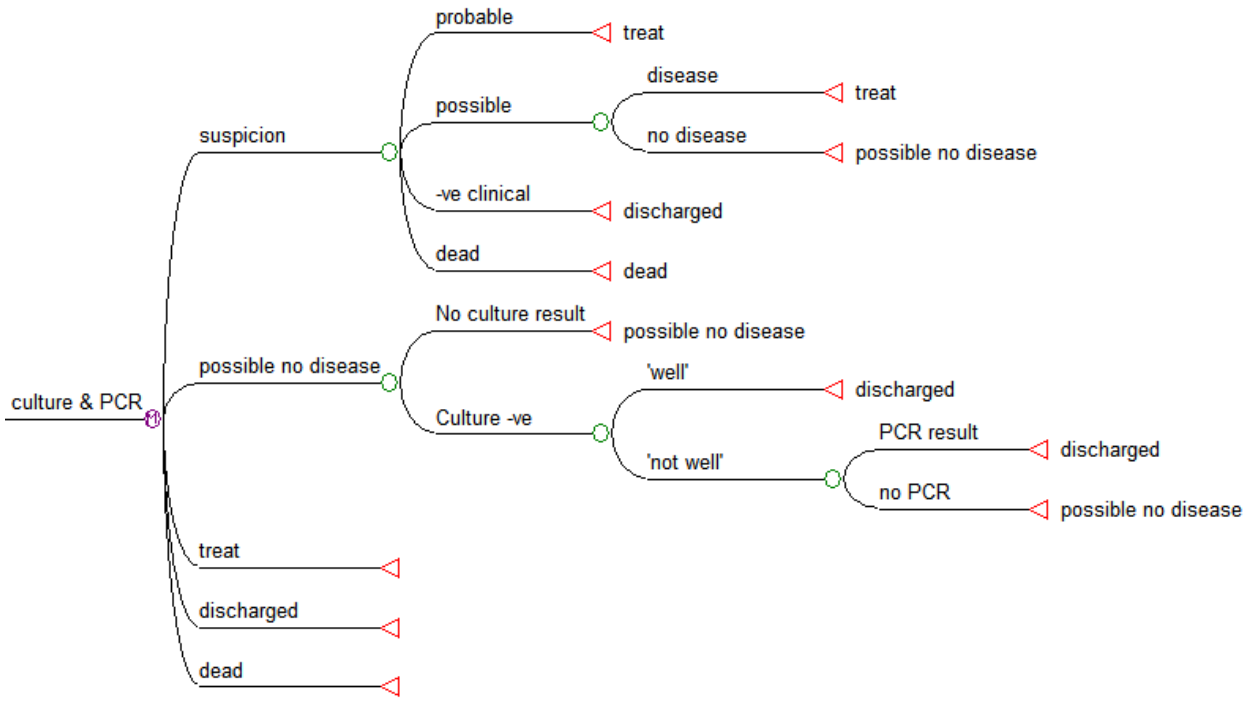


Figure I.2. Culture and PCR for everyone (Strategy 1)



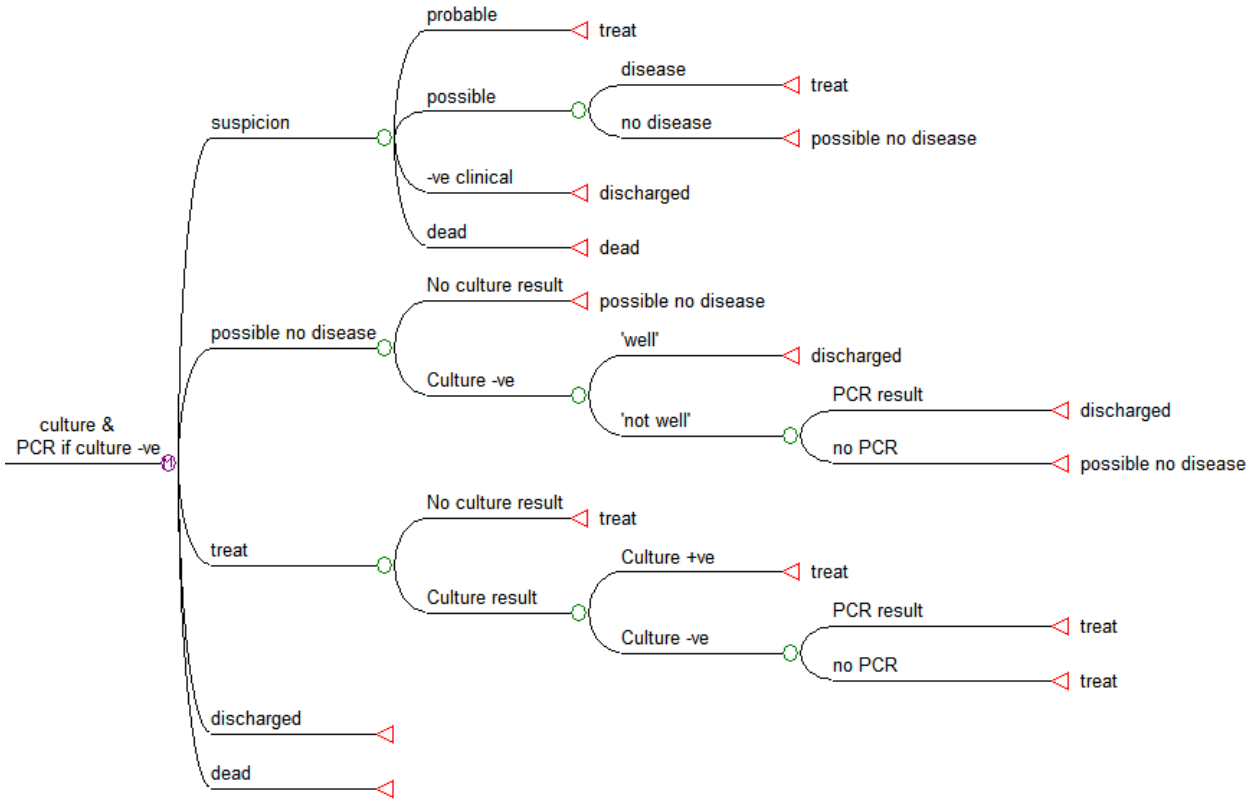
All patients in the cohort start the model with a suspicion of meningococcal disease and incur the costs associated with the PCR test*. At the end of the first cycle the cohort transfers to different health states. A proportion of patients are assumed to die in the first cycle (4 hours after admission to hospital) reflecting the high mortality associated with meningococcal disease. It is also assumed that for a proportion of patients it will become clear during the first cycle that they do not, in fact, have meningococcal disease.

Patients for whom a suspicion remains are sub-divided into two groups. The 'probable' group can, to all intents and purposes, be considered to have meningococcal disease and receive the full 7-day course of antibiotic treatment. The 'possible' group consists of those both with and without meningococcal disease. Those with disease will also receive the full 7-day course of

* Cost of the test plus transport cost

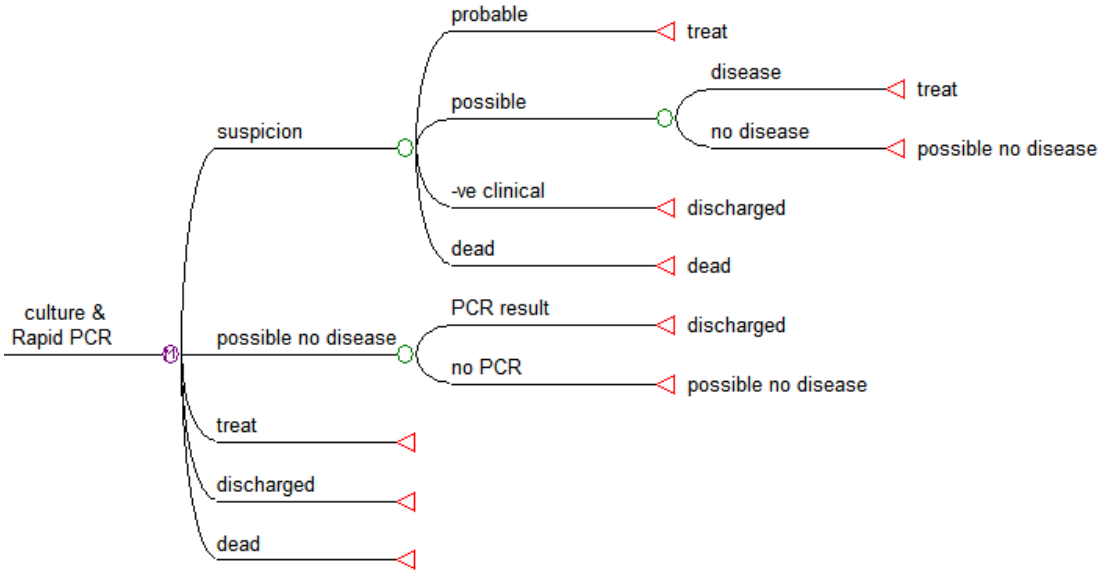
antibiotic treatment as PCR is used to rule out a positive diagnosis. Therefore, the 'possible' group with disease also transits to the 'treat' health state at the end of the first cycle. Thus the only group of patients who are not in an 'absorbing state' after the first cycle are the 'possible no disease'. A proportion of these will be in generally good health ('well') and are discharged when the negative culture is available. The 'not well' remain in the 'possible no disease' state until a negative PCR result is available.

Figure I.3. Culture and PCR if culture negative (Strategy 2)



In strategy 2 patients only have a PCR if the blood culture is negative. Blood culture has a high specificity and therefore most of the patients in the 'possible no disease' group will have a PCR following a negative blood culture, although that is not necessary in a subgroup of 'well' patients who, as in strategy 1, can be discharged once a negative blood culture result is available. In those in the 'treat' health state neither test result alters management and hence they remain in this 'absorbing' state. However, not all this group of patients will have a PCR as some will have a positive blood culture.

Figure I.4. Culture and rapid PCR for everyone (Strategy 3)



In strategy 3 all patients have a PCR test incurring the asscociated costs. As the PCR results are available earlier in this strategy, this facilitates an earlier discharge of patients in the 'possible no disease' group.

I.4 Model probabilities

Table I.1 shows the initial probabilities which determine the distribution of the cohort amongst the various states at the start of the Markov process. As meningococcal disease is suspected in all patients these probabilities are set so as ensure that all the cohort start in the suspicion state.

Table I.1. Initial state probabilities

State	Probability
Suspicion	100%
Possible no disease	0%
Treat	0%
Negative clinical	0%
Dead	0%

At the end of the first cycle all patients in the cohort transfer to a health state which is governed by the probabilities shown in table I.2.

Table I.2. First cycle probabilities

State	Probability (value used in sensitivity analysis)	Source	Notes
Probable case	10% (15%)	GDG	Transition to 'treat' health state
Possible	70% (50%)	GDG	A chance node then determines transition according to actual disease status
Possible no (disease)	90% (80%)	GDG	Transition to 'possible no disease' health state. The probability is of the subset (70%) defined as possible – it therefore represents 63% of the cohort

State	Probability (value used in sensitivity analysis)	Source	Notes
Possible (disease)	10% (20%)	GDG	Transition to 'treat' health state. The probability is of the subset (70%) defined as possible – it therefore represents 7% of the cohort
Negative clinical	10% (25%)	GDG	Transition probability to 'discharged' health state
Dead	10%	GDG	Transition probability

The 'treat', 'discharged' and 'dead' states are absorbing and patients in any of those states remain in that state until all model cycles are complete. It is only the 'possible no disease' health state from which any further transition occurs.

Within the model there are also implicit and explicit probabilities attached to the diagnostic accuracy of blood culture and PCR and these values are given in table I.3. The sensitivity of blood culture is a particularly important parameter for strategy 2 as it determines the extent to which additional PCR is undertaken in order to confirm the diagnosis. PCR has a very high diagnostic accuracy and culture has a negligible false positive rate which is the justification for the simplifying assumptions indicated in table I.3.

Table I.3. Test characteristics

Test characteristic	Value	Source	Notes
Culture sensitivity	30%	GDG	Varied as part of sensitivity analysis
Culture specificity	100%	GDG	Simplifying assumption
PCR sensitivity	100%	GDG	Simplifying assumption
PCR specificity	100%	GDG	Simplifying assumption

The model uses probabilities that are conditional on the cycle number to determine patient flow and transition dependent on test results. So the probabilities assigned to branches from a chance node indicating whether a test result is available will be set to zero until a certain time has elapsed (measured in cycles) at which point that probability will become 100%. Table I.4 shows the time-to-test result (in cycles) which is assumed in the model. These values can be varied in sensitivity analyses.

Table I.4. Time to test result

Test	Cycle available	Source
Culture	12	GDG
PCR	18	GDG
PCR if ordered after a negative culture	30	GDG
Rapid PCR	6	GDG

Finally, the model assumes that 20% of patients in the 'probable no disease' state would be 'well' enough to be discharged on the receipt of a negative culture result. Again, this value can be altered as part of sensitivity analysis.

I.5 Costs

The costs included in the model were restricted to those relevant to an incremental analysis. So, for example, the costs of taking a culture were not included as all children would have this. The costs used in the model are given in table I.5. All costs can be varied in sensitivity analysis.

Table I.5. Model costs

Item	Cost	Source	Notes
PCR	£25	Personal communication with Malcolm Guiver, HPA	
Rapid PCR	£25	GDG	
PCR transport	£25	GDG	
Rapid PCR rapid transport	£25	GDG	
Meningitis treatment cost per cycle	£76	NHS Tariff 2008–09 (HRG Code A25 Nervous system Infection)	Non-elective spell tariff is £2838 which is eligible for a 12% admitted patient tariff top-up. It is assumed that the tariff covers an inpatient stay of 7 days consisting of 42 cycles

I.6 Results

A comparison of the incremental costs of the three strategies using 'base–case' model inputs is shown in table I.6. These include the costs of meningitis treatment as the different strategies have different implications for patient discharge. The model assumes that the test strategy does not affect clinical outcomes and therefore the least costly strategy is considered to be the most cost effective.

Table I.6. Model costs

Strategy	Cost	Incremental cost
3. Rapid PCR to everyone	£943	
1. PCR to everyone	£1460	£517
2. PCR if culture negative	£1901	£441

I.7 Sensitivity analysis

Sensitivity analysis is used to explore the impact on the results of a change in model assumptions. This is particularly important where considerable uncertainty exists as to what the exact value of model inputs should be. If the conclusion of the model is not sensitive to changes in the assumptions within plausible ranges then there is greater confidence in the model output. Where results are sensitive to changes in the model's inputs then further research may be indicated to resolve the uncertainty. A number of one-way sensitivity analyses are described below, in which one input value is changed while holding all other values constant. The value is changed in a direction which favours strategy 2, as other changes would simply strengthen the base case result. Using this approach it can be possible to identify the cost effectiveness threshold for a model parameter holding all other base case inputs constant. If such a threshold value is outside the plausible range than that can be considered as lessening the uncertainty surrounding the base case finding.

Sensitivity of culture

Increasing the sensitivity of culture from 30% to 90% only reduces the cost of strategy 2 (PCR if culture negative) by £5 and therefore does not alter the ranking of the strategies in terms of their cost.

Days from culture-to-test result

If the results of culture were available after cycle 6 (day 1) the costs are:

- Strategy 3: £943
- Strategy 1: £1460
- Strategy 2: £1671

Even if the culture results were available after cycle 1, strategy 2 would be £19.50 dearer than strategy 1 (the cost of which is not altered by changes in the time-to-culture test result

Days from PCR-to-test result

In this sensitivity analysis, strategy 2 would only be cheaper than strategy 1 if PCR results were not available in strategy 1 until cycle 40 (almost 7 days).

Cost of PCR test and PCR transport

These costs can be treated as a single entity as collectively they represent the incremental test cost of PCR. The cost of the PCR test and transport has to be £1225 (compared to £50 in the base case analysis) before strategy 2 becomes a less costly strategy than strategy 1.

Proportion of 'well' patients who can be discharged after a negative culture

Ninety-three percent or more of the 'possible no disease' state patients would have to 'well' enough to be discharged following a negative culture in order for strategy 2 to be less costly than strategy 1, keeping all other base case inputs constant.

Cost of meningitis per cycle

The treatment cost of meningitis per cycle would have to be £3.12 or lower for strategy 2 to be less costly than strategy 1, and £1.47 or lower for strategy 2 to be less costly than strategy 3 (culture plus rapid PCR).

Cost of rapid PCR test and transport

The cost of the rapid PCR test plus transport would have to be £542 or greater for strategy 1 to be the cheapest strategy and the cost of the rapid PCR test plus transport would have to be £1008 or more in order for strategy 3 to be more expensive than strategy 2.

Clearly, uncertainty is not restricted to a single parameter value and if several inputs were changed in a direction favouring strategy 2 then the cost effectiveness thresholds would be different. For example, if we change the model inputs as follows this multi-way sensitivity analysis gives the results shown in Table I.7:

- Cost of meningitis per cycle: £50
- Proportion of 'possible no disease' who are well: 40%
- Cost of PCR + PCR transport: £100
- Cycles from PCR-to-test result: 24 (4 days)
- Cycles from PCR-to-test result strategy 2: 36 (6 days)
- Cycles from culture-to-test result: 6 (1 day)
- Sensitivity of culture: 40%

Table I.7. Multi-way sensitivity analysis

Strategy	Cost	Incremental cost
3. Rapid PCR to everyone	£638	
1. PCR to everyone	£1,255	£617
2. PCR if culture negative	£1,606	£351

Lastly we vary the probabilities (see table I.2) which govern the transition to the various 'states' at the end of the first cycle while holding all other model inputs constant at their base case values. This gives the results shown in Table I.8.

Table I.8. Sensitivity analysis varying first cycle transition probabilities

Strategy	Cost	Incremental cost
3. Rapid PCR to everyone	£1,087	
1. PCR to everyone	£1,416	£329
2. PCR if culture negative	£1,682	£266

I.8 Discussion

In the base case analysis only 17% of the cohort is in the 'treat' state, where the model assumes that all children have meningococcal disease. Strategy 2 (PCR only if culture negative) allows lower test costs in this cohort only to the extent that culture detects cases which, given the poor sensitivity, is limited. Lower test costs are also incurred for patients in the 'dead' and 'discharged' state which collectively account for another 20% of the base case population. However, 63% of the cohort are in the 'possible no disease' state and all these patients will have a negative culture. Most of the patients in this state will then have a PCR anyway in order to confirm the diagnosis. However, this delays the confirmatory negative diagnosis by 2 days (relative to strategy 1) with important implications for length of hospital stay.

If it is assumed that a negative culture would be available at cycle 6 (24 hours) rather than the base case which is cycle 12 (48 hours) then the relative cost effectiveness of strategy 2 would improve. However, even with this earlier availability of the culture result, reduced test costs would still not offset the costs associated with an additional 6 cycle (24 hours) hospital length of stay.

Naturally assuming a higher PCR test and/or PCR transport cost also improves the relative cost effectiveness of strategy 2 by increasing the savings associated with averted PCR testing. However, these costs would have to be far higher than they actually would be for the averted test savings to more than compensate for the longer length of stay associated with strategy 2.

In a similar vein, increasing the proportion of 'well' children in the 'possible no disease' state who can be discharged following a negative culture increases the relative cost effectiveness of strategy 2. This is because it reduces the number of children who would be eligible for PCR in strategy 2 and also reduces the additional length of stay associated with this strategy. However, a very high proportion would have to fit this 'well' category in order for strategy 2 to be cheaper than strategy 1.

Again the cost of meningitis treatment does affect the relative costs of the different strategies. The lower the cost of treatment, the lower the saving from averted hospital stay. However, treatments costs have to be implausibly low in order to alter the ranking of cost-effective treatments.

In the model rapid PCR and blood culture to all children (strategy 3) is more cost effective than PCR and blood culture to all children (strategy 1) because the base case assumes identical test and transport costs and the earlier availability of confirmed negative diagnoses facilitates earlier discharge.

I.9 Conclusion

The results presented above suggest that rapid PCR given to all children presenting in secondary care with a suspicion of meningococcal disease is the cheapest and, given the cost minimisation approach, most cost-effective strategy. This finding was not sensitive to changes in the model's inputs within plausible ranges. The principle driver of this result is that the rapid PCR allows a much earlier discharge of patients in the 'possible no disease' group.

Of the two strategies that are currently used in England and Wales (strategy 1 and strategy 2) blood culture and PCR (strategy 1) to all patients presenting in secondary care with a suspicion of meningococcal disease is more cost effective than only undertaking PCR in those with a negative blood culture (strategy 2). Low test sensitivity and a relatively low proportion of the cohort with actual disease means that strategy 2 averts only a small number of PCR tests. On the other hand, the delay of a confirmatory PCR negative as a result of not ordering the test at admission means that a large number of the cohort who do not have disease have a longer length of hospital stay than is necessary. Again, this finding is not sensitive to changes in the model's inputs within plausible ranges.

Appendix J

Cost effectiveness of antibiotics for treatment of bacterial meningitis and meningococcal disease

J.1 Introduction

This analysis assesses the cost effectiveness of three antibiotics (determined by current prescribing practices and antibiotic resistance patterns of causative organisms in England and Wales) for the treatment of suspected meningococcal disease or suspected bacterial meningitis in children.

In economic evaluation it is necessary to take into account benefits and effects as well as costs. However, the clinical review undertaken for this guideline did not find evidence to support a difference in efficacy between the comparator antibiotics. Where there is no difference in effectiveness between different comparators, a cost-minimisation approach is justified. By selecting the cheapest option more resources are freed up for alternative uses in the NHS without any concomitant loss in health gain in the population of concern.

Therefore, a cost model was developed in Microsoft Excel® to compare the costs of the relevant antibiotics (ceftriaxone, cefotaxime and benzylpenicillin).

This model looks at the cost effectiveness of empiric antibiotics for suspected bacterial meningitis or meningococcal septicaemia. See section J.6 for discussion of the cost of antibiotics for confirmed bacterial meningitis or meningococcal septicaemia.

J.2 Method

The cost analysis is undertaken from the perspective of the NHS and personal social services which is in accordance with NICE guidelines methodology.[*] The costing is done using a bottom-up or 'ingredients' approach which involves detailing the physical quantity of resources used in providing treatment alongside the unit cost of those resources. From this it is possible to estimate the total cost of treatment. This analysis has restricted itself to pharmaceutical, other consumables and staffing costs. Those costs that are the same across different treatments (such as the occupation of hospital bed) have been omitted as they have no impact on the cost differential between alternatives.

Unit cost data is taken from the most recently available published sources. Other model parameters are estimated using the expert opinion of the GDG.

The model did not address issues of antibiotic resistance which may, of course, have consequences for both health and resource use.

[*] www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

J.3 Model parameters and assumptions

The model's input values are given in tables J.1 to J.6.

Table J.1. Staff unit costs

Resource	Cost per hour[a]	Source
Band 5 nurse	£24.00	PSSRU Unit Costs of Health and Social Care (2009)[b]
Band 6 nurse	£30.00	PSSRU Unit Costs of Health and Social Care (2009)
Specialty registrar	£51.00	PSSRU Unit Costs of Health and Social Care (2009)

[a] Unit cost per hour including qualification costs
[b] Personal Social Services Research Unit. Unit Costs of Health and Social Care. Canterbury: University of Kent; 2009. www.pssru.ac.uk/pdf/uc/uc2009/uc2009.pdf

Table J.2. Staff tasks

Resource	Time (mins)	Source	Staff responsible
Giving intravenous drug[a]	10	GDG	1 x Band 5 nurse 1 x Band 6 nurse
Cannula placement[b]	10	GDG	1 x Specialty registrar
Supervision of infusion[c]	0	GDG	1 x Band 6 nurse

[a] Includes getting the drug and equipment to draw and make it up, checking the prescription and the patient; and delivery which takes 3–5 minutes
[b] This was estimated as 5–10 minutes. The higher value has been used for base case analysis
[c] Ceftriaxone is given as an infusion at a dose of 80 mg/kg. Benzylpenicillin and cefotaxime are given as a bolus

Table J.3. Treatment

Item	Value	Source	Notes
Weight of child (kg)	20	GDG	The implications of different weight is assessed using sensitivity analysis
Treatment duration (days)	2	GDG	–
Number of cannula insertions (benzylpenicillin)	2	GDG[a]	Best Practice Guidelines suggest that peripheral IVs should be changed every 72 hours
Number of cannula insertions (cefotaxime)	1	GDG	Best Practice Guidelines suggest that peripheral IVs should be changed every 72 hours
Number of cannula insertions (ceftriaxone)	1	GDG	Best Practice Guidelines suggest that peripheral IVs should be changed every 72 hours

[a] While the Best Practice Guidelines might suggest that only one cannula would be required for treatment of 2-day duration, the GDG felt that in practice, because of the number of doses, more than one cannula would be typically needed with benzylpenicillin

Table J.4. Drug costs and dose

Drug	Dose (mg/kg)	Vial quantity[a]	Cost per vial	Frequency (per day)	Source
Benzylpenicillin	50	600 mg	£0.46	4	BNFC (2009)
Cefotaxime	50	500 mg	£2.14	3	BNFC (2009)
Ceftriaxone	80	1 g	£10.17	1	BNFC (2009)

[a] For a child of a given weight the total dose (mg) is calculated. This is then used to determine the minimum number of vials needed to meet that dose given the size of the vials

Table J.5. Consumable costs

Item	Quantity	Unit cost	Total cost	Antibiotic dose	Cannula insertion	Infusion	Source
Normal saline flush: 10 ml ampoule	1	£0.46	£0.46	Yes	Yes	Yes	BNFC (2009)
10 ml leur lock syringe	1	£0.28	£0.28	No	No	Yes	Medisave UK Ltd[a]
Manometer extension line (50 cm)	1	£1.68	£1.68	No	No	Yes	NHS Supply Chain (Oct 2007)[b]
Hepsal flush: 5 ml ampoule	1	£0.25	£0.25	Yes	Yes	No	BNFC (2009)
5 ml syringe	1	£0.23	£0.23	Yes	No	No	First Aid Warehouse[c]
2 ml syringe	1	£0.22	£0.22	Yes	No	No	First Aid Warehouse[d]
Needle	1	£0.05	£0.05	Yes	No	No	First Aid Warehouse[e]
Non-sterile gloves	1	£0.16	£0.16	No	Yes	No	NHS Supply Chain (Oct 2007)[f]
Clinell wipe	1	£0.07	£0.07	No	Yes	No	SP Services[g]
IV burette giving set	1	£2.06	£2.06	No	Yes	No	SP Services[h]
500 ml bag of dextrose/saline	1	£1.15	£1.15	No	Yes	No	Baxter[i]
Cannula t-piece extension (t-connector)	1	£1.47	£1.47	No	Yes	No	NHS Supply Chain (Oct 2007)[j]
Splint	1	£1.00	£1.00	No	Yes	No	Personal communication with Diarrhoea & Vomiting in children GDG member
Micropore tape	0.01	£0.60	£0.01	No	Yes	No	BNFC (2009)[k]
Bandage to secure splint	0.01	£0.30	£0.00	No	Yes	No	BNFC (2009)[l]
Sterile occlusive dressing	0.01	£1.30	£0.01	No	Yes	No	BNFC (2009)[m]
Total cost per dose/insertion/infusion				£1.21	£6.64	£2.42	

[a] www.medisave.co.uk/advanced_search_result.php?keywords=leur+lock&x=15&y=13 £27.99 per box of 100 (accessed 9 February 2010)
[b] Price each if bought in a box of 50: £1.56; updated to 2008/09 prices using HCHS index (PSSRU 2009)
[c] www.firstaidwarehouse.co.uk/xpp-sterile_single_use_hypodermic_syringe_5ml_pack_of_100.html £22.91 per pack of 100 (accessed 9 February 2010)
[d] www.firstaidwarehouse.co.uk/xpp-sterile_single_use_hypodermic_syringe_2ml_pack_of_100.html £21.62 per pack of 100 (accessed 9 February 2010)
[e] www.firstaidwarehouse.co.uk/xpp-needles_sterile_23g_x_1.html £4.79 per pack of 100 (accessed 9 February 2010
[f] Gloves examination latex powder free sterile pairs (£7.32 for box of 50, 6 box order) updated to 2008/09 prices using HCHS index (PSSRU 2009)
[g] £2.99 for box of 40: www.spservices.co.uk/product_info.php/products_id/3708
[h] www.spservices.co.uk/product_info.php/products_id/2292 (accessed 9 February 2010)
[i] www.ecomm.baxter.com/ecatalog/browseCatalog.do?lid=10011&hid=10000&cid=10001&key=cfcf53b16b6ef78076c8decf6a58e2ff&pid=462468 (accessed 9 February 2010)
[j] IV accessory: T connector £1.37 each for 50 box order; updated to 2008/09 prices using HCHS index (PSSRU 2009)
[k] Micropore®, 1.25 cm = 60p for 5 metres; assume 5 cm used per cannula
[l] Type 1, 5 m (all): 2.5 cm = 30p - assume 5 cm
[m] Extensible water-impermeable plastic film spread with an adhesive mass. 2.5 cm × 3 m = £1.30; assume 3 cm length

The purchase of medical equipment also carries an opportunity cost but differs from operating costs, such as labour and consumables, in certain respects. The purchase of equipment often involves an upfront payment (or investment) before use. However, that cost is fixed as it does not vary with the quantity of treatment provided. The equipment can often be used over a number of years before it needs to be replaced.

Capital costs have two facets:

- Opportunity cost: the money spent on the equipment could have been invested in some other venture, yielding positive benefits. This is calculated by applying an interest rate to the sum invested in the equipment.
- Depreciation cost: the equipment has a certain lifespan and depreciates over time. Eventually, the equipment has to be replaced.

In economic evaluation, the usual practice is to annuitise the initial capital outlay over the expected life of the equipment. This gives an 'equivalent annual cost' which can then be apportioned to the procedure on a pro rata basis based on the typical equipment use over the course of the year in order to derive a unit cost of using that equipment. Calculating the equivalent annual cost means making an allowance for the differential timing of costs by discounting.

The formula for calculating the equivalent annual cost is:

$$E = (K - [S \div (1 + r)n]) \div A(n, r)$$

where:

E = equivalent annual cost
K = purchase price of equipment
S = resale value
r = discount (interest rate)
n = equipment lifespan
A(n, r) = annuity factor (n years at interest rate r)

Assigning equipment costs to an individual procedure is less straightforward. Firstly, it is necessary to calculate an equivalent annual cost, reflecting the initial purchase cost of the equipment. Table J.6 shows the values that were used to calculate the equipment cost per infusion for an annuity factor of 2.8.

Table J.6. Equipment costs

Item	Quantity	Unit cost	Total cost (K)	Resale value (S)	Life (years) (n)	Discount rate[a] (r)	Infusion time (minutes)	Use per day (hours)
Infusion pump	1	£1,069	£1,069	£0	3	3.5%	30	12
Equipment cost per infusion £0.05								

Source: Medisave UK Ltd: www.medisave.co.uk/needles-amp-syringes-syringe-drivers-c-137_386.html (accessed 12 February 2010)
[a] The discount rate is that stipulated in the 2009 NICE Guidelines Manual

J.4 Results

A comparison of the costs of the different antibiotics is shown in table J.7 and graphically in figure J.1. The calculation of these costs is described here.

Drug cost

The steps are as follows:

1. Calculate the total number of mg per dose = mg/kg × weight of child
2. Calculate the minimum number of vials to provide that dose*
3. Calculate the cost per dose
4. Calculate the total doses = doses per day × days of treatment
5. Calculate the total drugs cost = cost per dose × number of doses

So, for example, benzylpenicillin in the base case analysis:

Weight of child = 20 kg

Dose = 50 mg/kg so 50 x 20 = 1,000 mg per dose

Vial quantity = 600 mg so 2 vials required

Cost per vial = £0.46 so £0.92 per dose

Frequency = 4 times per day

Treatment duration = 2 days

Number of doses = 4 × 2 = 8

Drugs cost = £0.92 × 8 = **£7.36**

Staffing cost

Staffing costs relate to two tasks: placement of cannula and giving intravenous treatment. The cost of doing each of these tasks is calculated according to the staff doing them and the time it takes. The total staff cost is then calculated according to the number of times these tasks are repeated in a course of treatment. In the base case analysis it is assumed that a child would require two cannula placements with benzylpenicillin or a single cannula with ceftriaxone and cefotaxime. The number of times intravenous treatment is given is the same as the total number of doses (see calculation above).

So, using benzylpenicillin as the example in the base case analysis:

For cannula placement:

One specialty registrar @ £51 per hour

Time to place cannula = 10 minutes so £51 × (10÷60) = £8.50

Number of cannulas = 2

Cost of cannula placement = 2 × £8.50 = **£17.00**

For giving intravenous treatment:

One band 5 nurse @ £24 per hour

One band 6 nurse @ £30 per hour

Time to give IV treatment = 10 minutes so £54 × (10÷60) = £9.00

Number of of doses = 8

Cost of IV treatment = 8 × £9.00 = **£72.00**

Total staff cost† = £17.00 + £72.00 = **£89.00**

* The dose is determined by a child's weight, so cost is an increasing function of weight. However, , the increase in cost is not smooth as it is determined by the number of vials needed to provide the required dose rather than the total dosage.
† Totals may reflect rounding to two decimal places

Consumable cost

In addition to the drugs, other consumable resources are used for each antibiotic dose given and for each cannula insertion.

In table J.5 this is calculated as:

Antibiotic dose = £1.21

Cannula insertion = £6.64

Using the example of benzylpenicillin in the base case analysis:

For cannula placement :

Number of cannulas = 2

Cannula consumable cost = 2 × £6.64 = £13.28

For antibiotics:

Number of doses = 8

Antibiotic consumable cost = 8 × £1.21 = £9.68

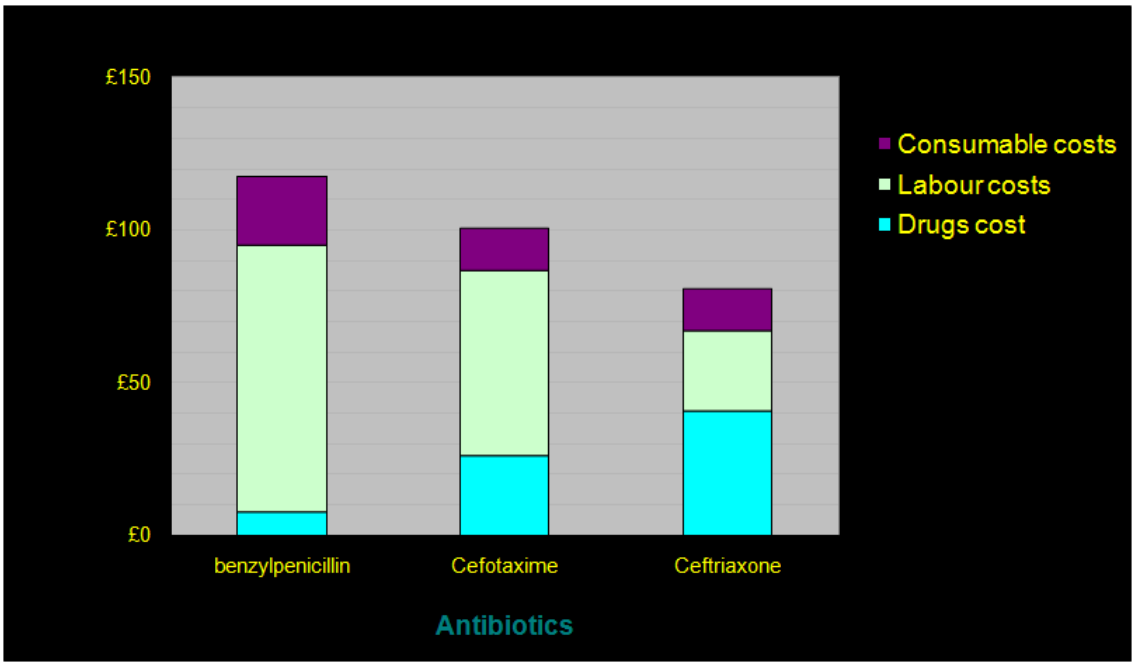
Total consumable cost = **£22.96**

Total cost of benzylpenicillin = £7.36 + £89.00 + £22.96 = **£119.32**

Table J.7. Total costs of antibiotic treatment for a 20 kg child

Cost	Benzylpenicillin	Cefotaxime	Ceftriaxone
Drug	£7.36	£25.68	£40.68
Staff	£87.33	£62.50	£26.50
Consumable	£22.78	£13.90	£13.99
Total	**£117.48**	**£102.08**	**£81.17**

Figure J.1. Total costs of antibiotic treatment for a 20 kg child



J.5 Sensitivity analysis

In economic evaluation a technique known as sensitivity analysis is used to assess the importance of uncertainty around baseline parameter values. If the model's conclusions are not affected by changing assumptions and parameter values then there is greater confidence in the result suggested by the model. On the other hand if the model's results are particularly sensitive to small changes in some parameter values this may indicate what the key drivers of the results are and where further research is needed to resolve uncertainty.

In this model there is some uncertainty around the timing and frequency of certain tasks. The results may also vary according to the weight of the child as drug dose is a function of weight. Two one-way sensitivity analyses are shown in figures J.2 and J.3 which indicate the effect of changing a single parameter value holding everything else in the model constant.

Figure J.2. Sensitivity analysis: varying child's weight

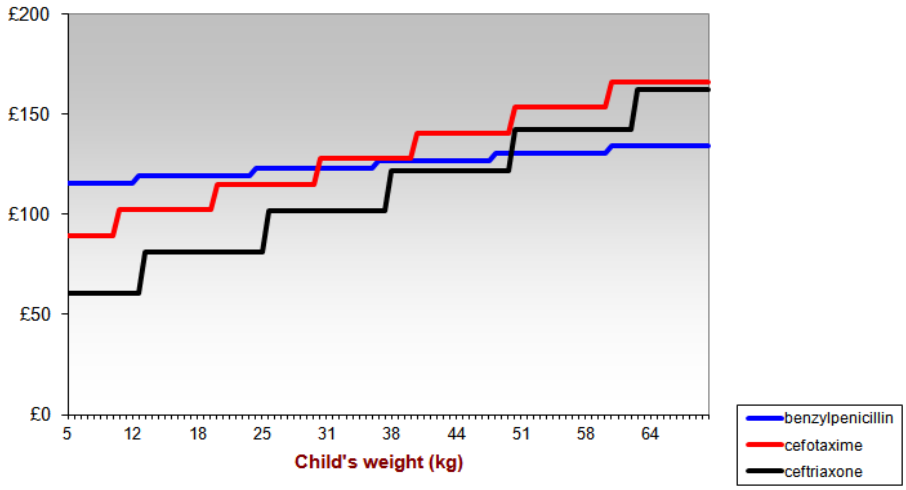
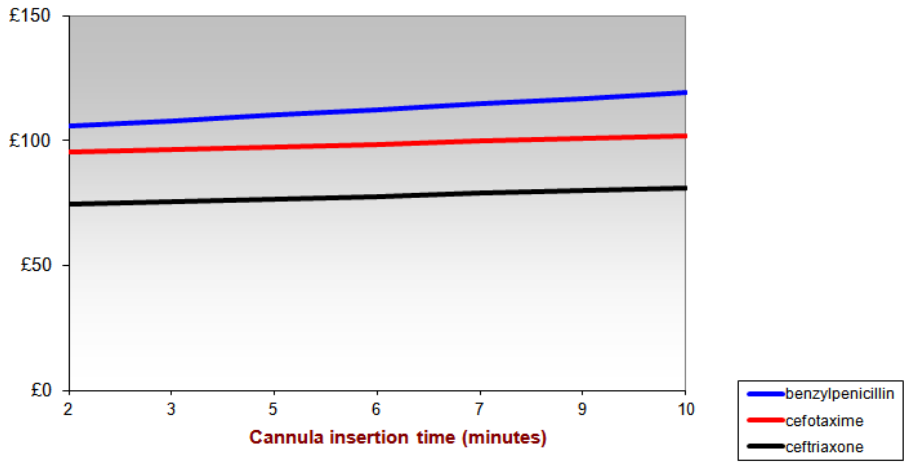


Figure J.3. Sensitivity analysis: varying cannula insertion time



J.6 Discussion

With the base case assumptions ceftriaxone appears to be the cheapest antibiotic. This is because the saving in staff time associated with a treatment only administered once a day more than offsets the substantially higher cost of the drug itself. Sensitivity analyses generally showed that these results were not sensitive to one-way changes in model parameters, with ceftriaxone remaining the cheapest option under most scenarios. However, an exception was a sensitivity analysis suggesting that the results were sensitive to the weight of the child. Benzylpenicillin was cheaper than cefotaxime in children with a weight greater than 30 kg and cheaper than ceftriaxone in children weighing more than 50 kg.

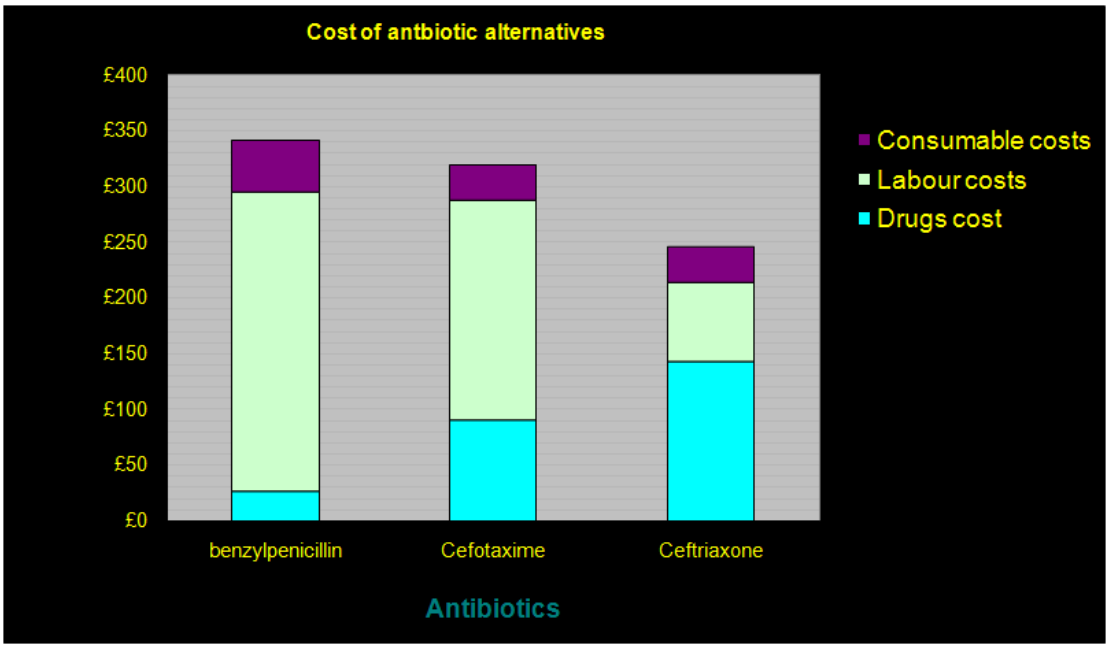
This analysis strongly suggests that ceftriaxone is the most cost-effective antibiotic for the treatment of suspected meningococcal disease or suspected meningitis in a majority of children as, despite a bi-modal age distribution of disease, peak incidence would occur in children less than 20 kg in weight. However, it should be borne in mind that the cost model did not take into account any complicated 'downstream' effects on health or costs arising from antibiotic resistance, patterns of which may vary locally.

Cost of antibiotics for confirmed bacterial meningitis/meningococcal septicaemia

The model is essentially that used for empiric antibiotics for suspected disease. Treatment duration is longer and most costs increase as a linear function of duration. For patients treated with ceftriaxone earlier discharge may be possible, although actual practice varies, as only one dose per day is required. In the event of early discharge antibiotic treatment could be completed either by a home visit from a community nurse or as an out-patient in a 'day-bed' area of the hospital. In the absence of any increased risk early discharge is likely to increase the cost effectiveness of ceftriaxone relative to other antibiotic alternatives.

The results shown in figure J.4 indicate why this is likely to be the case.

Figure J.4. Total costs of antibiotic treatment for a 20 kg child with confirmed bacterial meningitis or meningococcal septicaemia



Appendix K

Cost effectiveness of crystalloid versus colloid intravenous fluid for resuscitation in suspected meningococcal septicaemia

K.1 Introduction

The GDG concluded that there is insufficient evidence to decide whether crystalloid or colloid solutions have greater efficacy for volume resuscitation in children and young people with meningococcal septicaemia. An absence of evidence of a difference is not the same as evidence of no difference but it does mean that with the current state of knowledge the GDG felt unable to adequately assess the relative clinical effectiveness of the two alternatives.

However, there is a large differential between the acquisition costs of the two alternatives per treatment:

- Crystalloid: £0.49
- Colloid: £34.00

As there is insufficient evidence to suggest better clinical effectiveness with colloid then there is a rationale for recommending crystalloid over colloid on economic grounds. However, we acknowledge that the alternatives may not, in fact, be equally effective and this is important because mortality is the primary outcome. If crystalloid were to prove the more effective option then the economic case would be clear cut, with crystalloid dominating colloid (cheaper and more effective). However, if colloid were more effective then the cost effectiveness would depend on whether the additional benefit was worth the additional cost. Below we undertake a simple 'what-if' threshold analysis to determine what additional benefit would be needed for colloid to be considered as the cost-effective option.

K.2 Calculations

The first step is to calculate the incremental cost of colloid relative to crystalloid:

Incremental cost: £34 − £0.49 = £33.51

The 2009 NICE guidelines manual advises that an intervention will generally be considered cost-effective if the incremental cost effectiveness ratio is £20,000 per quality adjusted life year (QALY) or less. In other words, the NHS is willing to pay up to at least £20,000 per QALY gained.

Incremental cost ÷ incremental QALY gain = incremental cost per QALY

£33.51 ÷ incremental QALY gain = £20,000

Or, rearranging:

£33.51 ÷ £20,000 = incremental QALY gain

Incremental QALY gain = 0.0017

This means that as long as a patient gains at least 0.0017 QALY as a result of having the more expensive colloid, it would still be considered cost effective relative to colloid. However, what we are really talking about is the average QALY gain across all patients having colloid as opposed to crystalloid. For most patients it will make no difference (otherwise we'd have evidence to this effect) and in these the incremental QALY gain will be zero. However, if colloid is more effective, then in a very small minority of patients the difference is a matter of life and death and a very substantial gain would result. The average QALY gain of colloid over crystalloid is a weighted

average of the QALY gain in patients for whom the treatment makes no difference and the patients for whom treatment is life saving. So, if we saved one patient as a result of colloid what total number of patients treated is needed to give an average QALY gain of 0.0017?

QALY gain from averted death

The QALY is NICE's preferred measure of benefit for economic evaluation. This is because it is because it can be seen as a generic measure of health which allows a comparison across treatments which affect different dimensions of health, such as morbidity versus mortality.

It embodies the two principle objectives of health care:

- increase longevity
- increase quality of life.

Estimating a QALY involves placing a quality of life weight on a particular health state. This quality weight lies between 0 and 1, where 1 denotes full or 'perfect health' and 0 denotes death[*].

Assume that the mean age of children and young people covered by this guideline and requiring resuscitation is 10 years. The remaining life expectancy at age 10 years, taken from the ONS 2005–2007 interim life tables[†], is approximately 70 years. If we further assume that all these years would be lived in a state of 'perfect health' we can obtain an upper bound estimate of the QALY gain from an averted death at age 10 years. However, in line with the NICE Guidelines Manual (2009), these QALY are discounted at a rate of 3.5% per annum.

So the present value of one QALY per annum for 70 years is:

$$\sum_{i=0}^{70} \frac{1}{1.035^i} = 26.91 \text{ QALYs}$$

This looks spuriously precise, especially as we know that most lives are not lived in perfect health for their entirety. Therefore, it seems reasonable to round the above value down to give an approximate gain of 25 QALYs rising from an averted death. Figure K.1 shows the impact of discounting on the total QALY gain.

N is the maximum total number treated to achieve the cost-effectiveness threshold for each additional death averted through use of colloid.

$$\text{Average QALY gain} = \left(25 \times \frac{1}{\mathrm{N}}\right) + \left(0 + \left(\frac{(\mathrm{N}-1)}{\mathrm{N}}\right)\right)$$

$$0.0017 = \frac{25}{\mathrm{N}}$$

Or, rearranging:

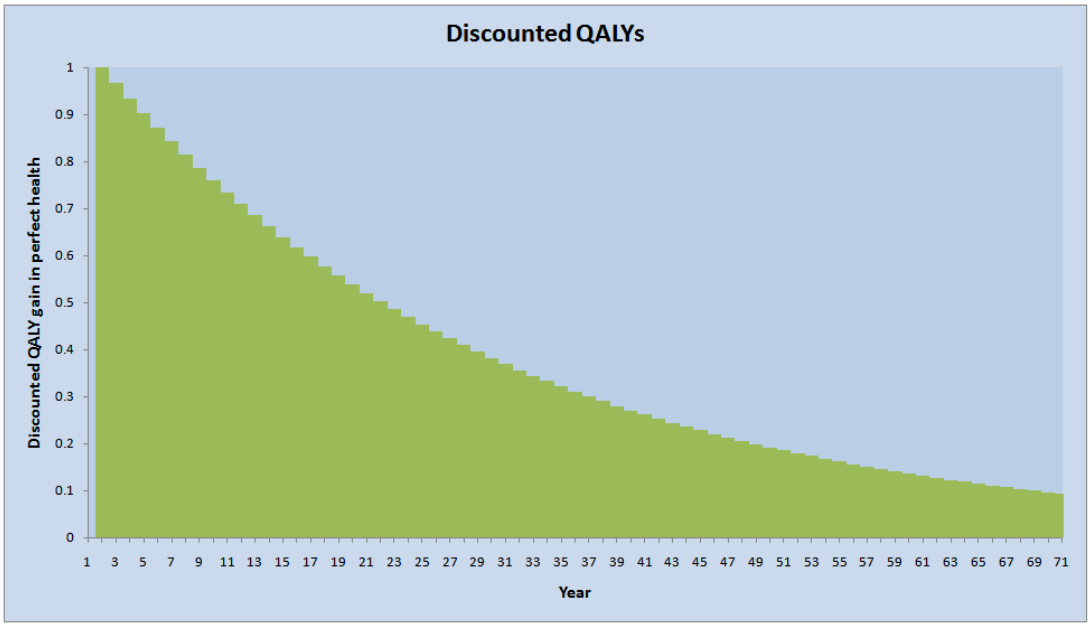
$$\mathrm{N} = \frac{25}{0.0017}$$

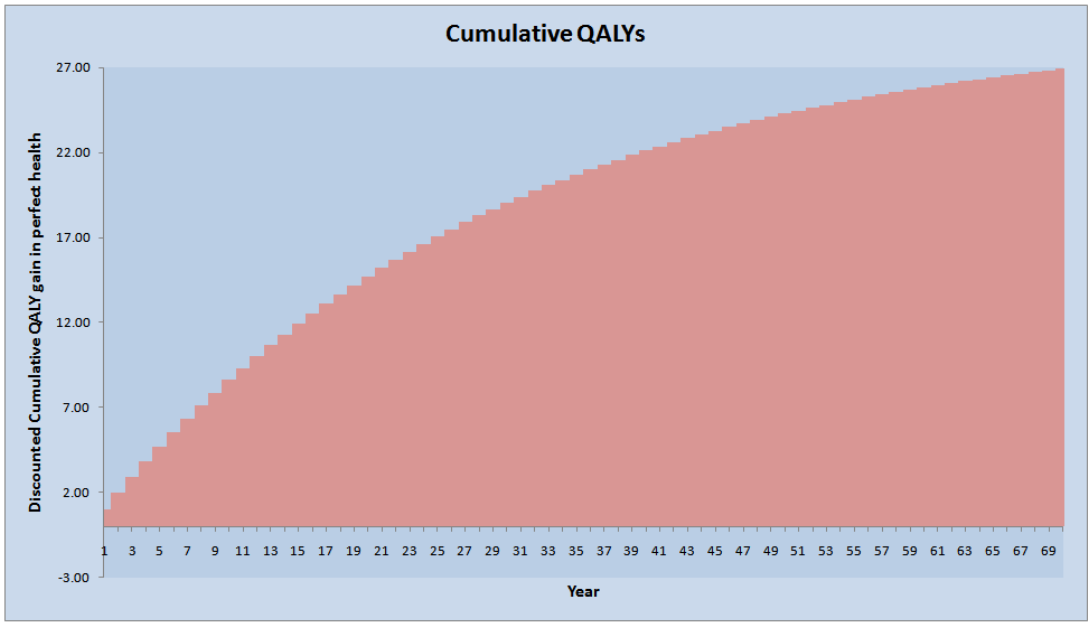
$$\mathrm{N} = 14{,}700$$

[*] It is possible to give a QALY weight of less than or equal to 0 to health states if they are deemed to be no better or worse than death

[†] www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459

Figure K.1. Graphs to show annual and cumulative QALY gain of 70 years lived in perfect health





K.3 Discussion

The calculations above assume that the only outcome with an impact on health related quality of life is survival. For example, it is implicitly assumed that both alternatives have an identical side effect profile. Were this not the case, differences in morbidity, short and long term, would also have to be incorporated into calculating the differential QALY between these two treatments.

The 'what-if' threshold analysis presented above suggests that colloid could be considered cost effective, despite its much higher cost, providing that it saved at least one life per 14,700 treated patients. This is not to say that it is cost effective, but rather it gives the level of clinical effectiveness relative to crystalloid that would be necessary given the current differential in cost and NICE's willingness to pay threshold of £20,000 per QALY. However, given that there is no reason currently to prefer one treatment over the other in terms of their efficacy, then it makes sense currently to recommend crystalloid. This is a considerably cheaper option and thereby frees up resources for alternative NHS use and patient benefit.

Appendix L

Cost effectiveness of complement deficiency screening in survivors of meningococcal disease

L.1 Introduction

Deficiencies in the complement system are the most well known of the inherited defects of the immune system reported in certain patients with meningococcal disease. Those with complement deficiency are prone to recurrent meningococcal disease or other serious bacterial diseases. It is argued that the potential benefits of identifying complement deficiency include lowering the threshold for diagnosis of subsequent infection and identifying family members who may be at risk of meningococcal disease or other infection. It is further posited that some improvement in health outcomes could be achieved in such people by offering immunisation and long-term antibiotic prophylaxis.

However, these potential benefits of screening and treatment entail an opportunity cost in that the resources used to identify and treat complement deficiency could be deployed in some alternate use which would also generate improvements in health outcomes. Therefore, it is important to consider the cost effectiveness of screening (and subsequent treatment[*]) for complement deficiency.

Clearly, as with any screening test, the prevalence of the condition being screened for is an important determinant of cost effectiveness. The lower the prevalence the greater the resources used in identifying a single case. Evidence on the prevalence of complement deficiency was estimated as part of a systematic review undertaken for this guideline.

Unfortunately there is insufficient evidence to reasonably estimate the cost effectiveness of screening for complement deficiency, particularly in relation to treatment efficacy. Therefore, the GDG requested that a threshold cost-effectiveness analysis be undertaken to aide guideline recommendations. A 'what-if' approach allows the cost effectiveness to be explored under alternative scenarios and for the cost-effectiveness thresholds for parameter values to be estimated in these scenarios. The GDG members could use such results in conjunction with their clinical judgement to ascertain the likely cost effectiveness of complement screening. This could then form the basis of a practice or research recommendation.

L.2 Method

A model has been developed in Microsoft Excel® in order to evaluate the cost effectiveness of complement screening under various 'what-if' scenarios. A single worksheet allows the user to simultaneously change model inputs while observing the impact these changes have on model outcomes (see figure L.1).

Changing the model's inputs

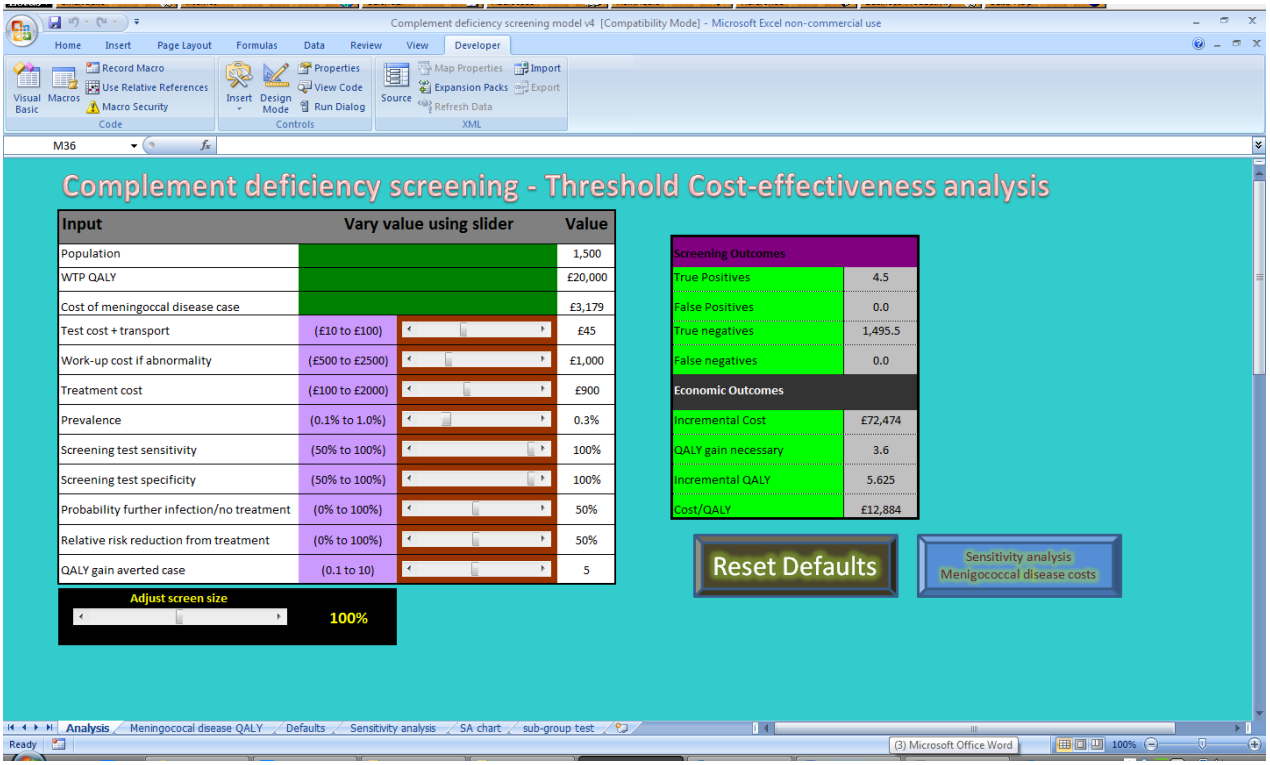
On the left hand side of the screen is a data entry grid which facilitates sensitivity and threshold analyses. Most of the values can be changed within certain ranges by using a slider. All inputs can additionally be entered directly in the 'value' column and here the input values are not restricted.

[*] The benefits of screening are contingent on effective treatment and therefore the cost effectiveness of screening cannot be adequately addressed in isolation from treatment costs and effects

The model results grid

On the right hand side of the screen is a results grid. The 'QALY gain necessary' is the amount of quality adjucted life years (QALYs) that are needed for cost effectiveness according to the 'willingness to pay' (WTP) for a QALY, which has a default value of £20,000. If the 'QALY gain necessary' is greater than the actual 'incremental QALY' then the incremental cost-effectiveness ratio will be greater than £20,000 per QALY. Any change in the input(s) is immediately reflected in the results grid making it easy to explore thresholds for cost effectiveness under different scenarios.

Figure L.1. Screen shot of model



Base-case inputs

The base case inputs are given in table L.1. Some of these inputs can be considered evidence-based but others simply reflect an illustrative 'what-if' scenario. Therefore, no greater weight should necessarily be given to the base case output than the output in different scenarios.

Table L.1. Model inputs and values

Input	Value	Slider range	Source
Population	1500	n/a	GDG
Willingness to pay (WTP) for a QALY	£20,000	n/a	NICE
Cost of meningococcal disease	£2,838	n/a	NHS Tariff 2008–09 (HRG Code A25 Nervous System Infection)
Test and test transport cost	£45	£10 to £100	Personal communication, Paul Holloway, GDG[a]
Work-up cost if abnormality	£1000	£500 to £2500	Personal communication, Paul Holloway
Antibiotic prophylaxis cost	£900	£100 to £2000	GDG, BNF (57) Netten (2008)[b]
Complement deficiency prevalence	0.3%	0.1% to 1.0%	GDG
Sensitivity	100%	50% to 100%	Assumption, GDG

Input	Value	Slider range	Source
Specificity	100%	50% to 100%	Assumption, GDG
Probability of further infection or no treatment	50%	0% to 100%	GDG
Relative risk reduction from treatment	50%	0% to 100%	GDG
QALY gain from an averted case	5.0	0.1 to 10	Estimate (See below)

[a] The initial 'screen' for cases of meningococcal disease would include an evaluation of the Alternative Complement Pathway and thus in addition to the total haemolytic complement (THC; or CH50) would include an AP50 (alternative pathway). The cost of this would be roughly the same as for the CH50 so the cost of the two would be approximately £30 plus the cost of the C3 and C4 (see www.clinlabnavigator.com/Tests/ComplementProfile.html) at £5.50, giving approximately £35.50 in total for initial testing plus £10 transport cost

[b] Treatment is assumed to consist of a Meningococcal polysaccharide A, C, W135 and Y vaccine (£16.73) and an antibiotic prophylaxis phenoxmethylpenicillin (250 mg) taken twice daily (£1.25 for 28 tablets) for 70 years, an approximation of the remaining life expectancy. Drug costs are taken from BNF 57 and discounted at 3.5% per annum where appropriate. It was additionally assumed that vaccination would require 10 minutes of a community nurse's time

QALY estimate

Meningococcal disease is associated with a number of long term sequelae impacting on health related quality of life and a health state utility was assigned to each of the sequelae identified in a review produced for this guideline. It was assumed that in the absence of meningococcal disease, children would live a further 70 years in perfect health.* With the exception of death, it was assumed that the sequelae were lifelong but that they had no additional impact on life expectancy. It was then possible to estimate a discounted QALY loss associated with each outcome. QALYs were discounted an annual rate of 3.5% in accordance with the NICE Guidelines Manual. The review undertaken for this guideline produced estimates of the proportion of children with meningococcal disease with these sequelae. These proportions were used to produce a weighted average estimate for the QALY gain from an averted case of meningococcal disease (see table L.2).

Table L.2. Weighted QALY loss from a case of meningococcal disease

Outcome	Health utility[a]	QALY loss	Weight	Weighted QALY loss	Source and notes
Death	0	26.91	0.10	2.69	
Hearing loss	0.72	7.53	0.04	0.30	Shephard et al 2005
Amputations	0.71	7.80	0.02	0.16	Shephard et al 2005 Based on single amputation
Other orthopaedic complications	0.99	0.27	0.017	0.0002	Health state not clearly defined so 'dummy' estimate
Skin complications	1.00	0.00	0.10	0.00	Shephard et al 2005 Based on utility for 'skin scarring'
Neurological sequelae	0.06	25.30	0.07	1.77	Shephard et al 2005 Based on utility for 'neurological disability'
Pain	0.99	0.27	0.21	0.002	Health state not clearly defined so 'dummy' estimate
Total weighted QALY loss				5.0	

[a] Health state utilities given are point estimates with some inherent uncertainty as to the precise values

* This is an approximation based on an assumption that the average age at infection is 10 years and that life expectancy at birth is 80 years

L.3 Results

The results are presented below for a range of scenarios (tables L.3 to L.12). In all scenarios where an input is varied, all other model inputs are kept constant at their default value.

Scenario analyses

Base-case values

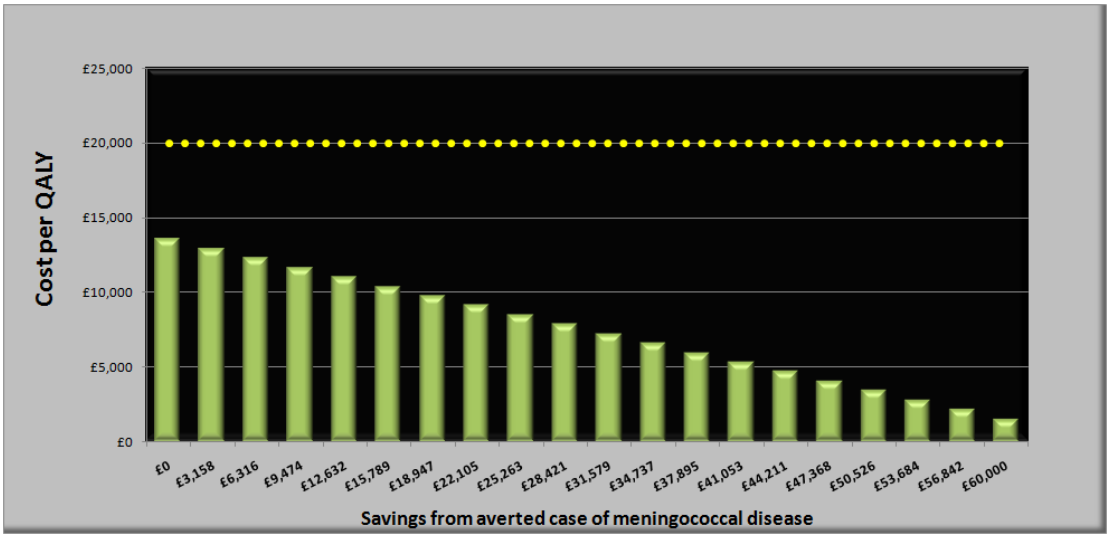
Table L.3. Results for scenario using model's default data values

Output	Value
Incremental cost	£72,474
Incremental QALY	5.6
Incremental cost/QALY	£12,884
Minimum QALY gain needed	3.6

Varying the cost of a case of meningococcal disease

In this sensitivity analysis the cost of a case of meningococcal disease is varied between £0 and £60,000. The results are illustrated in figure L.2. If the cost of a case were £67,600 or more then screening would generate net savings with costs of screening and treatment more than offset by the averted costs of meningococcal disease.

Figure L.2. Incremental cost per QALY varying the costs of meningococcal disease



Varying the initial screen/transport cost

In this analysis the cost of the initial screening test and transport is varied between a low of £10 and a high of £100.

Table L.4. Results varying the cost of the initial screen/transport cost

Output	Test cost £10	Test cost £100
Incremental cost	£19,974	£154,974
Incremental QALY	5.6	5.6
Incremental cost/QALY	£3,551	£27,551
Minimum QALY gain needed	1.0	7.7

The threshold test/transport cost for an incremental cost-effectiveness ratio of £20,000 per QALY is £71.

Varying the cost of work-up if an abnormality is found

In this analysis the cost of work-up if an abnormality is found is varied between £500 and £2,500.

Table L.5. Results varying the cost of work-up if an abnormality is found

Output	Work-up cost £500	Work-up cost £2,500
Incremental cost	£70,224	£79,224
Incremental QALY	5.6	5.6
Incremental cost/QALY	£12,484	£14,084
Minimum QALY gain needed	3.5	4.0

The work-up costs would have to exceed £9,900 in order to generate an incremental cost-effectiveness ratio of £20,000 per QALY.

Varying the cost of treatment in identified cases of complement deficiency

Here the cost of treatment in identified cases is varied between £100 and £2,000.

Table L.6. Results varying the cost of treatment in identified cases of complement deficiency

Output	Treatment cost £100	Treatment cost £2,000
Incremental cost	£68,874	£77,424
Incremental QALY	5.6	5.6
Incremental cost/QALY	£12,244	£13,764
Minimum QALY gain needed	3.4	3.9

Treatment costs would have to exceed £9,800 to give an incremental cost-effectiveness ratio of £20,000 per QALY.

Varying the prevalence of disease

The impact of varying the prevalence of complement deficiency between 0.1% and 1.0% is assessed here.

Table L.7. Results varying the prevalence of complement deficiency

Output	Prevalence 0.1%	Prevalence 1.0%
Incremental cost	£69,158	£84,079
Incremental QALY	1.9	18.8
Incremental cost/QALY	£36,884	£4,484
Minimum QALY gain needed	3.5	4.2

The threshold prevalence for an ICER of £20,000 per QALY is 0.2%.

Varying the screening test sensitivity

In this analysis we evaluate how estimates of cost effectiveness vary with the detection rate of the screening test between 50% and 100%.

Table L.8. Results varying the sensitivity of the screening test

Output	Sensitivity 50%	Sensitivity 100%
Incremental cost	£69,987	£72,474
Incremental QALY	2.8	5.6
Incremental cost/QALY	£24,884	£12,884
Minimum QALY gain needed	3.5	3.6

The threshold for cost effectiveness at £20,000 per QALY for test sensitivity is 63% holding all other model values constant.

Varying the screening test specificity

Here the effect of varying the specificity of the initial screening test between 50% and 100% is assessed.

Table L.9. Results varying the specificity of the screening test

Output	Specificity 50%	Specificity 100%
Incremental cost	£1,493,199	£72,474
Incremental QALY	5.6	5.6
Incremental cost/QALY	£265,458	£12,884
Minimum QALY gain needed	74.7	3.6

At a specificities of 98% and below, the incremental cost effectiveness exceeds £20,000 per QALY.

Varying the probability of further infection if no treatment

This analysis explores the consequences of varying the probability of reinfection* in the absence of treatment between 0% and 100%.

Table L.10. Results varying the probability of reinfection in the absence of treatment

Output	Probability of reinfection 0%	Probability of reinfection 100%
Incremental cost	£76,050	£68,897
Incremental QALY	0	11.25
Incremental cost/QALY	Dominated†	£6,124
Minimum QALY gain needed	3.8	3.4

The threshold probability of reinfection to produce an ICER of £20,000 per QALY is 32%.

Varying the efficacy of treatment

This analysis investigates the relationship between treatment and efficacy and the cost effectiveness of screening for complement deficiency. The relative risk reduction from treatment is varied from 0% (treatment does not work) to 100% (treatment offers complete protection from future infection).

* A simplifying assumption is made that there would only be one further case of reinfection in the absence of treatment
† More costly without any health gain, so unambiguously not cost-effective

Table L.11. Results varying the relative risk reduction with treatment

Output	Relative risk reduction 0%	Relative risk reduction 100%
Incremental cost	£76,050	£68,897
Incremental QALY	0	11.25
Incremental cost/QALY	Dominated	£6,124
Minimum QALY gain needed	3.8	3.4

The threshold relative risk reduction for an ICER of £20,000 per QALY is 32%.

Varying the QALY gain from an averted meningitis case

In table L.12 two scenarios show how the cost effectiveness varies with changes in the assumptions about the QALY gain from an averted case of meningococcal disease from 0.1 QALY per case to 10 QALYs per case.

Table L.12. Results varying the QALY gain from an averted case of meningococcal disease

Output	QALY gain from averted case 0.1	QALY gain from averted case 10
Incremental cost	£72,474	£72,474
Incremental QALY	0.11	11.25
Incremental cost/QALY	£644,210	£6,442
Minimum QALY gain needed	3.6	3.6

The threshold QALY gain for an ICER of £20,000 per QALY is 3.1.

L.4 Sensitivity analysis

In addition to considerable uncertainty about any treatment effect size there is also uncertainty with respect to the savings and the QALY gain (which is a weighted average based on the incidence of all sequelae including death) from an averted meningitis case. While there is published data on the cost and QALY implications of averted disease[205;206], children who are susceptible to repeat infection often have milder disease[207;208]. Therefore, the sensitivity analysis presented below shows the threshold for cost effectiveness for both selective and routine testing strategies, varying the gain from an averted case between 0 and 10 QALYs and the relative risk reduction with treatment between 0% and 100%. The analysis was undertaken using a lower bound estimate of the saving from an averted case of meningococcal disease (based on the treatment cost of an acute episode) and a higher saving of £10,000 per averted case. It was assumed that the prevalence of complement deficiency was 0.3% amongst all children with meningococcal disease, but 1% in the subgroup who accounted for 10% of all cases. The results are illustrated below in figures L.3 to L.6.

Saving per averted case = £3,179

Figure L.3. Threshold cost effectiveness for selective testing

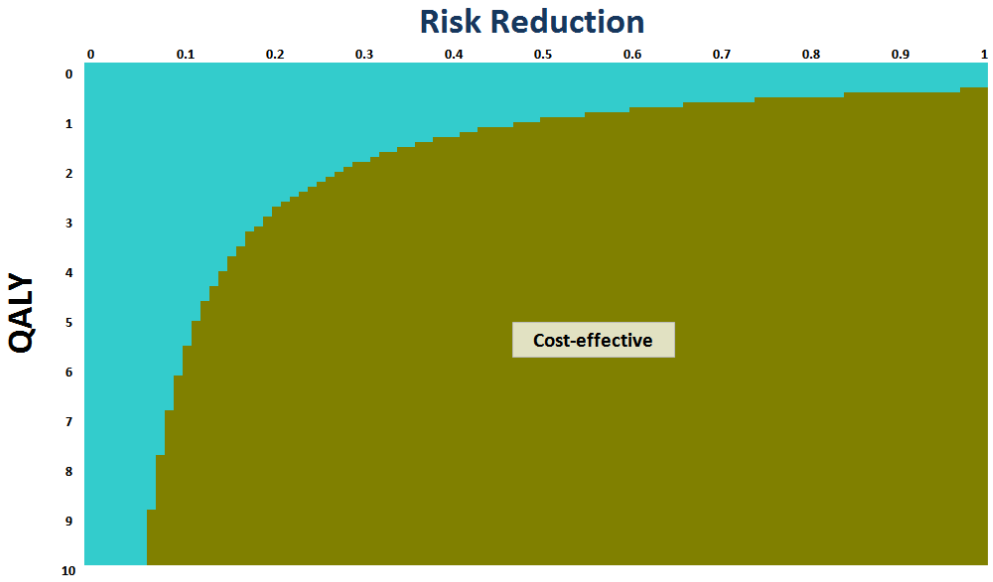
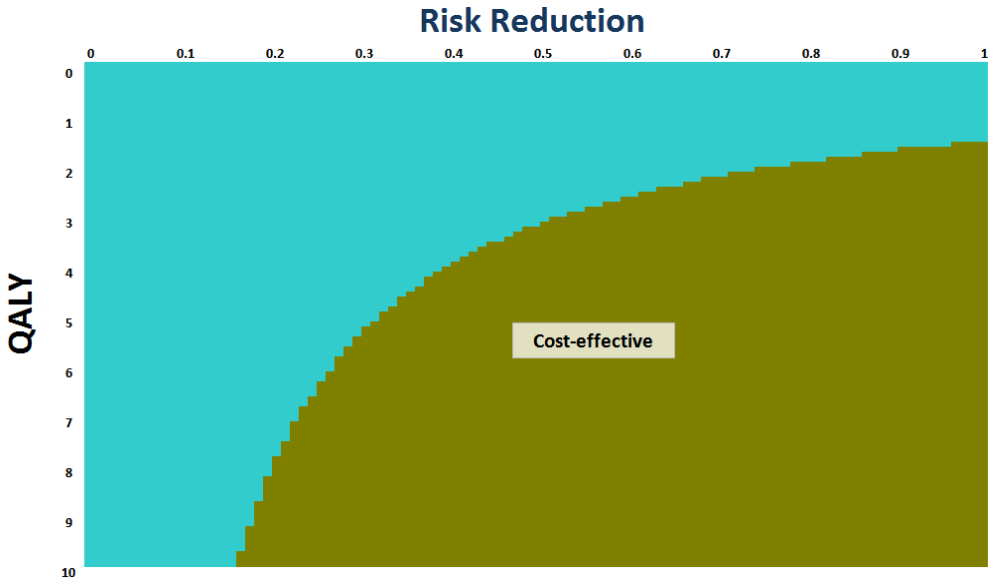


Figure L.4. Threshold cost effectiveness for routine testing



Saving per averted case = £10,000

Figure L.5. Threshold cost effectiveness for selective testing

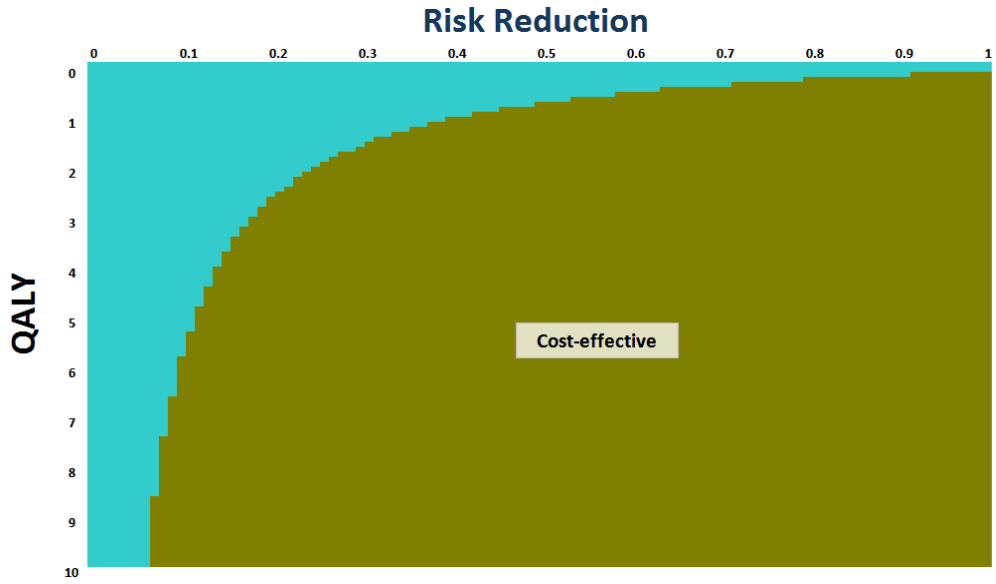
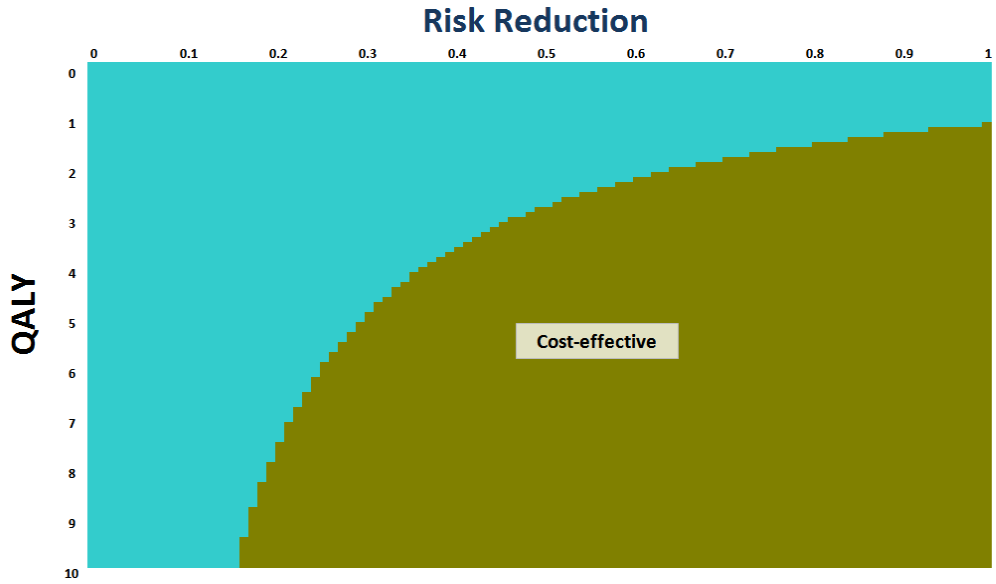


Figure L.6. Threshold cost effectiveness for routine testing



L.5 Discussion

This model provides insights into the type of scenarios in which screening for complement deficiency could be considered cost effective. It also indicates where the model is most sensitive to changes in the input data and, therefore, where future research may best be directed.

However, considerable care needs to be exercised in interpreting the above results. The data has limitations which makes it difficult to make an accurate assessment of the cost effectiveness of screening for complement deficiency in children who have survived an episode of meningococcal disease based on evidence. In particular there is a lack of evidence on the

effectiveness of treatment in those children identified with complement deficiency (such as vaccination, MedicAlert subscription, liberal precautionary use of antibiotics).

Various scenarios have been explored by varying a single input while keeping all other inputs constant at their default values. However, uncertainty is not necessarily confined to a single input and there are a huge number of scenarios that could potentially be assessed by varying many inputs simultaneously. This is especially important because the sensitivity of the model's results to changes in a single input value is not generally independent of the value of the other model inputs. So figure L.2, for example, suggests that the cost effectiveness of screening for complement deficiency is fairly sensitive to the assumptions made about the costs of an averted case of meningococcal disease. However, if much lower treatment efficacy is assumed (that is, a relative risk reduction from treatment of 4%), then changes to the incremental cost-effectiveness ratio (ICER) in response to changes in this assumption are much less marked. Conversely, the ICER becomes even more sensitive to changes in the assumptions about the costs of an averted case of meningococcal disease if higher treatment efficacy is assumed.

The results presented above suggest that the cost effectiveness of screening is not very sensitive to changes in the assumptions about the treatment costs or the cost of work-up if an abnormality is found. Neither of these inputs affects health outcomes and because of the small number of cases of complement deficiency identified, their overall contribution to the total costs is relatively small. The importance of these costs would increase with declining test specificity as there would be increasing 'downstream' costs associated with false positives. However, this would merely tend to reinforce a view that screening in low prevalence populations is often inappropriate because of the poor positive predictive value of the test. In any event, not too much uncertainty surrounds these costs.

The model does suggest that results are sensitive to fairly small absolute changes in the costs of the initial screening. This is an intuitive finding given the importance of the screening cost to the total strategy costs, especially in the absence of false positives. However, this data is not subject to considerable uncertainty with the availability of a well sourced cost estimate.

Changes in assumptions concerning disease prevalence are also an important determinant of cost effectiveness. Clearly, the more cases of complement deficiency, the greater the potential health gain in identifying children who would benefit from preventative treatment. While it is interesting to estimate a prevalence threshold for cost effectiveness, there is some evidence-base for the default model input.

The base-case analysis assumes a screening test with perfect diagnostic accuracy. Departures from this assumption would inevitably lessen the cost effectiveness of screening with more missed cases and/or costs associated with false positives. With other default inputs held constant, the specificity seems a particularly important determinant of the cost effectiveness of screening with every percentage point fall in specificity producing a larger increase in the ICER than every percentage point fall in sensitivity. This reflects the importance of the costs of false positives in a low prevalence population.

Not surprisingly, the model shows that the cost effectiveness is sensitive to changes in assumptions regarding the probability of further infection in children with complement deficiency. This probability is a function of both the underlying risk of infection in the absence of treatment and the degree of protection from that risk provided by that treatment. While there is some data indicating the risk of reinfection, there is a lack of evidence on the clinical effectiveness of treatment in this group of children and research here could help establish the cost effectiveness of screening for complement deficiency. The model shows that screening for complement deficiency could be highly cost effective in a scenario where there was a high risk of reinfection and where treatment was highly efficacious.

Varying the QALY gain from an averted meningococcal case is also an important determinant of the cost effectiveness of screening. While some uncertainty surrounds the default input, the threshold approach can indicate the likely importance of the uncertainty.

In the sensitivity analysis both the QALY gain and treatment efficacy were varied for different disease prevalence and savings per averted case. This shows that the cost effectiveness is not greatly influenced by the savings per case averted but that a considerably lower QALY gain and/or treatment efficacy is required for cost effectiveness at higher disease prevalence.

This analysis has compared screening for complement deficiency in children who survive a meningococcal disease versus no screening. The validity of ICER estimates always depends on the choice of the appropriate comparator and it should be borne in mind that the ICER for screening for complement deficiency in children who survive a meningococcal infection could be markedly different when compared against some alternative, possibly more appropriate, strategy. However, this is less of an issue if screening for complement deficiency in children who survive a meningococcal infection was judged not to be cost effective relative to no screening. The rationale for selective testing is that there exists a clearly identified subgroup with a higher pre-test probability of complement deficiency. If selective testing is not cost effective relative to no testing then routine testing will not be cost effective. If selective testing is cost effective relative to no testing the decision between selective and routine testing hinges on whether the additional cases identified by routine testing can be achieved at an acceptable cost, which we take to be £20,000 per QALY in this case. This analysis was not presented here because the GDG did not think the evidence justified a routine screening approach and the cost effectiveness of routine screening versus selective screening would have been less favourable than the cost effectiveness of routine screening presented in this analysis.

A final point to note relates to the use of a £20,000 per QALY willingness to pay threshold. This is not an absolute decision rule as far as NICE is concerned. However, interventions with a cost per QALY of less than £20,000 per QALY would usually be considered cost effective. If the intervention had a cost per QALY of more than £20,000 but less than £30,000 per QALY then it may be considered cost effective under certain circumstances (see NICE Guidelines Manual 2009). If the intervention had an ICER of above £30,000 per QALY than a stronger case for considering other factors would have to be made to justify the intervention for NHS resource use.

Appendix E

Search strategies

Clinical Question

1 In children and young people up to 16 years of age, what symptoms and signs or combination of symptoms and signs are predictive of bacterial meningitis?

2 In children and young people up to 16 years of age, what symptoms and signs or combination of symptoms and signs are predictive of meningococcal septicaemia?

3 Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome?

4 Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?

5 In children and young people up to 16 years of age with a petechial rash, can non-specific laboratory tests (C-reactive protein, white blood cell count, blood gas) help to confirm or refute the diagnosis of meningococcal disease?

6 In children and young people up to 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?

7 In children and young people with suspected meningitis, can CSF variables (white cell count, glucose, protein) distinguish between bacterial and viral meningitis?

8 What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?

9 What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?

10 In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs?

11 When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?

12 When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?

13 Should lumbar puncture be performed prior to stopping antibiotic treatment in children less than 3 months of age with bacterial meningitis?

1 In children and young people up to 16 years of age, what symptoms and signs or combinations of symptoms and signs are predictive of bacterial meningitis?

MENG_signs_symptoms_meningitis_medline_290708
MEDLINE(R) 1950 to June Week 4 2009

	Searches	Results
1	exp CHILD/	1299269
2	child$.ti,ab.	744852
3	(pediatric? or paediatric?).ti,ab.	137403
4	exp INFANT/	800205
5	(neonat$ or newborn?).ti,ab.	226616
6	infan$.ti,ab.	261163
7	(baby or babies).ti,ab.	40050
8	toddler?.ti,ab.	3574
9	exp ADOLESCENT/	1310506
10	teen$.ti,ab.	15833
11	adolescen$.ti,ab.	114405
12	exp SCHOOLS/	62462
13	school$.ti,ab.	137286
14	exp PUBERTY/	13306
15	pubescen$.ti,ab.	873
16	or/1-15	2728168
17	exp MENINGITIS, BACTERIAL/	17583
18	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5972
19	((bacterial$ or infect$) adj3 meninges).ti,ab.	46
20	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	21
21	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	295
22	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	673
23	((meningitis or meningitides) adj3 listeria).ti,ab.	362
24	((meningitis or meningitides) adj3 meningococc$).ti,ab.	1350
25	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1349

26	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4128
27	meningoencephalitis.ti,ab.	4258
28	MENINGOENCEPHALITIS/	4848
29	MENINGITIS/	15038
30	or/17-29	39566
31	"SIGNS AND SYMPTOMS"/	407
32	(sign? or symptom$ or complain$).ti,ab.	721383
33	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	172765
34	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	4891
35	presentation?.ti,ab.	158710
36	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	13119
37	FEVER/	25867
38	fever$.ti,ab.	91880
39	(pyrexi?? or febrile).ti,ab.	20814
40	VOMITING/	16537
41	(vomit$ or emesis or throw$ up).ti,ab.	39458
42	HEADACHE/	20330
43	(headache? or Cephalalgia or cephalgia or Cephalodynia or Hemicrania).ti,ab.	45555
44	((head or cranial or intracranial) adj3 pain$).ti,ab.	1266
45	(cephalea or cerebralgia or encephalalgia or encephalodynia).ti,ab.	114
46	(stiff$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	1145
47	(rigid$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	828
48	PHOTOPHOBIA/	285
49	photophob$.ti,ab.	1596
50	(light adj3 (intoleran$ or sensitiv$)).ti,ab.	3322
51	((tense or bulging or full$) adj3 fontanelle?).ti,ab.	108
52	INTRACRANIAL PRESSURE/	12003
53	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	2562
54	exp CONSCIOUSNESS DISORDERS/	30215
55	((level? or decreas$) adj3 consciousness).ti,ab.	2551

56	SEIZURES/	34144
57	SEIZURES, FEBRILE/	1925
58	seizure?.ti,ab.	63265
59	IRRITABLE MOOD/	643
60	(irritab$ or petulan$ or bad mood or moody).ti,ab.	11245
61	CRYING/	1706
62	(crying or high pitched cry or high pitched cries).ti,ab.	2364
63	Kernig$.ti,ab.	70
64	Brudzinski$.ti,ab.	37
65	((symphyseal or cheek) adj3 sign?).ti,ab.	7
66	meningism.ti,ab.	205
67	DECEREBRATE STATE/	4600
68	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	282
69	(abnormal adj3 postur$).ti,ab.	731
70	LETHARGY/	68
71	(letharg$ or sluggish$ or listless$).ti,ab.	5574
72	FATIGUE/	13987
73	fatigue.ti,ab.	37718
74	(drows$ or tiredness).ti,ab.	5906
75	hypnesthesia.ti,ab.	0
76	CONFUSION/	3042
77	(confusion or disorient$).ti,ab.	18984
78	((chang$ or alter$) adj3 mental state?).ti,ab.	268
79	or/31-78	1292284
80	and/16,30	19110
81	and/79-80	4136
82	limit 81 to (english language and humans)	2880
83	COHORT STUDIES/	99112
84	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	64423
85	or/83-84	136244

86	and/82,85	78
87	CASE REPORTS/	1433309
88	(case report or case study).ti.	128223
89	(letter or editorial or comment or historical article).pt.	1225504
90	or/87-89	2537684
91	82 not 90	2037
92	91 not 86	1961

MENG_signs_symptoms_meningitis_cctr_290708

# ▲	Searches	Results
1	exp CHILD/	30693
2	child$.ti,ab.	35075
3	(pediatric? or paediatric?).ti,ab.	6686
4	exp INFANT/	18139
5	(neonat$ or newborn?).ti,ab.	7087
6	infan$.ti,ab.	12672
7	(baby or babies).ti,ab.	1721
8	toddler?.ti,ab.	272
9	ADOLESCEN$.hw.	63377
10	teen$.ti,ab.	525
11	adolescen$.ti,ab.	5179
12	exp SCHOOLS/	625
13	school$.ti,ab.	6437
14	exp PUBERTY/	224
15	pubescen$.ti,ab.	15
16	or/1-15	108969
17	exp MENINGITIS, BACTERIAL/	225
18	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	184
19	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
20	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
21	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0

22	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	21
23	((meningitis or meningitides) adj3 listeria).ti,ab.	2
24	((meningitis or meningitides) adj3 meningococc$).ti,ab.	31
25	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	21
26	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	48
27	meningoencephalitis.ti,ab.	19
28	MENINGOENCEPHALITIS/	10
29	MENINGITIS/	99
30	or/17-29	424
31	SYMPTOM$.hw.	2548
32	(sign? or symptom$ or complain$).ti,ab.	58575
33	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	3967
34	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	103
35	presentation?.ti,ab.	3497
36	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	504
37	FEVER/	1245
38	fever$.ti,ab.	4500
39	(pyrexi?? or febrile).ti,ab.	1988
40	VOMITING/	2226
41	(vomit$ or emesis or throw$ up).ti,ab.	8163
42	HEADACHE/	1304
43	(headache? or Cephalalgia or cephalgia or Cephalodynia or Hemicrania).ti,ab.	5563
44	((head or cranial or intracranial) adj3 pain$).ti,ab.	107
45	(cephalea or cerebralgia or encephalalgia or encephalodynia).ti,ab.	11
46	(stiff$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	53
47	(rigid$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	31
48	PHOTOPHOBIA/	18
49	photophob$.ti,ab.	262
50	(light adj3 (intoleran$ or sensitiv$)).ti,ab.	125
51	((tense or bulging or full$) adj3 fontanelle?).ti,ab.	13

52	INTRACRANIAL PRESSURE/	223
53	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	80
54	exp CONSCIOUSNESS DISORDERS/	439
55	((level? or decreas$) adj3 consciousness).ti,ab.	159
56	SEIZURES/	302
57	SEIZURES, FEBRILE/	57
58	seizure?.ti,ab.	2087
59	IRRITABLE MOOD/	69
60	(irritab$ or petulan$ or bad mood or moody).ti,ab.	1362
61	CRYING/	178
62	(crying or high pitched cry or high pitched cries).ti,ab.	410
63	Kernig$.ti,ab.	0
64	Brudzinski$.ti,ab.	0
65	((symphyseal or cheek) adj3 sign?).ti,ab.	0
66	meningism.ti,ab.	3
67	DECEREBRATE STATE/	1
68	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	0
69	(abnormal adj3 postur$).ti,ab.	26
70	LETHARGY/	1
71	(letharg$ or sluggish$ or listless$).ti,ab.	195
72	FATIGUE/	981
73	fatigue.ti,ab.	3874
74	(drows$ or tiredness).ti,ab.	1729
75	hypnesthesia.ti,ab.	0
76	CONFUSION/	90
77	(confusion or disorient$).ti,ab.	593
78	((chang$ or alter$) adj3 mental state?).ti,ab.	45
79	or/31-78	88052
80	and/16,30	314
81	and/79-80	87

82	COHORT STUDIES/	3236
83	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	4010
84	or/82-83	6574
85	and/81,84	3
86	(case report or case study).ti.	197
87	(letter or editorial or comment or historical article).pt.	5240
88	or/86-87	5435
89	81 not 88	87
90	89 not 85	84

MENG_signs_symptoms_meningitis_cdsrdare_290708

# ▲	Searches	Results
1	CHILD$.kw.	1472
2	child$.ti,ab.	1649
3	(pediatric? or paediatric?).ti,ab.	238
4	INFANT?.kw.	943
5	(neonat$ or newborn?).ti,ab.	542
6	infan$.ti,ab.	591
7	(baby or babies).ti,ab.	151
8	toddler?.ti,ab.	5
9	ADOLESCEN$.kw.	936
10	teen$.ti,ab.	11
11	adolescen$.ti,ab.	267
12	SCHOOL$.kw.	66
13	school$.ti,ab.	131
14	PUBERTY.kw.	0
15	pubescen$.ti,ab.	0
16	or/1-15	3210
17	(MENINGITIS, BACTERIAL or BACTERIAL MENINGITIS).kw.	13
18	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	12

19	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
20	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
21	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0
22	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	0
23	((meningitis or meningitides) adj3 listeria).ti,ab.	0
24	((meningitis or meningitides) adj3 meningococc$).ti,ab.	4
25	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	0
26	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	2
27	meningoencephalitis.ti,ab.	2
28	MENINGOENCEPHALITIS.kw.	1
29	MENINGITIS.kw.	22
30	or/17-29	27
31	SYMPTOM$.kw.	104
32	(sign? or symptom$ or complain$).ti,ab.	1123
33	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	49
34	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	1
35	presentation?.ti,ab.	66
36	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	2
37	(FEVER or PYREXIA).kw.	59
38	fever$.ti,ab.	91
39	(pyrexi?? or febrile).ti,ab.	50
40	VOMIT$.kw.	114
41	(vomit$ or emesis or throw$ up).ti,ab.	152
42	HEADACHE$.kw.	73
43	(headache? or Cephalalgia or cephalgia or Cephalodynia or Hemicrania).ti,ab.	106
44	((head or cranial or intracranial) adj3 pain$).ti,ab.	1
45	(cephalea or cerebralgia or encephalalgia or encephalodynia).ti,ab.	0
46	(stiff$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	2
47	(rigid$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	0
48	PHOTOPHOBI$.kw.	0

49	photophob$.ti,ab.	0
50	(light adj3 (intoleran$ or sensitiv$)).ti,ab.	0
51	((tense or bulging or full$) adj3 fontanelle?).ti,ab.	0
52	INTRACRANIAL PRESSURE.kw.	9
53	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	8
54	CONSCIOUSNESS DISORDER$.kw.	1
55	((level? or decreas$) adj3 consciousness).ti,ab.	0
56	SEIZURE$.kw.	45
57	FEBRILE SEIZURE$.kw.	1
58	seizure?.ti,ab.	106
59	(IRRITAB$ or MOODY or MOODINESS).ti,ab.	53
60	(irritab$ or petulan$ or bad mood or moody).ti,ab.	54
61	CRYING.kw.	6
62	(crying or high pitched cry or high pitched cries).ti,ab.	9
63	Kernig$.ti,ab.	0
64	Brudzinski$.ti,ab.	0
65	((symphyseal or cheek) adj3 sign?).ti,ab.	0
66	meningism.ti,ab.	0
67	DECEREBRATE STATE$.kw.	0
68	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	0
69	(abnormal adj3 postur$).ti,ab.	1
70	LETHARG$.kw.	0
71	(letharg$ or sluggish$ or listless$).ti,ab.	1
72	(FATIGUE or TIRED$ or DROWSY).kw.	51
73	fatigue.ti,ab.	83
74	(drows$ or tiredness).ti,ab.	17
75	hypnesthesia.ti,ab.	0
76	CONFUS$.kw.	3
77	(confusion or disorient$).ti,ab.	14
78	((chang$ or alter$) adj3 mental state?).ti,ab.	11

79	or/31-78	1879
80	and/16,30	10
81	and/79-80	1
82	COHORT STUD$.kw.	151
83	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	112
84	or/82-83	250
85	and/81,84	0
86	(case report or case study).ti.	7
87	81 not 86	1

MENG_signs_symptoms_meningitis_290708_RERUN_on_300709

CINAHL 1982 -

#	Query	Results
S80	S73 and S74 and S78	99
S79	S73 and S74 and S78	0
S78	S75 or S76 or S77	16
S77	S51 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72	144
S76	TI (cephalea or cerebralgia or encephalalgia or encephalodynia) or AB (cephalea or cerebralgia or encephalalgia or encephalodynia)	5
S75	S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47	242
S74	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23	145
S73	s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15	1770
S72	TI (drows*) or AB (drows*)	324
S71	TI (letharg* or sluggish* or listless*) or AB (letharg* or sluggish* or listless*)	354
S70	TI (abnormal N3 postur*) or AB (abnormal N3 postur*)	67
S69	TI (decerebrate or decorticate or decerebration) or AB (decerebrate or decorticate or decerebration)	18
S68	TI (meningism) or AB (meningism)	6
S67	TI (crying or cry or cries) or AB (crying or cry or cries)	1047
S66	MH CRYING	543
S65	TI (irritab* or petulant* or bad mood or moody) or AB (irritab* or petulant* or bad mood or moody)	1634
S64	TI (seizure*) or AB (seizure*)	3728
S63	MH SEIZURES+	2949
S62	TI (intracranial pressure*) or AB (intracranial pressure*)	701
S61	MH INTRACRANIAL PRESSURE, INCREASED	600
S60	AB (tense N3 fontanelle) or AB (bulging N3 fontanelle) or AB (full* N3 fontanelle)	4

S59	TI (tense N3 fontanelle) or TI (bulging N3 fontanelle) or TI (full* N3 fontanelle)	2
S58	TI (light N3 sensitivity) or AB (light N3 sensitivity)	46
S57	TI (light N3 intolerant) or AB (light N3 intolerant)	0
S56	TI (photophobi*) or AB (photophobi*)	141
S55	MH PHOTOPHOBIA	45
S54	S52 and S53	1
S53	AB (neck* or nuchal or cervical or spine or spinal)	23994
S52	AB (stiff or rigid)	1405
S51	S49 and S50	0
S50	TI (neck* or nuchal or cervical or spine or spinal)	21119
S49	TI (stiff or rigid)	373
S48	TI (cephalea or cerebralgia or encephalalgia or encephalodynia) or AB ((cephalea or cerebralgia or encephalalgia or encephalodynia)	0
S47	AB (head N3 pain*) or AB (cranial N3 pain*) or AB (intracranial N3 pain*)	239
S46	TI (head N3 pain*) or TI (cranial N3 pain*) or TI (intracranial N3 pain*)	88
S45	AB (headache* or cephalagia or cephalgia or cephalodynia or hemicrania)	5048
S44	TI (headache* or cephalagia or cephalgia or cephalodynia or hemicrania)	4258
S43	MH HEADACHE	4307
S42	TI (confusion) or AB (confusion)	3562
S41	TI (confused or deliri*) or AB (confused or deliri*)	2580
S40	MH CONFUSION+	2047
S39	TI (consciousness or mental state*) or AB (consciousness or mental state*)	4025
S38	MH CONSCIOUSNESS DISORDERS+	3160
S37	TI (fatigue or letharg* or sluggish or listless* or tiredness) or AB (fatigue or letharg* or sluggish or listless* or tiredness)	9224
S36	MH FATIGUE	4452
S35	TI (vomit* or emesis or throw* up) or AB (vomit* or emesis or throw* up)	3581
S34	MH VOMITING+	1252
S33	TI (fever* or pyrexi* or febrile) or AB (fever* or pyrexi* or febrile)	6139
S32	MH FEVER	2461
S31	AB (physical N3 manifestation*) or AB (physical N3 characteristic*) or AB (physical N3 feature*) or AB (physical N3 finding*)	1955
S30	TI (physical N3 manifestation*) or TI (physical N3 characteristic*) or TI (physical N3 feature*) or TI (physical N3 finding*)	174
S29	AB (presenting N3 finding*) or AB (presenting N3 feature*) or AB (presenting N3 factor*)	383
S28	TI (presenting N3 finding*) or TI (presenting N3 feature*) or TI (presenting N3 factor*)	53
S27	AB (clinical N3 finding*) or AB (clinical N3 manifestation*) or AB (clinical N3 aspect*) or AB (clinical N3 aspect*)	6260
S26	TI (clinical N3 finding*) or TI (clinical N3 manifestation*) or TI (clinical N3 aspect*) or TI (clinical N3 aspect*)	911
S25	TI (sign* or symptom* or complain*) or AB (sign* or symptom* or	256606

	complain*)	
S24	MH SYMPTOMS	2681
S23	AB (infect* N3 leptomeninges) or AB (infect* N3 subarachnoid space*)	0
S22	TI (infect* N3 leptomeninges) or TI (infect* N3 subarachnoid space*)	0
S21	TI (infect* N3 leptomeninges) or TI (infect* N3 subarachnoid space*)	0
S20	TI (pachymeningitis or meningoencephalitis) or AB (pachymeningitis or meningoencephalitis)	126
S19	TI (meningitis or meningitides or meninges) or AB (meningitis or meningitides or meninges)	1755
S18	MH MENINGITIS, BACTERIAL+	971
S17	MH MENINGOENCEPHALITIS	88
S16	MH MENINGITIS	927
S15	TI (paediatric* or pediatric*) or AB (paediatric* or pediatric*)	29743
S14	AB (newborn*) or AB (neonate*)	7636
S13	TI (newborn*) or TI (neonate*)	5897
S12	TI (pubescen*) or AB (pubescen*)	55
S11	MH PUBERTY+	1004
S10	TI (school*) or AB (school*)	38329
S9	MH SCHOOLS+	21736
S8	TI (adolescen*) or AB (adolescen*)	28859
S7	TI (teenag*) or AB (teenag*)	3515
S6	MH ADOLESCENCE+	128199
S5	TI (baby or babies) or AB (baby or babies)	10049
S4	TI (infan*) or AB (infan*)	28358
S3	MH INFANT+	82965
S2	TI (child*) or AB (child*)	117798
S1	MH CHILD+	199308

MENG_signs_symptoms_meningitis_embase_290708

# ▲	Searches	Results
1	exp CHILD/	645644
2	child$.tw.	504737
3	exp INFANT/	178469
4	infan$.tw.	175939
5	NEWBORN/	182308
6	(newborn? or neonat$).ti,ab.	168036
7	(baby or babies).tw.	28322
8	(paediatric? or pediatric?).ti,ab.	117716
9	exp ADOLESCENT/	450563
10	teenag$.tw.	8281
11	adolescen$.tw.	87516
12	exp SCHOOLS/	38854
13	school$.tw.	77909
14	pubescen$.tw.	684
15	exp PUBERTY/	14913
16	or/1-15	1338884
17	BACTERIAL MENINGITIS/	7922
18	TUBERCULOUS MENINGITIS/	1961
19	MENINGOENCEPHALITIS/	3097
20	MENINGITIS/	13973
21	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5103
22	((bacterial$ or infect$) adj3 meninges).ti,ab.	33
23	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
24	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	240
25	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	470
26	((meningitis or meningitides) adj3 listeria).ti,ab.	216
27	((meningitis or meningitides) adj3 meningococc$).ti,ab.	910
28	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1066

29	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1668
30	meningoencephalitis.ti,ab.	2593
31	or/17-30	27820
32	exp SYMPTOMATOLOGY/	511266
33	(sign? or symptom$ or complain$).ti,ab.	623840
34	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	135929
35	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	4380
36	presentation?.ti,ab.	135715
37	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	11116
38	FEVER/	67331
39	HYPERPYREXIA/	543
40	fever$.ti,ab.	64870
41	(pyrexi?? or febrile).ti,ab.	17455
42	VOMITING/	69539
43	(vomit$ or emesis or throw$ up).ti,ab.	34598
44	exp CONSCIOUSNESS DISORDER/	41136
45	(letharg$ or sluggish$ or listless$).ti,ab.	4202
46	FATIGUE/	47716
47	fatigue.ti,ab.	32274
48	tiredness.ti,ab.	1825
49	((decreas$ or alter$ or chang$) adj3 (consciousness or mental state?)).ti,ab.	1883
50	exp CONFUSION/	12338
51	(confused or deliri$).ti,ab.	10932
52	((state or mental) adj3 confusion).ti,ab.	537
53	LISTLESSNESS/	49
54	exp "HEADACHE AND FACIAL PAIN"/	105673
55	(headache? or Cephalalgia or cephalgia or Cephalodynia or Hemicrania).ti,ab.	39196
56	((head or cranial or intracranial) adj3 pain$).ti,ab.	1053
57	(cephalea or cerebralgia or encephalalgia or encephalodynia).ti,ab.	109
58	(stiff$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	1012

59	(rigid$ adj3 (neck? or nuchal or cervical or spine or spinal)).ti,ab.	700
60	PHOTOPHOBIA/	2842
61	photophob$.ti,ab.	1427
62	(light adj3 (intoleran$ or sensitiv$)).ti,ab.	2417
63	((tense or bulging or full$) adj3 fontanelle?).ti,ab.	91
64	INTRACRANIAL PRESSURE/	8083
65	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	2266
66	CONSCIOUSNESS DISORDERS/	3692
67	((level? or decreas$) adj3 consciousness).ti,ab.	2179
68	exp "SEIZURE, EPILEPSY AND CONVULSION"/	129022
69	seizure?.ti,ab.	59731
70	IRRITABILITY/	7598
71	(irritab$ or petulan$ or bad mood or moody).ti,ab.	10513
72	CRYING/	1669
73	(crying or high pitched cry or high pitched cries).ti,ab.	1767
74	Kernig$.ti,ab.	53
75	Brudzinski$.ti,ab.	21
76	((symphyseal or cheek) adj3 sign?).ti,ab.	6
77	MENINGISM/	416
78	meningism.ti,ab.	148
79	DECEREBRATION/	1594
80	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	164
81	decerebration.ti,ab.	277
82	(abnormal adj3 postur$).ti,ab.	656
83	(letharg$ or sluggish$ or listless$).ti,ab.	4202
84	FATIGUE/	47716
85	fatigue.ti,ab.	32274
86	(drows$ or tiredness).ti,ab.	5450
87	hypnesthesia.ti,ab.	0
88	exp CONFUSION/	12338

89	(confusion or disorient$).ti,ab.	15422
90	((chang$ or alter$) adj3 mental state?).ti,ab.	253
91	or/32-90	1491897
92	and/16,31	11482
93	and/91-92	4674
94	limit 93 to (human and english language)	3612
95	COHORT ANALYSIS/	55493
96	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	57381
97	or/95-96	90188
98	and/94,97	72
99	CASE REPORT/	1046017
100	(case report or case study).ti.	104007
101	(letter or editorial or comment or historical article).pt.	685117
102	or/99-101	1646656
103	94 not 102	2428
104	103 not 98	2357

2 In children and young people up to 16 years of age, what symptoms and signs or combination of symptoms and signs are predictive of meningococcal septicaemia?

MENG_signs_symptoms_septicaemia_medline_030708

Ovid MEDLINE(R) 1950 to June Week 4 2008

#	Searches	Results
1	SHOCK, SEPTIC/	15026
2	(septic adj shock).ti,ab.	9295
3	(sepsis adj5 hypotension).ti,ab.	292
4	BACTEREMIA/	12148
5	(severe adj2 sepsis).ti,ab.	2899
6	(septic?emi? or bacter?emi?).ti,ab.	29355
7	MENINGOCOCCAL INFECTIONS/	4465
8	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3562
9	meningococc?emi?.ti,ab.	608
10	or/1-9	58501
11	"SIGNS AND SYMPTOMS"/	409
12	(sign? or symptom$ or complain$).ti,ab.	682294
13	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	166021
14	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	4626
15	presentation?.ti,ab.	148696
16	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	12370
17	((ill or sick) adj3 (looking or appearance)).ti,ab.	93
18	unwell.ti,ab.	438
19	FEVER/	25194
20	fever$.ti,ab.	87555
21	(pyrexi?? or febrile).ti,ab.	19597
22	VOMITING/	16368
23	(vomit$ or emesis or throw$ up).ti,ab.	37074
24	CHILLS/	88
25	(chills or rigors or shivering).ti,ab.	4696
26	SHIVERING/	1402
27	exp DIARRHEA/	37452
28	diarrh?ea?.ti,ab.	54752
29	LETHARGY/	44
30	(letharg$ or sluggish$ or listless$).ti,ab.	5261
31	FATIGUE/	13139
32	fatigue.ti,ab.	34937
33	tiredness.ti,ab.	1761
34	MUSCLE HYPOTONIA/	2199

35	(floppy or hypotonia? or hypotony).ti,ab.	6393
36	(floppy or hypotonia? or hypotony).ti,ab.	6393
37	(muscle? adj3 (atonic or flaccid$)).ti,ab.	105
38	CONSCIOUSNESS DISORDERS/	1433
39	((decreas$ or alter$ or chang$) adj3 (consciousness or mental state?)).ti,ab.	2028
40	exp CONFUSION/	6601
41	(confused or deliri$).ti,ab.	12775
42	((state or mental) adj3 confusion).ti,ab.	640
43	exp TACHYCARDIA/	34560
44	tachycardia?.ti,ab.	36681
45	((elevated or rapid or fast$) adj3 (heart?beat or heart rate)).ti,ab.	1073
46	exp PURPURA/	12832
47	(non?blanching or non blanching).ti,ab.	27
48	(petechia? or purpura).ti,ab.	16319
49	((hemorrhagic or haemorrhagic) adj3 rash??).ti,ab.	47
50	(capillar$ adj2 refill$).ti,ab.	184
51	PERFUSION/	42409
52	peripheral perfusion.ti,ab.	303
53	EXTREMITIES/	16202
54	BODY TEMPERATURE REGULATION/	18700
55	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.	884
56	((limb? or extremities or arms or legs) adj3 pain$).ti,ab.	2202
57	phantom limb?.ti,ab.	747
58	56 not 57	1731
59	PALLOR/	218
60	((abnormal$ or atypical$ or odd or unusual$ or strange) adj3 (skin colo?r or colo?r of skin)).ti,ab.	13
61	SKIN/bs	13369
62	(pallor or pale or paleness).ti,ab.	5760
63	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.	67
64	SKIN PIGMENTATION/	4079
65	or/11-55,58-64	1301229
66	and/10,65	11833
67	(case report or case study).ti.	121707
68	(letter or editorial or comment or historical article).pt.	1160514
69	CASE REPORTS/	1402669
70	or/67-69	2446660
71	66 not 70	8129
72	COHORT STUDIES/	87991
73	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	57818
74	or/72-73	121312
75	and/71,74	283

76 limit 75 to (english language and humans)	266
77 71 not 75	7846
78 limit 77 to (english language and humans)	5561

MENG_signs_symptoms_septicaemia_cctr_030708

EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2008

#	Searches	Results
1	SHOCK, SEPTIC/	252
2	(septic adj shock).ti,ab.	375
3	(sepsis adj5 hypotension).ti,ab.	17
4	BACTEREMIA/	380
5	(severe adj2 sepsis).ti,ab.	267
6	(septic?emi? or bacter?emi?).ti,ab.	1258
7	MENINGOCOCCAL INFECTIONS/	72
8	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	61
9	meningococc?emi?.ti,ab.	6
10	or/1-9	2040
11	SYMPTOM$.kw.	1183
12	(sign? or symptom$ or complain$).ti,ab.	54574
13	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	3769
14	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	96
15	presentation?.ti,ab.	3310
16	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	461
17	((ill or sick) adj3 (looking or appearance)).ti,ab.	0
18	unwell.ti,ab.	24
19	FEVER/	1210
20	fever$.ti,ab.	4272
21	(pyrexi?? or febrile).ti,ab.	1855
22	VOMITING/	2181
23	(vomit$ or emesis or throw$ up).ti,ab.	7577
24	CHILLS/	9
25	(chills or rigors or shivering).ti,ab.	750
26	SHIVERING/	222
27	exp DIARRHEA/	1950
28	diarrh?ea?.ti,ab.	4624
29	LETHARGY/	945
30	(letharg$ or sluggish$ or listless$).ti,ab.	198
31	FATIGUE/	878
32	fatigue.ti,ab.	3470
33	tiredness.ti,ab.	385
34	MUSCLE HYPOTONIA/	18
35	(floppy or hypotonia? or hypotony).ti,ab.	176
36	(floppy or hypotonia? or hypotony).ti,ab.	176
37	(muscle? adj3 (atonic or flaccid$)).ti,ab.	6
38	CONSCIOUSNESS DISORDERS/	12
39	((decreas$ or alter$ or chang$) adj3 (consciousness or mental state?)).ti,ab.	128

40	exp CONFUSION/	162
41	(confused or deliri$).ti,ab.	349
42	((state or mental) adj3 confusion).ti,ab.	33
43	exp TACHYCARDIA/	1110
44	tachycardia?.ti,ab.	2480
45	((elevated or rapid or fast$) adj3 (heart?beat or heart rate)).ti,ab.	172
46	exp PURPURA/	71
47	(non?blanching or non blanching).ti,ab.	3
48	(petechia? or purpura).ti,ab.	320
49	((hemorrhagic or haemorrhagic) adj3 rash??).ti,ab.	0
50	(capillar$ adj2 refill$).ti,ab.	7
51	PERFUSION/	250
52	peripheral perfusion.ti,ab.	25
53	EXTREMITIES/	188
54	BODY TEMPERATURE REGULATION/	546
55	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.	200
56	((limb? or extremities or arms or legs) adj3 pain$).ti,ab.	295
57	phantom limb?.ti,ab.	45
58	56 not 57	255
59	PALLOR/	8
60	((abnormal$ or atypical$ or odd or unusual$ or strange) adj3 (skin colo?r or colo?r of skin)).ti,ab.	0
61	SKIN/bs	585
62	(pallor or pale or paleness).ti,ab.	103
63	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.	6
64	SKIN PIGMENTATION/	107
65	or/11-55,58-64	83625
66	and/10,65	556
67	(case report or case study).ti.	187
68	(letter or editorial or comment or historical article).pt.	5038
69	case reports.pt.	1312
70	or/67-69	6424
71	66 not 70	552
72	COHORT STUDIES/	2865
73	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	3603
74	or/72-73	5870
75	and/71,74	12
76	71 not 75	540

MENG_signs_symptoms_septicaemia_cdsrdare_030708

CDSR, DARE

#	Searches	Results
1	SHOCK, SEPTIC.kw.	15
2	(septic adj shock).ti,ab.	9
3	(sepsis adj5 hypotension).ti,ab.	1
4	BACTEREMIA.kw.	29
5	(severe adj2 sepsis).ti,ab.	12
6	(septic?emi? or bacter?emi?).ti,ab.	23
7	MENINGOCOCCAL INFECTION$.kw.	4
8	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	6
9	meningococc?emi?.ti,ab.	0
10	or/1-9	74
11	symptom$.kw.	89
12	(sign? or symptom$ or complain$).ti,ab.	1012
13	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	42
14	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	1
15	presentation?.ti,ab.	60
16	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	1
17	((ill or sick) adj3 (looking or appearance)).ti,ab.	0
18	unwell.ti,ab.	4
19	FEVER.kw.	47
20	fever$.ti,ab.	82
21	(pyrexi?? or febrile).ti,ab.	44
22	VOMITING.kw.	101
23	(vomit$ or emesis or throw$ up).ti,ab.	145
24	CHILLS.kw.	0
25	(chills or rigors or shivering).ti,ab.	6
26	SHIVERING.kw.	3
27	DIARRH?EA.kw.	55
28	diarrh?ea?.ti,ab.	106
29	LETHARG$.kw.	0
30	(letharg$ or sluggish$ or listless$).ti,ab.	2
31	FATIGUE.kw.	35
32	fatigue.ti,ab.	67
33	tiredness.ti,ab.	4
34	HYPOTONI?.kw.	0
35	(floppy or hypotonia? or hypotony).ti,ab.	2
36	(muscle? adj3 (atonic or flaccid$)).ti,ab.	0
37	CONSCIOUSNESS.kw.	3
38	((decreas$ or alter$ or chang$) adj3 (consciousness or mental state?)).ti,ab.	12
39	CONFUSION.kw.	3

40	(confused or deliri$).ti,ab.	25
41	((state or mental) adj3 confusion).ti,ab.	0
42	TACHYCARDIA.kw.	16
43	tachycardia?.ti,ab.	17
44	((elevated or rapid or fast$) adj3 (heart?beat or heart rate)).ti,ab.	0
45	PURPURA.kw.	9
46	(non?blanching or non blanching).ti,ab.	0
47	(petechia? or purpura).ti,ab.	12
48	((hemorrhagic or haemorrhagic) adj3 rash??).ti,ab.	0
49	(capillar$ adj2 refill$).ti,ab.	0
50	PERFUSION.kw.	4
51	peripheral perfusion.ti,ab.	0
52	EXTREMIT$.kw.	32
53	BODY TEMPERATURE REGULATION.kw.	7
54	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.	0
55	((limb? or extremities or arms or legs) adj3 pain$).ti,ab.	14
56	phantom limb?.ti,ab.	3
57	55 not 56	11
58	PALLOR.kw.	1
59	((abnormal$ or atypical$ or odd or unusual$ or strange) adj3 (skin colo?r or colo?r of skin)).ti,ab.	0
60	SKIN.kw.	145
61	(pallor or pale or paleness).ti,ab.	4
62	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.	0
63	SKIN PIGMENTATION.kw.	3
64	or/11-54,57-63	1768
65	and/10,64	9
66	COHORT STUD$.kw.	118
67	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	96
68	or/66-67	202
69	and/65,68	0
70	65 not 68	9

MENG_signs_symptoms_septicaemia_cinahl_030708_7

EBSCO Host

#	Query	Limiters/Expanders	Results
S73	S20 and S72	Search modes - Boolean/Phrase	0
S72	S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S63 or S64 or S66 or S67 or S68 or S69 or S70 or S71	Search modes - Boolean/Phrase	444
S71	MH SKIN PIGMENTATION	Search modes - Boolean/Phrase	167
S70	TI (mottled or mottling) or AB (mottled or mottling)	Search modes - Boolean/Phrase	28
S69	TI (pallor or pale or paleness) or AB (pallor or pale or paleness)	Search modes - Boolean/Phrase	179
S68	AB (limb N3 pain*) or AB (extremities N3 pain*) or AB (arms N3 pain*) or AB (legs N3 pain*)	Search modes - Boolean/Phrase	468
S67	TI (limb N3 pain*) or TI (extremities N3 pain*) or TI (arms N3 pain*) or TI (legs N3 pain*)	Search modes - Boolean/Phrase	165
S66	S62 and S65	Search modes - Boolean/Phrase	0
S65	TI (hand* or feet or extremities) or AB (hand* or feet or extremities)	Search modes - Boolean/Phrase	36454
S64	(MH "SKIN/BS")	Search modes - Boolean/Phrase	166
S63	TI (skin colour) or TI (skin color) or AB (skin colour) or AB (skin color)	Search modes - Boolean/Phrase	133
S62	TI (cold or clammy or temperature) or AB (cold or clammy or temperature)	Search modes - Boolean/Phrase	8066
S61	MH BODY TEMPERATURE REGULATION	Search modes - Boolean/Phrase	982
S60	MH EXTREMITIES	Search modes - Boolean/Phrase	758
S59	TI (peripheral perfusion) or AB (peripheral perfusion)	Search modes - Boolean/Phrase	25
S58	MH PERFUSION	Search modes -	609

		Boolean/Phrase	
S57	TI (capillar* N2 refill*) or AB (capillar* N2 refill*)	Search modes - Boolean/Phrase	58
S56	AB (hemorrhagic N3 rash*) or AB (haemorrhagic N3 rash*)	Search modes - Boolean/Phrase	1
S55	TI (hemorrhagic N3 rash*) or TI (haemorrhagic N3 rash*)	Search modes - Boolean/Phrase	3
S54	TI (non blanching or petechia* or purpura) or AB (non blanching or petechia* or purpura)	Search modes - Boolean/Phrase	664
S53	MH PURPURA+	Search modes - Boolean/Phrase	770
S52	TI (heart beat or heart rate) or AB (heart beat or heart rate)	Search modes - Boolean/Phrase	7564
S51	TI (tachycardia*) or AB (tachycardia*)	Search modes - Boolean/Phrase	4504
S50	MH TACHYCARDIA	Search modes - Boolean/Phrase	1357
S49	AB (state N3 confusion) or AB (mental N3 confusion)	Search modes - Boolean/Phrase	68
S48	TI (state N3 confusion) or TI (mental N3 confusion)	Search modes - Boolean/Phrase	16
S47	TI (confused or deliri*) or AB (confused or deliri*)	Search modes - Boolean/Phrase	2580
S46	MH CONFUSION+	Search modes - Boolean/Phrase	2047
S45	TI (consciousness or mental state) or AB (consciousness or mental state)	Search modes - Boolean/Phrase	3941
S44	MH CONSCIOUSNESS DISORDERS+	Search modes - Boolean/Phrase	3160
S43	AB (muscle N3 atonic) or AB (muscle N3 flaccid*)	Search modes - Boolean/Phrase	13
S42	TI (muscle N3 atonic) or TI (muscle N3 flaccid*)	Search modes - Boolean/Phrase	0
S41	TI (floppy or hypton*) or AB (floppy or hypton*)	Search modes - Boolean/Phrase	56
S40	(MH "MUSCLE HYPOTONIA")	Search modes - Boolean/Phrase	117
S39	TI (fatigue or letharg* or sluggish or listless*) or AB (fatigue or letharg* or sluggish or listless*)	Search modes - Boolean/Phrase	8929
S38	MH FATIGUE	Search modes -	4452

		Boolean/Phrase	
S37	TI (diarrhoea* or diarrhea*) or AB (diarrhoea* or diarrhea*)	Search modes - Boolean/Phrase	3504
S36	MH DIARRHEA	Search modes - Boolean/Phrase	2836
S35	TI (chills or rigors or shivering) or AB (chills or rigors or shivering)	Search modes - Boolean/Phrase	398
S34	MH SHIVERING	Search modes - Boolean/Phrase	144
S33	TI (vomit* or emesis or throw* up) or AB (vomit* or emesis or throw* up)	Search modes - Boolean/Phrase	3581
S32	MH VOMITING+	Search modes - Boolean/Phrase	1252
S31	TI (fever* or pyrexi* or febrile) or AB (fever* or pyrexi* or febrile)	Search modes - Boolean/Phrase	6139
S30	MH FEVER	Search modes - Boolean/Phrase	2461
S29	TI (ill or sick or unwell) or AB (ill or sick or unwell)	Search modes - Boolean/Phrase	18895
S28	AB (physical N3 manifestation*) or AB (physical N3 characteristic*) or AB (physical N3 feature*) or AB (physical N3 finding*)	Search modes - Boolean/Phrase	1955
S27	TI (physical N3 manifestation*) or TI (physical N3 characteristic*) or TI (physical N3 feature*) or TI (physical N3 finding*)	Search modes - Boolean/Phrase	174
S26	AB (presenting N3 finding*) or AB (presenting N3 feature*) or AB (presenting N3 factor*)	Search modes - Boolean/Phrase	383
S25	TI (presenting N3 finding*) or TI (presenting N3 feature*) or TI (presenting N3 factor*)	Search modes - Boolean/Phrase	53
S24	AB (clinical N3 finding*) or AB (clinical N3 manifestation*) or AB (clinical N3 aspect*) or AB (clinical N3 aspect*)	Search modes - Boolean/Phrase	6260
S23	TI (clinical N3 finding*) or TI (clinical N3 manifestation*) or TI (clinical N3 aspect*) or TI (clinical N3 aspect*)	Search modes - Boolean/Phrase	911
S22	TI (sign* or symptom* or complain*) or AB (sign* or symptom* or complain*)	Search modes - Boolean/Phrase	256606
S21	MH SYMPTOMS	Search modes - Boolean/Phrase	2681
S20	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8	Search modes -	1815

	or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19	Boolean/Phrase	
S19	TI (meningococcemi*) or AB (meningococcemi*)	Search modes - Boolean/Phrase	40
S18	TI (meningococcaemi*) or AB (meningococcaemi*)	Search modes - Boolean/Phrase	6
S17	TI (bacteremic N3 shock) or AB (bacteremic N3 shock)	Search modes - Boolean/Phrase	0
S16	TI (bacteraemic N3 shock) or AB (bacteraemic N3 shock)	Search modes - Boolean/Phrase	0
S15	TI (septic N3 shock) or AB (septic N3 shock)	Search modes - Boolean/Phrase	881
S14	TI (meningococc* N3 infection) or AB (meningococc* N3 infection)	Search modes - Boolean/Phrase	36
S13	TI (meningococc* N3 disease) or AB (meningococc* N3 disease)	Search modes - Boolean/Phrase	265
S12	TI (meningococc* N3 endotoxic) or AB (meningococc* N3 endotoxic)	Search modes - Boolean/Phrase	1
S11	TI (meningococc* N3 toxic) or AB (meningococc* N3 toxic)	Search modes - Boolean/Phrase	0
S10	TI (meningococc* N3 septic) or AB (meningococc* N3 septic)	Search modes - Boolean/Phrase	18
S9	TI (meningococc* N3 sepsis) or AB (meningococc* N3 sepsis)	Search modes - Boolean/Phrase	20
S8	TI (septicemia or bacteremia) or AB (septicemia or bacteremia)	Search modes - Boolean/Phrase	1233
S7	TI (septicaemia or bacteraemia) or AB (septicaemia or bacteraemia)	Search modes - Boolean/Phrase	461
S6	TI (severe N2 sepsis) or AB (severe N2 sepsis)	Search modes - Boolean/Phrase	606
S5	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S4	MH NEONATAL SEPSIS	Search modes - Boolean/Phrase	284
S3	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S2	TI (sepsis N5 hypotension) or AB (sepsis N5 hypotension)	Search modes - Boolean/Phrase	29
S1	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046

MENG_signs_symptoms_septicaemia_embase_030708

EMBASE 1980 to 2008 Week 26

#	Searches	Results
1	SEPTIC SHOCK/	12538
2	SEPTICEMIA/	8591
3	((septic or bacter?emic) adj shock).ti,ab.	8379
4	(sepsis adj5 hypotension).ti,ab.	252
5	BACTEREMIA/	13888
6	(severe adj2 sepsis).ti,ab.	2787
7	(septic?emi? or bacter?emi?).ti,ab.	22628
8	MENINGOCOCCAL INFECTION/	2724
9	MENINGOCOCCOSIS/	2724
10	MENINGOCOCCEMIA/	809
11	(meningococc$ adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	2544
12	(meningococc?emi? or meningococcosis).ti,ab.	425
13	or/1-12	49161
14	exp SYMPTOMATOLOGY/	466292
15	(sign? or symptom$ or complain$).ti,ab.	583892
16	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.	127602
17	(presenting adj3 (feature? or finding? or factor?)).ti,ab.	4057
18	presentation?.ti,ab.	125308
19	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.	10442
20	((ill or sick) adj3 (looking or appearance)).ti,ab.	66
21	unwell.ti,ab.	427
22	FEVER/	61373
23	HYPERPYREXIA/	505
24	fever$.ti,ab.	60949
25	(pyrexi?? or febrile).ti,ab.	16314
26	VOMITING/	63671
27	(vomit$ or emesis or throw$ up).ti,ab.	32662
28	RIGOR/	1868
29	CHILL/	6173
30	(chills or rigors or shivering).ti,ab.	3896
31	SHIVERING/	1926
32	exp DIARRHEA/	79192
33	diarrh?ea?.ti,ab.	41413
34	exp CONSCIOUSNESS DISORDER/	37810
35	(letharg$ or sluggish$ or listless$).ti,ab.	3967
36	FATIGUE/	42052
37	fatigue.ti,ab.	29832
38	tiredness.ti,ab.	1716
39	MUSCLE HYPOTONIA/	4193

40	INFANTILE HYPOTONIA/	291
41	MUSCLE ATONIA/	193
42	(floppy or hypotonia? or hypotony).ti,ab.	5268
43	(muscle? adj3 (atonic or flaccid$)).ti,ab.	96
44	((decreas$ or alter$ or chang$) adj3 (consciousness or mental state?)).ti,ab.	1734
45	exp CONFUSION/	11223
46	(confused or deliri$).ti,ab.	10225
47	((state or mental) adj3 confusion).ti,ab.	516
48	exp TACHYCARDIA/	45140
49	tachycardia?.ti,ab.	30320
50	((elevated or rapid or fast$) adj3 (heart?beat or heart rate)).ti,ab.	949
51	exp PURPURA/	18311
52	(non?blanching or non blanching).ti,ab.	23
53	(petechia? or purpura).ti,ab.	11749
54	((hemorrhagic or haemorrhagic) adj3 rash??).ti,ab.	43
55	CAPILLARY FLOW/	1954
56	CAPILLARY PRESSURE/	730
57	PERIPHERAL CIRCULATION/	2876
58	peripheral perfusion.ti,ab.	283
59	THERMOREGULATION/	9358
60	SKIN TEMPERATURE/	4270
61	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.	784
62	COLD CLAMMY SKIN/	14
63	COLD LIMB/	317
64	LIMB PAIN/	1027
65	((limb? or extremities or arms or legs) adj3 pain$).ti,ab.	2084
66	PALLOR/	1372
67	LISTLESSNESS/	34
68	((abnormal$ or atypical$ or odd or unusual$ or strange) adj3 (skin colo?r or colo?r of skin)).ti,ab.	15
69	SKIN BLOOD FLOW/	4321
70	(pallor or pale or paleness).ti,ab.	4325
71	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.	57
72	SKIN PIGMENTATION/	4536
73	or/14-72	1361119
74	and/13,73	14558
75	(case report or case study).ti.	97310
76	(letter or editorial or comment or historical article).pt.	630094
77	CASE REPORT/	995482
78	or/75-77	1547244
79	74 not 78	9487
80	limit 79 to (human and english language)	7180

81	COHORT ANALYSIS/	49364
82	((cohort or incidence or concurrent or panel) adj3 (study or studies or analys?s)).ti,ab.	50810
83	or/81-82	80130
84	and/80,83	250
85	80 not 83	6930

3 Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome?

MENG_antibiotics_men_prehosp_cctr_130308

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	MENINGITIS/	99
2	exp MENINGITIS, BACTERIAL/	224
3	meningitis.tw.	480
4	meningoencephalitis.tw.	20
5	or/1-4	570
6	exp ANTIBIOTICS/	16936
7	(antibiotic$ or anti?bacterial$).ti.	3564
8	(empiric adj2 (therapy or antibiotics)).tw.	242
9	exp PENICILLINS/	3770
10	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	1483
11	exp CEPHALOSPORINS/	3300
12	exp CEFOTAXIME/	1418
13	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	575
14	exp CEFTRIAXONE/	472
15	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	764
16	exp CEFUROXIME/	373
17	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	644
18	(chloramphenicol or kemicetine).tw.	325
19	exp AMOXICILLIN/	1647
20	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).tw.	1703
21	exp AMPICILLIN/	2848
22	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or	1359

	amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).tw.	
23	or/6-22	21282
24	5 and 23	238

MENG_antibiotics_men_prehosp_cdsrdare_130308
Cochrane Database of Systematic Reviews 1st Quarter 2008
Database of Abstracts of Reviews of Effects 1st Quarter 2008

#	Searches	Results
1	MENINGITIS.kw.	17
2	MENINGITIS, BACTERIAL.kw.	10
3	meningitis.tw.	133
4	meningoencephalitis.tw.	7
5	or/1-4	137
6	ANTIBIOTIC$.kw.	195
7	(antibiotic$ or anti?bacterial$).ti.	251
8	(empiric adj2 (therapy or antibiotics)).tw.	26
9	PENICILLIN$.kw.	29
10	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	160
11	CEPHALOSPORIN$.kw.	14
12	CEFOTAXIME.kw.	1
13	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	43
14	CEFTRIAXONE.kw.	4
15	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or	56

	cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	
16	CEFUROXIME.kw.	0
17	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	52
18	(chloramphenicol or kemicetine).tw.	35
19	AMOXICILLIN.kw.	23
20	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).tw.	139
21	AMPICILLIN.kw.	7
22	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).tw.	124
23	or/6-22	478
24	5 and 23	34

MENG_antibiotics_men_prehosp_cinahl_130308

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to February Week 5 2008

#	Searches	Results
1	MENINGITIS/	739
2	exp MENINGITIS, BACTERIAL/	721
3	meningitis.tw.	1293
4	meningoencephalitis.tw.	70
5	or/1-4	1915
6	exp ANTIBIOTICS/	13282
7	(antibiotic$ or anti?bacterial$).ti.	3337
8	(empiric adj2 (therapy or antibiotics)).tw.	247
9	exp PENICILLINS/	1135
10	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	657
11	exp CEPHALOSPORINS/	837
12	exp CEFOTAXIME/	266
13	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	93
14	exp CEFTRIAXONE/	159
15	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	217
16	exp CEFUROXIME/	72
17	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	116
18	(chloramphenicol or kemicetine).tw.	86
19	exp AMOXICILLIN/	393
20	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).tw.	372
21	exp AMPICILLIN/	516
22	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or	231

	amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).tw.	
23	or/6-22	14563
24	5 and 23	319

MENG_antibiotics_men_prehosp_cinahl_130308_2
EBSCO Host Friday, July 31, 2009 9:17:39 AM

#	Query	Limiters/Expanders	Results
S19	S5 and S18	Search modes - Boolean/Phrase	0
S18	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17	Search modes - Boolean/Phrase	329
S17	MH AMPICILLIN+	Search modes - Boolean/Phrase	675
S16	MH AMOXICILLIN+	Search modes - Boolean/Phrase	503
S15	TI (chloramphenicol or kemicetine) or AB (chloramphenicol or kemicetine)	Search modes - Boolean/Phrase	131
S14	MH CEFUROXIME+	Search modes - Boolean/Phrase	97
S13	MH CEFTRIAXONE+	Search modes - Boolean/Phrase	238
S12	MH CEFOTAXIME+	Search modes - Boolean/Phrase	385
S11	MH CEPHALOSPORINS+	Search modes - Boolean/Phrase	1103
S10	MH PENICILLINS+	Search modes - Boolean/Phrase	1462
S9	AB (empiric N2 therapy) or AB (empiric N2 antibiotic*)	Search modes - Boolean/Phrase	351
S8	TI (empiric N2 therapy) or TI (empiric N2 antibiotic*)	Search modes - Boolean/Phrase	73
S7	TI (antibiotic* or anti bacterial*) or AB (antibiotic* or anti bacterial*)	Search modes - Boolean/Phrase	10353
S6	MH ANTIBIOTICS+	Search modes - Boolean/Phrase	17851
S5	S1 or S2 or S3 or S4	Search modes - Boolean/Phrase	1453

S4	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110
S3	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S2	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S1	MH MENINGITIS	Search modes - Boolean/Phrase	927

MENG_antibiotics_men_prehosp_embase_130308

EMBASE 1980 to 2008 Week 10

#	Searches	Results
1	MENINGITIS/	12996
2	exp MENINGITIS, BACTERIAL/	7280
3	meningitis.tw.	20956
4	meningoencephalitis.tw.	2405
5	or/1-4	29395
6	exp ANTI-BACTERIAL AGENTS/	1046958
7	(antibiotic$ or anti?bacterial$).ti.	46897
8	(empiric adj2 (therapy or antibiotics)).tw.	2008
9	exp PENICILLINS/	136227
10	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	20911
11	exp CEPHALOSPORINS/	106366
12	exp CEFOTAXIME/	22815
13	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	6684
14	exp CEFTRIAXONE/	22433
15	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	6457
16	exp CEFUROXIME/	12765
17	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	6249
18	(chloramphenicol or kemicetine).tw.	13463
19	exp AMOXICILLIN/	30341
20	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).tw.	8620
21	exp AMPICILLIN/	43501
22	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or	14782

	austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).tw.	
23	or/6-22	1063853
24	exp CHILD/	600933
25	child$.tw.	463748
26	exp INFANT/	166142
27	infan$.tw.	164257
28	(baby or babies).tw.	26266
29	exp ADOLESCENT/	414214
30	teenag$.tw.	7614
31	adolescen$.tw.	78191
32	exp SCHOOLS/	35143
33	school$.tw.	70608
34	exp PUBERTY/	13610
35	pubescen$.tw.	614
36	or/24-35	1091204
37	5 and 23 and 36	5024
38	limit 37 to english language	3803

MENG_antibiotics_men_prehosp_medline_130308

Ovid MEDLINE(R) 1950 to March Week 1 2008

#	Searches	Results
1	MENINGITIS/	14651
2	exp MENINGITIS, BACTERIAL/	16568
3	meningitis.tw.	30492
4	meningoencephalitis.tw.	4012
5	or/1-4	44163
6	exp ANTI-BACTERIAL AGENTS/	417667
7	(antibiotic$ or anti?bacterial$).ti.	69080
8	(empiric adj2 (therapy or antibiotics)).tw.	1949
9	exp PENICILLINS/	60779
10	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	32115
11	exp CEPHALOSPORINS/	31823
12	exp CEFOTAXIME/	9781
13	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	5518
14	exp CEFTRIAXONE/	3437
15	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	5079
16	exp CEFUROXIME/	1648
17	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	3012
18	(chloramphenicol or kemicetine).tw.	20032
19	exp AMOXICILLIN/	7192
20	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).tw.	7452
21	exp AMPICILLIN/	20564
22	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or	16197

	austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).tw.	
23	or/6-22	463832
24	exp CHILD/	1240933
25	child$.tw.	686056
26	exp INFANT/	770483
27	infan$.tw.	244714
28	(baby or babies).tw.	36169
29	exp ADOLESCENT/	1242197
30	teenag$.tw.	10069
31	adolescen$.tw.	102228
32	exp SCHOOLS/	57930
33	school$.tw.	123158
34	exp PUBERTY/	12723
35	pubescen$.tw.	773
36	or/24-35	2495561
37	5 and 23 and 36	5475
38	limit 37 to (english language and humans)	3513

4 Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?

MENG_antibiotics_sep_prehosp_cctr_200208

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	MENINGITIS/	99
2	exp MENINGITIS, BACTERIAL/	224
3	meningitis.tw.	480
4	meningoencephalitis.tw.	20
5	exp MENINGOCOCCAL INFECTIONS/	152
6	meningococc$.tw.	270
7	septic?emia.tw.	451
8	or/1-7	1180
9	ANTI-BACTERIAL AGENTS/	4968
10	(antibiotic$ or anti?bacterial$).ti.	3564
11	exp PENICILLINS/	3770
12	penicillin$.tw.	1568
13	amoxicillin.ti.	979
14	ampicillin.ti.	654
15	exp CEPHALOSPORINS/	3300
16	cephalosporin$.tw.	795
17	cefotaxime.ti.	383
18	ceftriaxone.ti.	560
19	cefuroxime.ti.	430
20	VANCOMYCIN/	294
21	vancomycin.ti.	300
22	RIFAMPIN/	608
23	rifampicin.ti.	295
24	GENTAMICINS/	851
25	gentamicin.ti.	643
26	THIENAMYCINS/	173
27	meropenem.ti.	126
28	CHLORAMPHENICOL/	259
29	chloramphenicol.ti.	216
30	(empiric and therapy).tw.	349
31	or/9-30	14861
32	exp MENINGITIS/	342
33	exp CENTRAL NERVOUS SYSTEM DISEASES/	14532
34	33 not 32	14190
35	immunodeficien$.mp.	2770
36	IMMUNOLOGIC DISEASES/	0

37 or/34-36	16898
38 and/8,31	433
39 38 not 37	429

MENG_antibiotics_sep_prehosp_cdsrdare_200208

EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2008

#	Searches	Results
1	MENINGITIS.kw.	17
2	MENINGITIS, BACTERIAL.kw.	10
3	meningitis.tw.	132
4	meningoencephalitis.tw.	7
5	MENINGOCOCCAL INFECTIONS.kw.	3
6	meningococc$.tw.	23
7	septic?emia.tw.	149
8	or/1-7	262
9	ANTI-BACTERIAL AGENTS.kw.	293
10	(antibiotic$ or anti?bacterial$).ti.	251
11	PENICILLIN.kw.	4
12	penicillin$.tw.	185
13	amoxicillin.ti.	4
14	ampicillin.ti.	1
15	CEPHALOSPORINS.kw.	14
16	cephalosporin$.tw.	124
17	cefotaxime.ti.	0
18	ceftriaxone.ti.	2
19	cefuroxime.ti.	0
20	VANCOMYCIN.kw.	4
21	vancomycin.ti.	2
22	RIFAMPIN.kw.	14
23	rifampicin.ti.	4
24	GENTAMICINS.kw.	5
25	gentamicin.ti.	3
26	THIENAMYCINS.kw.	4
27	meropenem.ti.	2
28	CHLORAMPHENICOL.kw.	2
29	chloramphenicol.ti.	0
30	(empiric and therapy).tw.	58
31	or/9-30	506
32	immunodeficien$.mp.	304
33	IMMUNE SYSTEM DISEASES.kw.	1
34	AIDS.kw.	45
35	HIV.kw.	132
36	ACQUIRED IMMUNE DEFICIENCY SYNDROME.kw.	0
37	ACQUIRED IMMUNODEFICIENCY SYNDROME.kw.	30
38	HUMAN IMMUNODEFICIENCY VIRUS.kw.	0
39	INTRACRANIAL SHUNT.kw.	0
40	intracranial shunt.tw.	1

41 BRAIN TUMO?R.kw.	0
42 brain tumo?r.tw.	24
43 EPILEPSY.kw.	79
44 epilep$.tw.	225
45 or/32-44	608
46 and/8,31	71
47 46 not 45	66

MENG_antibiotics_sep_prehosp_cinahl_200208_3

EBSCO Host Friday, July 31, 2009 9:46:48 AM

#	Query	Limiters/Expanders	Results
		Limiters - Language: English **Search modes** - Boolean/Phrase	
S34	S32 not S31		16
S33	S32 not S31	**Search modes** - Boolean/Phrase	16
S32	S8 and S24	**Search modes** - Boolean/Phrase	1
S31	S27 or S28 or S29 or S30	**Search modes** - Boolean/Phrase	69
S30	MH HIV INFECTIONS+	**Search modes** - Boolean/Phrase	34079
S29	MH IMMUNOLOGIC DISEASES+	**Search modes** - Boolean/Phrase	90805
S28	TI (immunodeficien*) or AB (immunodeficien*)	**Search modes** - Boolean/Phrase	5174
S27	S26 NOT S25	**Search modes** - Boolean/Phrase	13
S26	MH CENTRAL NERVOUS SYSTEM DISEASES+	**Search modes** - Boolean/Phrase	94418
S25	MH MENINGITIS+	**Search modes** - Boolean/Phrase	1962
S24	S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	**Search modes** -	277

	or S17 or S18 or S19 or S20 or S21 or S22 or S23	Boolean/Phrase	
S23	TI (antibiotic* or anti bacterial*)	**Search modes** - Boolean/Phrase	3959
S22	TI (empiric AND therapy) or AB (empiric AND therapy)	**Search modes** - Boolean/Phrase	458
S21	TI (chloramphenicol)	**Search modes** - Boolean/Phrase	31
S20	TI (meropenem)	**Search modes** - Boolean/Phrase	41
S19	TI (gentamicin)	**Search modes** - Boolean/Phrase	226
S18	TI (rifampicin)	**Search modes** - Boolean/Phrase	32
S17	TI (vancomycin)	**Search modes** - Boolean/Phrase	629
S16	TI (cefuroxime)	**Search modes** - Boolean/Phrase	49
S15	TI (ceftriaxone)	**Search modes** - Boolean/Phrase	79
S14	TI (cefotaxime)	**Search modes** - Boolean/Phrase	24
S13	TI (cephalosporin*) or AB (cephalosporin*)	**Search modes** - Boolean/Phrase	582
S12	TI (ampicillin)	**Search modes** - Boolean/Phrase	56
S11	TI (amoxicillin)	**Search modes** - Boolean/Phrase	149
S10	TI (pencillin*) or AB (pencillin*)	**Search modes** - Boolean/Phrase	3
S9	MH ANTIBIOTICS+	**Search modes** - Boolean/Phrase	17851
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7	**Search modes** -	1632

		Boolean/Phrase	
S7	TI (septicaemia or septicemia) or AB (septicaemia or septicemia)	**Search modes** - Boolean/Phrase	477
S6	TI (meningococc*) or AB (meningococc*)	**Search modes** - Boolean/Phrase	627
S5	MH MENINGOCOCCAL INFECTIONS+	**Search modes** - Boolean/Phrase	793
S4	TI (meningoencephalitis) or AB (meningoencephalitis)	**Search modes** - Boolean/Phrase	110
S3	TI (meningitis) or AB (meningitis)	**Search modes** - Boolean/Phrase	1700
S2	(MH "MENINGITIS, BACTERIAL+")	**Search modes** - Boolean/Phrase	971
S1	MH MENINGITIS	**Search modes** - Boolean/Phrase	927

MENG_antibiotics_embase_sep_prehosp_200208

EMBASE 1980 to 2008 Week 09

#	Searches	Results
1	MENINGITIS/	12981
2	exp BACTERIAL MENINGITIS/	7268
3	meningitis.tw.	20928
4	meningoencephalitis.tw.	2400
5	exp MENINGOCOCCAL INFECTION/	2671
6	meningococc$.tw.	5730
7	septic?emia.tw.	9173
8	or/1-7	41780
9	exp ANTI-BACTERIAL AGENT/	1045217
10	(antibiotic$ or anti?bacterial$).ti.	46845
11	penicillin$.tw.	23227
12	amoxicillin.ti.	2031
13	ampicillin.ti.	2429
14	cephalosporin$.tw.	12919
15	cefotaxime.ti.	1847
16	ceftriaxone.ti.	1926
17	cefuroxime.ti.	1151
18	vancomycin.ti.	4515
19	rifampicin.ti.	2133
20	gentamicin.ti.	4764
21	meropenem.ti.	845
22	chloramphenicol.ti.	2144
23	(empiric and therapy).tw.	3085
24	or/9-23	1054372
25	exp MENINGITIS/	29947
26	exp CENTRAL NERVOUS SYSTEM DISEASE/	763580
27	26 not 25	733633
28	immunodeficien$.tw.	72805
29	exp IMMUNOPATHOLOGY/	584078
30	exp HUMAN IMMUNODEFICIENCY VIRUS INFECTION/	143023
31	or/27-30	1364546
32	and/8,24	18284
33	32 not 31	14973
34	limit 33 to english language	11168

MENG_antibiotics_sep_prehosp_medline_200208

Ovid MEDLINE(R) 1950 to February Week 4 2008

#	Searches	Results
1	MENINGITIS/	14398
2	exp MENINGITIS, BACTERIAL/	16342
3	meningitis.tw.	30049
4	meningoencephalitis.tw.	3945
5	exp MENINGOCOCCAL INFECTIONS/	7856
6	meningococc$.tw.	7889
7	septic?emia.tw.	12634
8	or/1-7	59918
9	exp ANTI-BACTERIAL AGENTS/	412179
10	(antibiotic$ or anti?bacterial$).ti.	67851
11	exp PENICILLINS/	59805
12	penicillin$.tw.	35281
13	amoxicillin.ti.	1926
14	ampicillin.ti.	3734
15	exp CEPHALOSPORINS/	31472
16	cephalosporin$.tw.	13309
17	cefotaxime.ti.	1500
18	ceftriaxone.ti.	1644
19	cefuroxime.ti.	862
20	VANCOMYCIN/	7220
21	vancomycin.ti.	4459
22	RIFAMPIN/	12150
23	rifampicin.ti.	3361
24	GENTAMICINS/	14393
25	gentamicin.ti.	5897
26	THIENAMYCINS/	2103
27	meropenem.ti.	600
28	CHLORAMPHENICOL/	16821
29	chloramphenicol.ti.	4996
30	(empiric and therapy).tw.	2950
31	or/9-30	447563
32	exp MENINGITIS/	39476
33	exp CENTRAL NERVOUS SYSTEM DISEASES/	835915
34	33 not 32	796439
35	immunodeficien$.mp.	138301
36	exp IMMUNE SYSTEM DISEASES/	923601
37	or/34-36	1711357
38	and/8,31	13005
39	38 not 37	11986

40 limit 39 to humans	9991
41 limit 40 to english language	6963

5 In children and young people up to 16 years of age with a petechial rash, can non-specific laboratory tests (C-reactive protein, white blood cell count, blood gas) help to confirm or refute the diagnosis of meningococcal disease?

MENG_nonspecific_labs_septicaemia_cctr_281108

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

#	Searches	Results
1	(petechia$ adj2 rash??).ti,ab.	3
2	(purpur$ adj2 (Henoch or Schoenlein or Anaphylactoid or Hemorrhag$ or haemorrhag$ or Fulminans or rash??)).ti,ab.	32
3	((nonblanch$ or non blanch$ or blanch$) adj3 rash??).ti,ab.	0
4	petechiae.ti,ab.	52
5	((hemorrhag$ or haemorrhag$) adj2 (vasculitis or rash??)).ti,ab.	0
6	exp PURPURA/	72
7	septic?emi?.ti,ab.	477
8	exp BACTEREMIA/	484
9	bacter?emi?.ti,ab.	821
10	MENINGOCOCCAL INFECTIONS/	73
11	(meningococc$ adj2 (septic or toxic or endotoxic or disease or infection? or meningitis)).ti,ab.	82
12	meningococc?emi?.ti,ab.	5
13	(Neisseria meningitid$ or n meningitid$).ti,ab.	138
14	NEISSERIA MENINGITIDIS/	124
15	(meningococcus or meningococci).ti,ab.	52
16	exp MENINGITIS, MENINGOCOCCAL/	90
17	or/1-16	1922
18	C-REACTIVE PROTEIN/	1492
19	(c-reactive adj3 protein?).ti,ab.	2252
20	CRP.ti,ab.	1267
21	ALC.ti,ab.	63
22	exp LEUKOCYTE COUNT/	3561
23	((leukocyt$ or leucocyt$ or lymphocyt$ or neutrophil$ or white blood cell?) adj2 count$).ti,ab.	2475
24	white count.ti,ab.	5
25	LEUKOCYTES/an, cy, pa	102
26	LYMPHOCYTES/cy, pa	100
27	NEUTROPHILS/cy, pa	162
28	NEUTROPENIA/	1010
29	neutropenia.ti,ab.	1985
30	leukocytosis.ti,ab.	122
31	lymphocytosis.ti,ab.	50
32	WBC count.ti,ab.	202

33 (differential adj2 count?).ti,ab.	212
34 (WCC or WBCC).ti,ab.	20
35 reactive c protein?.ti,ab.	3
36 exp BLOOD GAS ANALYSIS/	1361
37 (blood adj2 (gas or gases or oxygen or carbon dioxide)).ti,ab.	2320
38 (oximetry or oximetries).ti,ab.	649
39 OXYGEN/bl	2087
40 CARBON DIOXIDE/bl	991
41 (ABG or ABGs or VBG or VBGs).ti,ab.	72
42 or/18-41	15540
43 and/17,42	281
44 from 43 keep 1-281	281

DARE, CDSR

MENG_nonspecific_labs_septicaemia_cdsrdare_281108

#	Searches	Results
1	(petechia$ adj2 rash??).ti,ab.	0
2	(purpur$ adj2 (Henoch or Schoenlein or Anaphylactoid or Hemorrhag$ or haemorrhag$ or Fulminans or rash??)).ti,ab.	2
3	((nonblanch$ or non blanch$ or blanch$) adj3 rash??).ti,ab.	0
4	petechiae.ti,ab.	0
5	((hemorrhag$ or haemorrhag$) adj2 (vasculitis or rash??)).ti,ab.	0
6	PURPURA.kw.	11
7	septic?emi?.ti,ab.	12
8	BACTEREMIA.kw.	32
9	bacter?emi?.ti,ab.	14
10	MENINGOCOCCAL INFECTIONS.kw.	5
11	(meningococc$ adj2 (septic or toxic or endotoxic or disease or infection? or meningitis)).ti,ab.	8
12	meningococc?emi?.ti,ab.	0
13	(Neisseria meningitid$ or n meningitid$).ti,ab.	0
14	NEISSERIA MENINGITIDIS.kw.	4
15	(meningococcus or meningococci).ti,ab.	0
16	MENINGITIS, MENINGOCOCCAL.kw.	4
17	or/1-16	70
18	C-REACTIVE PROTEIN.kw.	15
19	(c-reactive adj3 protein?).ti,ab.	12
20	CRP.ti,ab.	1
21	ALC.ti,ab.	1
22	LEUKOCYTE COUNT.kw.	6
23	((leukocyt$ or leucocyt$ or lymphocyt$ or neutrophil$ or white blood cell?) adj2 count$).ti,ab.	5
24	white count.ti,ab.	0
25	LEUKOCYTE$.kw.	17
26	LYMPHOCYTE$.kw.	20
27	NEUTROPHIL$.kw.	3
28	NEUTROPENIA.kw.	48
29	neutropenia.ti,ab.	39
30	leukocytosis.ti,ab.	0
31	lymphocytosis.ti,ab.	0
32	WBC count.ti,ab.	0
33	(differential adj2 count?).ti,ab.	0
34	(WCC or WBCC).ti,ab.	0
35	reactive c protein?.ti,ab.	0
36	BLOOD GAS ANALYSIS.kw.	2
37	(blood adj2 (gas or gases or oxygen or carbon dioxide)).ti,ab.	10

38 (oximetry or oximetries).ti,ab.	10
39 OXYGEN.kw.	89
40 CARBON DIOXIDE.kw.	6
41 (ABG or ABGs or VBG or VBGs).ti,ab.	0
42 or/18-41	227
43 and/17,42	5

EMBASE 1980 to 2008 Week 48

MENG_nonspecific_labs_septicaemia_embase_281108

#	Searches	Results
1	SEPTICEMIA/	8802
2	(septic?emi$ or bacter?emi$).ti,ab.	23576
3	NEISSERIA MENINGITIDIS/	6851
4	(Neisseria meningitid$ or n meningitid$).ti,ab.	4352
5	MENINGOCOCCAL INFECTION/	2820
6	(meningococcal adj2 (septic or toxic or endotoxic or disease or infection? or meningitis)).ti,ab.	2924
7	meningococc?emi?.ti,ab.	428
8	(meningococcus or meningococci).ti,ab.	1469
9	MENINGOCOCCOSIS/	2820
10	MENINGOCOCCEMIA/	838
11	PURPURA/	2874
12	PURPURIC RASH/	99
13	PETECHIA/	1622
14	(petechia$ adj2 rash??).ti,ab.	145
15	((purpur$ or haemorrhag$ or hemorrhag$ or Henoch or Schoenlein or Anaphylactoid or fulminans) adj2 (vasculitis or rash??)).ti,ab.	435
16	((nonblanch$ or non blanch$ or blanch$) adj3 rash??).ti,ab.	14
17	petechiae.ti,ab.	854
18	or/1-17	41081
19	C-REACTIVE PROTEIN/	28105
20	(c-reactive adj3 protein?).ti,ab.	18556
21	reactive c protein?.ti,ab.	33
22	CRP.ti,ab.	13200
23	exp LEUKOCYTE COUNT/	44035
24	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	18775
25	white count.ti,ab.	77
26	(leukocyte? or leucocyte? or lymphocyte?).ti.	84295
27	leukocytosis.ti,ab.	3980
28	lymphocytosis.ti,ab.	2379
29	(neutrophil? or neutropenia).ti,ab.	75226
30	(differential adj count$).ti,ab.	1114
31	WBC count.ti,ab.	1918
32	(WCC or WBCC).ti,ab.	234
33	ALC.ti,ab.	854
34	BLOOD GAS ANALYSIS/	5195
35	(blood adj3 (gas or gases or oxygen or carbon dioxide)).ti,ab.	19304
36	(oximetry or oximetries).ti,ab.	4382
37	(ABG or ABGs or VBG or VBGs).ti,ab.	778
38	OXYGEN BLOOD LEVEL/	1536

39 CARBON DIOXIDE BLOOD LEVEL/	399
40 ARTERIAL GAS/	4735
41 ARTERIAL OXYGEN SATURATION/	3521
42 (oxygen adj3 (arterial or venous or saturation)).ti,ab.	16052
43 or/19-42	272134
44 and/18,43	3308
45 limit 44 to english language	2960
46 CASE REPORT/	1015542
47 (case report or case study).ti.	100118
48 letter.pt.	431555
49 editorial.pt.	220296
50 or/46-49	1586737
51 45 not 50	2344
52 limit 51 to animals	269
53 51 not 52	2075

Ovid MEDLINE(R) 1950 to November Week 3 2008
MENG_nonspecific_labs_septicaemia_medline_281108

#	Searches	Results
1	(petechia$ adj2 rash??).ti,ab.	158
2	(purpur$ adj2 (Henoch or Schoenlein or Anaphylactoid or Hemorrhag$ or haemorrhag$ or Fulminans or rash??)).ti,ab.	2941
3	((nonblanch$ or non blanch$ or blanch$) adj3 rash??).ti,ab.	12
4	petechiae.ti,ab.	1100
5	((hemorrhag$ or haemorrhag$) adj2 (vasculitis or rash??)).ti,ab.	329
6	exp PURPURA/	13005
7	septic?emi?.ti,ab.	14147
8	exp BACTEREMIA/	15023
9	bacter?emi?.ti,ab.	16655
10	MENINGOCOCCAL INFECTIONS/	4559
11	(meningococc$ adj2 (septic or toxic or endotoxic or disease or infection? or meningitis)).ti,ab.	4474
12	meningococc?emi?.ti,ab.	620
13	(Neisseria meningitid$ or n meningitid$).ti,ab.	5326
14	NEISSERIA MENINGITIDIS/	6157
15	(meningococcus or meningococci).ti,ab.	2100
16	exp MENINGITIS, MENINGOCOCCAL/	4425
17	or/1-16	63949
18	C-REACTIVE PROTEIN/	17501
19	(c-reactive adj3 protein?).ti,ab.	20741
20	CRP.ti,ab.	14154
21	ALC.ti,ab.	924
22	exp LEUKOCYTE COUNT/	67800
23	((leukocyt$ or leucocyt$ or lymphocyt$ or neutrophil$ or white blood cell?) adj2 count$).ti,ab.	27673
24	white count.ti,ab.	103
25	LEUKOCYTES/an, cy, pa	8710
26	LYMPHOCYTES/cy, pa	16129
27	NEUTROPHILS/cy, pa	10182
28	NEUTROPENIA/	12186
29	neutropenia.ti,ab.	17981
30	leukocytosis.ti,ab.	5361
31	lymphocytosis.ti,ab.	3221
32	WBC count.ti,ab.	2224
33	(differential adj2 count?).ti,ab.	3374
34	(WCC or WBCC).ti,ab.	257
35	reactive c protein?.ti,ab.	30
36	exp BLOOD GAS ANALYSIS/	26302
37	(blood adj2 (gas or gases or oxygen or carbon dioxide)).ti,ab.	21829

38 (oximetry or oximetries).ti,ab.	5253
39 OXYGEN/bl	41691
40 CARBON DIOXIDE/bl	22067
41 (ABG or ABGs or VBG or VBGs).ti,ab.	993
42 or/18-41	250517
43 and/17,42	3890
44 limit 43 to humans	3286
45 limit 44 to english language	2806
46 CASE REPORTS/	1432523
47 (case report or case study).ti.	125221
48 letter.pt.	654631
49 editorial.pt.	234808
50 or/46-49	2204944
51 45 not 50	2344

6 In children and young people up to 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008
MENG_nonspecific_labs_meningitis_cctr_041108

#	Searches	Results
1	exp CHILD/	29922
2	child$.ti,ab.	33306
3	exp INFANT/	17712
4	infan$.ti,ab.	12147
5	(baby or babies).ti,ab.	1673
6	toddler?.ti,ab.	252
7	(neonat$ or newborn?).ti,ab.	6827
8	ADOLESCENT/	55610
9	adolescen$.ti,ab.	4812
10	teen$.ti,ab.	497
11	exp SCHOOLS/	562
12	school$.ti,ab.	6141
13	exp PUBERTY/	215
14	pubescen$.ti,ab.	11
15	(pediatric? or paediatric?).ti,ab.	6289
16	or/1-15	100848
17	meningoencephalitis.ti,ab.	18
18	MENINGOENCEPHALITIS/	10
19	meningitis.ti,ab.	478
20	exp MENINGITIS/	350
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	10
23	or/17-22	580
24	C-REACTIVE PROTEIN/	1492
25	(c-reactive adj3 protein?).ti,ab.	2252
26	CRP.ti,ab.	1267
27	ALC.ti,ab.	63
28	exp LEUKOCYTE COUNT/	3561
29	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	1787
30	white count.ti,ab.	5
31	LEUKOCYTES/an, cy, pa	102
32	LYMPHOCYTES/cy, pa	100
33	leukocytosis.ti.	12
34	lymphocytosis.ti.	1
35	CALCITONIN/	378

36 (procalcitonin or pro calcitonin or calcitonin).ti,ab.	699
37 WBC count.ti,ab.	202
38 (WCC or WBCC).ti,ab.	20
39 reactive c protein?.ti,ab.	3
40 or/24-39	8202
41 and/16,23	399
42 40 and 41	23

MENG_nonspecific_labs_meningitis_cdsrdare_041108
DARE, CDSR

#	Searches	Results
1	CHILD.kw.	1169
2	child$.ti,ab.	1445
3	INFANT.kw.	820
4	infan$.ti,ab.	540
5	(baby or babies).ti,ab.	134
6	toddler?.ti,ab.	5
7	(neonat$ or newborn?).ti,ab.	507
8	ADOLESCENT.kw.	754
9	adolescen$.ti,ab.	219
10	teen$.ti,ab.	10
11	SCHOOL$.kw.	55
12	school$.ti,ab.	119
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	218
16	or/1-15	2768
17	meningoencephalitis.ti,ab.	1
18	MENINGOENCEPHALITIS.kw.	1
19	meningitis.ti,ab.	31
20	MENINGITIS.kw.	21
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	0
23	or/17-22	34
24	C-REACTIVE PROTEIN.kw.	14
25	(c-reactive adj3 protein?).ti,ab.	10
26	CRP.ti,ab.	1
27	ALC.ti,ab.	1
28	LEUKOCYTE COUNT.kw.	6
29	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	3
30	white count.ti,ab.	0
31	LEUKOCYTES.kw.	6
32	LYMPHOCYTES.kw.	5
33	leukocytosis.ti.	0
34	lymphocytosis.ti.	0
35	(PROCALCITONIN or CALCITONIN).kw.	21
36	(procalcitonin or pro calcitonin or calcitonin).ti,ab.	16
37	WBC count.ti,ab.	0
38	(WCC or WBCC).ti,ab.	0
39	reactive c protein?.ti,ab.	0

40 or/24-39	56
41 and/16,23	15
42 40 and 41	0

MENG_nonspecific_labs_meningitis_cinahl_051108

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to October Week 5 2008

#	Searches	Results
1	exp CHILD/	181083
2	child$.tw.	104982
3	exp INFANT/	76346
4	infan$.tw.	25807
5	(baby or babies).tw.	9090
6	exp ADOLESCENT/	114199
7	teenag$.tw.	3073
8	adolescen$.tw.	25047
9	exp SCHOOLS/	19567
10	school$.tw.	33952
11	exp PUBERTY/	907
12	pubescen$.tw.	48
13	(newborn? or neonate?).ti,ab.	9954
14	(pediatric? or paediatric?).ti,ab.	25271
15	or/1-14	301195
16	meningoencephalitis.ti,ab.	91
17	MENINGOENCEPHALITIS/	71
18	meningitis.ti,ab.	1504
19	exp MENINGITIS/	1771
20	((bacterial$ or infect$) adj3 meninges).ti,ab.	3
21	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	59
22	or/16-21	2312
23	C-REACTIVE PROTEIN/	2669
24	(c-reactive adj3 protein?).ti,ab.	2251
25	CRP.ti,ab.	1031
26	reactive c protein?.ti,ab.	0
27	exp LEUKOCYTE COUNT/	2277
28	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	1021
29	white count.ti,ab.	3
30	ALC.ti,ab.	60
31	LEUKOCYTES/	977
32	LYMPHOCYTES/	695
33	leukocytosis.ti,ab.	161
34	lymphocytosis.ti,ab.	52
35	CALCITONIN/	433
36	(procalcitonin or pro calcitonin or calcitonin).ti,ab.	426
37	WBC count.ti,ab.	134
38	(WCC or WBCC).ti,ab.	20
39	or/23-38	8479

40 and/15,22	1118
41 and/39-40	50
42 letter.pt.	66789
43 editorial.pt.	93976
44 CASE REPORTS/	7038
45 (case report or case study).ti.	12368
46 or/42-45	178691
47 41 not 46	49
48 limit 47 to english	49

EMBASE 1980 to 2008 Week 44

MENG_nonspecific_labs_meningitis_embase_051108

#	Searches	Results
1	exp CHILD/	621482
2	child$.tw.	483162
3	exp INFANT/	171568
4	infan$.tw.	169643
5	(baby or babies).tw.	27298
6	exp ADOLESCENT/	431471
7	teenag$.tw.	7935
8	adolescen$.tw.	82587
9	exp SCHOOLS/	37034
10	school$.tw.	74297
11	exp PUBERTY/	14217
12	pubescen$.tw.	647
13	NEWBORN/	177516
14	(newborn? or neonate?).ti,ab.	96623
15	(pediatric? or paediatric?).ti,ab.	109644
16	or/1-15	1264718
17	exp MENINGITIS/	31239
18	meningitis.ti,ab.	21633
19	MENINGOENCEPHALITIS/	2926
20	meningoencephalitis.ti,ab.	2490
21	meningo encephalitis.ti,ab.	308
22	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
23	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	656
24	or/17-23	36180
25	C-REACTIVE PROTEIN/	27803
26	(c-reactive adj3 protein?).ti,ab.	18431
27	reactive c protein?.ti,ab.	31
28	CRP.ti,ab.	13106
29	exp LEUKOCYTE COUNT/	43705
30	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	18713
31	white count.ti,ab.	77
32	(leukocyte? or leucocyte? or lymphocyte?).ti.	84180
33	leukocytosis.ti,ab.	3967
34	lymphocytosis.ti,ab.	2373
35	CALCITONIN/	12540
36	PROCALCITONIN/	1279
37	(procalcitonin or pro calcitonin or calcitonin).ti,ab.	16878
38	WBC count.ti,ab.	1909
39	(WCC or WBCC).ti,ab.	232

40 ALC.ti,ab.	850
41 or/25-40	188726
42 and/16,24	13714
43 42 and 41	727
44 (letter or editorial or comment or historical article).pt.	648101
45 CASE REPORT/	1012221
46 (case report or case study).ti.	99647
47 or/44-46	1580055
48 43 not 47	571
49 limit 48 to english language	486

Ovid MEDLINE(R) 1950 to October Week 4 2008

MENG_nonspecific_labs_meningitis_medline_041108

#	Searches	Results
1	exp CHILD/	1295492
2	child$.ti,ab.	722953
3	exp INFANT/	803310
4	infan$.ti,ab.	256511
5	(baby or babies).ti,ab.	38120
6	toddler?.ti,ab.	3402
7	(neonat$ or newborn?).ti,ab.	224315
8	ADOLESCENT/	1300520
9	adolescen$.ti,ab.	109016
10	teen$.ti,ab.	14460
11	exp SCHOOLS/	60673
12	school$.ti,ab.	130115
13	exp PUBERTY/	13231
14	pubescen$.ti,ab.	822
15	(pediatric? or paediatric?).ti,ab.	131703
16	or/1-15	2702422
17	meningoencephalitis.ti,ab.	4183
18	MENINGOENCEPHALITIS/	4840
19	meningitis.ti,ab.	31905
20	exp MENINGITIS/	41796
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	958
23	or/17-22	51643
24	C-REACTIVE PROTEIN/	17295
25	(c-reactive adj3 protein?).ti,ab.	20525
26	CRP.ti,ab.	13996
27	ALC.ti,ab.	916
28	exp LEUKOCYTE COUNT/	67464
29	((leukocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	22408
30	white count.ti,ab.	103
31	LEUKOCYTES/an, cy, pa	8634
32	LYMPHOCYTES/cy, pa	16006
33	leukocytosis.ti.	694
34	lymphocytosis.ti.	873
35	CALCITONIN/	12439
36	(procalcitonin or pro calcitonin or calcitonin).ti,ab.	19339
37	WBC count.ti,ab.	2206
38	(WCC or WBCC).ti,ab.	255
39	reactive c protein?.ti,ab.	30

40 9007-41-4.rn.	17295
41 56645-65-9.rn.	969
42 or/24-41	153480
43 and/16,23	24227
44 and/42-43	858
45 letter.pt.	651944
46 editorial.pt.	233012
47 CASE REPORTS/	1425518
48 (case report or case study).ti.	124260
49 or/45-48	2193879
50 44 not 49	754
51 limit 50 to humans	729
52 limit 51 to english language	578

MENG_nonspecific_labs_meningitis_medline_051108

Ovid MEDLINE(R) 1950 to October Week 4 2008

#	Searches	Results
1	exp CHILD/	1295492
2	child$.ti,ab.	722953
3	exp INFANT/	803310
4	infan$.ti,ab.	256511
5	(baby or babies).ti,ab.	38120
6	toddler?.ti,ab.	3402
7	(neonat$ or newborn?).ti,ab.	224315
8	ADOLESCENT/	1300520
9	adolescen$.ti,ab.	109016
10	teen$.ti,ab.	14460
11	exp SCHOOLS/	60673
12	school$.ti,ab.	130115
13	exp PUBERTY/	13231
14	pubescen$.ti,ab.	822
15	(pediatric? or paediatric?).ti,ab.	131703
16	or/1-15	2702422
17	meningoencephalitis.ti,ab.	4183
18	MENINGOENCEPHALITIS/	4840
19	meningitis.ti,ab.	31905
20	exp MENINGITIS/	41796
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	958
23	or/17-22	51643
24	C-REACTIVE PROTEIN/	17295
25	(c-reactive adj3 protein?).ti,ab.	20525
26	CRP.ti,ab.	13996
27	ALC.ti,ab.	916
28	exp LEUKOCYTE COUNT/	67464
29	((leukocyt$ or leucocyt$ or lymphocyt$ or white blood cell?) adj3 count$).ti,ab.	24319
30	white count.ti,ab.	103
31	LEUKOCYTES/an, cy, pa	8634
32	LYMPHOCYTES/cy, pa	16006
33	leukocytosis.ti,ab.	5315
34	lymphocytosis.ti,ab.	3201
35	CALCITONIN/	12439
36	(procalcitonin or pro calcitonin or calcitonin).ti,ab.	19339
37	WBC count.ti,ab.	2206
38	(WCC or WBCC).ti,ab.	255
39	reactive c protein?.ti,ab.	30

40 9007-41-4.rn.	17295
41 56645-65-9.rn.	969
42 or/24-41	159323
43 and/16,23	24227
44 and/42-43	929
45 letter.pt.	651944
46 editorial.pt.	233012
47 CASE REPORTS/	1425518
48 (case report or case study).ti.	124260
49 or/45-48	2193879
50 44 not 49	802
51 limit 50 to humans	769
52 limit 51 to english language	607

7 In children and young people with suspected meningitis, can CSF variables (white cell count, glucose, protein) distinguish between bacterial and viral meningitis?

8 What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?

MENG_CSF_parameter_cctr_101208

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

#	Searches	Results
1	exp CHILD/	29922
2	child$.ti,ab.	33306
3	exp INFANT/	17712
4	infan$.ti,ab.	12147
5	(baby or babies).ti,ab.	1673
6	toddler?.ti,ab.	252
7	(neonat$ or newborn?).ti,ab.	6827
8	ADOLESCENT/	55610
9	adolescen$.ti,ab.	4812
10	teen$.ti,ab.	497
11	exp SCHOOLS/	562
12	school$.ti,ab.	6141
13	exp PUBERTY/	215
14	pubescen$.ti,ab.	11
15	(pediatric? or paediatric?).ti,ab.	6289
16	or/1-15	100848
17	meningoencephalitis.ti,ab.	18
18	MENINGOENCEPHALITIS/	10
19	meningitis.ti,ab.	478
20	exp MENINGITIS/	350
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	10
23	((fungal or aseptic) adj3 meninges).ti,ab.	0
24	or/17-23	580
25	SPINAL PUNCTURE/	196
26	(lumbar adj3 punctur$).ti,ab.	268
27	CEREBROSPINAL FLUID/	105
28	(cerebrospinal$ adj3 fluid$).ti.	355
29	(cerebro spinal$ adj3 fluid$).ti.	6
30	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (parameter$ or parametre$)).ti,ab.	38

31	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (white cell$ or leukocyte$ or neutrophil$ or lymphocyte$ or glucose$ or protein$)).ti,ab.	245
32	or/25-31	981
33	and/16,24,32	79

MENG_CSF_parameter_cdsrdare_101208

EBM Reviews - Cochrane Database of Systematic Reviews 4th Quarter 2008

#	Searches	Results
1	CHILD.kw.	385
2	child$.ti,ab.	1066
3	INFANT.kw.	406
4	infan$.ti,ab.	481
5	(baby or babies).ti,ab.	137
6	toddler?.ti,ab.	4
7	(neonat$ or newborn?).ti,ab.	450
8	ADOLESCEN$.kw.	142
9	adolescen$.ti,ab.	103
10	teen$.ti,ab.	8
11	SCHOOL$.kw.	9
12	school$.ti,ab.	79
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	172
16	or/1-15	1527
17	meningoencephalitis.ti,ab.	1
18	MENINGOENCEPHALITIS.kw.	1
19	meningitis.ti,ab.	20
20	MENINGITIS.kw.	10
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	0
23	((fungal or aseptic) adj3 meninges).ti,ab.	0
24	or/17-23	22
25	SPINAL PUNCTURE.kw.	2
26	(lumbar adj3 punctur$).ti,ab.	2
27	CEREBROSPINAL FLUID.kw.	4
28	(cerebrospinal$ adj3 fluid$).ti.	1
29	(cerebro spinal$ adj3 fluid$).ti.	0
30	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (parameter$ or parametre$)).ti,ab.	0
31	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (white cell$ or leukocyte$ or neutrophil$ or lymphocyte$ or glucose$ or protein$)).ti,ab.	2
32	or/25-31	8
33	and/16,24,32	0

MENG_CSF_parameter_cinahl_101208

EBSCO Host Friday, July 31, 2009 10:27:58 AM

#	Query	Limiters/Expanders	Results
S30	(S16 and S23 and S29)	Search modes - Boolean/Phrase	0
S29	(S24 or S25 or S26 or S27 or S28)	Search modes - Boolean/Phrase	70
S28	(TI cerebrospinal* N3 fluid*) or (AB cerebrospinal* N3 fluid*)	Search modes - Boolean/Phrase	1211
S27	(TI CSF)	Search modes - Boolean/Phrase	256
S26	(MH CEREBROSPINAL FLUID)	Search modes - Boolean/Phrase	861
S25	(TI lumbar N3 punctur*) or (AB lumbar N3 punctur*)	Search modes - Boolean/Phrase	431
S24	(MH "SPINAL PUNCTURE")	Search modes - Boolean/Phrase	545
S23	(S17 or S18 or S19 or S20 or S21 or S22)	Search modes - Boolean/Phrase	114
S22	(TI "viral*" or "virus*" N3 "meninges" or "meningitis") or (AB "viral*" or "virus*" N3 "meninges" or "meningitis")	Search modes - Boolean/Phrase	6909
S21	(TI "bacterial*" or "infect*" N3 "meninges") or (AB "bacterial*" or "infect*" N3 "meninges")	Search modes - Boolean/Phrase	6214
S20	(MH "MENINGITIS+")	Search modes - Boolean/Phrase	1962
S19	(TI "meningitis") or (AB "meningitis")	Search modes - Boolean/Phrase	1700
S18	(MH "MENINGOENCEPHALITIS")	Search modes - Boolean/Phrase	88
S17	(TI "meningoencephalitis") or (AB "meningoencephalitis")	Search modes - Boolean/Phrase	110
S16	(S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1)	Search modes - Boolean/Phrase	1770

S15	(TI "pediatric*" or "paediatric*") or (AB "pediatric*" or "paediatric*")	Search modes - Boolean/Phrase	29743
S14	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	55
S13	(MH "PUBERTY+")	Search modes - Boolean/Phrase	1004
S12	(TI "school*") or (AB "school*")	Search modes - Boolean/Phrase	38329
S11	(MH "SCHOOLS+")	Search modes - Boolean/Phrase	21736
S10	(TI "teen*") or (AB "teen*")	Search modes - Boolean/Phrase	6332
S9	(TI "adolescen*") or (AB "adolescen*")	Search modes - Boolean/Phrase	28859
S8	(MH "ADOLESCENCE+")	Search modes - Boolean/Phrase	128199
S7	(TI "neonat*" or "newborn?") or (AB "neonat*" or "newborn?")	Search modes - Boolean/Phrase	16412
S6	(TI "toddler*") or (AB "toddler*")	Search modes - Boolean/Phrase	1632
S5	(TI "baby" or "babies") or (AB "baby" or "babies")	Search modes - Boolean/Phrase	10049
S4	(TI "infant*") or (AB "infant*")	Search modes - Boolean/Phrase	27020
S3	(MH "INFANT+")	Search modes - Boolean/Phrase	82965
S2	(TI "child*") or (AB "child*")	Search modes - Boolean/Phrase	117798
S1	(MH "CHILD+")	Search modes -	199308

MENG_CSF_parameter_embase_101208

EMBASE 1980 to 2008 Week 49

#	Searches	Results
1	exp CHILD/	624232
2	child$.tw.	485853
3	exp INFANT/	172303
4	infan$.tw.	170443
5	(baby or babies).tw.	27438
6	exp ADOLESCENT/	433813
7	teenag$.tw.	7974
8	adolescen$.tw.	83184
9	exp SCHOOLS/	37292
10	school$.tw.	74809
11	exp PUBERTY/	14295
12	pubescen$.tw.	654
13	NEWBORN/	178121
14	(newborn? or neonate?).ti,ab.	97081
15	(pediatric? or paediatric?).ti,ab.	110541
16	or/1-15	1271158
17	exp MENINGITIS/	31434
18	meningitis.ti,ab.	21723
19	MENINGOENCEPHALITIS/	2959
20	meningoencephalitis.ti,ab.	2507
21	meningo encephalitis.ti,ab.	310
22	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
23	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	657
24	or/17-23	36393
25	LUMBAR PUNCTURE/	5367
26	(lumbar adj3 punctur$).ti,ab.	3750
27	CEREBROSPINAL FLUID/	26817
28	(cerebrospinal$ adj3 fluid$).ti.	12180
29	(cerebro spinal$ adj3 fluid$).ti.	75
30	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (parameter$ or parametre$)).ti,ab.	331
31	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (white cell$ or leukocyte$ or neutrophil$ or lymphocyte$ or glucose$ or protein$)).ti,ab.	4607
32	or/25-31	39697
33	and/16,24,32	2382
34	letter.pt.	432301
35	editorial.pt.	220749
36	CASE REPORT/	1016868
37	(case report or case study).ti.	100316
38	or/34-37	1589125
39	33 not 38	1672
40	limit 39 to english language	1378

MENG_CSF_parameter_medline_101208

MEDLINE 1950 to November Week 3 2008

#	Searches	Results
1	exp CHILD/	1301996
2	child$.ti,ab.	727524
3	exp INFANT/	806815
4	infan$.ti,ab.	257852
5	(baby or babies).ti,ab.	38372
6	toddler?.ti,ab.	3425
7	(neonat$ or newborn?).ti,ab.	225635
8	ADOLESCENT/	1308783
9	adolescen$.ti,ab.	111216
10	teen$.ti,ab.	14767
11	exp SCHOOLS/	61026
12	school$.ti,ab.	131452
13	exp PUBERTY/	13352
14	pubescen$.ti,ab.	833
15	(pediatric? or paediatric?).ti,ab.	132913
16	or/1-15	2718027
17	meningoencephalitis.ti,ab.	4208
18	MENINGOENCEPHALITIS/	4864
19	meningitis.ti,ab.	32111
20	exp MENINGITIS/	42057
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	961
23	((fungal or aseptic) adj3 meninges).ti,ab.	1
24	or/17-23	51994
25	SPINAL PUNCTURE/	4346
26	(lumbar adj3 punctur$).ti,ab.	4470
27	CEREBROSPINAL FLUID/	14821
28	(cerebrospinal$ adj3 fluid$).ti.	20717
29	(cerebro spinal$ adj3 fluid$).ti.	168
30	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (parameter$ or parametre$)).ti,ab.	402
31	((CSF or (cerebrospinal$ adj3 fluid$)) adj3 (white cell$ or leukocyte$ or neutrophil$ or lymphocyte$ or glucose$ or protein$)).ti,ab.	5882
32	or/25-31	38996
33	and/16,24,32	3097
34	letter.pt.	654713
35	editorial.pt.	234908
36	CASE REPORTS/	1432649
37	(case report or case study).ti.	125291
38	or/34-37	2205298
39	33 not 38	2424

40 limit 39 to humans	2278
41 limit 40 to english language	1704

9 What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?

MENG_dx_csf_aspirates_economics_embase_241108

EMBASE 1980 to 2008 Week 47

#	Searches	Results
1	BACTERIAL MENINGITIS/	7625
2	TUBERCULOUS MENINGITIS/	1887
3	MENINGOENCEPHALITIS/	2945
4	MENINGITIS/	13498
5	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	4927
6	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
7	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
8	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	230
9	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	462
10	((meningitis or meningitides) adj3 listeria).ti,ab.	211
11	((meningitis or meningitides) adj3 meningococc$).ti,ab.	881
12	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1023
13	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1626
14	meningoencephalitis.ti,ab.	2500
15	SEPTICEMIA/	8791
16	BACTEREMIA/	14315
17	(septic?emi? or bacter?emi?).ti,ab.	23006
18	MENINGOCOCCAL INFECTION/	2818
19	MENINGOCOCCOSIS/	2818
20	MENINGOCOCCEMIA/	838
21	(meningococc$ adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	2603
22	(meningococc?emi? or meningococcosis).ti,ab.	434
23	NEISSERIA MENINGITIDIS/	6847
24	(Neisseria meningitidis or n meningitidis).ti,ab.	4304
25	or/1-24	62025
26	exp GENE AMPLIFICATION/	268526
27	(gene amplification or polymerase chain reaction?).ti,ab.	103919
28	PCR.ti,ab.	167012
29	BACTERIAL ANTIGEN/	9132
30	VIRUS ANTIGEN/	12069
31	rapid antigen.ti,ab.	279
32	(antigen? adj3 test$).ti,ab.	6597
33	exp IMMUNOLOGICAL PROCEDURES/	583611
34	exp ANALYTICAL EQUIPMENT/	58521

35 CEREBROSPINAL FLUID/	26765
36 (cerebro?spinal adj2 fluid?).ti,ab.	37117
37 exp MICROBIOLOGICAL EXAMINATION/	196602
38 exp BLOOD ANALYSIS/	56170
39 (blood adj3 cultur$).ti,ab.	16323
40 exp SKIN TEST/	27554
41 exp MICROSCOPY/	232877
42 ((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	18174
43 SKIN CULTURE/	1291
44 SKIN/	24245
45 dermoscop$.ti,ab.	742
46 EPILUMINESCENCE MICROSCOPY/	1253
47 dermatoscop$.ti,ab.	262
48 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	346
49 gram? stain$.ti,ab.	2755
50 GRAM STAINING/	2860
51 AGGLUTINATION TEST/	2524
52 LATEX AGGLUTINATION TEST/	1883
53 (latex adj3 fixation).ti,ab.	84
54 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	231
55 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	4546
56 (early adj2 diagnosis).ti,ab.	30122
57 EARLY DIAGNOSIS/	36630
58 or/26-57	1399902
59 and/25,58	22222
60 limit 59 to "diagnosis (optimized)"	3372
61 limit 60 to "economics (2 or more terms min difference)"	96
62 limit 61 to english language	91

MENG_dx_csf_aspirates_economics_htaeed_241108

CLEED, CLHTA

#	Searches	Results
1	exp MENINGITIS, BACTERIAL/	29
2	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	0
3	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
4	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
5	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	0
6	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	0
7	((meningitis or meningitid?s) adj3 listeria).ti,ab.	0
8	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	3
9	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	0
10	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1
11	meningoencephalitis.ti,ab.	1
12	MENINGOENCEPHALITIS/	1
13	MENINGITIS/	8
14	BACTEREMIA/	81
15	(septic?emi? or bacter?emi?).ti,ab.	29
16	MENINGOCOCCAL INFECTIONS/	13
17	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	9
18	meningococc?emi?.ti,ab.	0
19	exp NEISSERIA MENINGITIDIS/	2
20	(Neisseria meningitidis or n meningitidis).ti,ab.	1
21	or/1-20	132
22	exp POLYMERASE CHAIN REACTION/	115
23	NUCLEIC ACID AMPLIFICATION TECHNIQUES/	8
24	PCR.ti,ab.	27
25	polymerase chain reaction?.ti,ab.	25
26	ANTIGENS, BACTERIAL/ or ANTIGENS, VIRAL/	16
27	rapid antigen.ti,ab.	1
28	(antigen? adj3 test$).ti,ab.	9
29	exp IMMUNOLOGIC TESTS/	298
30	exp REAGENT KITS, DIAGNOSTIC/	57
31	CEREBROSPINAL FLUID/	4
32	(cerebro?spinal adj2 fluid?).ti,ab.	7
33	exp BACTERIOLOGICAL TECHNIQUES/	46
34	exp BLOOD/	125
35	(blood adj3 cultur$).ti,ab.	9
36	exp SKIN TESTS/	53
37	exp MICROSCOPY/	16
38	((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	11

39 exp SKIN/	23
40 dermoscop$.ti,ab.	1
41 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	0
42 gram? stain$.ti,ab.	1
43 (agglutination adj3 (test$ or latex)).ti,ab.	1
44 exp AGGLUTINATION TESTS/	9
45 (latex adj3 fixation).ti,ab.	0
46 (skin adj3 aspirate?).ti,ab.	0
47 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	0
48 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	10
49 (early adj2 diagnosis).ti,ab.	20
50 EARLY DIAGNOSIS/	24
51 or/22-50	677
52 and/21,51	13
53 limit 52 to english language	13

MENG_dx_csf_aspirates_economics_medline_241108

Ovid MEDLINE(R) 1950 to November Week 2 2008

#	Searches	Results
1	ECONOMICS/	25927
2	"COSTS AND COST ANALYSIS"/	37714
3	COST ALLOCATION/	1868
4	COST-BENEFIT ANALYSIS/	45114
5	COST CONTROL/	18116
6	COST SAVINGS/	6198
7	COST OF ILLNESS/	11241
8	COST SHARING/	1452
9	HEALTH CARE COSTS/	17529
10	DIRECT SERVICE COSTS/	869
11	DRUG COSTS/	9032
12	EMPLOYER HEALTH COSTS/	998
13	HOSPITAL COSTS/	5782
14	HEALTH RESOURCES/	6549
15	"HEALTH SERVICES NEEDS AND DEMAND"/	31064
16	HEALTH PRIORITIES/	7065
17	HEALTH EXPENDITURES/	10495
18	CAPITAL EXPENDITURES/	1846
19	FINANCIAL MANAGEMENT/	14569
20	FINANCIAL MANAGEMENT, HOSPITAL/	7012
21	QUALITY-ADJUSTED LIFE YEARS/	3703
22	"DEDUCTIBLES AND COINSURANCE"/	1215
23	MEDICAL SAVINGS ACCOUNTS/	402
24	ECONOMICS, HOSPITAL/	8768
25	ECONOMICS, MEDICAL/	7354
26	ECONOMICS, NURSING/	3859
27	ECONOMICS, PHARMACEUTICAL/	2005
28	MODELS, ECONOMIC/	3350
29	MODELS, ECONOMETRIC/	2869
30	RESOURCE ALLOCATION/	6095
31	HEALTH CARE RATIONING/	9134
32	"FEES AND CHARGES"/	7497
33	BUDGETS/	7798
34	VALUE OF LIFE/	5086
35	(financ$ or fiscal$ or funding).tw.	56232
36	(QALY$ or life?year$).tw.	2253
37	(econom$ or cost$).tw.	294370
38	pharmacoeconomic$.tw.	1968
39	or/1-38	490283
40	exp MENINGITIS, BACTERIAL/	17352

41	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5816
42	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
43	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	22
44	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	365
45	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	842
46	((meningitis or meningitid?s) adj3 listeria).ti,ab.	360
47	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	1404
48	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	1328
49	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4122
50	meningoencephalitis.ti,ab.	4203
51	MENINGOENCEPHALITIS/	4859
52	MENINGITIS/	15221
53	BACTEREMIA/	12542
54	(septic?emi? or bacter?emi?).ti,ab.	29969
55	MENINGOCOCCAL INFECTIONS/	4550
56	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3651
57	meningococc?emi?.ti,ab.	620
58	exp NEISSERIA MENINGITIDIS/	6594
59	(Neisseria meningitidis or n meningitidis).ti,ab.	5264
60	or/40-59	79466
61	exp POLYMERASE CHAIN REACTION/	251660
62	NUCLEIC ACID AMPLIFICATION TECHNIQUES/	3809
63	PCR.ti,ab.	193226
64	polymerase chain reaction?.ti,ab.	115482
65	ANTIGENS, BACTERIAL/ or ANTIGENS, VIRAL/	67242
66	rapid antigen.ti,ab.	297
67	(antigen? adj3 test$).ti,ab.	9079
68	exp IMMUNOLOGIC TESTS/	892795
69	exp REAGENT KITS, DIAGNOSTIC/	14399
70	CEREBROSPINAL FLUID/	14809
71	(cerebro?spinal adj2 fluid?).ti,ab.	49376
72	exp BACTERIOLOGICAL TECHNIQUES/	61547
73	exp BLOOD/	810010
74	(blood adj3 cultur$).ti,ab.	19469
75	exp SKIN TESTS/	50108
76	exp MICROSCOPY/	378744
77	((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	22185
78	exp SKIN/	158180
79	dermoscop$.ti,ab.	769
80	((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	492
81	gram? stain$.ti,ab.	3387

82 (agglutination adj3 (test$ or latex)).ti,ab.	6896
83 exp AGGLUTINATION TESTS/	34845
84 (latex adj3 fixation).ti,ab.	246
85 (skin adj3 aspirate?).ti,ab.	49
86 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	256
87 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	5863
88 (early adj2 diagnosis).ti,ab.	41045
89 EARLY DIAGNOSIS/	4224
90 or/61-89	2373456
91 and/60,90	23544
92 limit 91 to english language	18958
93 limit 92 to ("costs (specificity)" or "economics (specificity)")	88

MENG_dx_csf_skin_aspirates_cctr_180808

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	8501
2	sensitivity.ti,ab.	11345
3	specificity.ti,ab.	3407
4	((post-test or posttest) adj probability).ti,ab.	12
5	((pre-test or pretest) adj probability).ti,ab.	14
6	predictive value$.tw.	1719
7	likelihood ratio$.tw.	121
8	di.xs.	50593
9	or/1-8	62178
10	exp MENINGITIS, BACTERIAL/	227
11	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	174
12	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
13	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
14	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	1
15	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	28
16	((meningitis or meningitid?s) adj3 listeria).ti,ab.	2
17	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	33
18	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	22
19	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	42
20	meningoencephalitis.ti,ab.	18
21	MENINGOENCEPHALITIS/	10
22	MENINGITIS/	99
23	BACTEREMIA/	380
24	(septic?emi? or bacter?emi?).ti,ab.	1259
25	MENINGOCOCCAL INFECTIONS/	72
26	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	62
27	meningococc?emi?.ti,ab.	5
28	exp NEISSERIA MENINGITIDIS/	124
29	(Neisseria meningitidis or n meningitidis).ti,ab.	134
30	or/10-29	1929
31	exp POLYMERASE CHAIN REACTION/	1126
32	NUCLEIC ACID AMPLIFICATION TECHNIQUES/	12
33	PCR.ti,ab.	1479
34	polymerase chain reaction?.ti,ab.	1104
35	ANTIGENS, BACTERIAL/ or ANTIGENS, VIRAL/	423
36	rapid antigen.ti,ab.	13
37	(antigen? adj3 test$).ti,ab.	340
38	exp IMMUNOLOGIC TESTS/	5799

39 exp REAGENT KITS, DIAGNOSTIC/	177
40 CEREBROSPINAL FLUID/	103
41 (cerebro?spinal adj2 fluid?).ti,ab.	906
42 exp BACTERIOLOGICAL TECHNIQUES/	338
43 exp BLOOD/	9100
44 (blood adj3 cultur$).ti,ab.	681
45 exp SKIN TESTS/	1697
46 exp MICROSCOPY/	841
47 ((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	1697
48 exp SKIN/	3127
49 dermoscop$.ti,ab.	9
50 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	10
51 gram? stain$.ti,ab.	146
52 (agglutination adj3 (test$ or latex)).ti,ab.	66
53 exp AGGLUTINATION TESTS/	136
54 (latex adj3 fixation).ti,ab.	0
55 (skin adj3 aspirate?).ti,ab.	1
56 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	4
57 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	61
58 (early adj2 diagnosis).ti,ab.	386
59 EARLY DIAGNOSIS/	85
60 or/31-59	23403
61 and/30,60	520
62 HUMANS/ and ANIMALS/	5715
63 61 not 62	514

MENG_dx_csf_skin_aspirates_cdsrdare_180808

DARE, CDSR

#	Searches	Results
1	"SENSITIVITY AND SPECIFICITY".kw.	474
2	sensitivity.ti,ab.	166
3	specificity.ti,ab.	12
4	((post-test or posttest) adj probability).ti,ab.	0
5	((pre-test or pretest) adj probability).ti,ab.	0
6	predictive value$.tw.	314
7	likelihood ratio$.tw.	190
8	di.xs.	0
9	or/1-8	884
10	BACTERIAL MENINGITIS.kw.	1
11	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	12
12	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
13	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
14	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	0
15	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	0
16	((meningitis or meningitid?s) adj3 listeria).ti,ab.	0
17	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	4
18	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	0
19	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	2
20	meningoencephalitis.ti,ab.	1
21	MENINGOENCEPHALITIS.kw.	1
22	MENINGITIS.kw.	21
23	BACTEREMIA.kw.	30
24	(septic?emi? or bacter?emi?).ti,ab.	23
25	MENINGOCOCCAL INFECTION$.kw.	4
26	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	6
27	meningococc?emi?.ti,ab.	0
28	NEISSERIA MENINGITIDIS.kw.	4
29	(Neisseria meningitidis or n meningitidis).ti,ab.	0
30	or/10-29	74
31	POLYMERASE CHAIN REACTION.kw.	9
32	NUCLEIC ACID AMPLIFICATION TECHNIQUES.kw.	4
33	PCR.ti,ab.	2
34	polymerase chain reaction?.ti,ab.	4
35	(ANTIGENS, BACTERIAL or ANTIGENS, VIRAL).kw.	4
36	rapid antigen.ti,ab.	0
37	(antigen? adj3 test$).ti,ab.	4
38	IMMUNOLOGIC TESTS.kw.	5

39 DIAGNOSTIC REAGENT KIT$.kw.	0
40 CEREBROSPINAL FLUID$.kw.	13
41 (cerebro?spinal adj2 fluid?).ti,ab.	16
42 BACTERIOLOGICAL TECHNIQUE$.kw.	10
43 BLOOD.kw.	772
44 (blood adj3 cultur$).ti,ab.	9
45 SKIN TEST$.kw.	0
46 MICROSCOPY.kw.	8
47 ((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	3
48 SKIN.kw.	145
49 dermoscop$.ti,ab.	2
50 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	0
51 gram? stain$.ti,ab.	1
52 (agglutination adj3 (test$ or latex)).ti,ab.	1
53 AGGLUTINATION TEST$.kw.	2
54 (latex adj3 fixation).ti,ab.	0
55 (skin adj3 aspirate?).ti,ab.	0
56 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	0
57 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	1
58 (early adj2 diagnosis).ti,ab.	7
59 EARLY DIAGNOSIS.kw.	10
60 or/31-59	989
61 and/30,60	11

MENG_dx_csf_skin_aspirates_cinahl_180808_5

EBSCO-Host Thursday, July 30, 2009 10:32:54 AM

#	Query	Limiters/Expanders	Results
S72	S9 and S28 and S70	Limiters - English Language Search modes - Boolean/Phrase	0
S71	S9 and S28 and S70	Search modes - Boolean/Phrase	0
S70	S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69	Search modes - Boolean/Phrase	340
S69	TI (early N2 diagnosis) or AB (early N2 diagnosis)	Search modes - Boolean/Phrase	2568
S68	AB (rapid diagnos* or rapid diagnostic test*)	Search modes - Boolean/Phrase	269
S67	TI (rapid diagnos* or rapid diagnostic test*)	Search modes - Boolean/Phrase	91
S66	TI (derm* N3 scraping) or AB (derm* N3 aspirate*)	Search modes - Boolean/Phrase	0
S65	AB (epiderm* N3 scraping) or AB (epiderm* N3 aspirate*)	Search modes - Boolean/Phrase	1
S64	TI (epiderm* N3 scraping) or TI (epiderm* N3 aspirate*)	Search modes - Boolean/Phrase	0
S63	AB (lesion N3 scraping) or TI (lesion N3 aspirate*)	Search modes - Boolean/Phrase	1
S62	TI (lesion N3 scraping) or AB (lesion N3 aspirate*)	Search modes - Boolean/Phrase	1
S61	AB (skin N3 scraping) or AB (skin N3 aspirate*)	Search modes - Boolean/Phrase	4
S60	TI (skin N3 scraping) or TI (skin N3 aspirate*)	Search modes - Boolean/Phrase	2
S59	MH AGGLUTINATION TESTS	Search modes - Boolean/Phrase	76
S58	TI (latex N3 fixation) or AB (latex N3 fixation)	Search modes - Boolean/Phrase	1
S57	TI (agglutination N3 latex) or AB (agglutination N3 latex)	Search modes - Boolean/Phrase	55
S56	TI (agglutination N3 test*) or AB (agglutination N3 test*)	Search modes - Boolean/Phrase	71
S55	TI (gram* stain*) or AB (gram* stain*)	Search modes - Boolean/Phrase	216
S54	TI (dermatoscop*) or AB (dermatoscop*)	Search modes - Boolean/Phrase	7
S53	MH SKIN+	Search modes - Boolean/Phrase	4178
S52	TI (dermal N3 microscopy) or AB (dermal N3	Search modes -	2

	microscopy)	Boolean/Phrase	
S51	TI (dermal N3 test*) or AB (dermal N3 test*)	Search modes - Boolean/Phrase	16
S50	TI (epidermal N3 microscopy) or AB (epidermal N3 microscopy)	Search modes - Boolean/Phrase	0
S49	TI (epidermal N3 test*) or AB (epidermal N3 test*)	Search modes - Boolean/Phrase	4
S48	TI (skin N3 microscopy) or AB (skin N3 microscopy)	Search modes - Boolean/Phrase	15
S47	TI (skin N3 test*) or AB (skin N3 test*)	Search modes - Boolean/Phrase	1451
S46	MH MICROSCOPY+	Search modes - Boolean/Phrase	2453
S45	MH SKIN TESTS+	Search modes - Boolean/Phrase	2100
S44	TI (blood N3 cultur*) or AB (blood N3 cultur*)	Search modes - Boolean/Phrase	1134
S43	MH BLOOD+	Search modes - Boolean/Phrase	11761
S42	MH BACTERIOLOGICAL TECHNIQUES+	Search modes - Boolean/Phrase	641
S41	TI (cerebro-spinal n2 fluid*) or AB (cerebro-spinal n2 fluid*)	Search modes - Boolean/Phrase	4
S40	TI (cerebrospinal n2 fluid*) or AB (cerebrospinal n2 fluid*)	Search modes - Boolean/Phrase	1211
S39	MH CEREBROSPINAL FLUID	Search modes - Boolean/Phrase	861
S38	MH REAGENT KITS, DIAGNOSTIC+	Search modes - Boolean/Phrase	641
S37	MH IMMUNOLOGIC TESTS+	Search modes - Boolean/Phrase	13608
S36	TI (antigen* N3 test*) or AB (antigen* N3 test*)	Search modes - Boolean/Phrase	433
S35	TI (rapid antigen) or AB (rapid antigen)	Search modes - Boolean/Phrase	53
S34	MH ANTIGENS, VIRAL	Search modes - Boolean/Phrase	391
S33	MH ANTIGENS, BACTERIAL	Search modes - Boolean/Phrase	239
S32	TI (polymerase chain reaction*) or AB (polymerase chain reaction*)	Search modes - Boolean/Phrase	3709
S31	TI (PCR) or AB (PCR)	Search modes - Boolean/Phrase	2599
S30	MH NUCLEIC ACID AMPLIFICATION TECHNIQUES	Search modes - Boolean/Phrase	294
S29	MH POLYMERASE CHAIN REACTION+	Search modes - Boolean/Phrase	6807
S28	S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27	Search modes - Boolean/Phrase	304

S27	TI (neisseria meningitidis or n meningitidis) or AB (neisseria meningitidis or n meningitidis)	Search modes - Boolean/Phrase	118
S26	MH NEISSERIA	Search modes - Boolean/Phrase	192
S25	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S24	TI (meningococcal N3 infection*) or AB (meningococcal N3 infection*)	Search modes - Boolean/Phrase	48
S23	TI (meningococcal N3 disease) or AB (meningococcal N3 disease)	Search modes - Boolean/Phrase	264
S22	TI (meningococcal N3 endotoxic) or AB (meningococcal N3 endotoxic)	Search modes - Boolean/Phrase	0
S21	TI (meningococcal N3 toxic) or AB (meningococcal N3 toxic)	Search modes - Boolean/Phrase	0
S20	TI (meningococcal N3 septic) or AB (meningococcal N3 septic)	Search modes - Boolean/Phrase	17
S19	TI (meningococcal N3 sepsis) or AB (meningococcal N3 sepsis)	Search modes - Boolean/Phrase	20
S18	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S17	TI (septicemi* or septicaemi* or bacteremi* or bactaeremi*) or AB (septicemi* or septicaemi* or bacteremi* or bactaeremi*)	Search modes - Boolean/Phrase	1537
S16	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S15	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S14	MH MENINGITIS	Search modes - Boolean/Phrase	927
S13	MH MENINGOENCEPHALITIS	Search modes - Boolean/Phrase	88
S12	TI (meningeal or pachymeningitis or meningoencephalitis) or AB (meningeal or pachymeningitis or meningoencephalitis)	Search modes - Boolean/Phrase	258
S11	TI (meningitis or meningitides) or AB (meningitis or meningitides)	Search modes - Boolean/Phrase	1705
S10	MH MENINGITIS, BACTERIAL	Search modes - Boolean/Phrase	757
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8	Search modes - Boolean/Phrase	1657
S8	TI (likelihood ratio) or AB (likelihood ratio)	Search modes - Boolean/Phrase	420
S7	TI (predictive value) or AB (predictive value)	Search modes - Boolean/Phrase	3191
S6	TI (pretest probability) or AB (pretest probability)	Search modes - Boolean/Phrase	104
S5	TI (pre test probability) or AB (pre test probability)	Search modes - Boolean/Phrase	14
S4	TI (posttest probability) or AB (posttest probability)	Search modes - Boolean/Phrase	30

S3	TI (post test probability) or AB (post test probability)	Search modes - Boolean/Phrase	24
S2	TI (sensitivity or specificity) or AB (sensitivity or specificity)	Search modes - Boolean/Phrase	18703
S1	(MH "SENSITIVITY and SPECIFICITY")	Search modes - Boolean/Phrase	17102

MENG_dx_csf_skin_aspirates_embase_180808

EMBASE 1980 to 2008 Week 33

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	45738
2	sensitivity.ti,ab.	292366
3	specificity.ti,ab.	183913
4	((post-test or posttest) adj probability).ti,ab.	321
5	((pre-test or pretest) adj probability).ti,ab.	687
6	predictive value$.tw.	38513
7	likelihood ratio$.tw.	3992
8	DIAGNOSTIC ACCURACY/	119650
9	or/1-8	520805
10	BACTERIAL MENINGITIS/	7497
11	TUBERCULOUS MENINGITIS/	1845
12	MENINGOENCEPHALITIS/	2885
13	MENINGITIS/	13325
14	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	4869
15	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
16	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
17	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	228
18	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	461
19	((meningitis or meningitides) adj3 listeria).ti,ab.	211
20	((meningitis or meningitides) adj3 meningococc$).ti,ab.	869
21	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1009
22	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1606
23	meningoencephalitis.ti,ab.	2454
24	SEPTICEMIA/	8657
25	BACTEREMIA/	14036
26	(septic?emi? or bacter?emi?).ti,ab.	22727
27	MENINGOCOCCAL INFECTION/	2750
28	MENINGOCOCCOSIS/	2750
29	MENINGOCOCCEMIA/	820
30	(meningococc$ adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	2560
31	(meningococc?emi? or meningococcosis).ti,ab.	427
32	NEISSERIA MENINGITIDIS/	6739
33	(Neisseria meningitidis or n meningitidis).ti,ab.	4239
34	or/10-33	61055
35	exp GENE AMPLIFICATION/	260834
36	(gene amplification or polymerase chain reaction?).ti,ab.	101953
37	PCR.ti,ab.	162475
38	BACTERIAL ANTIGEN/	9039

39 VIRUS ANTIGEN/	11974
40 rapid antigen.ti,ab.	274
41 (antigen? adj3 test$).ti,ab.	6509
42 exp IMMUNOLOGICAL PROCEDURES/	572276
43 exp ANALYTICAL EQUIPMENT/	57123
44 CEREBROSPINAL FLUID/	26428
45 (cerebro?spinal adj2 fluid?).ti,ab.	36635
46 exp MICROBIOLOGICAL EXAMINATION/	192078
47 exp BLOOD ANALYSIS/	55007
48 (blood adj3 cultur$).ti,ab.	16113
49 exp SKIN TEST/	27088
50 exp MICROSCOPY/	228204
51 ((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	17931
52 SKIN CULTURE/	1251
53 SKIN/	24042
54 dermoscop$.ti,ab.	699
55 EPILUMINESCENCE MICROSCOPY/	1182
56 dermatoscop$.ti,ab.	250
57 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	341
58 gram? stain$.ti,ab.	2715
59 GRAM STAINING/	2811
60 AGGLUTINATION TEST/	2470
61 LATEX AGGLUTINATION TEST/	1859
62 (latex adj3 fixation).ti,ab.	84
63 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	228
64 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	4446
65 (early adj2 diagnosis).ti,ab.	29582
66 EARLY DIAGNOSIS/	35895
67 or/35-66	1371892
68 and/34,67	21846
69 limit 68 to "diagnosis (optimized)"	3327
70 and/9,68	1954
71 69 or 70	3592
72 CASE REPORT/	1001819
73 (letter or editorial or historical article).pt.	636862
74 (case report or case study).ti.	98284
75 or/72-74	1559708
76 71 not 75	3060
77 limit 76 to (human and english language)	2155

MENG_dx_csf_skin_aspirates_medline_180808
Ovid MEDLINE(R) 1950 to August Week 1 2008

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	267401
2	sensitivity.ti,ab.	347063
3	specificity.ti,ab.	225165
4	((post-test or posttest) adj probability).ti,ab.	342
5	((pre-test or pretest) adj probability).ti,ab.	716
6	predictive value$.tw.	42338
7	likelihood ratio$.tw.	4506
8	di.xs.	3397568
9	or/1-8	3857005
10	exp MENINGITIS, BACTERIAL/	17169
11	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5723
12	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
13	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	22
14	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	352
15	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	833
16	((meningitis or meningitid?s) adj3 listeria).ti,ab.	356
17	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	1390
18	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	1308
19	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4081
20	meningoencephalitis.ti,ab.	4143
21	MENINGOENCEPHALITIS/	4812
22	MENINGITIS/	15098
23	BACTEREMIA/	12245
24	(septic?emi? or bacter?emi?).ti,ab.	29554
25	MENINGOCOCCAL INFECTIONS/	4516
26	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3609
27	meningococc?emi?.ti,ab.	612
28	exp NEISSERIA MENINGITIDIS/	6513
29	(Neisseria meningitidis or n meningitidis).ti,ab.	5180
30	or/10-29	78429
31	exp POLYMERASE CHAIN REACTION/	243781
32	NUCLEIC ACID AMPLIFICATION TECHNIQUES/	3651
33	PCR.ti,ab.	186169
34	polymerase chain reaction?.ti,ab.	112436
35	ANTIGENS, BACTERIAL/ or ANTIGENS, VIRAL/	66341
36	rapid antigen.ti,ab.	282
37	(antigen? adj3 test$).ti,ab.	8875
38	exp IMMUNOLOGIC TESTS/	878495

39 exp REAGENT KITS, DIAGNOSTIC/	14215
40 CEREBROSPINAL FLUID/	14597
41 (cerebro?spinal adj2 fluid?).ti,ab.	48577
42 exp BACTERIOLOGICAL TECHNIQUES/	60487
43 exp BLOOD/	798218
44 (blood adj3 cultur$).ti,ab.	19137
45 exp SKIN TESTS/	49711
46 exp MICROSCOPY/	371660
47 ((skin or epidermal or dermal) adj3 (test$ or microscopy)).ti,ab.	21850
48 exp SKIN/	155719
49 dermoscop$.ti,ab.	730
50 ((skin or epidermal or dermal) adj3 (scraping? or aspirate?)).ti,ab.	481
51 gram? stain$.ti,ab.	3319
52 (agglutination adj3 (test$ or latex)).ti,ab.	6780
53 exp AGGLUTINATION TESTS/	34552
54 (latex adj3 fixation).ti,ab.	243
55 (skin adj3 aspirate?).ti,ab.	48
56 ((skin or lesion? or epiderm$ or derm$) adj3 aspirate?).ti,ab.	251
57 (rapid diagnos$ or rapid diagnostic test$).ti,ab.	5733
58 (early adj2 diagnosis).ti,ab.	40157
59 EARLY DIAGNOSIS/	3898
60 or/31-59	2329818
61 and/30,60	23195
62 limit 61 to "diagnosis (optimized)"	3832
63 and/9,61	9177
64 63 or 62	10543
65 ANIMALS/ not HUMANS/	3247594
66 HUMANS/ and ANIMALS/	1071960
67 66 or 65	4319554
68 64 not 67	8798
69 limit 68 to english language	6895
70 CASE REPORTS/	1411055
71 (letter or editorial or historical article).pt,ti.	1163474
72 71 or 70	2437461
73 69 not 72	5079

10 In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs

MENG_dx_throatswabs_MEDLINE_260609

EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2009

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	8869
2	sensitivity.ti,ab.	12021
3	specificity.ti,ab.	3582
4	((post-test or posttest) adj probability).ti,ab.	14
5	((pre-test or pretest) adj probability).ti,ab.	18
6	predictive value$.tw.	1824
7	likelihood ratio$.tw.	128
8	di.xs.	52803
9	or/1-8	65053
10	exp MENINGITIS, BACTERIAL/	229
11	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	183
12	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
13	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
14	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	1
15	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	29
16	((meningitis or meningitid?s) adj3 listeria).ti,ab.	2
17	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	34
18	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	22
19	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	48
20	meningoencephalitis.ti,ab.	18
21	MENINGOENCEPHALITIS/	10
22	MENINGITIS/	98
23	BACTEREMIA/	384
24	(septic?emi? or bacter?emi?).ti,ab.	1276
25	MENINGOCOCCAL INFECTIONS/	72
26	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	62
27	meningococc?emi?.ti,ab.	5
28	exp NEISSERIA MENINGITIDIS/	145
29	(Neisseria meningitidis or n meningitidis).ti,ab.	139
30	or/10-29	1974
31	PHARYNX/mi [Microbiology]	117
32	((phary$ or throat$) adj2 (swab$ or cultur$)).ti,ab.	225
33	or/31-32	307

34 and/9,30,33	0
35 limit 34 to (english language and humans) [Limit not valid; records were retained]	0
36 CASE REPORTS/	0
37 (letter or editorial or historical article).pt,ti.	6119
38 or/36-37	6119
39 35 not 38	0
40 limit 39 to yr="2006 -Current"	0

MENG_dx_ Friday, June 26, 2009 11:07:42 AM

MENG_dx_throatswabs_CINAHL_260609

#	Query	Limiters/Expanders	Results
S33	S9 and S28 and S32	Search modes - Boolean/Phrase	0
S32	S29 or S30 or S31	Search modes - Boolean/Phrase	295
S31	AB (pharyn* N2 swab*) or AB (pharyn* N2 cultur*) or AB (throat* N2 swab*) or AB (throat N2 cultur*)	Search modes - Boolean/Phrase	140
S30	TI (pharyn* N2 swab*) or TI (pharyn* N2 cultur*) or TI (throat* N2 swab*) or TI (throat N2 cultur*)	Search modes - Boolean/Phrase	33
S29	(MH "PHARYNX/MI")	Search modes - Boolean/Phrase	145
S28	S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27	Search modes - Boolean/Phrase	Display
S27	TI (neisseria meningitidis or n meningitidis) or AB (neisseria meningitidis or n meningitidis)	Search modes - Boolean/Phrase	Display
S26	MH NEISSERIA	Search modes - Boolean/Phrase	Display
S25	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	Display
S24	TI (meningococcal N3 infection*) or AB (meningococcal N3 infection*)	Search modes - Boolean/Phrase	Display
S23	TI (meningococcal N3 disease) or AB (meningococcal N3 disease)	Search modes - Boolean/Phrase	Display
S22	TI (meningococcal N3 endotoxic) or AB (meningococcal N3 endotoxic)	Search modes - Boolean/Phrase	Display
S21	TI (meningococcal N3 toxic) or AB (meningococcal N3 toxic)	Search modes - Boolean/Phrase	Display
S20	TI (meningococcal N3 septic) or AB (meningococcal N3 septic)	Search modes - Boolean/Phrase	Display
S19	TI (meningococcal N3 sepsis) or AB (meningococcal N3 sepsis)	Search modes - Boolean/Phrase	Display
S18	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	Display
S17	TI (septicemi* or septicaemi* or bacteremi* or bactaeremi*) or AB (septicemi* or septicaemi* or bacteremi* or bactaeremi*)	Search modes - Boolean/Phrase	Display
S16	MH BACTEREMIA	Search modes - Boolean/Phrase	Display

S15	MH BACTEREMIA	Search modes - Boolean/Phrase	Display
S14	MH MENINGITIS	Search modes - Boolean/Phrase	Display
S13	MH MENINGOENCEPHALITIS	Search modes - Boolean/Phrase	Display
S12	TI (meningeal or pachymeningitis or meningoencephalitis) or AB (meningeal or pachymeningitis or meningoencephalitis)	Search modes - Boolean/Phrase	Display
S11	TI (meningitis or meningitides) or AB (meningitis or meningitides)	Search modes - Boolean/Phrase	Display
S10	MH MENINGITIS, BACTERIAL	Search modes - Boolean/Phrase	Display
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8	Search modes - Boolean/Phrase	Display
S8	TI (likelihood ratio) or AB (likelihood ratio)	Search modes - Boolean/Phrase	Display
S7	TI (predictive value) or AB (predictive value)	Search modes - Boolean/Phrase	Display
S6	TI (pretest probability) or AB (pretest probability)	Search modes - Boolean/Phrase	Display
S5	TI (pre test probability) or AB (pre test probability)	Search modes - Boolean/Phrase	Display
S4	TI (posttest probability) or AB (posttest probability)	Search modes - Boolean/Phrase	Display
S3	TI (post test probability) or AB (post test probability)	Search modes - Boolean/Phrase	Display
S2	TI (sensitivity or specificity) or AB (sensitivity or specificity)	Search modes - Boolean/Phrase	Display
S1	(MH "SENSITIVITY and SPECIFICITY")	Search modes - Boolean/Phrase	Display

MENG_dx_throatswabs_EMBASE_260609

EMBASE 1980 to 2009 Week 25

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	52914
2	sensitivity.ti,ab.	308251
3	specificity.ti,ab.	193327
4	((post-test or posttest) adj probability).ti,ab.	340
5	((pre-test or pretest) adj probability).ti,ab.	738
6	predictive value$.tw.	41021
7	likelihood ratio$.tw.	4440
8	DIAGNOSTIC ACCURACY/	128208
9	or/1-8	550568
10	BACTERIAL MENINGITIS/	7885
11	TUBERCULOUS MENINGITIS/	1947
12	MENINGOENCEPHALITIS/	3071
13	MENINGITIS/	13881
14	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5080
15	((bacterial$ or infect$) adj3 meninges).ti,ab.	33
16	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
17	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	239
18	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	469
19	((meningitis or meningitides) adj3 listeria).ti,ab.	215
20	((meningitis or meningitides) adj3 meningococc$).ti,ab.	906
21	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1060
22	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1660
23	meningoencephalitis.ti,ab.	2578
24	SEPTICEMIA/	9062
25	BACTEREMIA/	14928
26	(septic?emi? or bacter?emi?).ti,ab.	23621
27	MENINGOCOCCAL INFECTION/	2941
28	MENINGOCOCCOSIS/	2941
29	MENINGOCOCCEMIA/	867
30	(meningococc$ adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	2676
31	(meningococc?emi? or meningococcosis).ti,ab.	438
32	NEISSERIA MENINGITIDIS/	7051
33	(Neisseria meningitidis or n meningitidis).ti,ab.	4434
34	or/10-33	64040
35	THROAT CULTURE/	2487
36	((pharyn$ or throat$) adj2 (swab$ or cultur$)).ti,ab.	1867
37	or/35-36	3261
38	and/9,34,37	16

39 limit 38 to yr="2006 -Current"	4

MENG_dx_throatswabs_MEDLINE_260609

Ovid MEDLINE(R) 1950 to June Week 3 2009

#	Searches	Results
1	exp "SENSITIVITY AND SPECIFICITY"/	287267
2	sensitivity.ti,ab.	362432
3	specificity.ti,ab.	232794
4	((post-test or posttest) adj probability).ti,ab.	374
5	((pre-test or pretest) adj probability).ti,ab.	781
6	predictive value$.tw.	44574
7	likelihood ratio$.tw.	4989
8	di.xs.	3454285
9	or/1-8	3935647
10	exp MENINGITIS, BACTERIAL/	17458
11	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5925
12	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
13	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	21
14	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	369
15	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	838
16	((meningitis or meningitid?s) adj3 listeria).ti,ab.	370
17	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	1391
18	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	1351
19	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4114
20	meningoencephalitis.ti,ab.	4219
21	MENINGOENCEPHALITIS/	4809
22	MENINGITIS/	14953
23	BACTEREMIA/	12880
24	(septic?emi? or bacter?emi?).ti,ab.	30323
25	MENINGOCOCCAL INFECTIONS/	4470
26	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3622
27	meningococc?emi?.ti,ab.	614
28	exp NEISSERIA MENINGITIDIS/	6530
29	(Neisseria meningitidis or n meningitidis).ti,ab.	5303
30	or/10-29	79719
31	PHARYNX/mi [Microbiology]	3194
32	((phary$ or throat$) adj2 (swab$ or cultur$)).ti,ab.	2539
33	or/31-32	4964
34	and/9,30,33	86
35	limit 34 to (english language and humans)	66
36	CASE REPORTS/	1423595
37	(letter or editorial or historical article).pt,ti.	1197705
38	or/36-37	2480773

39 35 not 38	52

11 When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?

MENG_lumbar_puncture_risks_meningitis_cctr_120908

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	exp CHILD/	38980
2	child$.ti,ab.	32759
3	exp INFANT/	17523
4	infan$.ti,ab.	11965
5	(baby or babies).ti,ab.	1648
6	toddler?.ti,ab.	244
7	(neonat$ or newborn?).ti,ab.	6723
8	ADOLESCENT/	54880
9	adolescen$.ti,ab.	4686
10	teen$.ti,ab.	488
11	exp SCHOOLS/	534
12	school$.ti,ab.	6033
13	exp PUBERTY/	209
14	pubescen$.ti,ab.	10
15	(pediatric? or paediatric?).ti,ab.	6156
16	or/1-15	99424
17	SPINAL PUNCTURE/	196
18	CEREBROSPINAL FLUID/cy, mi	48
19	MENINGITIS, BACTERIAL/cf	18
20	MENINGITIS, MENINGOCOCCAL/cf	8
21	MENINGITIS, PNEUMOCOCCAL/cf	11
22	MENINGITIS, LISTERIA/cf	0
23	MENINGITIS, HAEMOPHILUS/cf	14
24	MENINGITIS, ESCHERICHIA COLI/cf	0
25	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	353
26	((cerebrospinal fluid or cerebro spinal fluid or spinal fluid) adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	19
27	(CSF adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	34
28	or/17-27	544
29	exp MENINGITIS, BACTERIAL/	227
30	((bacterial$ or infect$) adj3 (meningitis or meningitid$)).ti,ab.	177
31	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
32	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
33	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0
34	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	20
35	((meningitis or meningitides) adj3 listeria).ti,ab.	2

36	((meningitis or meningitides) adj3 meningococc$).ti,ab.	31
37	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	21
38	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	42
39	meningoencephalitis.ti,ab.	18
40	MENINGOENCEPHALITIS/	10
41	MENINGITIS/	99
42	or/29-41	406
43	RISK FACTORS/	10464
44	PROGNOSIS/	6689
45	(risk? or danger$).ti,ab.	40016
46	(indications or indicated).ti,ab.	16803
47	(prognostic adj2 factor?).ti,ab.	2056
48	(safety or safe or safely).ti,ab.	42812
49	TREATMENT OUTCOME/	45916
50	FATAL OUTCOME/	11
51	(contraindicat$ or contra indicat$).ti,ab.	1397
52	complication?.ti,ab.	19380
53	unsafe.ti,ab.	88
54	predict$.ti,ab.	21055
55	((treatment or fatal) adj outcome?).ti,ab.	2176
56	adverse.ti,ab.	32752
57	ae.fs.	71246
58	or/43-57	195591
59	and/16,28	224
60	and/42,58	207
61	60 and 59	37

MENG_lumbar_puncture_risks_meningitis_cdsrdare_120908

DARE, CDSR

#	Searches	Results
1	CHILD.kw.	1169
2	child$.ti,ab.	1445
3	INFANT.kw.	820
4	infan$.ti,ab.	540
5	(baby or babies).ti,ab.	134
6	toddler?.ti,ab.	5
7	(neonat$ or newborn?).ti,ab.	507
8	ADOLESCEN$.kw.	755
9	adolescen$.ti,ab.	219
10	teen$.ti,ab.	10
11	SCHOOL$.kw.	55
12	school$.ti,ab.	119
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	218
16	or/1-15	2768
17	SPINAL PUNCTURE.kw.	6
18	CEREBROSPINAL FLUID.kw.	12
19	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	3
20	((cerebrospinal fluid or cerebro spinal fluid or spinal fluid) adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	0
21	(CSF adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	0
22	or/17-21	17
23	MENINGITIS, BACTERIAL.kw.	13
24	((bacterial$ or infect$) adj3 (meningitis or meningitid$)).ti,ab.	12
25	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
26	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
27	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0
28	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	0
29	((meningitis or meningitides) adj3 listeria).ti,ab.	0
30	((meningitis or meningitides) adj3 meningococc$).ti,ab.	4
31	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	0
32	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	2
33	meningoencephalitis.ti,ab.	1
34	MENINGOENCEPHALITIS.kw.	1
35	MENINGITIS.kw.	21
36	or/23-35	26
37	RISK FACTORS.kw.	577
38	PROGNOSIS.kw.	190

39 (risk? or danger$).ti,ab.	2207
40 (indications or indicated).ti,ab.	222
41 (prognostic adj2 factor?).ti,ab.	14
42 (safety or safe or safely).ti,ab.	1176
43 TREATMENT OUTCOME.kw.	2451
44 FATAL OUTCOME.kw.	2
45 (contraindicat$ or contra indicat$).ti,ab.	21
46 complication?.ti,ab.	643
47 unsafe.ti,ab.	4
48 predict$.ti,ab.	123
49 ((treatment or fatal) adj outcome?).ti,ab.	40
50 adverse.ti,ab.	1528
51 ae.fs.	0
52 or/37-51	6598
53 and/16,22	4
54 and/36,52	16
55 54 and 53	0

MENG_lumbar_puncture_risks_meningitis_cinahl_120908_6

EBSCO Host Friday, July 31, 2009 5:12:32 AM

#	Query	Limiters/Expanders	Results
S51	S49 and S50	Search modes - Boolean/Phrase	0
S50	S38 and S48	Search modes - Boolean/Phrase	0
S49	S16 and S22	Search modes - Boolean/Phrase	1
S48	S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47	Search modes - Boolean/Phrase	83
S47	TI (cerebrospinal fluid or cerebro spinal fluid or CSF) or AB (cerebrospinal fluid or cerebro spinal fluid or CSF)	Search modes - Boolean/Phrase	1955
S46	AB (spinal N3 punctur*) or AB (spinal N3 tap*) or AB (spinal N3 drain*)	Search modes - Boolean/Phrase	36
S45	TI (spinal N3 punctur*) or TI (spinal N3 tap*) or TI (spinal N3 drain*)	Search modes - Boolean/Phrase	19
S44	AB (lumbar N3 punctur*) or AB (lumbar N3 tap*) or AB (lumbar N3 drain*)	Search modes - Boolean/Phrase	338
S43	TI (lumbar N3 punctur*) or TI (lumbar N3 tap*) or TI (lumbar N3 drain*)	Search modes - Boolean/Phrase	182
S42	(MH "MENINGITIS, MENINGOCOCCAL/CF")	Search modes - Boolean/Phrase	5
S41	(MH "MENINGITIS, BACTERIAL/CF")	Search modes - Boolean/Phrase	32
S40	MH CEREBROSPINAL FLUID	Search modes - Boolean/Phrase	861
S39	MH SPINAL PUNCTURE	Search modes - Boolean/Phrase	545
S38	S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37	Search modes - Boolean/Phrase	192
S37	TI (adverse effect*) or AB (adverse effect*) or MW (adverse effect*)	Search modes - Boolean/Phrase	127467
S36	TI (adverse) or AB (adverse)	Search modes - Boolean/Phrase	23718
S35	TI (treatment outcome*) or TI (fatal outcome*) or AB (treatment outcome*) or AB (fatal outcome*)	Search modes - Boolean/Phrase	2756
S34	TI (predict*) or AB (predict*)	Search modes - Boolean/Phrase	61108
S33	TI (unsafe*) or AB (unsafe*)	Search modes - Boolean/Phrase	1219
S32	TI (complication*) or AB (complication*)	Search modes - Boolean/Phrase	33493
S31	TI (contraindicat* or contra indicat*) or AB (contraindicat* or contra indicat*)	Search modes - Boolean/Phrase	2366
S30	MH FATAL OUTCOME	Search modes - Boolean/Phrase	1496
S29	MH TREATMENT OUTCOMES	Search modes - Boolean/Phrase	64021
S28	TI (safety or safe or safely) or AB (safety or safe or	Search modes -	54318

	safely)	Boolean/Phrase	
S27	TI (prognostic N2 factor*) or AB (prognostic N2 factor*)	Search modes - Boolean/Phrase	1880
S26	TI (indications or indicated) or AB (indications or indicated)	Search modes - Boolean/Phrase	37655
S25	TI (risk* or danger*) or AB (risk* or danger*)	Search modes - Boolean/Phrase	142789
S24	MH PROGNOSIS	Search modes - Boolean/Phrase	9871
S23	MH RISK FACTORS	Search modes - Boolean/Phrase	37222
S22	S17 or S18 or S19 or S20 or S21	Search modes - Boolean/Phrase	98
S21	AB (meningitis or meningitides or pachymeningitis or meningoencephalitis)	Search modes - Boolean/Phrase	1072
S20	TI (meningitis or meningitides or pachymeningitis or meningoencephalitis)	Search modes - Boolean/Phrase	1148
S19	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S18	MH MENINGOENCEPHALITIS	Search modes - Boolean/Phrase	88
S17	MH MENINGITIS	Search modes - Boolean/Phrase	927
S16	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15	Search modes - Boolean/Phrase	1770
S15	TI (paediatric* or pediatric*) or AB (paediatric* or pediatric*)	Search modes - Boolean/Phrase	29743
S14	AB (newborn*) or AB (neonate*)	Search modes - Boolean/Phrase	7636
S13	TI (newborn*) or TI (neonate*)	Search modes - Boolean/Phrase	5897
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55
S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004
S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes - Boolean/Phrase	10049
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes -	82965

		Boolean/Phrase	
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_lumbar_puncture_risks_meningitis_embase_120908

EMBASE 1980 to 2008 Week 37

#	Searches	Results
1	exp CHILD/	617293
2	child$.tw.	479219
3	exp INFANT/	170372
4	infan$.tw.	168509
5	NEWBORN/	176652
6	(newborn? or neonat$).ti,ab.	161116
7	(baby or babies).tw.	27073
8	(paediatric? or pediatric?).ti,ab.	108377
9	teenag$.tw.	7861
10	adolescen$.tw.	81680
11	exp SCHOOLS/	36654
12	school$.tw.	73563
13	pubescen$.tw.	639
14	exp PUBERTY/	14112
15	or/1-14	1117020
16	BACTERIAL MENINGITIS/	7542
17	TUBERCULOUS MENINGITIS/	1857
18	MENINGOENCEPHALITIS/	2906
19	MENINGITIS/	13388
20	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	4888
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
22	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
23	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	228
24	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	461
25	((meningitis or meningitides) adj3 listeria).ti,ab.	211
26	((meningitis or meningitides) adj3 meningococc$).ti,ab.	873
27	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1015
28	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1616
29	meningoencephalitis.ti,ab.	2471
30	or/16-29	26506
31	RISK FACTOR/	230794
32	PROGNOSIS/	176645
33	(risk? or danger$).ti,ab.	692645
34	(indications or indicated).ti,ab.	392860
35	(prognostic adj2 factor?).ti,ab.	33926
36	(safety or safe or safely).ti,ab.	251885
37	TREATMENT OUTCOME/	327713
38	FATALITY/	41349
39	(contraindicat$ or contra indicat$).ti,ab.	21500

40	complication?.ti,ab.	332175
41	unsafe.ti,ab.	2311
42	predict$.ti,ab.	472152
43	((treatment or fatal) adj outcome?).ti,ab.	15810
44	adverse.ti,ab.	154992
45	ae.fs.	476936
46	or/31-45	2529370
47	PUNCTURE/	2575
48	LUMBAR PUNCTURE/	5221
49	CEREBROSPINAL FLUID/	26537
50	CEREBROSPINAL FLUID ANALYSIS/	9343
51	CEREBROSPINAL FLUID CULTURE/	1340
52	CEREBROSPINAL FLUID CYTOLOGY/	1019
53	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	4651
54	((cerebrospinal fluid or cerebro spinal fluid or spinal fluid) adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	1077
55	(CSF adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	1223
56	or/47-55	45744
57	and/15,30	10293
58	and/46,56	12123
59	58 and 57	883
60	(letter or editorial or comment or historical article).pt.	641036
61	CASE REPORT/	1005898
62	or/60-61	1558270
63	59 not 62	643
64	limit 63 to (human and english language)	513

MENG_lumbar_puncture_risks_meningitis_medline_120908

Ovid MEDLINE(R) 1950 to September Week 1 2008

#	Searches	Results
1	exp CHILD/	1286301
2	child$.ti,ab.	716770
3	exp INFANT/	798379
4	infan$.ti,ab.	254649
5	(baby or babies).ti,ab.	37789
6	toddler?.ti,ab.	3353
7	(neonat$ or newborn?).ti,ab.	222646
8	ADOLESCENT/	1290113
9	adolescen$.ti,ab.	107783
10	teen$.ti,ab.	14322
11	exp SCHOOLS/	60241
12	school$.ti,ab.	128849
13	exp PUBERTY/	13154
14	pubescen$.ti,ab.	812
15	(pediatric? or paediatric?).ti,ab.	130239
16	or/1-15	2682504
17	SPINAL PUNCTURE/	4308
18	CEREBROSPINAL FLUID/cy, mi	4072
19	MENINGITIS, BACTERIAL/cf	655
20	MENINGITIS, MENINGOCOCCAL/cf	318
21	MENINGITIS, PNEUMOCOCCAL/cf	313
22	MENINGITIS, LISTERIA/cf	56
23	MENINGITIS, HAEMOPHILUS/cf	232
24	MENINGITIS, ESCHERICHIA COLI/cf	9
25	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	5486
26	((cerebrospinal fluid or cerebro spinal fluid or spinal fluid) adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	1406
27	(CSF adj2 (microscop$ or cytolog$ or examin$)).ti,ab.	1446
28	or/17-27	14719
29	exp MENINGITIS, BACTERIAL/	17220
30	((bacterial$ or infect$) adj3 (meningitis or meningitid$)).ti,ab.	5987
31	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
32	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	22
33	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	284
34	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	671
35	((meningitis or meningitides) adj3 listeria).ti,ab.	350
36	((meningitis or meningitides) adj3 meningococc$).ti,ab.	1329
37	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1308
38	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4080

39 meningoencephalitis.ti,ab.	4157
40 MENINGOENCEPHALITIS/	4822
41 MENINGITIS/	15111
42 or/29-41	39184
43 RISK FACTORS/	367270
44 PROGNOSIS/	270481
45 (risk? or danger$).ti,ab.	783855
46 (indications or indicated).ti,ab.	486682
47 (prognostic adj2 factor?).ti,ab.	37143
48 (safety or safe or safely).ti,ab.	277710
49 TREATMENT OUTCOME/	352749
50 FATAL OUTCOME/	35360
51 (contraindicat$ or contra indicat$).ti,ab.	24748
52 complication?.ti,ab.	404516
53 unsafe.ti,ab.	2897
54 predict$.ti,ab.	529842
55 ((treatment or fatal) adj outcome?).ti,ab.	18248
56 adverse.ti,ab.	161698
57 ae.fs.	1051618
58 or/43-57	3350170
59 and/16,28	5373
60 and/42,58	9546
61 60 and 59	669
62 CASE REPORTS/	1416035
63 (letter or editorial or comment or historical article).pt.	1177893
64 or/62-63	2457292
65 61 not 64	515
66 limit 65 to (english language and humans)	407

12 When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?

MENG_lumbar_puncture_septicaemia_risks_cctr_110808

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	BACTEREMIA/	380
2	(septic?emi? or bacter?emi?).ti,ab.	1259
3	MENINGOCOCCAL INFECTIONS/	72
4	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	62
5	meningococc?emi?.ti,ab.	5
6	exp NEISSERIA MENINGITIDIS/	124
7	(Neisseria meningitidis or n meningitidis).ti,ab.	134
8	SHOCK, SEPTIC/	256
9	SEPSIS/	895
10	(blood adj2 poisoning).ti,ab.	4
11	(septic adj3 (shock or toxic or endo?toxic)).ti,ab.	383
12	(sep?i? adj3 hypotension).ti,ab.	22
13	(severe adj3 sepsis).ti,ab.	283
14	or/1-13	2708
15	INTRACRANIAL PRESSURE/	216
16	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	74
17	COMA/	97
18	(coma or comatose).ti,ab.	709
19	exp CONSCIOUSNESS DISORDERS/	420
20	((level? or decreas$) adj3 consciousness).ti,ab.	151
21	SEIZURES/	294
22	SEIZURES, FEBRILE/	57
23	(seizure? or convulsi$).ti,ab.	2190
24	PAPILLEDEMA/	8
25	(papilledema? or papilloedema?).ti,ab.	10
26	papilla edema?.ti,ab.	0
27	choked disk?.ti,ab.	0
28	optic$ papillitis.ti,ab.	0
29	(retinal adj (edema? or oedema?)).ti,ab.	13
30	exp HYPERTENSION/	11857
31	((raise? or rise or high or elevat$) adj3 blood pressure?).ti,ab.	1824
32	BRADYCARDIA/	271
33	((slow$ or decreas$) adj3 (heart?beat or heart rate)).ti,ab.	1638
34	bradycardia?.ti,ab.	1158
35	exp BLOOD COAGULATION DISORDERS/	645

36	(coagulopathy or coagulopathies).ti,ab.	209
37	((clotting or coagulat$) adj2 disorder?).ti,ab.	68
38	exp THROMBOCYTOPENIA/	643
39	(thrombocytop?enia? or thrombop?enia?).ti,ab.	1350
40	((low or subnormal or decreas$) adj2 platelet?).ti,ab.	546
41	BLOOD PLATELETS/	1334
42	CONTUSIONS/	64
43	(bruising or contusion? or bleeding).ti,ab.	9235
44	(prolonged adj3 (clotting or coagulation)).ti,ab.	28
45	SHOCK/	98
46	exp NEUROLOGIC MANIFESTATIONS/	18879
47	(neurologic$ adj3 (sign? or deficit? or symptom$ or manifestation?)).ti,ab.	820
48	(focal CNS sign? or focal sign?).ti,ab.	5
49	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	0
50	(abnormal adj3 postur$).ti,ab.	23
51	(dyskinesia? or asterixis or ballismus or hemiballismus).ti,ab.	843
52	((involuntary or abnormal$) adj3 movement?).ti,ab.	332
53	(neurologic$ adj3 gait).ti,ab.	2
54	(neuro?behavio?ral adj3 (sign? or manifestation? or symptom$)).ti,ab.	11
55	(abnormal$ adj3 reflex$).ti,ab.	32
56	vertigo.ti,ab.	526
57	((abnormal$ or dysfunction? or disorder$ or size?) adj3 (pupil? or pupillary)).ti,ab.	328
58	(paresis or hemiparesis or monoparesis).ti,ab.	316
59	((disorder$ or dysfunction$ or disturbance?) adj3 (vision or visual or hearing or aural or taste or smell or olfaction or olfactory or touch)).ti,ab.	329
60	OLFACTION DISORDERS/	35
61	(anosmia? or cacosmia? or dysosmia? or paraosmia?).ti,ab.	18
62	VISION DISORDERS/	350
63	(visual adj3 (hallucination? or agnosia? or illusion?)).ti,ab.	56
64	(macropsia or micropsia).ti,ab.	0
65	(cortical adj3 (deafness or blindness)).ti,ab.	4
66	contra?indicat$.ti,ab.	1295
67	RISK FACTORS/	10464
68	(risk? or danger$).ti,ab.	40016
69	indications.ti,ab.	1906
70	(prognostic adj2 factor?).ti,ab.	2056
71	(safety or safe or safely).ti,ab.	42812
72	or/15-71	123939
73	SPINAL PUNCTURE/	196
74	CEREBROSPINAL FLUID/	103
75	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	353
76	or/73-75	529

77 and/72,76	271
78 and/14,77	7

MENG_lumbar_puncture_septicaemia_risks_cdsrdare_110808
CDSR, DARE

#	Searches	Results
1	BACTEREMIA.kw.	30
2	(septic?emi? or bacter?emi?).ti,ab.	23
3	MENINGOCOCCAL INFECTIONS.kw.	4
4	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	6
5	meningococc?emi?.ti,ab.	0
6	NEISSERIA MENINGITIDIS.kw.	4
7	(Neisseria meningitidis or n meningitidis).ti,ab.	0
8	SEPTIC SHOCK.kw.	0
9	SEPSIS.kw.	57
10	(blood adj2 poisoning).ti,ab.	0
11	(septic adj3 (shock or toxic or endo?toxic)).ti,ab.	9
12	(sep?i? adj3 hypotension).ti,ab.	1
13	(severe adj3 sepsis).ti,ab.	13
14	or/1-13	111
15	INTRACRANIAL PRESSURE.kw.	7
16	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	8
17	COMA.kw.	9
18	(coma or comatose).ti,ab.	8
19	CONSCIOUSNESS DISORDER$.kw.	1
20	((level? or decreas$) adj3 consciousness).ti,ab.	0
21	SEIZURE$.kw.	36
22	FEBRILE SEIZURES.kw.	1
23	(seizure? or convulsi$).ti,ab.	114
24	PAPILL?EDEMA$.kw.	0
25	(papilledema? or papilloedema?).ti,ab.	0
26	papilla edema?.ti,ab.	0
27	choked disk?.ti,ab.	0
28	optic$ papillitis.ti,ab.	0
29	(retinal adj (edema? or oedema?)).ti,ab.	0
30	HYPERTENSION.kw.	262
31	((raise? or rise or high or elevat$) adj3 blood pressure?).ti,ab.	35
32	BRADYCARDIA.kw.	9
33	((slow$ or decreas$) adj3 (heart?beat or heart rate)).ti,ab.	2
34	bradycardia?.ti,ab.	26
35	(BLOOD COAGULATION or COAGULOPATH$).kw.	21
36	(coagulopathy or coagulopathies).ti,ab.	6
37	((clotting or coagulat$) adj2 disorder?).ti,ab.	1
38	THROMBOCYTOPENIA.kw.	10
39	(thrombocytop?enia? or thrombop?enia?).ti,ab.	24

40	((low or subnormal or decreas$) adj2 platelet?).ti,ab.	2
41	BLOOD PLATELET$.kw.	4
42	CONTUSION$.kw.	4
43	(bruising or contusion? or bleeding).ti,ab.	234
44	(prolonged adj3 (clotting or coagulation)).ti,ab.	0
45	SHOCK.kw.	31
46	NEUROLOGIC MANIFESTATION$.kw.	0
47	(neurologic$ adj3 (sign? or deficit? or symptom$ or manifestation?)).ti,ab.	33
48	(focal CNS sign? or focal sign?).ti,ab.	0
49	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	0
50	(abnormal adj3 postur$).ti,ab.	2
51	(dyskinesia? or asterixis or ballismus or hemiballismus).ti,ab.	36
52	((involuntary or abnormal$) adj3 movement?).ti,ab.	12
53	(neurologic$ adj3 gait).ti,ab.	0
54	(neuro?behavio?ral adj3 (sign? or manifestation? or symptom$)).ti,ab.	0
55	(abnormal$ adj3 reflex$).ti,ab.	0
56	vertigo.ti,ab.	14
57	((abnormal$ or dysfunction? or disorder$ or size?) adj3 (pupil? or pupillary)).ti,ab.	0
58	(paresis or hemiparesis or monoparesis).ti,ab.	3
59	((disorder$ or dysfunction$ or disturbance?) adj3 (vision or visual or hearing or aural or taste or smell or olfaction or olfactory or touch)).ti,ab.	6
60	OLFACTION DISORDER$.kw.	1
61	(anosmia? or cacosmia? or dysosmia? or paraosmia?).ti,ab.	1
62	VISION DISORDER$.kw.	11
63	(visual adj3 (hallucination? or agnosia? or illusion?)).ti,ab.	2
64	(macropsia or micropsia).ti,ab.	0
65	(cortical adj3 (deafness or blindness)).ti,ab.	0
66	contra?indicat$.ti,ab.	19
67	RISK FACTOR$.kw.	577
68	(risk? or danger$).ti,ab.	2163
69	indications.ti,ab.	63
70	(prognostic adj2 factor?).ti,ab.	15
71	(safety or safe or safely).ti,ab.	1142
72	or/15-71	3845
73	SPINAL PUNCTURE$.kw.	6
74	CEREBROSPINAL FLUID.kw.	13
75	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	3
76	or/73-75	18
77	and/72,76	4
78	and/14,77	0

MENG_lumbar_puncture_septicaemia_risks_cinahl_110808_9

EBSCO Host Friday, July 31, 2009 5:27:11 AM

#	Query	Limiters/Expanders	Results
S80	S19 and S77 and S79	Search modes - Boolean/Phrase	0
S79	S72 OR S78	Search modes - Boolean/Phrase	9
S78	MH NEUROLOGIC MANIFESTATIONS+	Search modes - Boolean/Phrase	102784
S77	S73 or S74 or S75 or S76	Search modes - Boolean/Phrase	34
S76	AB (lumbar N3 puncture) or AB (lumbar N3 tap*) or AB (lumbar N3 drain*)	Search modes - Boolean/Phrase	285
S75	TI (lumbar N3 puncture) or TI (lumbar N3 tap*) or TI (lumbar N3 drain*)	Search modes - Boolean/Phrase	158
S74	(MH "CEREBROSPINAL FLUID/MI")	Search modes - Boolean/Phrase	63
S73	MH SPINAL PUNCTURE	Search modes - Boolean/Phrase	545
S72	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71	Search modes - Boolean/Phrase	479
S71	TI (safety or safe or safely) or AB (safety or safe or safely)	Search modes - Boolean/Phrase	54318
S70	TI (prognostic N2 factor*) or AB (prognostic N2 factor*)	Search modes - Boolean/Phrase	1880
S69	TI (indications) or AB (indications)	Search modes - Boolean/Phrase	6289
S68	TI (risk* or danger*)	Search modes - Boolean/Phrase	52078
S67	MH RISK FACTORS	Search modes - Boolean/Phrase	37222
S66	TI (contraindicat* or contra indicat*) or AB (contraindicat* or contra indicat*)	Search modes - Boolean/Phrase	2366
S65	(MH "SPINAL PUNCTURE/CT")	Search modes - Boolean/Phrase	8
S64	TI (deafness or blindness) or AB (deafness or blindness)	Search modes - Boolean/Phrase	2024
S63	AB (hallucination* or agnosia* or illusion* or macropsia* or micropsia*)	Search modes - Boolean/Phrase	789
S62	TI (hallucination* or agnosia* or illusion* or macropsia* or micropsia*)	Search modes - Boolean/Phrase	435
S61	MH VISION DISORDERS	Search modes - Boolean/Phrase	2495
S60	TI (anosmia* or cacosmia* or dysosmia* or parasomia*) or AB (anosmia* or cacosmia* or dysosmia* or	Search modes - Boolean/Phrase	67

	parasomia*)		
S59	MH OLFACTION DISORDERS	Search modes - Boolean/Phrase	215
S58	TI (vision or visual or hearing or aural or taste or smell or olfaction or olfactory or touch)	Search modes - Boolean/Phrase	15963
S57	TI (paresis or hemiparesis or monoparesis) or AB (paresis or hemiparesis or monoparesis)	Search modes - Boolean/Phrase	1012
S56	TI (pupil* or pupillary) or AB (pupil* or pupillary)	Search modes - Boolean/Phrase	1115
S55	TI (vertigo) or AB (vertigo)	Search modes - Boolean/Phrase	803
S54	TI (abnormal N3 reflex*) or AB (abnormal N3 reflex*)	Search modes - Boolean/Phrase	55
S53	TI (neurobehaviour* or neurobehavior*) or AB (neurobehaviour* or neurobehavior*)	Search modes - Boolean/Phrase	664
S52	AB (involuntary N3 movement*) or AB (abnormal* N3 movement*)	Search modes - Boolean/Phrase	301
S51	TI (involuntary N3 movement*) or (TI abnormal* N3 movement*)	Search modes - Boolean/Phrase	41
S50	TI (dyskinesia* or asterixis or ballismus or hemiballismus) or AB (dyskinesia* or asterixis or ballismus or hemiballismus)	Search modes - Boolean/Phrase	481
S49	TI (abnormal N3 postur*) or AB (abnormal N3 postur*)	Search modes - Boolean/Phrase	67
S48	TI (decerebrate or decorticate) or AB (decerebrate or decorticate)	Search modes - Boolean/Phrase	14
S47	TI (focal N2 sign*) or AB (focal N2 sign*)	Search modes - Boolean/Phrase	77
S46	TI (neurologic*) or AB (neurologic*)	Search modes - Boolean/Phrase	12384
S45	MH NEUROLOGIC MANIFESTATIONS	Search modes - Boolean/Phrase	748
S44	MH SHOCK	Search modes - Boolean/Phrase	903
S43	TI (bruising or contusion* or bleeding) or AB (bruising or contusion* or bleeding)	Search modes - Boolean/Phrase	7028
S42	(MH "CONTUSIONS and ABRASIONS")	Search modes - Boolean/Phrase	456
S41	MH BLOOD PLATELETS	Search modes - Boolean/Phrase	1360
S40	TI (platelet*) or AB (platelet*)	Search modes - Boolean/Phrase	3839
S39	TI (thrombopaeni* or thromvopeni*) or AB (thrombopaeni* or thromvopeni*)	Search modes - Boolean/Phrase	0
S38	TI (thrombocytopaeni* or thrombocytopeni*) or AB (thrombocytopaeni* or thrombocytopeni*)	Search modes - Boolean/Phrase	1519
S37	MH THROMBOCYTOPENIA	Search modes - Boolean/Phrase	1036
S36	TI (coagulopathy or coagulopathies or clotting or coagulat*) or AB (coagulopathy or coagulopathies or	Search modes - Boolean/Phrase	2629

	clotting or coagulat*)		
S35	MH BLOOD COAGULATION DISORDERS+	Search modes - Boolean/Phrase	1887
S34	TI (bradycardia*) or AB (bradycardia*)	Search modes - Boolean/Phrase	985
S33	MH BRADYCARDIA	Search modes - Boolean/Phrase	786
S32	TI (blood pressure*) or AB (blood pressure*)	Search modes - Boolean/Phrase	14546
S31	MH HYPERTENSION+	Search modes - Boolean/Phrase	19636
S30	TI (optic* papillitis) or AB (optic* papillitis)	Search modes - Boolean/Phrase	0
S29	TI (choked disk*) or AB (choked disk*)	Search modes - Boolean/Phrase	0
S28	TI (papilledema or papilloedema or papilla edema) or AB (papilledema or papilloedema or papilla edema)	Search modes - Boolean/Phrase	58
S27	TI (seizure*) or AB (seizure*)	Search modes - Boolean/Phrase	3728
S26	MH SEIZURES+	Search modes - Boolean/Phrase	2949
S25	TI (consciousness) or AB (consciousness)	Search modes - Boolean/Phrase	2198
S24	MH CONSCIOUSNESS DISORDERS+	Search modes - Boolean/Phrase	3160
S23	TI (coma or comatose) or AB (coma or comatose)	Search modes - Boolean/Phrase	2017
S22	MH COMA	Search modes - Boolean/Phrase	863
S21	TI (intracranial pressure) or AB (intracranial pressure)	Search modes - Boolean/Phrase	697
S20	MH INTRACRANIAL PRESSURE	Search modes - Boolean/Phrase	547
S19	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18	Search modes - Boolean/Phrase	1806
S18	TI (severe N3 sepsis) or AB (severe N3 sepsis)	Search modes - Boolean/Phrase	620
S17	AB (septic N3 hypotension) or AB (sepsis N3 hypotension)	Search modes - Boolean/Phrase	30
S16	TI (septic N3 hypotension) or TI (sepsis N3 hypotension)	Search modes - Boolean/Phrase	3
S15	AB (septic N3 shock*) or AB (septic N3 toxic) or AB (septic N3 endo toxic)	Search modes - Boolean/Phrase	621
S14	TI (septic N3 shock*) or TI (septic N3 toxic) or TI (septic N3 endo toxic)	Search modes - Boolean/Phrase	493
S13	TI (blood N2 poisoning) or AB (blood N2 poisoning)	Search modes - Boolean/Phrase	11
S12	MH SEPSIS	Search modes - Boolean/Phrase	3327
S11	MH SHOCK, SEPTIC	Search modes -	1046

		Boolean/Phrase	
S10	TI (meningitidis) or AB (meningitidis)	Search modes - Boolean/Phrase	118
S9	MH NEISSERIA	Search modes - Boolean/Phrase	192
S8	AB (meningococcemi* or meningococcaemi*)	Search modes - Boolean/Phrase	32
S7	TI (meningococcemi* or meningococcaemi*)	Search modes - Boolean/Phrase	24
S6	AB (meningococcal N3 sepsis) or AB (meningococcal N3 septic) or AB (meningococcal N3 toxic) or AB (meningococcal N3 endotoxic) or AB (meningococcal N3 disease) or AB (meningococcal N3 infection*)	Search modes - Boolean/Phrase	153
S5	TI (meningococcal N3 sepsis) or TI (meningococcal N3 septic) or TI (meningococcal N3 toxic) or TI (meningococcal N3 endotoxic) or TI (meningococcal N3 disease) or TI (meningococcal N3 infection*)	Search modes - Boolean/Phrase	248
S4	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S3	AB (septicaemi* or septicemi* or bacteraemi* or bacteremi*)	Search modes - Boolean/Phrase	1422
S2	TI (septicaemi* or septicemi* or bacteraemi* or bacteremi*)	Search modes - Boolean/Phrase	785
S1	MH BACTEREMIA	Search modes - Boolean/Phrase	1700

MENG_lumbar_puncture_septicaemia_risks_embase_110808

EMBASE 1980 to 2008 Week 32

#	Searches	Results
1	SEPTIC SHOCK/	12659
2	SEPTICEMIA/	8651
3	((septic or bacter?emic) adj shock).ti,ab.	8446
4	(sepsis adj3 hypotension).ti,ab.	188
5	BACTEREMIA/	14023
6	(severe adj3 sepsis).ti,ab.	3118
7	(septic?emi? or bacter?emi?).ti,ab.	22718
8	MENINGOCOCCAL INFECTION/	2749
9	MENINGOCOCCOSIS/	2749
10	MENINGOCOCCEMIA/	818
11	(meningococc$ adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	2559
12	(meningococc?emi? or meningococcosis).ti,ab.	427
13	NEISSERIA MENINGITIDIS/	6735
14	(Neisseria meningitidis or n meningitidis).ti,ab.	4236
15	(blood adj2 poisoning).ti,ab.	61
16	or/1-15	54515
17	INTRACRANIAL PRESSURE/	7621
18	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	2147
19	COMA/	9347
20	(coma or comatose).ti,ab.	14129
21	CONSCIOUSNESS DISORDER/	3309
22	((level? or decreas$) adj3 consciousness).ti,ab.	2049
23	SEIZURE/	42980
24	FEBRILE CONVULSION/	2505
25	(seizure? or convulsi$).ti,ab.	64531
26	PAPILLEDEMA/	2745
27	(papilledema? or papilloedema?).ti,ab.	1540
28	papilla edema?.ti,ab.	3
29	choked disk?.ti,ab.	10
30	optic$ papillitis.ti,ab.	13
31	(retinal adj (edema? or oedema?)).ti,ab.	330
32	exp HYPERTENSION/	233636
33	((raise? or rise or high or elevat$) adj3 blood pressure?).ti,ab.	17103
34	BRADYCARDIA/	17129
35	((slow$ or decreas$) adj3 (heart?beat or heart rate)).ti,ab.	6669
36	bradycardia?.ti,ab.	11785
37	BLOOD CLOTTING DISORDER/	8810
38	(coagulopathy or coagulopathies).ti,ab.	5212
39	((clotting or coagulat$) adj2 disorder?).ti,ab.	1809

40	exp THROMBOCYTOPENIA/	54299
41	(thrombocytop?enia? or thrombop?enia?).ti,ab.	22870
42	((low or subnormal or decreas$) adj2 platelet?).ti,ab.	4749
43	THROMBOCYTE/	25972
44	CONTUSION/	1434
45	(bruising or contusion? or bleeding).ti,ab.	80948
46	(prolonged adj3 (clotting or coagulation)).ti,ab.	383
47	SHOCK/	11253
48	NEUROLOGIC DISEASE/	40945
49	(neurologic$ adj3 (sign? or deficit? or symptom$ or manifestation?)).ti,ab.	31157
50	(focal CNS sign? or focal sign?).ti,ab.	238
51	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	163
52	(abnormal adj3 postur$).ti,ab.	613
53	(dyskinesia? or asterixis or ballismus or hemiballismus).ti,ab.	7797
54	((involuntary or abnormal$) adj3 movement?).ti,ab.	4191
55	(neurologic$ adj3 gait).ti,ab.	138
56	(neuro?behavio?ral adj3 (sign? or manifestation? or symptom$)).ti,ab.	187
57	(abnormal$ adj3 reflex$).ti,ab.	747
58	vertigo.ti,ab.	6271
59	((abnormal$ or dysfunction? or disorder$ or size?) adj3 (pupil? or pupillary)).ti,ab.	1496
60	(paresis or hemiparesis or monoparesis).ti,ab.	9425
61	((disorder$ or dysfunction$ or disturbance?) adj3 (vision or visual or hearing or aural or taste or smell or olfaction or olfactory or touch)).ti,ab.	6382
62	exp SMELLING DISORDER/	2559
63	(anosmia? or cacosmia? or dysosmia? or paraosmia?).ti,ab.	914
64	VISUAL DISORDER/	8020
65	(visual adj3 (hallucination? or agnosia? or illusion?)).ti,ab.	1966
66	(macropsia or micropsia).ti,ab.	37
67	(cortical adj3 (deafness or blindness)).ti,ab.	639
68	contra?indicat$.ti,ab.	19653
69	RISK FACTOR/	228535
70	(risk? or danger$).ti,ab.	686985
71	indications.ti,ab.	71243
72	(prognostic adj2 factor?).ti,ab.	33640
73	(safety or safe or safely).ti,ab.	249876
74	or/17-73	1541302
75	LUMBAR PUNCTURE/	5159
76	CEREBROSPINAL FLUID/	26402
77	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	4618
78	or/75-77	32736
79	and/16,74	13833
80	and/78-79	238

81 (letter or editorial or comment or historical article).pt.	636164
82 CASE REPORT/	1001006
83 or/81-82	1549133
84 80 not 83	182
85 limit 84 to (human and english language)	138

MENG_lumbar_puncture_septicaemia_risks_medline_110808

Ovid MEDLINE(R) 1950 to July Week 5 2008

#	Searches	Results
1	BACTEREMIA/	12236
2	(septic?emi? or bacter?emi?).ti,ab.	29530
3	MENINGOCOCCAL INFECTIONS/	4513
4	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3607
5	meningococc?emi?.ti,ab.	612
6	exp NEISSERIA MENINGITIDIS/	6506
7	(Neisseria meningitidis or n meningitidis).ti,ab.	5171
8	SHOCK, SEPTIC/	15094
9	SEPSIS/	33449
10	(blood adj2 poisoning).ti,ab.	91
11	(septic adj3 (shock or toxic or endo?toxic)).ti,ab.	9592
12	(sep?i? adj3 hypotension).ti,ab.	341
13	(severe adj3 sepsis).ti,ab.	3244
14	or/1-13	83668
15	INTRACRANIAL PRESSURE/	11997
16	((raise? or rise or high or elevat$) adj3 intracranial pressure?).ti,ab.	2456
17	COMA/	9648
18	(coma or comatose).ti,ab.	19840
19	exp CONSCIOUSNESS DISORDERS/	29639
20	((level? or decreas$) adj3 consciousness).ti,ab.	2386
21	SEIZURES/	33299
22	SEIZURES, FEBRILE/	1857
23	seizure?.ti,ab.	60411
24	PAPILLEDEMA/	3220
25	(papilledema? or papilloedema?).ti,ab.	2043
26	papilla edema?.ti,ab.	1
27	choked disk?.ti,ab.	17
28	optic$ papillitis.ti,ab.	7
29	(retinal adj (edema? or oedema?)).ti,ab.	375
30	exp HYPERTENSION/	177563
31	((raise? or rise or high or elevat$) adj3 blood pressure?).ti,ab.	20131
32	BRADYCARDIA/	8196
33	((slow$ or decreas$) adj3 (heart?beat or heart rate)).ti,ab.	7450
34	bradycardia?.ti,ab.	13972
35	exp BLOOD COAGULATION DISORDERS/	69166
36	(coagulopathy or coagulopathies).ti,ab.	6247
37	((clotting or coagulat$) adj2 disorder?).ti,ab.	2588
38	exp THROMBOCYTOPENIA/	32977
39	(thrombocytop?enia? or thrombop?enia?).ti,ab.	27160

40	((low or subnormal or decreas$) adj2 platelet?).ti,ab.	5313
41	BLOOD PLATELETS/	58948
42	CONTUSIONS/	3467
43	(bruising or contusion? or bleeding).ti,ab.	97427
44	(prolonged adj3 (clotting or coagulation)).ti,ab.	485
45	SHOCK/	12032
46	exp NEUROLOGIC MANIFESTATIONS/	633792
47	(neurologic$ adj3 (sign? or deficit? or symptom$ or manifestation?)).ti,ab.	36123
48	(focal CNS sign? or focal sign?).ti,ab.	287
49	((decerebrate or decorticate) adj3 (rigidity or state? or posturing?)).ti,ab.	281
50	(abnormal adj3 postur$).ti,ab.	686
51	(dyskinesia? or asterixis or ballismus or hemiballismus).ti,ab.	9504
52	((involuntary or abnormal$) adj3 movement?).ti,ab.	4889
53	(neurologic$ adj3 gait).ti,ab.	161
54	(neuro?behavio?ral adj3 (sign? or manifestation? or symptom$)).ti,ab.	188
55	(abnormal$ adj3 reflex$).ti,ab.	798
56	vertigo.ti,ab.	7368
57	((abnormal$ or dysfunction? or disorder$ or size?) adj3 (pupil? or pupillary)).ti,ab.	1852
58	(paresis or hemiparesis or monoparesis).ti,ab.	11721
59	((disorder$ or dysfunction$ or disturbance?) adj3 (vision or visual or hearing or aural or taste or smell or olfaction or olfactory or touch)).ti,ab.	8312
60	OLFACTION DISORDERS/	2083
61	(anosmia? or cacosmia? or dysosmia? or paraosmia?).ti,ab.	1159
62	VISION DISORDERS/	18238
63	(visual adj3 (hallucination? or agnosia? or illusion?)).ti,ab.	2267
64	(macropsia or micropsia).ti,ab.	69
65	(cortical adj3 (deafness or blindness)).ti,ab.	819
66	SPINAL PUNCTURE/ct	45
67	contra?indicat$.ti,ab.	22609
68	RISK FACTORS/	364028
69	(risk? or danger$).ti,ab.	775888
70	indications.ti,ab.	94676
71	(prognostic adj2 factor?).ti,ab.	36836
72	(safety or safe or safely).ti,ab.	274963
73	or/15-72	2297555
74	SPINAL PUNCTURE/	4294
75	CEREBROSPINAL FLUID/cy, mi	4055
76	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	5452
77	or/74-76	11603
78	and/73,77	4583
79	and/14,78	158
80	CASE REPORTS/	1410121

81 (letter or editorial or comment or historical article).pt.	1171314
82 or/80-81	2445589
83 79 not 82	121
84 limit 83 to (english language and humans)	94

13 Should lumbar puncture be performed prior to stopping antibiotic treatment in children less than 3 months of age with bacterial meningitis?

MENG_lumbar_puncture_meningitis_cctr_050808

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	SPINAL PUNCTURE/	196
2	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	353
3	or/1-2	436
4	exp MENINGITIS, BACTERIAL/	227
5	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	174
6	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
7	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
8	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0
9	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	20
10	((meningitis or meningitides) adj3 listeria).ti,ab.	2
11	((meningitis or meningitides) adj3 meningococc$).ti,ab.	31
12	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	21
13	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	42
14	meningoencephalitis.ti,ab.	18
15	MENINGOENCEPHALITIS/	10
16	MENINGITIS/	99
17	or/4-16	405
18	and/3,17	16

MENG_lumbar_puncture_meningitis_cdsrdare_050808

CDSR, DARE

#	Searches	Results
1	SPINAL PUNCTURE.kw.	6
2	SPINAL TAP.kw.	0
3	LUMBAR PUNCTURE.kw.	0
4	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	3
5	or/1-4	6
6	BACTERIAL MENINGITIS.kw.	1
7	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	12
8	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
9	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
10	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	0
11	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	0
12	((meningitis or meningitides) adj3 listeria).ti,ab.	0
13	((meningitis or meningitides) adj3 meningococc$).ti,ab.	4
14	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	0
15	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	2
16	meningoencephalitis.ti,ab.	1
17	MENINGOENCEPHALITIS.kw.	1
18	MENINGITIS.kw.	21
19	or/6-18	26
20	and/5,19	2

MENG_lumbar_puncture_meningitis_cinahl_050808_4
EBSCO Host Friday, July 31, 2009 5:00:54 AM

#	Query	Limiters/Expanders	Results
S19	S6 and S17	Limiters **- Language: English** Search modes **- Boolean/Phrase**	1
S18	S6 and S17	Search modes **- Boolean/Phrase**	1
S17	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes **- Boolean/Phrase**	215
S16	TI (meningitidis or meningitides or meningitis or meningeal or pachymeningitis or meningoencephalitis) or AB (meningitidis or meningitides or meningitis or meningeal or pachymeningitis or meningoencephalitis)	Search modes **- Boolean/Phrase**	1989
S15	AB (infect* N3 leptomeninges) or AB (infect* N3 subarachnoid space*)	Search modes **- Boolean/Phrase**	0
S14	TI (infect* N3 leptomeninges) or TI (infect* N3 subarachnoid space*)	Search modes **- Boolean/Phrase**	0
S13	TI (infect* N3 meningitis) or TI (infect* N3 meningitides) or TI (infect* N3 meninges)	Search modes **- Boolean/Phrase**	23
S12	AB (infect* N3 meningitis) or AB (infect* N3 meningitides) or AB (infect* N3 meninges)	Search modes **- Boolean/Phrase**	107
S11	AB (bacterial N3 meningitis) or AB (bacterial N3 meningitides) or AB (bacterial N3 meninges)	Search modes **- Boolean/Phrase**	221
S10	TI (bacterial N3 meningitis) or TI (bacterial N3 meningitides) or TI (bacterial N3 meninges)	Search modes **- Boolean/Phrase**	243
S9	MH MENINGITIS, BACTERIAL+	Search modes **- Boolean/Phrase**	971
S8	MH MENINGOENCEPHALITIS	Search modes **- Boolean/Phrase**	88
S7	MH MENINGITIS	Search modes **- Boolean/Phrase**	927
S6	S1 or S2 or S3 or S4 or S5	Search modes **- Boolean/Phrase**	1512
S5	TI (spinal N3 puncture) or TI (spinal N3 tap*) or TI (spinal N3 drain*)	Search modes **- Boolean/Phrase**	19
S4	AB (spinal N3 puncture) or AB (spinal N3 tap*) or AB (spinal N3 drain*)	Search modes **- Boolean/Phrase**	35
S3	AB (lumbar N3 puncture) or AB (lumbar N3 tap*) or AB (lumbar N3 drain*)	Search modes **- Boolean/Phrase**	285
S2	TI (lumbar N3 puncture) or TI (lumbar N3 tap*) or TI (lumbar N3 drain*)	Search modes **- Boolean/Phrase**	158
S1	MH SPINAL PUNCTURE	Search modes **- Boolean/Phrase**	545

MENG_lumbar_puncture_meningitis_embase_050808

EMBASE 1980 to 2008 Week 31

#	Searches	Results
1	LUMBAR PUNCTURE/	5151
2	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	4615
3	or/1-2	7501
4	BACTERIAL MENINGITIS/	7473
5	TUBERCULOUS MENINGITIS/	1837
6	MENINGOENCEPHALITIS/	2879
7	MENINGITIS/	13296
8	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	4859
9	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
10	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
11	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	228
12	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	461
13	((meningitis or meningitides) adj3 listeria).ti,ab.	211
14	((meningitis or meningitides) adj3 meningococc$).ti,ab.	867
15	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1008
16	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1601
17	meningoencephalitis.ti,ab.	2451
18	or/4-17	26293
19	and/3,18	1370
20	CASE REPORT/	1000112
21	(letter or editorial or comment or historical article).pt.	635220
22	(case report or case study).ti.	98017
23	or/20-22	1556502
24	19 not 23	696
25	limit 24 to (human and english language)	541

MENG_lumbar_puncture_meningitis_medline_050808

Ovid MEDLINE(R) 1950 to July Week 4 2008

#	Searches	Results
1	SPINAL PUNCTURE/	4274
2	((lumbar or spinal) adj3 (punctur$ or tap? or drain$)).ti,ab.	5426
3	or/1-2	7798
4	exp MENINGITIS, BACTERIAL/	17087
5	((bacterial$ or infect$) adj3 (meningitis or meningitides)).ti,ab.	5689
6	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
7	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	22
8	((meningitis or meningitides) adj3 (e coli or escherichia coli)).ti,ab.	281
9	((meningitis or meningitides) adj3 (haemophilus or hemophilus)).ti,ab.	669
10	((meningitis or meningitides) adj3 listeria).ti,ab.	346
11	((meningitis or meningitides) adj3 meningococc$).ti,ab.	1322
12	((meningitis or meningitides) adj3 pneumococc$).ti,ab.	1299
13	((meningitis or meningitides or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4057
14	meningoencephalitis.ti,ab.	4131
15	MENINGOENCEPHALITIS/	4797
16	MENINGITIS/	15039
17	or/4-16	38786
18	and/3,17	1136
19	CASE REPORTS/	1405994
20	(letter or editorial or comment or historical article).pt.	1165112
21	or/19-20	2435543
22	18 not 21	696
23	limit 22 to (english language and humans)	506

14 In children and young people with suspected or confirmed bacterial meningitis, can a cranial computed tomography (CT) scan reliably demonstrate raised intracranial pressure?

MENG_CT_scan_meningitis_cctr_131108

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

#	Searches	Results
1	exp CHILD/	29922
2	child$.ti,ab.	33306
3	exp INFANT/	17712
4	infan$.ti,ab.	12147
5	(baby or babies).ti,ab.	1673
6	toddler?.ti,ab.	252
7	(neonat$ or newborn?).ti,ab.	6827
8	ADOLESCENT/	55610
9	adolescen$.ti,ab.	4812
10	teen$.ti,ab.	497
11	exp SCHOOLS/	562
12	school$.ti,ab.	6141
13	exp PUBERTY/	215
14	pubescen$.ti,ab.	11
15	(pediatric? or paediatric?).ti,ab.	6289
16	or/1-15	100848
17	meningoencephalitis.ti,ab.	18
18	MENINGOENCEPHALITIS/	10
19	meningitis.ti,ab.	478
20	exp MENINGITIS/	350
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	10
23	((fungal or aseptic) adj3 meninges).ti,ab.	0
24	or/17-23	580
25	exp CENTRAL NERVOUS SYSTEM INFECTIONS/	694
26	((CNS or central nervous system) adj3 infection?).ti,ab.	48
27	or/25-26	732
28	INTRACRANIAL PRESSURE/	222
29	INTRACRANIAL HYPERTENSION/	49
30	(ICP or intracranial pressure? or intra cranial pressure? or intra cranial hypertension or intracranial hypertension).ti,ab.	466
31	or/28-30	523
32	and/27,31	21
33	or/24,32	588
34	TOMOGRAPHY SCANNERS, X-RAY COMPUTED/	9
35	exp TOMOGRAPHY, X-RAY COMPUTED/	1809

36 ((CT or CAT or comput$ tomograph$) adj2 (scan$ or x ray or xray)).ti,ab.	1156
37 (electron beam adj2 (tomography or comput$ tomography)).ti,ab.	40
38 Cine CT.ti,ab.	3
39 Tomodensitometr$.ti,ab.	5
40 ((spiral or helical) adj2 (CT or CAT or comput$ tomography)).ti,ab.	253
41 CBCT.ti,ab.	5
42 ((brain or cranial) adj3 (CT or comput$ tomography)).ti,ab.	167
43 (cone beam adj2 (CT or comput$ tomography)).ti,ab.	6
44 (head adj3 (CT or comput$ tomography)).ti,ab.	79
45 or/34-44	2618
46 and/16,33	406
47 46 and 45	7

Thursday, November 13, 2008 1:19:12 PM

MENG_CT_scan_meningitis_cinahl_131108

#	Query	Limiters/Expanders	Results
S44	S43 and S42	Limiters - Publication Type: Abstract, Clinical Innovations, Clinical Trial, Corrected Article, Journal Article, Journal Description, Nursing Diagnoses, Nursing Interventions, Other, Pictorial, Practice Acts, Practice Guidelines, Proceedings, Research, Research Instrument, Research Term Definition, Response, Review, Standards, Statistics, Systematic Review, Tables/Charts; Language: English Search modes - Boolean/Phrase	190
S43		Limiters - Publication Type: Abstract, Clinical Innovations, Clinical Trial, Corrected Article, Journal Article, Journal Description, Nursing Diagnoses, Nursing Interventions, Other, Pictorial, Practice Acts, Practice Guidelines, Proceedings, Research, Research Instrument, Research Term Definition, Response, Review, Standards, Statistics, Systematic Review, Tables/Charts; Language: English Search modes - Boolean/Phrase	1867178
S42	S41 and S40	Search modes - Boolean/Phrase	191
S41	S27 and S16	Search modes - Boolean/Phrase	3446
S40	S39 or S38 or S37 or S36 or S35 or S34 or S33 or S32 or S31 or S30 or S29 or S28	Search modes - Boolean/Phrase	40756
S39	(AB "cone beam") or (TI "cone beam")	Search modes - Boolean/Phrase	86
S38	(AB "brain" or "cranial" or "head" N3 "CT" or "comput$ tomography")	Search modes - Boolean/Phrase	14829
S37	(TI "brain" or "cranial" or "head" N3 "CT" or "comput$ tomography")	Search modes - Boolean/Phrase	11646
S36	(AB "CBCT") or (TI "CBCT")	Search modes - Boolean/Phrase	29
S35	(AB "spiral" or "helical" N3 "scan*" or	Search modes - Boolean/Phrase	10636

	"comput* tomograph*" or "CT" or "CAT")		
S34	(TI "spiral" or "helical" N3 "scan*" or "comput* tomograph*" or "CT" or "CAT")	Search modes - Boolean/Phrase	10423
S33	(TI "Tomodensitometr*") or (AB "Tomodensitometr*")	Search modes - Boolean/Phrase	2
S32	(TI "Cine CT") or (AB "Cine CT")	Search modes - Boolean/Phrase	2
S31	(TI "electron beam") or (AB "electron beam")	Search modes - Boolean/Phrase	181
S30	(AB "CT" or "CAT" or "comput* tomograph*" N3 "scan*" or "x ray" or "xray")	Search modes - Boolean/Phrase	19830
S29	(TI "CT" or "CAT" or "comput* tomograph*" N3 "scan*" or "x ray" or "xray")	Search modes - Boolean/Phrase	18128
S28	(MH "TOMOGRAPHY, X-RAY COMPUTED")	Search modes - Boolean/Phrase	12049
S27	(S26 or S23 or S22 or S21 or S20 or S19 or S18 or S17)	Search modes - Boolean/Phrase	11270
S26	S25 and S24	Search modes - Boolean/Phrase	5
S25	(TI "CNS" or "central nervous system" N3 "infection?") or (AB "CNS" or "central nervous system" N3 "infection?")	Search modes - Boolean/Phrase	2186

S24	(TI "ICP" or "intracranial pressure?" or "intra cranial pressure?" or "intra cranial hypertension" or "intracranial hypertension") or (AB "ICP" or "intracranial pressure?" or "intra cranial pressure?" or "intra cranial hypertension" or "intracranial hypertension")	Search modes - Boolean/Phrase	575
S23	(MH "CENTRAL NERVOUS SYSTEM INFECTIONS+") and (MH "INTRACRANIAL PRESSURE" or "INTRACRANIAL HYPERTENSION")	Search modes - Boolean/Phrase	17
S22	(TI "viral*" or "virus*" N3 "meninges" or "meningitis") or (AB "viral*" or "virus*" N3 "meninges" or "meningitis")	Search modes - Boolean/Phrase	6322
S21	(TI "bacterial*" or "infect*" N3 "meninges") or (AB "bacterial*" or "infect*" N3 "meninges")	Search modes - Boolean/Phrase	5638
S20	(MH "MENINGITIS+")	Search modes - Boolean/Phrase	1781
S19	(TI "meningitis") or (AB "meningitis")	Search modes - Boolean/Phrase	1572
S18	(MH "MENINGOENCEPHALITIS")	Search modes - Boolean/Phrase	71

S17	(TI "meningoencephalitis") or (AB "meningoencephalitis")	Search modes - Boolean/Phrase	98
S16	(S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1)	Search modes - Boolean/Phrase	311634
S15	(TI "pediatric*" or "paediatric*") or (AB "pediatric*" or "paediatric*")	Search modes - Boolean/Phrase	27348
S14	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	49
S13	(MH "PUBERTY+")	Search modes - Boolean/Phrase	910
S12	(TI "school*") or (AB "school*")	Search modes - Boolean/Phrase	35292
S11	(MH "SCHOOLS+")	Search modes - Boolean/Phrase	19581
S10	(TI "teen*") or (AB "teen*")	Search modes - Boolean/Phrase	5851
S9	(TI "adolescen*") or (AB "adolescen*")	Search modes - Boolean/Phrase	26392
S8	(MH "ADOLESCENCE+")	Search modes - Boolean/Phrase	114373
S7	(TI "neonat*" or "newborn?") or (AB "neonat*" or "newborn?")	Search modes - Boolean/Phrase	15038
S6	(TI "toddler*") or (AB "toddler*")	Search modes - Boolean/Phrase	1513
S5	(TI "baby" or "babies") or (AB "baby" or "babies")	Search modes - Boolean/Phrase	9357
S4	(TI "infant*") or (AB "infant*")	Search modes - Boolean/Phrase	24996
S3	(MH "INFANT+")	Search modes - Boolean/Phrase	76526

S2	(TI "child*") or (AB "child*")	Search modes - Boolean/Phrase	108585
S1	(MH "CHILD+")	Search modes - Boolean/Phrase	181626

MENG_CT_scan_meningitis_embase_131108

EMBASE 1980 to 2008 Week 45

#	Searches	Results
1	exp CHILD/	622250
2	child$.tw.	483851
3	exp INFANT/	171792
4	infan$.tw.	169863
5	(baby or babies).tw.	27336
6	exp ADOLESCENT/	432106
7	teenag$.tw.	7948
8	adolescen$.tw.	82744
9	exp SCHOOLS/	37093
10	school$.tw.	74422
11	exp PUBERTY/	14243
12	pubescen$.tw.	649
13	NEWBORN/	177675
14	(newborn? or neonate?).ti,ab.	96750
15	(pediatric? or paediatric?).ti,ab.	109885
16	or/1-15	1266382
17	exp MENINGITIS/	31278
18	meningitis.ti,ab.	21653
19	MENINGOENCEPHALITIS/	2936
20	meningoencephalitis.ti,ab.	2494
21	meningo encephalitis.ti,ab.	308
22	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
23	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	656
24	or/17-23	36222
25	exp CENTRAL NERVOUS SYSTEM INFECTION/	62635
26	((CNS or central nervous system) adj3 infection?).ti,ab.	3866
27	25 or 26	64126
28	INTRACRANIAL PRESSURE/	7719
29	INTRACRANIAL HYPERTENSION/	5702
30	(ICP or intracranial pressure? or intra cranial pressure? or intra cranial hypertension or intracranial hypertension).ti,ab.	15317
31	or/28-30	19968
32	and/27,31	1103
33	or/24,32	36541
34	COMPUTER ASSISTED TOMOGRAPHY/	244693
35	ELECTRON BEAM TOMOGRAPHY/	1454
36	HIGH RESOLUTION COMPUTER TOMOGRAPHY/	2930
37	SPIRAL COMPUTER ASSISTED TOMOGRAPHY/	5771
38	((CT or CAT or comput$ tomograph$) adj2 (scan$ or x ray or xray)).ti,ab.	54420
39	(electron beam adj2 (tomography or comput$ tomography)).ti,ab.	1001

40 Cine CT.ti,ab.	94
41 Tomodensitometr$.ti,ab.	441
42 ((spiral or helical) adj2 (CT or CAT or comput$ tomography)).ti,ab.	7061
43 CBCT.ti,ab.	199
44 ((brain or cranial) adj3 (CT or comput$ tomography)).ti,ab.	5989
45 (cone beam adj2 (CT or comput$ tomography)).ti,ab.	463
46 (head adj3 (CT or comput$ tomography)).ti,ab.	1784
47 COMPUTED TOMOGRAPHY SCANNER/	1960
48 BRAIN TOMOGRAPHY/	2068
49 or/34-48	267358
50 and/16,33	13862
51 and/49-50	1364
52 letter.pt.	429947
53 editorial.pt.	219283
54 CASE REPORT/	1013272
55 (case report or case study).ti.	99794
56 or/52-55	1582133
57 51 not 55	1299
58 limit 57 to english language	1072

MENG_CT_scan_meningitis_medline_131108

Ovid MEDLINE(R) 1950 to November Week 1 2008

#	Searches	Results
1	exp CHILD/	1297405
2	child$.ti,ab.	724373
3	exp INFANT/	804306
4	infan$.ti,ab.	256875
5	(baby or babies).ti,ab.	38185
6	toddler?.ti,ab.	3409
7	(neonat$ or newborn?).ti,ab.	224669
8	ADOLESCENT/	1302705
9	adolescen$.ti,ab.	109375
10	teen$.ti,ab.	14492
11	exp SCHOOLS/	60777
12	school$.ti,ab.	130426
13	exp PUBERTY/	13253
14	pubescen$.ti,ab.	827
15	(pediatric? or paediatric?).ti,ab.	132123
16	or/1-15	2706615
17	meningoencephalitis.ti,ab.	4189
18	MENINGOENCEPHALITIS/	4843
19	meningitis.ti,ab.	31948
20	exp MENINGITIS/	41832
21	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
22	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	960
23	((fungal or aseptic) adj3 meninges).ti,ab.	1
24	or/17-23	51699
25	exp CENTRAL NERVOUS SYSTEM INFECTIONS/	113882
26	((CNS or central nervous system) adj3 infection?).ti,ab.	4522
27	or/25-26	116205
28	INTRACRANIAL PRESSURE/	12106
29	INTRACRANIAL HYPERTENSION/	1923
30	(ICP or intracranial pressure? or intra cranial pressure? or intra cranial hypertension or intracranial hypertension).ti,ab.	17823
31	or/28-30	24019
32	and/27,31	1211
33	or/24,32	52131
34	TOMOGRAPHY SCANNERS, X-RAY COMPUTED/	1164
35	exp TOMOGRAPHY, X-RAY COMPUTED/	216424
36	((CT or CAT or comput$ tomograph$) adj2 (scan$ or x ray or xray)).ti,ab.	64037
37	(electron beam adj2 (tomography or comput$ tomography)).ti,ab.	1092
38	Cine CT.ti,ab.	116
39	Tomodensitometr$.ti,ab.	708

40 ((spiral or helical) adj2 (CT or CAT or comput$ tomography)).ti,ab.	7827
41 CBCT.ti,ab.	264
42 ((brain or cranial) adj3 (CT or comput$ tomography)).ti,ab.	6941
43 (cone beam adj2 (CT or comput$ tomography)).ti,ab.	615
44 (head adj3 (CT or comput$ tomography)).ti,ab.	2032
45 or/34-44	245144
46 and/16,33	24487
47 46 and 45	1353
48 letter.pt.	653119
49 editorial.pt.	233767
50 CASE REPORTS/	1427861
51 (case report or case study).ti.	124561
52 or/48-51	2197905
53 47 not 52	642
54 limit 53 to humans	642
55 limit 54 to english language	497

15 What antibiotic regimen (type) should be used to treat children and young people with suspected bacterial meningitis or meningococcal septicaemia in the secondary care setting?

MENG_antibiotic_regimen_2ary_care_economics_medline_300908

Ovid MEDLINE(R) 1950 to September Week 3 2008

#	Searches	Results
1	ECONOMICS/	25850
2	"COSTS AND COST ANALYSIS"/	37525
3	COST ALLOCATION/	1865
4	COST-BENEFIT ANALYSIS/	44619
5	COST CONTROL/	18046
6	COST SAVINGS/	6165
7	COST OF ILLNESS/	11045
8	COST SHARING/	1439
9	HEALTH CARE COSTS/	17315
10	DIRECT SERVICE COSTS/	862
11	DRUG COSTS/	8937
12	EMPLOYER HEALTH COSTS/	995
13	HOSPITAL COSTS/	5739
14	HEALTH RESOURCES/	6504
15	"HEALTH SERVICES NEEDS AND DEMAND"/	30538
16	HEALTH PRIORITIES/	6992
17	HEALTH EXPENDITURES/	10412
18	CAPITAL EXPENDITURES/	1840
19	FINANCIAL MANAGEMENT/	14519
20	FINANCIAL MANAGEMENT, HOSPITAL/	6964
21	QUALITY-ADJUSTED LIFE YEARS/	3637
22	"DEDUCTIBLES AND COINSURANCE"/	1205
23	MEDICAL SAVINGS ACCOUNTS/	399
24	ECONOMICS, HOSPITAL/	8707
25	ECONOMICS, MEDICAL/	7311
26	ECONOMICS, NURSING/	3854
27	ECONOMICS, PHARMACEUTICAL/	1977
28	MODELS, ECONOMIC/	3277
29	MODELS, ECONOMETRIC/	2833
30	RESOURCE ALLOCATION/	6048
31	HEALTH CARE RATIONING/	9069
32	"FEES AND CHARGES"/	7469
33	BUDGETS/	7752
34	VALUE OF LIFE/	5063
35	(financ$ or fiscal$ or funding).tw.	55436

36	(QALY$ or life?year$).tw.	2200
37	(econom$ or cost$).tw.	289816
38	pharmacoeconomic$.tw.	1939
39	ec.fs.	248306
40	or/1-39	577113
41	exp CHILD/	1287949
42	child$.ti,ab.	717967
43	exp INFANT/	799331
44	infan$.ti,ab.	254988
45	(baby or babies).ti,ab.	37856
46	toddler?.ti,ab.	3363
47	(neonat$ or newborn?).ti,ab.	222961
48	ADOLESCENT/	1291921
49	adolescen$.ti,ab.	108044
50	teen$.ti,ab.	14349
51	exp SCHOOLS/	60330
52	school$.ti,ab.	129087
53	exp PUBERTY/	13166
54	pubescen$.ti,ab.	817
55	or/41-54	2671173
56	BACTEREMIA/	12347
57	(septic?emi? or bacter?emi?).ti,ab.	29703
58	MENINGOCOCCAL INFECTIONS/	4530
59	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	3463
60	meningococc?emi?.ti,ab.	613
61	(Neisseria meningitid$ or n meningitid$).ti,ab.	5258
62	exp NEISSERIA MENINGITIDIS/	6548
63	(meningococcus or meningococci).ti,ab.	2082
64	exp MENINGITIS, BACTERIAL/	17239
65	MENINGITIS/	15112
66	MENINGOENCEPHALITIS/	4825
67	((bacterial$ or infect$) adj3 (meningitis or meningitid$)).ti,ab.	5996
68	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
69	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	22
70	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	354
71	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	834
72	((meningitis or meningitid?s) adj3 listeria).ti,ab.	358
73	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	1393
74	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	1319
75	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	4090
76	(meningoencephalitis or meningo encephalitis).ti,ab.	4609

77	or/56-76	79094
78	exp ANTI-BACTERIAL AGENTS/	433715
79	ANTI-INFECTIVE AGENTS/	28516
80	((anti infective$ or antiinfective$) adj2 (agent$ or drug$)).tw.	595
81	(antimicrob$ or anti microb$).ti,ab.	56197
82	(antibacterial? or anti bacterial?).ti,ab.	28569
83	microbicide?.tw.	959
84	(bacteriocide? or bacteriocidal agent?).ti,ab.	40
85	(empiric adj2 (therapy or antibiotics)).ti,ab.	2035
86	exp PENICILLINS/	63010
87	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	33258
88	exp CEPHALOSPORINS/	32658
89	exp CEFOTAXIME/	10060
90	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	5680
91	exp CEFTRIAXONE/	3578
92	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	5303
93	exp CEFUROXIME/	1703
94	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	3124
95	(chloramphenicol or kemicetine).ti,ab.	20541
96	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).ti,ab.	7855
97	exp AMPICILLIN/	21281
98	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or	16789

	morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).ti,ab.	
99	exp MACROLIDES/	74524
100	(erythromycin or Abboticin or Abomacetin or Ak-mycin or Akne-Mycin or Aknin or Benzamycin or Benzamycin Pak or Bristamycin or Dotycin or Dumotrycin or E-Base or E-Glades or E-Mycin or E-Solve 2 or Eritrocina or Ermycin or Eryc or Erycen or Erycette or Erycin or Erycinum or Eryderm or Erygel or Erymax or Erypar or Erythra-Derm or Erythro or Erythro-Statin or Erythrogran or Erythroguent or Erythromast or Erythromid or Ethril or Ilocaps or Ilosone or Ilotycin or IndermRetcin or Kesso-Mycin or Mephamycin or Pantomicina or Pce or Pfizer-e or Propiocine or R-P Mycin or Robimycin or Sansac or Serp-AFD or Stiemycin or Taimoxin-F or Theramycin Z or Torlamicina or Wemid or Wyamycin S).ti,ab.	17412
101	(Azithromycin or zit?romax or sumamed or Zithrax or zitrim or zitrocin or zmax).ti,ab.	3554
102	(Clarithromycin? or biaxin).ti,ab.	4839
103	(Roxithromycin or rulid? or surlid).ti,ab.	972
104	(Dirithromycin or dynabac).ti,ab.	134
105	(cephradine or cefradine).ti,ab.	606
106	BETA-LACTAMS/	3474
107	exp MONOBACTAMS/	1324
108	(beta lactam? or mono lactam? or monolactam? or aztreonam or azactam or Azthreonam or Az threonam or SQ-26,776 or Urobactam).ti,ab.	12914
109	exp GENTAMICINS/	15681
110	(gentam?cin? or garamycin or g-myticin or gentacycol or Gentavet or genticin or Bristagen or Apogen or Alcomicin or Gentacidin or Gentafair or Gentak or Gentamar or Jenamicin or Spectro-Genta or U-gencin).ti,ab.	17472
111	or/78-110	544710
112	and/55,77	32217
113	and/111-112	9228
114	and/40,113	182
115	limit 113 to ("costs (optimized)" or "economics (optimized)")	147
116	114 or 115	182
117	limit 116 to english language	160

MENG_antibiotic_regimen_2ary_care_economics_eedhta_300908

CLEED, CLHTA

#	Searches	Results
1	exp CHILD/	2457
2	child$.ti,ab.	921
3	exp INFANT/	1659
4	infan$.ti,ab.	179
5	(baby or babies).ti,ab.	11
6	toddler?.ti,ab.	3
7	(neonat$ or newborn?).ti,ab.	264
8	ADOLESCENT/	2743
9	adolescen$.ti,ab.	130
10	teen$.ti,ab.	11
11	exp SCHOOLS/	31
12	school$.ti,ab.	98
13	exp PUBERTY/	0
14	pubescen$.ti,ab.	0
15	or/1-14	4736
16	BACTEREMIA/	80
17	(septic?emi? or bacter?emi?).ti,ab.	29
18	MENINGOCOCCAL INFECTIONS/	15
19	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	8
20	meningococc?emi?.ti,ab.	0
21	(Neisseria meningitid$ or n meningitid$).ti,ab.	1
22	exp NEISSERIA MENINGITIDIS/	3
23	(meningococcus or meningococci).ti,ab.	0
24	exp MENINGITIS, BACTERIAL/	29
25	MENINGITIS/	9
26	MENINGOENCEPHALITIS/	1
27	((bacterial$ or infect$) adj3 (meningitis or meningitid$)).ti,ab.	0
28	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
29	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	0
30	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	0
31	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	0
32	((meningitis or meningitid?s) adj3 listeria).ti,ab.	0
33	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	3
34	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	0
35	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1
36	(meningoencephalitis or meningo encephalitis).ti,ab.	1
37	or/16-36	134
38	exp ANTI-BACTERIAL AGENTS/	916
39	ANTI-INFECTIVE AGENTS/	146

40	((anti infective$ or antiinfective$) adj2 (agent$ or drug$)).tw.	211
41	(antimicrob$ or anti microb$).ti,ab.	96
42	(antibacterial? or anti bacterial?).ti,ab.	21
43	microbicide?.tw.	0
44	(bacteriocide? or bacteriocidal agent?).ti,ab.	0
45	(empiric adj2 (therapy or antibiotics)).ti,ab.	7
46	exp PENICILLINS/	123
47	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).tw.	65
48	exp CEPHALOSPORINS/	130
49	exp CEFOTAXIME/	79
50	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).tw.	22
51	exp CEFTRIAXONE/	51
52	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	64
53	exp CEFUROXIME/	13
54	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	34
55	(chloramphenicol or kemicetine).ti,ab.	2
56	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).ti,ab.	10
57	exp AMPICILLIN/	89
58	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or	9

	rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).ti,ab.	
59	exp MACROLIDES/	213
60	(erythromycin or Abboticin or Abomacetin or Ak-mycin or Akne-Mycin or Aknin or Benzamycin or Benzamycin Pak or Bristamycin or Dotycin or Dumotrycin or E-Base or E-Glades or E-Mycin or E-Solve 2 or Eritrocina or Ermycin or Eryc or Erycen or Erycette or Erycin or Erycinum or Eryderm or Erygel or Erymax or Erypar or Erythra-Derm or Erythro or Erythro-Statin or Erythrogran or Erythroguent or Erythromast or Erythromid or Ethril or Ilocaps or Ilosone or Ilotycin or IndermRetcin or Kesso-Mycin or Mephamycin or Pantomicina or Pce or Pfizer-e or Propiocine or R-P Mycin or Robimycin or Sansac or Serp-AFD or Stiemycin or Taimoxin-F or Theramycin Z or Torlamicina or Wemid or Wyamycin S).ti,ab.	6
61	(Azithromycin or zit?romax or sumamed or Zithrax or zitrim or zitrocin or zmax).ti,ab.	13
62	(Clarithromycin? or biaxin).ti,ab.	12
63	(Roxithromycin or rulid? or surlid).ti,ab.	5
64	(Dirithromycin or dynabac).ti,ab.	0
65	(cephradine or cefradine).ti,ab.	1
66	BETA-LACTAMS/	2
67	exp MONOBACTAMS/	4
68	(beta lactam? or mono lactam? or monolactam? or aztreonam or azactam or Azthreonam or Az threonam or SQ-26,776 or Urobactam).ti,ab.	4
69	exp GENTAMICINS/	29
70	(gentam?cin? or garamycin or g-myticin or gentacycol or Gentavet or genticin or Bristagen or Apogen or Alcomicin or Gentacidin or Gentafair or Gentak or Gentamar or Jenamicin or Spectro-Genta or U-gencin).ti,ab.	11
71	or/38-70	1156
72	and/15,37	59
73	and/71-72	11

MENG_antibiotic_regimen_2ary_care_economics_embase_300908
EMBASE 1980 to 2008 Week 39

#	Searches	Results
1	exp CHILD/	618649
2	child$.ti,ab.	480418
3	exp INFANT/	170747
4	infan$.ti,ab.	168617
5	(baby or babies).ti,ab.	27125
6	exp ADOLESCENT/	428919
7	teenag$.ti,ab.	7884
8	adolescen$.ti,ab.	81954
9	exp SCHOOLS/	36762
10	school$.ti,ab.	73744
11	exp PUBERTY/	14139
12	pubescen$.ti,ab.	641
13	NEWBORN/	176926
14	(newborn? or neonate?).ti,ab.	96227
15	(pediatric? or paediatric?).ti,ab.	108811
16	or/1-15	1257990
17	SEPTICEMIA/	8733
18	BACTEREMIA/	14151
19	(septic?emia or bacter?emia).ti,ab.	21404
20	(meningococc$ adj3 (sepsis or septic)).ti,ab.	344
21	NEISSERIA MENINGITIDIS/	6780
22	(Neisseria meningitid$ or n meningitid$).ti,ab.	4309
23	MENINGOCOCCAL INFECTION/	2784
24	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	2353
25	meningococc?emi?.ti,ab.	423
26	(meningococcus or meningococci).ti,ab.	1457
27	MENINGOCOCCOSIS/	2784
28	MENINGOCOCCEMIA/	830
29	BACTERIAL MENINGITIS/	7558
30	TUBERCULOUS MENINGITIS/	1862
31	MENINGOENCEPHALITIS/	2910
32	MENINGITIS/	13413
33	((bacterial$ or infect$) adj3 (meningitis or meningitid?s)).ti,ab.	5095
34	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
35	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
36	((meningitis or meningitid?s) adj3 (e coli or escherichia coli)).ti,ab.	287
37	((meningitis or meningitid?s) adj3 (haemophilus or hemophilus)).ti,ab.	595
38	((meningitis or meningitid?s) adj3 listeria).ti,ab.	215
39	((meningitis or meningitid?s) adj3 meningococc$).ti,ab.	923
40	((meningitis or meningitid?s) adj3 pneumococc$).ti,ab.	1021

41	((meningitis or meningitid?s or meningeal or Pachymeningitis) adj3 (tuberculosis or tuberculous or tubercular)).ti,ab.	1623
42	(meningoencephalitis or meningo encephalitis).ti,ab.	2745
43	or/17-42	60870
44	exp ANTI-BACTERIAL AGENTS/	1084611
45	ANTIINFECTIVE AGENT/	33399
46	((anti infective$ or antiinfective$) adj2 (agent$ or drug$)).tw.	603
47	(antimicrob$ or anti microb$).ti,ab.	51426
48	(antibacterial? or anti bacterial?).ti,ab.	24095
49	microbicide?.ti,ab.	813
50	(bacteriocide? or bacteriocidal agent?).ti,ab.	25
51	(empiric adj2 (therapy or antibiotics)).ti,ab.	2071
52	exp PENICILLIN DERIVATIVE/	140074
53	(penicillin or abbocillin or ayercillin or benzopenicillin or benzylpenicillin or bicillin or cillora or cilloral or cilopen or compocillin or cosmopen or crystapen or crysticillin or dropcillin or galofak or gelacillin or liquacillin or megacillin or pentids or permapen or pfizerpen or pharmacillin or pradupen or specilline or ursopen or wycillin).ti,ab.	20983
54	exp CEPHALOSPORIN DERIVATIVE/	109591
55	(cefotaxime or cephotaxime or claforan or benaxima or biosint or cefotaxim or fotexina or klaforan or primafen or taporin).ti,ab.	5861
56	(ceftriaxone or ceftriazone or biotrakson or rocephine or rocephin or benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or lendacin or longacef or longaceph or rocefalin or rocefin or tacex or terbac).tw.	6612
57	(cefuroxime or ancef or biofuroksym or cedax or cefizox or cefobid or cefotan or ceftin or cefurax or cefuril or cefzil or cepazine or cephuroxime or duricef or elobact or kefurox or kefzol or kerurox or ketocef or mandol or maxipime or mefoxin or monocid or oraxim or rocephin or sharox or velosef or zinacef or zinat or zinnat).tw.	6348
58	(chloramphenicol or kemicetine).ti,ab.	13615
59	(amoxicillin or ampc or actimoxi or amoclen or amolin or amopen or amopenixin or amoxi or amoxi-mast or amoxibiotic or amoxiden or amoxil or amoxivet or anemolin or aspenil or biomox or bristamox or cemoxin or clamoxyl or delacillin or dispermox or efpenix or flemoxin or hiconcil or histocillin or hydroxyampicillin or ibiamox or imacillin or lamoxy or metafarma or metifarma or moxacin or moxal or ospamox or pamoxicillin or penamox or piramox or polymox or robamox or sawamox or sumox or tolodina or trimox or unicillin or utimox or vetramox or wymox or zimox).ti,ab.	7838
60	(ampicillin or ab-pc or acillin or adobacillin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amipenix or ampen or ampi or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil or ampicin or ampifarm or ampikel or ampimed or ampipenin or ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or brl or binotal or bonapicillin or britacil or campicillin or cimex or copharcilin or d-cillin or delcillin or deripen or divercillin or doktacillin or duphacillin or geocillin or grampenil or guicitrina or guicitrine or lifeampil or morepen or norobrittin or novo-ampicillin or nuvapen or olin kid or omnipen or	12842

	orbicilina or pen a or pen ampil or penbristol or penbritin or penbrock or penicline or penimic or pensyn or pentrex or pentrexl or pentrexyl or pfizerpen or polycillin or ponecil or princillin or principen or qidamp or racenacillin or ro-ampen or rosampline or roscillin or semicillin or servicillin or spectrobid or sumipanto or supen or synpenin or texcillin or tokiocillin or tolomol or totacillin or totalciclina or totapen or trifacilina or ukapen or ultrabion or ultrabron or vampen or viccillin or wypicil).ti,ab.	
61	exp MACROLIDE/	79083
62	(erythromycin or Abboticin or Abomacetin or Ak-mycin or Akne-Mycin or Aknin or Benzamycin or Benzamycin Pak or Bristamycin or Dotycin or Dumotrycin or E-Base or E-Glades or E-Mycin or E-Solve 2 or Eritrocina or Ermycin or Eryc or Erycen or Erycette or Erycin or Erycinum or Eryderm or Erygel or Erymax or Erypar or Erythra-Derm or Erythro or Erythro-Statin or Erythrogran or Erythroguent or Erythromast or Erythromid or Ethril or Ilocaps or Ilosone or Ilotycin or IndermRetcin or Kesso-Mycin or Mephamycin or Pantomicina or Pce or Pfizer-e or Propiocine or R-P Mycin or Robimycin or Sansac or Serp-AFD or Stiemycin or Taimoxin-F or Theramycin Z or Torlamicina or Wemid or Wyamycin S).ti,ab.	15359
63	(Azithromycin or zit?romax or sumamed or Zithrax or zitrim or zitrocin or zmax).ti,ab.	3710
64	(Clarithromycin? or biaxin).ti,ab.	5238
65	(Roxithromycin or rulid? or surlid).ti,ab.	1192
66	(Dirithromycin or dynabac).ti,ab.	182
67	(cephradine or cefradine).ti,ab.	452
68	BETA LACTAM/	1539
69	BETA LACTAM DERIVATIVE/	905
70	exp MONOBACTAM DERIVATIVE/	8499
71	(beta lactam? or mono lactam? or monolactam? or aztreonam or azactam or Azthreonam or Az threonam or SQ-26,776 or Urobactam).ti,ab.	13589
72	exp AMINOGLYCOSIDE ANTIBIOTIC AGENT/	123346
73	(gentam?cin? or garamycin or g-myticin or gentacycol or Gentavet or genticin or Bristagen or Apogen or Alcomicin or Gentacidin or Gentafair or Gentak or Gentamar or Jenamicin or Spectro-Genta or U-gencin).ti,ab.	13652
74	aminoglycoside?.ti,ab.	10880
75	or/44-74	1116773
76	and/16,43	19647
77	and/75-76	9519
78	limit 77 to "economics (2 or more terms min difference)"	202

16 What antibiotic regimen should be used to treat confirmed bacterial meningitis or meningococcal septicaemia?

MENG_antibiotics_conf_mc_cctr_120508

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	exp MENINGOCOCCAL INFECTIONS/	152
2	meningococc$.tw.	270
3	exp NEISSERIA MENINGITIDIS/	122
4	meningitidis.tw.	136
5	or/1-4	370
6	exp PENICILLIN G/	3181
7	(benzathine benzylpenicilline panpharma or kedacillin or amoxicillin clavulanic acid or or-pen or penicillin g sodium or clavulanate potentiated amoxycillin or clamoxyl or bencelin or ampicillin pivaloyl ester or benzathine benzylpenicillin or pengesod or pivampicillin monohydrochloride or disodium alpha-sulfobenzylpenicillin or sulbenicillin or benzathine benzylpenicilline panpharma or sulfobenzylpenicillin or benpen or penibiot or ampicillin trihydrate or parcillin or disodium alpha sulfobenzylpenicillin or pipera-hameln or peniroger or bicillin l-a or bicillin la or brevicilina or penicillin g benzathine or sodium benzylpenicillin or t1220 or t-1220 or pendysin or benzathine penicillin g or potassium clavulanate-amoxicillin combination or penicillin grunenthal or amoxicillin trihydrate or procaine penicillin g or phthalidyl ampicillin or augmentin or piperacillin curasan or clamoxyl parenteral or clamoxyl or ks r1 or coliriocilina or co-amoxiclav or coamoxiclav or pipracil or lpg or berocillin or pekamin or polymox or aminobenzylpenicillin or carboxybenzyl penicillin or ampicillin trihydrate or pentrexyl or polycillin or amoxycillin or tardocillin or carbenicillin disodium or uticillin or azlin or amoxicillin potassium clavulanate combination or debecillin or amoxycillin-clavulanic acid or amoxicillin or brl 2333 or securopen or pivampicillin hydrochloride or potassium clavulanate amoxicillin combination or amoxicillin monopotassium salt or amoxi clavulanate or pondocillin or bay-f 1353 or bayf 1353 or crystapen or van-pen-g or pivamiser or extencilline or pipril or bicillin l a or benzylpenicillin procaine or sodipen or carfecillin sodium salt or talampicillin hydrochloride or piperacillin sodium or clavulanate potentiated amoxycillin or carboxybenzyl penicillin or penilevel or clamoxyl or talampicillin or carfecillin sodium salt or benzathine penicillin g or amoxicillin or amoxi-clavulanate or baypen or benzathine benzylpenicillin or provipen benzatina or synulox or ampicillin pivaloyl ester or benzathine penicillin or mezlocillin or azlocillin sodium or benzathine benzylpenicilline panpharma or brl 3475 or potassium clavulanate-amoxicillin combination or aminobenzyl penicillin or penicillin g procaine or brl 25000 or piperacillin monosodium salt or pivampicillin hydrochloride or ampicillin sodium or piperacillin or benzathine penicillin or kedacillin or cl 227193 or brl 8988 or pfizerpen or penicillin g procaine or penduran or amox clav or carbenicillin or mezlocillin sodium or carbapen or clamoxyl parenteral or penicillin g or procaine penicillin or amoxicillin-clavulanic acid or amoxicilline or trimox or penicillin g procaine or t 1220 or bay f 1353 or carfecillin or benzylpenicillin or pipercillin or peniroger retard or provipen benzatina or actimoxi or aminobenzyl penicillin or mezlocilline or ampicillin sodium or cl-227193 or cl227193 or piperacillin hexal or omnipen or amoxicillin-potassium clavulanate combination or piperacillin fresenius or amoxycillin clavulanic acid or penicillin g potassium or brl-8988 or	4792

	brl8988 or piperacillin ratiopharm or unicilina or potassium clavulanate-amoxicillin combination or bay-e 6905 or baye 6905 or amcill or spektramox or jenacillin or ab-piperacillin or carfecillin sodium salt or microcillin or hydroxyampicillin or benzylpenicillin potassium or talpen or permapen or pivampicillin monohydrochloride or penidural or melocin or sodiopen or peniroger retard or wymox or piperacillin monosodium salt or penicilina g llorente or amoxil or carbenicillin phenyl sodium or procaine penicillin or phthalidyl ampicillin or ks-r1 or ksr1 or benzylpenicillin procaine or ursopen or pyopen or talampicillin hydrochloride or amoxicillin trihydrate or ampicillin or benzetacil or carphecillin or sodium penicillin or penamox or geopen or carbenicillin disodium or azlocillin or brl-25000 or brl25000 or piperacillin sodium or procaine penicillin g or clavulanate potentiated amoxycillin or pendepon or penicillin g jenapharm or pivampicillin or clavulin or piperacillin monosodium salt or ukapen or meslocillin or piperacillin-ratiopharm or ab piperacillin or co amoxiclav or brl-2333 or brl2333 or pipera hameln or amox-clav or anabactyl or penicillin g benzathine or penicillin g benzathine or brl-3475 or brl3475 or bay e 6905 or carbecin or mezlin or pipcil or disodium alpha-sulfobenzylpenicillin or cepacilina or bicillin or amoxicillin monosodium salt).tw.	
8	exp CEFTRIAXONE/	472
9	(ro 13 9904 or lendacin or ceftrex or longacef or ceftriaxone sodium or benaxona or cefatriaxone or rocefalin or ceftriaxona ldp torlan or ro13-9904 or ro139904 or ro-13-9904 or rocephin or rocefin or ceftriaxone or anhydrous ceftriaxone sodium or cefaxona or ceftriaxona andreu or ceftriaxon hexal or ceftriaxon curamed or ceftriaxon or ro 13-9904 or ro 139904 or ro13 9904 or ceftriaxone irex or tacex or hemiheptahydrate disodium salt ceftriaxone or terbac or disodium salt ceftriaxone or rocephine or anhydrous ceftriaxone sodium or longaceph or ceftriaxone sodium).tw.	763
10	exp CEFOTAXIME/	1418
11	(abbott 48999 or abbott 50192 or abbott48999 or abbott-48999 or abbott50192 or abbott-50192 or anhydrous ceftriaxone sodium or benaxima or benaxona or biosint or cefatriaxone or cefaxona or cefixime or cefizox or cefmax or cefmenoxime or cefmenoxime hydrochloride or cefmenoxime hydrochloride or cefotaxim or cefotaxime or cefotaxime sodium or cefotiam or cefotiam hydrochloride or cefradil or ceftizoxime or ceftizoxime monosodium salt or ceftizoxime sodium or ceftrex or ceftriaxon or ceftriaxon curamed or ceftriaxon hexal or ceftriaxona andreu or ceftriaxona ldp torlan or ceftriaxone or ceftriaxone irex or ceftriaxone sodium or cefuroxime or cephotaxim or cephuroxime or ceradolan or cgp 14221 e or cgp14221e or cgp-14221-e or claforan or disodium salt ceftriaxone or "fk 027" or fk 749 or fk027 or fk-027 or fk749 or fk-749 or fotexina or fr 13749 or fr 17027 or fr13749 or fr-13749 or fr17027 or fr-17027 or haloapor or halospor or hemiheptahydrate disodium salt ceftriaxone or hr 756 or hr756 or hr-756 or kendrick or ketocef or klaforan or lendacin or longacef or longaceph or primafen or ro 13 9904 or ro 139904 or ro 13-9904 or ro13 9904 or ro139904 or ro-13-9904 or ro13-9904 or rocefalin or rocefin or rocephin or rocephine or ru 24756 or ru24756 or ru-24756 or sce 1365 or sce 963 or sce1365 or sce-1365 or sce963 or sce-963 or sk&f 88373 2 or sk&f 883732 or sk&f 88373-2 or skf 88373 or skf88373 or skf-88373 or suprax or tacex or taporin or terbac or zinacef).tw.	2148
12	(exp CEPHALOSPORINS/ or cephalosporin$.tw.) and third generation.tw.	148
13	or/6-12	7065

14 5 and 13	72

MENG_antibiotics_conf_mc_cdsrdare_120508

Cochrane Database of Systematic Reviews 1st Quarter 2008
Database of Abstracts of Reviews of Effects 2nd Quarter 2008

#	Searches	Results
1	meningococc$.ti,ab,kw.	10
2	meningitidis.ti,ab,kw.	4
3	or/1-2	10
4	(benzathine benzylpenicilline panpharma or kedacillin or amoxicillin clavulanic acid or or-pen or penicillin g sodium or clavulanate potentiated amoxycillin or clamoxyl or bencelin or ampicillin pivaloyl ester or benzathine benzylpenicillin or pengesod or pivampicillin monohydrochloride or disodium alpha-sulfobenzylpenicillin or sulbenicillin or benzathine benzylpenicilline panpharma or sulfobenzylpenicillin or benpen or penibiot or ampicillin trihydrate or parcillin or disodium alpha sulfobenzylpenicillin or pipera-hameln or peniroger or bicillin l-a or bicillin la or brevicilina or penicillin g benzathine or sodium benzylpenicillin or t1220 or t-1220 or pendysin or benzathine penicillin g or potassium clavulanate-amoxicillin combination or penicillin grunenthal or amoxicillin trihydrate or procaine penicillin g or phthalidyl ampicillin or augmentin or piperacillin curasan or clamoxyl parenteral or clamoxyl or ks r1 or coliriocilina or co-amoxiclav or coamoxiclav or pipracil or lpg or berocillin or pekamin or polymox or aminobenzylpenicillin or carboxybenzyl penicillin or ampicillin trihydrate or pentrexyl or polycillin or amoxycillin or tardocillin or carbenicillin disodium or uticillin or azlin or amoxicillin potassium clavulanate combination or debecillin or amoxycillin-clavulanic acid or amoxicillin or brl 2333 or securopen or pivampicillin hydrochloride or potassium clavulanate amoxicillin combination or amoxicillin monopotassium salt or amoxi clavulanate or pondocillin or bay-f 1353 or bayf 1353 or crystapen or van-pen-g or pivamiser or extencilline or pipril or bicillin l a or benzylpenicillin procaine or sodipen or carfecillin sodium salt or talampicillin hydrochloride or piperacillin sodium or clavulanate potentiated amoxycillin or carboxybenzyl penicillin or penilevel or clamoxyl or talampicillin or carfecillin sodium salt or benzathine penicillin g or amoxicillin or amoxi-clavulanate or baypen or benzathine benzylpenicillin or provipen benzatina or synulox or ampicillin pivaloyl ester or benzathine penicillin or mezlocillin or azlocillin sodium or benzathine benzylpenicilline panpharma or brl 3475 or potassium clavulanate-amoxicillin combination or aminobenzyl penicillin or penicillin g procaine or brl 25000 or piperacillin monosodium salt or pivampicillin hydrochloride or ampicillin sodium or piperacillin or benzathine penicillin or kedacillin or cl 227193 or brl 8988 or pfizerpen or penicillin g procaine or penduran or amox clav or carbenicillin or mezlocillin sodium or carbapen or clamoxyl parenteral or penicillin g or procaine penicillin or amoxicillin-clavulanic acid or amoxicilline or trimox or penicillin g procaine or t 1220 or bay f 1353 or carfecillin or benzylpenicillin or pipercillin or peniroger retard or provipen benzatina or actimoxi or aminobenzyl penicillin or mezlocilline or ampicillin sodium or cl-227193 or cl227193 or piperacillin hexal or omnipen or amoxicillin-potassium clavulanate combination or piperacillin fresenius or amoxycillin clavulanic acid or penicillin g potassium or brl-8988 or brl8988 or piperacillin ratiopharm or unicilina or potassium clavulanate-amoxicillin combination or bay-e 6905 or baye 6905 or amcill or spektramox or jenacillin or ab-piperacillin or carfecillin sodium salt or microcillin or hydroxyampicillin or benzylpenicillin potassium or talpen or permapen or pivampicillin monohydrochloride or penidural or melocin or sodiopen or peniroger retard or wymox or piperacillin monosodium salt or penicilina g llorente or amoxil or	43

	carbenicillin phenyl sodium or procaine penicillin or phthalidyl ampicillin or ks-r1 or ksr1 or benzylpenicillin procaine or ursopen or pyopen or talampicillin hydrochloride or amoxicillin trihydrate or ampicillin or benzetacil or carphecillin or sodium penicillin or penamox or geopen or carbenicillin disodium or azlocillin or brl-25000 or brl25000 or piperacillin sodium or procaine penicillin g or clavulanate potentiated amoxycillin or pendepon or penicillin g jenapharm or pivampicillin or clavulin or piperacillin monosodium salt or ukapen or meslocillin or piperacillin-ratiopharm or ab piperacillin or co amoxiclav or brl-2333 or brl2333 or pipera hameln or amox-clav or anabactyl or penicillin g benzathine or penicillin g benzathine or brl-3475 or brl3475 or bay e 6905 or carbecin or mezlin or pipcil or disodium alpha-sulfobenzylpenicillin or cepacilina or bicillin or amoxicillin monosodium salt).ti,ab,kw.	
5	(ro 13 9904 or lendacin or ceftrex or longacef or ceftriaxone sodium or benaxona or cefatriaxone or rocefalin or ceftriaxona ldp torlan or ro13-9904 or ro139904 or ro-13-9904 or rocephin or rocefin or ceftriaxone or anhydrous ceftriaxone sodium or cefaxona or ceftriaxona andreu or ceftriaxon hexal or ceftriaxon curamed or ceftriaxon or ro 13-9904 or ro 139904 or ro13 9904 or ceftriaxone irex or tacex or hemiheptahydrate disodium salt ceftriaxone or terbac or disodium salt ceftriaxone or rocephine or anhydrous ceftriaxone sodium or longaceph or ceftriaxone sodium).ti,ab,kw.	10
6	(abbott 48999 or abbott 50192 or abbott48999 or abbott-48999 or abbott50192 or abbott-50192 or anhydrous ceftriaxone sodium or benaxima or benaxona or biosint or cefatriaxone or cefaxona or cefixime or cefizox or cefmax or cefmenoxime or cefmenoxime hydrochloride or cefmenoxime hydrochloride or cefotaxim or cefotaxime or cefotaxime sodium or cefotiam or cefotiam hydrochloride or cefradil or ceftizoxime or ceftizoxime monosodium salt or ceftizoxime sodium or ceftrex or ceftriaxon or ceftriaxon curamed or ceftriaxon hexal or ceftriaxona andreu or ceftriaxona ldp torlan or ceftriaxone or ceftriaxone irex or ceftriaxone sodium or cefuroxime or cephotaxim or cephuroxime or ceradolan or cgp 14221 e or cgp14221e or cgp-14221-e or claforan or disodium salt ceftriaxone or "fk 027" or fk 749 or fk027 or fk-027 or fk749 or fk-749 or fotexina or fr 13749 or fr 17027 or fr13749 or fr-13749 or fr17027 or fr-17027 or haloapor or halospor or hemiheptahydrate disodium salt ceftriaxone or hr 756 or hr756 or hr-756 or kendrick or ketocef or klaforan or lendacin or longacef or longaceph or primafen or ro 13 9904 or ro 139904 or ro 13-9904 or ro13 9904 or ro139904 or ro-13-9904 or ro13-9904 or rocefalin or rocefin or rocephin or rocephine or ru 24756 or ru24756 or ru-24756 or sce 1365 or sce 963 or sce1365 or sce-1365 or sce963 or sce-963 or sk&f 88373 2 or sk&f 883732 or sk&f 88373-2 or skf 88373 or skf88373 or skf-88373 or suprax or tacex or taporin or terbac or zinacef).ti,ab,kw.	16
7	(cephalosporin$ and third generation).ti,ab,kw.	3
8	or/4-7	55
9	3 and 8	2

MENG_antibiotics_conf_mc_cinahl_120508_2
EBSCO Host Friday, July 31, 2009 9:06:26 AM

#	Query	Limiters/Expanders	Results
S25	S13 and S17 and S24	Search modes - Boolean/Phrase	0
S24	S18 or S19 or S20 or S21 or S22 or S23	Search modes - Boolean/Phrase	119
S23	AB (cephalosporin*) AND AB (third generation)	Search modes - Boolean/Phrase	178
S22	TI (cephalosporin*) AND TI (third generation)	Search modes - Boolean/Phrase	25
S21	MH CEPHALOSPORINS+	Search modes - Boolean/Phrase	1103
S20	MH CEFOTAXIME+	Search modes - Boolean/Phrase	385
S19	MH CEFTRIAXONE+	Search modes - Boolean/Phrase	238
S18	MH PENICILLIN G+	Search modes - Boolean/Phrase	754
S17	S14 or S15 or S16	Search modes - Boolean/Phrase	52
S16	TI (meningitidis) or AB (meningitidis)	Search modes - Boolean/Phrase	118
S15	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S14	MH MENINGOCOCCAL INFECTIONS+	Search modes - Boolean/Phrase	793
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12	Search modes - Boolean/Phrase	1733
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55

S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004
S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes - Boolean/Phrase	10049
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes - Boolean/Phrase	82965
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_antibiotics_conf_mc_embase_120508

EMBASE 1980 to 2008 Week 19

#	Searches	Results
1	exp CHILD/	606114
2	child$.tw.	468525
3	exp INFANT/	167510
4	infan$.tw.	165608
5	(baby or babies).tw.	26493
6	exp ADOLESCENT/	418552
7	teenag$.tw.	7700
8	adolescen$.tw.	79268
9	exp SCHOOLS/	35629
10	school$.tw.	71468
11	exp PUBERTY/	13763
12	pubescen$.tw.	624
13	or/1-12	1101670
14	exp MENINGOCOCCAL INFECTIONS/	2701
15	meningococc$.tw.	5765
16	exp NEISSERIA MENINGITIDIS/	6657
17	meningitidis.tw.	4255
18	or/14-17	9838
19	exp PENICILLIN G/	46394
20	(benzathine benzylpenicilline panpharma or kedacillin or amoxicillin clavulanic acid or or-pen or penicillin g sodium or clavulanate potentiated amoxycillin or clamoxyl or bencelin or ampicillin pivaloyl ester or benzathine benzylpenicillin or pengesod or pivampicillin monohydrochloride or disodium alpha-sulfobenzylpenicillin or sulbenicillin or benzathine benzylpenicilline panpharma or sulfobenzylpenicillin or benpen or penibiot or ampicillin trihydrate or parcillin or disodium alpha sulfobenzylpenicillin or pipera-hameln or peniroger or bicillin l-a or bicillin la or brevicilina or penicillin g benzathine or sodium benzylpenicillin or t1220 or t-1220 or pendysin or benzathine penicillin g or potassium clavulanate-amoxicillin combination or penicillin grunenthal or amoxicillin trihydrate or procaine penicillin g or phthalidyl ampicillin or augmentin or piperacillin curasan or clamoxyl parenteral or clamoxyl or ks r1 or coliriocilina or co-amoxiclav or coamoxiclav or pipracil or lpg or berocillin or pekamin or polymox or aminobenzylpenicillin or carboxybenzyl penicillin or ampicillin trihydrate or pentrexyl or polycillin or amoxycillin or tardocillin or carbenicillin disodium or uticillin or azlin or amoxicillin potassium clavulanate combination or debecillin or amoxycillin-clavulanic acid or amoxicillin or brl 2333 or securopen or pivampicillin hydrochloride or potassium clavulanate amoxicillin combination or amoxicillin monopotassium salt or amoxi clavulanate or pondocillin or bay-f 1353 or bayf 1353 or crystapen or van-pen-g or pivamiser or extencilline or pipril or bicillin l a or benzylpenicillin procaine or sodipen or carfecillin sodium salt or talampicillin hydrochloride or piperacillin sodium or clavulanate potentiated amoxycillin or carboxybenzyl penicillin or penilevel or clamoxyl or talampicillin or carfecillin sodium salt or benzathine penicillin g or amoxicillin or amoxi-clavulanate or baypen or benzathine benzylpenicillin or provipen benzatina or synulox or	31438

	ampicillin pivaloyl ester or benzathine penicillin or mezlocillin or azlocillin sodium or benzathine benzylpenicilline panpharma or brl 3475 or potassium clavulanate-amoxicillin combination or aminobenzyl penicillin or penicillin g procaine or brl 25000 or piperacillin monosodium salt or pivampicillin hydrochloride or ampicillin sodium or piperacillin or benzathine penicillin or kedacillin or cl 227193 or brl 8988 or pfizerpen or penicillin g procaine or penduran or amox clav or carbenicillin or mezlocillin sodium or carbapen or clamoxyl parenteral or penicillin g or procaine penicillin or amoxicillin-clavulanic acid or amoxicilline or trimox or penicillin g procaine or t 1220 or bay f 1353 or carfecillin or benzylpenicillin or pipercillin or peniroger retard or provipen benzatina or actimoxi or aminobenzyl penicillin or mezlocilline or ampicillin sodium or cl-227193 or cl227193 or piperacillin hexal or omnipen or amoxicillin-potassium clavulanate combination or piperacillin fresenius or amoxycillin clavulanic acid or penicillin g potassium or brl-8988 or brl8988 or piperacillin ratiopharm or unicilina or potassium clavulanate-amoxicillin combination or bay-e 6905 or baye 6905 or amcill or spektramox or jenacillin or ab-piperacillin or carfecillin sodium salt or microcillin or hydroxyampicillin or benzylpenicillin potassium or talpen or permapen or pivampicillin monohydrochloride or penidural or melocin or sodiopen or peniroger retard or wymox or piperacillin monosodium salt or penicilina g llorente or amoxil or carbenicillin phenyl sodium or procaine penicillin or phthalidyl ampicillin or ks-r1 or ksr1 or benzylpenicillin procaine or ursopen or pyopen or talampicillin hydrochloride or amoxicillin trihydrate or ampicillin or benzetacil or carphecillin or sodium penicillin or penamox or geopen or carbenicillin disodium or azlocillin or brl-25000 or brl25000 or piperacillin sodium or procaine penicillin g or clavulanate potentiated amoxycillin or pendepon or penicillin g jenapharm or pivampicillin or clavulin or piperacillin monosodium salt or ukapen or meslocillin or piperacillin-ratiopharm or ab piperacillin or co amoxiclav or brl-2333 or brl2333 or pipera hameln or amox-clav or anabactyl or penicillin g benzathine or penicillin g benzathine or brl-3475 or brl3475 or bay e 6905 or carbecin or mezlin or pipcil or disodium alpha-sulfobenzylpenicillin or cepacilina or bicillin or amoxicillin monosodium salt).tw.	
21	exp CEFTRIAXONE/	22752
22	(ro 13 9904 or lendacin or ceftrex or longacef or ceftriaxone sodium or benaxona or cefatriaxone or rocefalin or ceftriaxona ldp torlan or ro13-9904 or ro139904 or ro-13-9904 or rocephin or rocefin or ceftriaxone or anhydrous ceftriaxone sodium or cefaxona or ceftriaxona andreu or ceftriaxon hexal or ceftriaxon curamed or ceftriaxon or ro 13-9904 or ro 139904 or ro13 9904 or ceftriaxone irex or tacex or hemiheptahydrate disodium salt ceftriaxone or terbac or disodium salt ceftriaxone or rocephine or anhydrous ceftriaxone sodium or longaceph or ceftriaxone sodium).tw.	6509
23	exp CEFOTAXIME/	22989
24	(abbott 48999 or abbott 50192 or abbott48999 or abbott-48999 or abbott50192 or abbott-50192 or anhydrous ceftriaxone sodium or benaxima or benaxona or biosint or cefatriaxone or cefaxona or cefixime or cefizox or cefmax or cefmenoxime or cefmenoxime hydrochloride or cefmenoxime hydrochloride or cefotaxim or cefotaxime or cefotaxime sodium or cefotiam or cefotiam hydrochloride or cefradil or ceftizoxime or ceftizoxime monosodium salt or ceftizoxime sodium or ceftrex or ceftriaxon or ceftriaxon curamed or ceftriaxon hexal or ceftriaxona andreu or ceftriaxona ldp torlan or ceftriaxone or ceftriaxone irex or ceftriaxone sodium or cefuroxime or cephotaxim or cephuroxime or ceradolan or cgp 14221 e or cgp14221e or cgp-14221-e or claforan or disodium	16993

	salt ceftriaxone or "fk 027" or fk 749 or fk027 or fk-027 or fk749 or fk-749 or fotexina or fr 13749 or fr 17027 or fr13749 or fr-13749 or fr17027 or fr-17027 or haloapor or halospor or hemiheptahydrate disodium salt ceftriaxone or hr 756 or hr756 or hr-756 or kendrick or ketocef or klaforan or lendacin or longacef or longaceph or primafen or ro 13 9904 or ro 139904 or ro 13-9904 or ro13 9904 or ro139904 or ro-13-9904 or ro13-9904 or rocefalin or rocefin or rocephin or rocephine or ru 24756 or ru24756 or ru-24756 or sce 1365 or sce 963 or sce1365 or sce-1365 or sce963 or sce-963 or sk&f 88373 2 or sk&f 883732 or sk&f 88373-2 or skf 88373 or skf88373 or skf-88373 or suprax or tacex or taporin or terbac or zinacef).tw.	
25	(exp CEPHALOSPORINS/ or cephalosporin$.tw.) and third generation.tw.	2754
26	or/19-25	100436
27	13 and 18 and 26	855
28	limit 27 to english language	639

MENG_antibiotics_conf_mc_medline_120508

Ovid MEDLINE(R) 1950 to April Week 5 2008

#	Searches	Results
1	exp CHILD/	1253336
2	child$.tw.	694460
3	exp INFANT/	777578
4	infan$.tw.	247293
5	(baby or babies).tw.	36629
6	exp ADOLESCENT/	1256792
7	teenag$.tw.	10216
8	adolescen$.tw.	104023
9	exp SCHOOLS/	58614
10	school$.tw.	124850
11	exp PUBERTY/	12834
12	pubescen$.tw.	786
13	or/1-12	2523047
14	exp MENINGOCOCCAL INFECTIONS/	8086
15	meningococc$.tw.	8119
16	exp NEISSERIA MENINGITIDIS/	6329
17	meningitidis.tw.	5111
18	or/14-17	13158
19	exp PENICILLIN G/	30379
20	(benzathine benzylpenicilline panpharma or kedacillin or amoxicillin clavulanic acid or or-pen or penicillin g sodium or clavulanate potentiated amoxycillin or clamoxyl or bencelin or ampicillin pivaloyl ester or benzathine benzylpenicillin or pengesod or pivampicillin monohydrochloride or disodium alpha-sulfobenzylpenicillin or sulbenicillin or benzathine benzylpenicilline panpharma or sulfobenzylpenicillin or benpen or penibiot or ampicillin trihydrate or parcillin or disodium alpha sulfobenzylpenicillin or pipera-hameln or peniroger or bicillin l-a or bicillin la or brevicilina or penicillin g benzathine or sodium benzylpenicillin or t1220 or t-1220 or pendysin or benzathine penicillin g or potassium clavulanate-amoxicillin combination or penicillin grunenthal or amoxicillin trihydrate or procaine penicillin g or phthalidyl ampicillin or augmentin or piperacillin curasan or clamoxyl parenteral or clamoxyl or ks r1 or coliriocilina or co-amoxiclav or coamoxiclav or pipracil or lpg or berocillin or pekamin or polymox or aminobenzylpenicillin or carboxybenzyl penicillin or ampicillin trihydrate or pentrexyl or polycillin or amoxycillin or tardocillin or carbenicillin disodium or uticillin or azlin or amoxicillin potassium clavulanate combination or debecillin or amoxycillin-clavulanic acid or amoxicillin or brl 2333 or securopen or pivampicillin hydrochloride or potassium clavulanate amoxicillin combination or amoxicillin monopotassium salt or amoxi clavulanate or pondocillin or bay-f 1353 or bayf 1353 or crystapen or van-pen-g or pivamiser or extencilline or pipril or bicillin l a or benzylpenicillin procaine or sodipen or carfecillin sodium salt or talampicillin hydrochloride or piperacillin sodium or clavulanate potentiated amoxycillin or carboxybenzyl penicillin or penilevel or clamoxyl or talampicillin or carfecillin sodium salt or benzathine penicillin g or amoxicillin or amoxi-clavulanate or	33580

	baypen or benzathine benzylpenicillin or provipen benzatina or synulox or ampicillin pivaloyl ester or benzathine penicillin or mezlocillin or azlocillin sodium or benzathine benzylpenicilline panpharma or brl 3475 or potassium clavulanate-amoxicillin combination or aminobenzyl penicillin or penicillin g procaine or brl 25000 or piperacillin monosodium salt or pivampicillin hydrochloride or ampicillin sodium or piperacillin or benzathine penicillin or kedacillin or cl 227193 or brl 8988 or pfizerpen or penicillin g procaine or penduran or amox clav or carbenicillin or mezlocillin sodium or carbapen or clamoxyl parenteral or penicillin g or procaine penicillin or amoxicillin-clavulanic acid or amoxicilline or trimox or penicillin g procaine or t 1220 or bay f 1353 or carfecillin or benzylpenicillin or pipercillin or peniroger retard or provipen benzatina or actimoxi or aminobenzyl penicillin or mezlocilline or ampicillin sodium or cl-227193 or cl227193 or piperacillin hexal or omnipen or amoxicillin-potassium clavulanate combination or piperacillin fresenius or amoxycillin clavulanic acid or penicillin g potassium or brl-8988 or brl8988 or piperacillin ratiopharm or unicilina or potassium clavulanate-amoxicillin combination or bay-e 6905 or baye 6905 or amcill or spektramox or jenacillin or ab-piperacillin or carfecillin sodium salt or microcillin or hydroxyampicillin or benzylpenicillin potassium or talpen or permapen or pivampicillin monohydrochloride or penidural or melocin or sodiopen or peniroger retard or wymox or piperacillin monosodium salt or penicilina g llorente or amoxil or carbenicillin phenyl sodium or procaine penicillin or phthalidyl ampicillin or ks-r1 or ksr1 or benzylpenicillin procaine or ursopen or pyopen or talampicillin hydrochloride or amoxicillin trihydrate or ampicillin or benzetacil or carphecillin or sodium penicillin or penamox or geopen or carbenicillin disodium or azlocillin or brl-25000 or brl25000 or piperacillin sodium or procaine penicillin g or clavulanate potentiated amoxycillin or pendepon or penicillin g jenapharm or pivampicillin or clavulin or piperacillin monosodium salt or ukapen or meslocillin or piperacillin-ratiopharm or ab piperacillin or co amoxiclav or brl-2333 or brl2333 or pipera hameln or amox-clav or anabactyl or penicillin g benzathine or penicillin g benzathine or brl-3475 or brl3475 or bay e 6905 or carbecin or mezlin or pipcil or disodium alpha-sulfobenzylpenicillin or cepacilina or bicillin or amoxicillin monosodium salt).tw.	
21	exp CEFTRIAXONE/	3478
22	(ro 13 9904 or lendacin or ceftrex or longacef or ceftriaxone sodium or benaxona or cefatriaxone or rocefalin or ceftriaxona ldp torlan or ro13-9904 or ro139904 or ro-13-9904 or rocephin or rocefin or ceftriaxone or anhydrous ceftriaxone sodium or cefaxona or ceftriaxona andreu or ceftriaxon hexal or ceftriaxon curamed or ceftriaxon or ro 13-9904 or ro 139904 or ro13 9904 or ceftriaxone irex or tacex or hemiheptahydrate disodium salt ceftriaxone or terbac or disodium salt ceftriaxone or rocephine or anhydrous ceftriaxone sodium or longaceph or ceftriaxone sodium).tw.	5141
23	exp CEFOTAXIME/	9855
24	(abbott 48999 or abbott 50192 or abbott48999 or abbott-48999 or abbott50192 or abbott-50192 or anhydrous ceftriaxone sodium or benaxima or benaxona or biosint or cefatriaxone or cefaxona or cefixime or cefizox or cefmax or cefmenoxime or cefmenoxime hydrochloride or cefmenoxime hydrochloride or cefotaxim or cefotaxime or cefotaxime sodium or cefotiam or cefotiam hydrochloride or cefradil or ceftizoxime or ceftizoxime monosodium salt or ceftizoxime sodium or ceftrex or ceftriaxon or ceftriaxon curamed or ceftriaxon hexal or ceftriaxona andreu or ceftriaxona ldp torlan or ceftriaxone or ceftriaxone irex or ceftriaxone sodium or cefuroxime or cephotaxim or cephuroxime or	13463

	ceradolan or cgp 14221 e or cgp14221e or cgp-14221-e or claforan or disodium salt ceftriaxone or "fk 027" or fk 749 or fk027 or fk-027 or fk749 or fk-749 or fotexina or fr 13749 or fr 17027 or fr13749 or fr-13749 or fr17027 or fr-17027 or haloapor or halospor or hemiheptahydrate disodium salt ceftriaxone or hr 756 or hr756 or hr-756 or kendrick or ketocef or klaforan or lendacin or longacef or longaceph or primafen or ro 13 9904 or ro 139904 or ro 13-9904 or ro13 9904 or ro139904 or ro-13-9904 or ro13-9904 or rocefalin or rocefin or rocephin or rocephine or ru 24756 or ru24756 or ru-24756 or sce 1365 or sce 963 or sce1365 or sce-1365 or sce963 or sce-963 or sk&f 88373 2 or sk&f 883732 or sk&f 88373-2 or skf 88373 or skf88373 or skf-88373 or suprax or tacex or taporin or terbac or zinacef).tw.	
25	(exp CEPHALOSPORINS/ or cephalosporin$.tw.) and third generation.tw.	2536
26	or/19-25	59324
27	13 and 18 and 26	525
28	limit 27 to (english language and humans)	377

17 What are the indications for administering intravenous fluids to resuscitate children and young people with suspected meningococcal septicaemia?

MENG_iv_fluid_resuscitation_cctr_240908

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	exp CHILD/	38980
2	child$.ti,ab.	32759
3	exp INFANT/	17523
4	infan$.ti,ab.	11965
5	(baby or babies).ti,ab.	1648
6	toddler?.ti,ab.	244
7	(neonat$ or newborn?).ti,ab.	6723
8	ADOLESCENT/	54880
9	adolescen$.ti,ab.	4686
10	teen$.ti,ab.	488
11	exp SCHOOLS/	534
12	school$.ti,ab.	6033
13	exp PUBERTY/	209
14	pubescen$.ti,ab.	10
15	(pediatric? or paediatric?).ti,ab.	6156
16	or/1-15	99424
17	SHOCK, SEPTIC/	256
18	SHOCK/	98
19	(septic adj shock).ti,ab.	377
20	shock.ti.	839
21	SEPSIS/	895
22	BACTEREMIA/	380
23	(septic?emi? or bacter?emi?).ti,ab.	1259
24	sepsis.ti,ab.	2105
25	MENINGOCOCCAL INFECTIONS/	72
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	60
27	meningococc?emi?.ti,ab.	5
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	135
29	NEISSERIA MENINGITIDIS/	124
30	(blood adj3 poisoning?).ti,ab.	5
31	(meningococcus or meningococci).ti,ab.	51

32	or/17-31	4680
33	exp INFUSIONS, PARENTERAL/	8560
34	((infusion? or rehydrat$ or hydrat$) adj3 (IV or intravenous$ or parenteral$ or intraosseous$ or intra venous$)).ti,ab.	5812
35	(drip? adj3 (infusion? or intravenous$ or intra venous$ or IV)).ti,ab.	258
36	(rapid$ adj3 infusion?).ti,ab.	274
37	(bolus or boluses).ti,ab.	6611
38	INJECTIONS, INTRAVENOUS/	5979
39	(injection? adj3 (intra?venous$ or IV)).ti,ab.	2347
40	(fluid? adj3 (drip? or IV or intravenous$ or intra venous$)).ti,ab.	530
41	FLUID THERAPY/	781
42	((fluid or volume) adj3 resuscitation?).ti,ab.	143
43	(colloid? or albumin? or crystalloid? or saline).ti,ab.	14971
44	REHYDRATION SOLUTIONS/	191
45	ISOTONIC SOLUTIONS/	460
46	SALINE SOLUTION, HYPERTONIC/	254
47	HYPOTONIC SOLUTION/	47
48	((hyper?tonic or hypo?tonic or iso?tonic) adj3 (solution? or fluid?)).ti,ab.	457
49	COLLOIDS/	259
50	hydrocolloid?.ti,ab.	252
51	exp ALBUMINS/	2643
52	SERUM ALBUMIN/	742
53	albumin?.ti,ab.	3633
54	exp BLOOD SUBSTITUTES/	1037
55	((plasma or blood) adj2 (substitute? or expander?)).ti,ab.	196
56	ELECTROLYTES/	704
57	electrolyte?.ti,ab.	1877
58	exp SODIUM CHLORIDE/	1529
59	sodium chloride.ti,ab.	691
60	(penta?starch? or penta?span? or hydroxy?ethyl starch).ti,ab.	448
61	(heta?starch? or 2-hydroxyethyl ether).tw.	53
62	((hartmann's or hartmanns or potassium) adj3 (solution? or fluid?)).ti,ab.	155
63	(sodium adj lactate?).ti,ab.	75
64	((glucose or dextrose) adj2 solution?).ti,ab.	594
65	(dextran? or gelatin?).ti,ab.	1283
66	Gelofusine.ti,ab.	27
67	Haemaccel.ti,ab.	50

68	(ringer$ adj2 lactate?).ti,ab.	399
69	plasma protein fraction.ti,ab.	6
70	PPF.ti,ab.	17
71	or/33-70	42254
72	and/16,32	1535
73	and/71-72	279

MENG_iv_fluid_resuscitation_cdsrdare_240908

DARE, CDSR

#	Searches	Results
1	CHILD.kw.	1169
2	child$.ti,ab.	1445
3	INFANT.kw.	820
4	infan$.ti,ab.	540
5	(baby or babies).ti,ab.	134
6	toddler?.ti,ab.	5
7	(neonat$ or newborn?).ti,ab.	507
8	ADOLESCEN$.kw.	755
9	adolescen$.ti,ab.	219
10	teen$.ti,ab.	10
11	SCHOOL$.kw.	55
12	school$.ti,ab.	119
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	218
16	or/1-15	2768
17	SEPTIC SHOCK.kw.	0
18	SHOCK.kw.	31
19	(septic adj shock).ti,ab.	8
20	shock.ti.	27
21	SEPSIS.kw.	57
22	BACTEREMIA.kw.	30
23	(septic?emi? or bacter?emi?).ti,ab.	24
24	sepsis.ti,ab.	88
25	MENINGOCOCCAL INFECTION$.kw.	5
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	6
27	meningococc?emi?.ti,ab.	0
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	0
29	NEISSERIA MENINGITIDIS.kw.	4
30	(blood adj3 poisoning?).ti,ab.	0
31	(meningococcus or meningococci).ti,ab.	0
32	or/17-31	185
33	PARENTERAL INFUSION$.kw.	0
34	((infusion? or rehydrat$ or hydrat$) adj3 (IV or intravenous$ or parenteral$ or intraosseous$ or intra venous$)).ti,ab.	33
35	(drip? adj3 (infusion? or intravenous$ or intra venous$ or IV)).ti,ab.	0
36	(rapid$ adj3 infusion?).ti,ab.	1
37	(bolus or boluses).ti,ab.	17
38	INTRAVENOUS INJECTION$.kw.	0
39	(injection? adj3 (intra?venous$ or IV)).ti,ab.	3

40 (fluid? adj3 (drip? or IV or intravenous$ or intra venous$)).ti,ab.	21
41 FLUID THERAPY.kw.	43
42 ((fluid or volume) adj3 resuscitation?).ti,ab.	7
43 (colloid? or albumin? or crystalloid? or saline).ti,ab.	90
44 REHYDRATION SOLUTION$.kw.	16
45 ISOTONIC SOLUTION$.kw.	11
46 HYPERTONIC SALINE SOLUTION$.kw.	0
47 HYPOTONIC SOLUTION$.kw.	0
48 ((hyper?tonic or hypo?tonic or iso?tonic) adj3 (solution? or fluid?)).ti,ab.	9
49 COLLOID$.kw.	20
50 hydrocolloid?.ti,ab.	4
51 ALBUMIN$.kw.	28
52 SERUM ALBUMIN.kw.	9
53 albumin?.ti,ab.	35
54 BLOOD SUBSTITUTE$.kw.	0
55 ((plasma or blood) adj2 (substitute? or expander?)).ti,ab.	6
56 ELECTROLYTE$.kw.	3
57 electrolyte?.ti,ab.	10
58 SODIUM CHLORIDE.kw.	31
59 sodium chloride.ti,ab.	1
60 (penta?starch? or penta?span? or hydroxy?ethyl starch).ti,ab.	6
61 (heta?starch? or 2-hydroxyethyl ether).tw.	12
62 ((hartmann's or hartmanns or potassium) adj3 (solution? or fluid?)).ti,ab.	3
63 (sodium adj lactate?).ti,ab.	0
64 ((glucose or dextrose) adj2 solution?).ti,ab.	1
65 (dextran? or gelatin?).ti,ab.	10
66 Gelofusine.ti,ab.	0
67 Haemaccel.ti,ab.	0
68 (ringer$ adj2 lactate?).ti,ab.	1
69 plasma protein fraction.ti,ab.	1
70 PPF.ti,ab.	2
71 or/33-70	229
72 and/16,32	83
73 and/71-72	4

MENG_iv_fluid_resuscitation_cinahl_240908

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to September Week 3 2008

#	Searches	Results
1	exp CHILD/	178880
2	child$.tw.	103646
3	exp INFANT/	75622
4	infan$.tw.	25536
5	(baby or babies).tw.	8976
6	exp ADOLESCENT/	112655
7	teenag$.tw.	3035
8	adolescen$.tw.	24735
9	exp SCHOOLS/	19236
10	school$.tw.	33517
11	exp PUBERTY/	891
12	pubescen$.tw.	47
13	(newborn? or neonate?).ti,ab.	9822
14	or/1-13	294047
15	SHOCK, SEPTIC/	871
16	(sepsis adj5 hypotension).ti,ab.	25
17	BACTEREMIA/	1483
18	NEONATAL SEPSIS/	257
19	(severe adj2 sepsis).ti,ab.	462
20	(septic?emia or bacter?emia).ti,ab.	1490
21	(meningococc$ adj3 (sepsis or septic)).ti,ab.	26
22	((septic or bacter?emic) adj shock).ti,ab.	721
23	SHOCK/	798
24	shock.ti.	2055
25	MENINGOCOCCAL INFECTIONS/	577
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	267
27	meningococc?emi?.ti,ab.	45
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	101
29	(blood adj3 poisoning?).ti,ab.	11
30	(meningococcus or meningococci).ti,ab.	32
31	or/15-30	6457
32	exp INFUSIONS, PARENTERAL/	3482
33	((infusion? or rehydrat$ or hydrat$) adj3 (IV or intravenous$ or parenteral$ or intraosseous$ or intra venous$)).ti,ab.	1237
34	(drip? adj3 (infusion? or intravenous$ or intra venous$ or IV)).ti,ab.	33
35	(rapid$ adj3 infusion?).ti,ab.	80
36	(bolus or boluses).ti,ab.	1321
37	INJECTIONS, INTRAVENOUS/	879
38	(injection? adj3 (intra?venous$ or IV)).ti,ab.	343

39	(fluid? adj3 (drip? or IV or intravenous$ or intra venous$)).ti,ab.	494
40	FLUID THERAPY/	1456
41	FLUID RESUSCITATION/	564
42	INTRAVENOUS THERAPY/	1649
43	HOME INTRAVENOUS THERAPY/	946
44	((fluid or volume) adj3 resuscitation?).ti,ab.	453
45	(colloid? or albumin? or crystalloid? or saline).ti,ab.	5077
46	REHYDRATION SOLUTIONS/	114
47	ISOTONIC SOLUTIONS/	164
48	SALINE SOLUTION, HYPERTONIC/	186
49	HYPOTONIC SOLUTION/	64
50	((hypertonic or hypotonic or isotonic or hyper tonic or iso tonic or hypo tonic) adj3 (solution? or fluid?)).ti,ab.	164
51	hydrocolloid?.ti,ab.	212
52	exp ALBUMINS/	3972
53	albumin?.ti,ab.	2164
54	exp BLOOD SUBSTITUTES/	1998
55	((plasma or blood) adj2 (substitute? or expander?)).ti,ab.	104
56	ELECTROLYTES/	398
57	electrolyte?.ti,ab.	1319
58	SODIUM CHLORIDE/	623
59	sodium chloride.ti,ab.	246
60	(penta?starch? or penta?span? or hydroxy?ethyl starch).ti,ab.	77
61	(heta?starch? or 2-hydroxyethyl ether).ti,ab.	35
62	((hartmann's or hartmanns or potassium) adj3 (solution? or fluid?)).ti,ab.	43
63	(sodium adj lactate?).ti,ab.	10
64	((glucose or dextrose) adj2 solution?).ti,ab.	88
65	(dextran? or gelatin?).ti,ab.	334
66	Gelofusine.ti,ab.	8
67	Haemaccel.ti,ab.	6
68	(ringer$ adj2 lactate?).ti,ab.	178
69	plasma protein fraction.ti,ab.	5
70	PPF.ti,ab.	14
71	Actovegin.ti,ab.	4
72	(Blood adj Derivative?).ti,ab.	3
73	Diaspirin.ti,ab.	11
74	Fluosol.ti,ab.	2
75	Perfluorodecalin.ti,ab.	3
76	(plasma adj2 (fresh or frozen)).ti,ab.	179
77	or/32-76	21484
78	and/14,31	1813
79	77 and 78	162

80 CASE REPORT/	6954
81 (letter or editorial or comment or historical article).pt.	158427
82 (case report or case study).ti.	12205
83 or/80-82	176192
84 79 not 83	155
85 limit 84 to english	154

MENG_iv_fluid_resuscitation_embase_240908

EMBASE 1980 to 2008 Week 38

#	Searches	Results
1	exp CHILD/	617693
2	child$.tw.	479594
3	exp INFANT/	170481
4	infan$.tw.	168613
5	(baby or babies).tw.	27102
6	exp ADOLESCENT/	428206
7	teenag$.tw.	7872
8	adolescen$.tw.	81766
9	exp SCHOOLS/	36686
10	school$.tw.	73626
11	exp PUBERTY/	14125
12	pubescen$.tw.	640
13	NEWBORN/	176747
14	(newborn? or neonate?).ti,ab.	96116
15	(pediatric? or paediatric?).ti,ab.	108510
16	or/1-15	1256245
17	SEPTIC SHOCK/	12777
18	SEPTICEMIA/	8715
19	((septic or bacter?emic) adj shock).ti,ab.	8509
20	(sepsis adj5 hypotension).ti,ab.	256
21	BACTEREMIA/	14124
22	(severe adj2 sepsis).ti,ab.	2861
23	(septic?emia or bacter?emia).ti,ab.	21377
24	(meningococc$ adj3 (sepsis or septic)).ti,ab.	343
25	NEISSERIA MENINGITIDIS/	6770
26	(Neisseria meningitid$ or n meningitid$).ti,ab.	4300
27	MENINGOCOCCAL INFECTION/	2776
28	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	2349
29	meningococc?emi?.ti,ab.	423
30	(meningococcus or meningococci).ti,ab.	1455
31	MENINGOCOCCOSIS/	2776
32	MENINGOCOCCEMIA/	827
33	(blood adj2 poisoning).ti,ab.	61
34	SHOCK/	11326
35	shock.ti.	27553
36	or/17-35	84644
37	INFUSION/	5204
38	((infusion? or rehydrat$ or hydrat$) adj3 (IV or intravenous$ or parenteral$ or intraosseous$ or intra venous$)).ti,ab.	29329
39	(drip? adj3 (infusion? or intravenous$ or intra venous$ or IV)).ti,ab.	1801

40	(rapid$ adj3 infusion?).ti,ab.	1394
41	(bolus or boluses).ti,ab.	34150
42	INTRAVENOUS DRUG ADMINISTRATION/	269632
43	(injection? adj3 (intra?venous$ or IV)).ti,ab.	30082
44	(fluid? adj3 (drip? or IV or intravenous$ or intra venous$)).ti,ab.	3025
45	FLUID THERAPY/	6164
46	REHYDRATION/	2585
47	((fluid or volume) adj3 resuscitation?).ti,ab.	2421
48	(colloid? or albumin? or crystalloid? or saline).ti,ab.	163359
49	ISOTONIC SOLUTION/	967
50	HYPERTONIC SOLUTION/	1837
51	HYPOTONIC SOLUTION/	810
52	SODIUM CHLORIDE/	55098
53	((hypertonic or hypotonic or isotonic or hyper tonic or iso tonic or hypo tonic) adj3 (solution? or fluid?)).ti,ab.	4340
54	COLLOID/	7278
55	HYDROCOLLOID/	640
56	hydrocolloid?.ti,ab.	518
57	ALBUMINOID/	248
58	ALBUMIN/	34285
59	SERUM ALBUMIN/	5420
60	albumin?.ti,ab.	67332
61	ARTIFICIAL BLOOD/	279
62	BLOOD SUBSTITUTE/	852
63	exp PLASMA SUBSTITUTE/	23839
64	((plasma or blood) adj2 (substitute? or expander?)).ti,ab.	1918
65	ELECTROLYTE/	10597
66	electrolyte?.ti,ab.	26210
67	sodium chloride.ti,ab.	7836
68	(penta?starch? or penta?span? or hydroxy?ethyl starch).ti,ab.	1550
69	(hetastarch? or heta starch? or 2-hydroxyethyl ether).ti,ab.	322
70	HARTMANN SOLUTION/	228
71	((hartmann's or hartmanns or potassium) adj3 (solution? or fluid?)).ti,ab.	1991
72	(sodium adj lactate?).ti,ab.	496
73	((glucose or dextrose) adj2 solution?).ti,ab.	2952
74	(dextran? or gelatin?).ti,ab.	27573
75	Actovegin.ti,ab.	31
76	(Blood adj Derivative?).ti,ab.	146
77	(Blood adj Extract?).ti,ab.	85
78	Diaspirin.ti,ab.	172
79	Fluosol.ti,ab.	438
80	Gelatinol.ti,ab.	6

81	Oxyamal.ti,ab.	2
82	Oxypolygelatin.ti,ab.	14
83	Perfluorobutyltetrahydrofuran.ti,ab.	2
84	Perfluorodecalin.ti,ab.	202
85	Perfluorooctyl Bromide.ti,ab.	67
86	Perfluoroperhydrofluoranthene.ti,ab.	1
87	Perfluorotributylamine.ti,ab.	93
88	Perfluorotripropylamine.ti,ab.	32
89	Plasmion.ti,ab.	28
90	Polygeline.ti,ab.	89
91	Polymerized Hemoglobin.ti,ab.	87
92	Rheodextran.ti,ab.	3
93	Thrombocyte Concentrate.ti,ab.	7
94	Ultroser G.ti,ab.	52
95	(plasma adj2 (fresh or frozen)).ti,ab.	3288
96	Gelofusine.ti,ab.	71
97	Haemaccel.ti,ab.	171
98	RINGER LACTATE SOLUTION/	3024
99	(ringer$ adj2 lactate?).ti,ab.	2553
100	PLASMA PROTEIN/	8760
101	plasma protein fraction.ti,ab.	88
102	PPF.ti,ab.	587
103	or/37-102	604648
104	and/16,36	15381
105	and/103-104	2102
106	CASE REPORT/	1006507
107	(letter or editorial or comment or historical article).pt.	641796
108	(case report or case study).ti.	98894
109	or/106-108	1568754
110	105 not 109	1470
111	limit 110 to (human and english language)	1006

MENG_iv_fluid_resuscitation_medline_240908

Ovid MEDLINE(R) 1950 to September Week 2 2008

#	Searches	Results
1	exp CHILD/	1287015
2	child$.ti,ab.	717279
3	exp INFANT/	798791
4	infan$.ti,ab.	254787
5	(baby or babies).ti,ab.	37817
6	toddler?.ti,ab.	3356
7	(neonat$ or newborn?).ti,ab.	222770
8	ADOLESCENT/	1290912
9	adolescen$.ti,ab.	107907
10	teen$.ti,ab.	14329
11	exp SCHOOLS/	60285
12	school$.ti,ab.	128956
13	exp PUBERTY/	13158
14	pubescen$.ti,ab.	814
15	(pediatric? or paediatric?).ti,ab.	130409
16	or/1-15	2684046
17	SHOCK, SEPTIC/	15164
18	SHOCK/	12057
19	(septic adj shock).ti,ab.	9419
20	shock.ti.	42521
21	SEPSIS/	33612
22	BACTEREMIA/	12333
23	(septic?emi? or bacter?emi?).ti,ab.	29686
24	sepsis.ti,ab.	43188
25	MENINGOCOCCAL INFECTIONS/	4529
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	3461
27	meningococc?emi?.ti,ab.	613
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	5256
29	NEISSERIA MENINGITIDIS/	6106
30	(blood adj3 poisoning?).ti,ab.	179
31	(meningococcus or meningococci).ti,ab.	2082
32	or/17-31	147906
33	exp INFUSIONS, PARENTERAL/	71220
34	((infusion? or rehydrat$ or hydrat$) adj3 (IV or intravenous$ or parenteral$ or intraosseous$ or intra venous$)).ti,ab.	33973
35	(drip? adj3 (infusion? or intravenous$ or intra venous$ or IV)).ti,ab.	2185
36	(rapid$ adj3 infusion?).ti,ab.	1659
37	(bolus or boluses).ti,ab.	36990
38	INJECTIONS, INTRAVENOUS/	70915
39	(injection? adj3 (intra?venous$ or IV)).ti,ab.	37329

40	(fluid? adj3 (drip? or IV or intravenous$ or intra venous$)).ti,ab.	3733
41	FLUID THERAPY/	11043
42	((fluid or volume) adj3 resuscitation?).ti,ab.	2616
43	(colloid? or albumin? or crystalloid? or saline).ti,ab.	195755
44	REHYDRATION SOLUTIONS/	1005
45	ISOTONIC SOLUTIONS/	6220
46	SALINE SOLUTION, HYPERTONIC/	4045
47	HYPOTONIC SOLUTION/	2680
48	((hyper?tonic or hypo?tonic or iso?tonic) adj3 (solution? or fluid?)).ti,ab.	6222
49	COLLOIDS/	9585
50	hydrocolloid?.ti,ab.	972
51	exp ALBUMINS/	110727
52	SERUM ALBUMIN/	35667
53	albumin?.ti,ab.	86735
54	exp BLOOD SUBSTITUTES/	31237
55	((plasma or blood) adj2 (substitute? or expander?)).ti,ab.	3151
56	ELECTROLYTES/	17697
57	electrolyte?.ti,ab.	34788
58	exp SODIUM CHLORIDE/	44787
59	sodium chloride.ti,ab.	9876
60	(pentastarch? or penta starch? or pentaspan? or penta span? or hydroxy?ethyl starch).ti,ab.	1723
61	(hetastarch? or heta starch? or 2-hydroxyethyl ether).ti,ab.	345
62	((hartmann's or hartmanns or potassium) adj3 (solution? or fluid?)).ti,ab.	2466
63	(sodium adj lactate?).ti,ab.	685
64	((glucose or dextrose) adj2 solution?).ti,ab.	3851
65	(dextran? or gelatin?).ti,ab.	35367
66	Gelofusine.ti,ab.	70
67	Haemaccel.ti,ab.	237
68	(ringer$ adj2 lactate?).ti,ab.	2863
69	plasma protein fraction.ti,ab.	145
70	Actovegin.ti,ab.	58
71	(Blood adj Derivative?).ti,ab.	263
72	(Blood adj Extract?).ti,ab.	138
73	Diaspirin.ti,ab.	195
74	Fluosol.ti,ab.	444
75	Perfluorodecalin.ti,ab.	229
76	Perfluorooctyl Bromide.ti,ab.	72
77	Perfluorotributylamine.ti,ab.	105
78	Polygeline.ti,ab.	93
79	Polymerized Hemoglobin.ti,ab.	97
80	Ultroser G.ti,ab.	63

81 (plasma adj2 (fresh or frozen)).ti,ab.	3828
82 PPF.ti,ab.	706
83 or/33-82	615612
84 and/16,32	37104
85 and/83-84	3080
86 CASE REPORTS/	1416820
87 (letter or editorial or comment or historical article).pt.	1178972
88 (case report or case study).ti.	123223
89 or/86-88	2477804
90 85 not 89	2606
91 limit 90 to humans	2411
92 limit 91 to english language	1884

18 What are the indications for commencing inotropes in children and young people with suspected/confirmed meningococcal septicaemia?

MENG_inotropes_septicaemia_cctr_091008

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2008

#	Searches	Results
1	exp CHILD/	38980
2	child$.ti,ab.	32759
3	exp INFANT/	17523
4	infan$.ti,ab.	11965
5	(baby or babies).ti,ab.	1648
6	toddler?.ti,ab.	244
7	(neonat$ or newborn?).ti,ab.	6723
8	ADOLESCENT/	54880
9	adolescen$.ti,ab.	4686
10	teen$.ti,ab.	488
11	exp SCHOOLS/	534
12	school$.ti,ab.	6033
13	exp PUBERTY/	209
14	pubescen$.ti,ab.	10
15	(pediatric? or paediatric?).ti,ab.	6156
16	or/1-15	99424
17	SHOCK, SEPTIC/	256
18	SHOCK/	98
19	(septic adj shock).ti,ab.	377
20	shock.ti,ab.	2075
21	SEPSIS/	895
22	BACTEREMIA/	380
23	(septic?emi? or bacter?emi?).ti,ab.	1259
24	sepsis.ti,ab.	2105
25	MENINGOCOCCAL INFECTIONS/	72
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	60
27	meningococc?emi?.ti,ab.	5
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	135
29	NEISSERIA MENINGITIDIS/	124
30	(blood adj3 poisoning?).ti,ab.	5
31	(meningococcus or meningococci).ti,ab.	51
32	or/17-31	5650
33	exp CARDIOTONIC AGENTS/	4246
34	(inotrope? or inotropic).ti,ab.	1036
35	((cardiotonic or cardio tonic or cardiotropic or cardio tropic) adj3 (agent? or drug? or regime$ or therap$ or medication?)).ti,ab.	27
36	EPINEPHRINE/	2340

37	(Adrenalin$ or D-Adrenaline or D-Epifrin or D-Epinephrine or Epinefrin or Epinefrina or Epinephran or Epinephrine or Epinephrinum or L-Adrenalin or L-Adrenaline or L-Adrenaline Base or L-Epinephine or L-Epinephrine or L-Epirenamine or evoadrenaline or Levoepinephrine or Racepinefrina or Racepinefrine or Racepinefrinum or Racepinephrine).ti,ab.	4266
38	(ADROP or Adnephrine or Adrenal or Adrenalin-Medihaler or Adrenamine or Adrenan or Adrenapax or Adrenasol or Adrenatrate or Adrenine or Adrenodis or Adrenohorma or Adrenor or Adrenosan or Adrenutol or Adrin or Adrine or Aktamin or Ana-Guard or Antiasthmatique or Astminhal or Balmadren or Bernarenin or Biorenine or Bosmin or Brevirenin or Bronkaid or Chelafrin or Citanest Forte or Corisol or Drenamist or Duranest or Dylephrin or Epi EZ Pen Jr or Epifrin or Epiglaufrin or Epipen or Epirenamine or Epirenan or Epirenin or Epitrate or Eppy or Esphygmogenina or Exadrin or Glaucon or Glaucosan or Glauposine or Glycirenan or Haemostasin or Haemostatin or Hektalin or Hemisine or Hemostasin or Hemostatin or Hypernephrin or Hyporenin or IOP or Intranefrin or Iontocaine or Isoptoepinal or Kidoline or Levonor or Levorenen or Levorenin or Levorenine or Lidocaton or Lyophrin or Medihaler-Epi or Metanephrin or Micronefrin or Mucidrina or Myosthenine or Mytrate or Nephridine or Nephron or Nieraline or Nor-Epirenan or Norartrinal or Paranephrin or Primatene Mist or Renagladin or Renaglandin or Renaglandulin or Renaleptine or Renalina or Renoform or Renostypricin or Renostypticin or Renostyptin or Scurenaline or Septocaine or Simplene or Sindrenina or Soladren or Sphygmogenin or Stryptirenal or Styptirenal or Supracapsulin or Supradin or Supranefran or Supranephrane or Supranephrine or Supranol or Suprarenaline or Suprarenin or Suprel or Surenine or Surrenine or Sus-Phrine or Susphrine or Sympathin E or Sympathin I or Takamina or Takamine or Tokamina or Tolansin or Tolax or Tolcil or Tolhart or Tonogen or Twinject or Vaponefrin or Vasoconstrictine or Vasodrine or Vasoton or Vasotonin).ti,ab.	3660
39	exp NOREPINEPHRINE/	2138
40	(Arterenol or L-Norepinephrine or L-noradrenaline or Noradrenaline or nor adrenaline or Nor epinephrine or Norepinephrine or levarterenol or levonorepinephrine or levophed).ti,ab.	6467
41	exp DOPAMINE AGENTS/	8644
42	DOPAMINE/	788
43	(dopamine or dopaminergic).ti,ab.	3174
44	DOBUTAMINE/	376
45	(dobutamine or Deoxyepinephrine or Dopamin or Dopamine HCl or Dophamine or Hydroxytyramin or Hydroxytyramine or Oxytyramine or dobucor or dobuject or dobutrex or Lilly 81929 or oxiken or posiject).ti,ab.	572
46	VASOPRESSINS/	302
47	VASOTOCIN/	26
48	(3-Isoleucyl vasopressin or Arginine oxytocin or Arginine vasotocin or Argiprestocin Pitressin tannate or Vasopressin? or Vasotocin? or pitressin or pressyn or beta-Hypophamine).ti,ab.	965
49	or/33-48	25315
50	and/16,32	1670
51	and/49-50	37

MENG_inotropes_septicaemia_cdsrdare_091008

DARE, CDSR

#	Searches	Results
1	CHILD$.kw.	1233
2	child$.ti,ab.	1445
3	INFANT?.kw.	820
4	infan$.ti,ab.	540
5	(baby or babies).ti,ab.	134
6	toddler?.ti,ab.	5
7	(neonat$ or newborn?).ti,ab.	507
8	ADOLESCEN$.kw.	755
9	adolescen$.ti,ab.	219
10	teen$.ti,ab.	10
11	SCHOOL?.kw.	55
12	school$.ti,ab.	119
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	218
16	or/1-15	2785
17	SHOCK, SEPTIC.kw.	16
18	SHOCK.kw.	31
19	(septic adj shock).ti,ab.	8
20	shock.ti,ab.	38
21	SEPSIS.kw.	57
22	BACTEREMIA.kw.	30
23	(septic?emi? or bacter?emi?).ti,ab.	24
24	sepsis.ti,ab.	88
25	MENINGOCOCCAL INFECTION?.kw.	5
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	6
27	meningococc?emi?.ti,ab.	0
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	0
29	NEISSERIA MENINGITIDIS.kw.	4
30	(blood adj3 poisoning?).ti,ab.	0
31	(meningococcus or meningococci).ti,ab.	0
32	or/17-31	194
33	CARDIOTONIC AGENT?.kw.	13
34	(inotrope? or inotropic).ti,ab.	14
35	((cardiotonic or cardio tonic or cardiotropic or cardio tropic) adj3 (agent? or drug? or regime$ or therap$ or medication?)).ti,ab.	0
36	EPINEPHRINE.kw.	18
37	(Adrenalin$ or D-Adrenaline or D-Epifrin or D-Epinephrine or Epinefrin or Epinefrina or Epinephran or Epinephrine or Epinephrinum or L-Adrenalin or L-Adrenaline or L-Adrenaline Base or L-Epinephine or L-Epinephrine or L-	22

	Epirenamine or evoadrenaline or Levoepinephrine or Racepinefrina or Racepinefrine or Racepinefrinum or Racepinephrine).ti,ab.	
38	(ADROP or Adnephrine or Adrenal or Adrenalin-Medihaler or Adrenamine or Adrenan or Adrenapax or Adrenasol or Adrenatrate or Adrenine or Adrenodis or Adrenohorma or Adrenor or Adrenosan or Adrenutol or Adrin or Adrine or Aktamin or Ana-Guard or Antiasthmatique or Astminhal or Balmadren or Bernarenin or Biorenine or Bosmin or Brevirenin or Bronkaid or Chelafrin or Citanest Forte or Corisol or Drenamist or Duranest or Dylephrin or Epi EZ Pen Jr or Epifrin or Epiglaufrin or Epipen or Epirenamine or Epirenan or Epirenin or Epitrate or Eppy or Esphygmogenina or Exadrin or Glaucon or Glaucosan or Glauposine or Glycirenan or Haemostasin or Haemostatin or Hektalin or Hemisine or Hemostasin or Hemostatin or Hypernephrin or Hyporenin or IOP or Intranefrin or Iontocaine or Isoptoepinal or Kidoline or Levonor or Levorenen or Levorenin or Levorenine or Lidocaton or Lyophrin or Medihaler-Epi or Metanephrin or Micronefrin or Mucidrina or Myosthenine or Mytrate or Nephridine or Nephron or Nieraline or Nor-Epirenan or Norartrinal or Paranephrin or Primatene Mist or Renagladin or Renaglandin or Renaglandulin or Renaleptine or Renalina or Renoform or Renostypricin or Renostypticin or Renostyptin or Scurenaline or Septocaine or Simplene or Sindrenina or Soladren or Sphygmogenin or Stryptirenal or Styptirenal or Supracapsulin or Supradin or Supranefran or Supranephrane or Supranephrine or Supranol or Suprarenaline or Suprarenin or Suprel or Surenine or Surrenine or Sus-Phrine or Susphrine or Sympathin E or Sympathin I or Takamina or Takamine or Tokamina or Tolansin or Tolax or Tolcil or Tolhart or Tonogen or Twinject or Vaponefrin or Vasoconstrictine or Vasodrine or Vasoton or Vasotonin).ti,ab.	22
39	NOREPINEPHRINE.kw.	5
40	(Arterenol or L-Norepinephrine or L-noradrenaline or Noradrenaline or nor adrenaline or Nor epinephrine or Norepinephrine or levarterenol or levonorepinephrine or levophed).ti,ab.	29
41	DOPAMINE AGENT?.kw.	11
42	DOPAMINE.kw.	55
43	(dopamine or dopaminergic).ti,ab.	51
44	DOBUTAMINE.kw.	5
45	(dobutamine or Deoxyepinephrine or Dopamin or Dopamine HCl or Dophamine or Hydroxytyramin or Hydroxytyramine or Oxytyramine or dobucor or dobuject or dobutrex or Lilly 81929 or oxiken or posiject).ti,ab.	4
46	VASOPRESSIN?.kw.	21
47	VASOTOCIN.kw.	2
48	(3-Isoleucyl vasopressin or Arginine oxytocin or Arginine vasotocin or Argiprestocin Pitressin tannate or Vasopressin? or Vasotocin? or pitressin or pressyn or beta-Hypophamine).ti,ab.	13
49	or/33-48	174
50	and/16,32	85
51	and/49-50	3

MENG_inotropes_septicaemia_cinahl_101008_2

EBSCO-Host July 30, 2009

#	Query	Limiters/Expanders	Results
S45	S16 and S37 and S44	Search modes - Boolean/Phrase	0
S44	S38 or S39 or S40 or S41 or S42 or S43	Search modes - Boolean/Phrase	62
S43	TI (vasopressin*) or AB (vasopressin*)	Search modes - Boolean/Phrase	408
S42	MH VASOPRESSINS	Search modes - Boolean/Phrase	582
S41	TI (dopamine or dopaminergic) or AB (dopamine or dopaminergic)	Search modes - Boolean/Phrase	1555
S40	MH DOPAMINE AGENTS+	Search modes - Boolean/Phrase	5880
S39	TI (inotrope* or inotropic) or AB (inotrope* or inotropic)	Search modes - Boolean/Phrase	597
S38	MH CARDIOTONIC AGENTS+	Search modes - Boolean/Phrase	4731
S37	S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36	Search modes - Boolean/Phrase	282
S36	AB (meningococcus or meningococci)	Search modes - Boolean/Phrase	30
S35	TI (meningococcus or meningococci)	Search modes - Boolean/Phrase	8
S34	TI (blood N3 poisoning*) or AB (blood N3 poisoning*)	Search modes - Boolean/Phrase	13
S33	AB (neisseria meningitid*) or AB (n meningitid*)	Search modes - Boolean/Phrase	102
S32	TI (neisseria meningitid*) or TI (n meningitid*)	Search modes - Boolean/Phrase	48
S31	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S30	AB (meningococcal N3 septic) or AB (meningococcal N3 toxic) or AB (meningococcal N3 endotoxic) or AB (meningococcal N3 disease) or AB (meningococcal N3 infection*)	Search modes - Boolean/Phrase	147
S29	TI (meningococcal N3 septic) or TI (meningococcal N3 toxic) or TI (meningococcal N3 endotoxic) or TI (meningococcal N3 disease) or TI (meningococcal N3 infection*)	Search modes - Boolean/Phrase	234
S28	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S27	TI SHOCK	Search modes - Boolean/Phrase	2460
S26	MH SHOCK	Search modes - Boolean/Phrase	903
S25	AB (meningococc* N3 sepsis) or AB (meningococc* N3 septic)	Search modes - Boolean/Phrase	18
S24	TI (meningococc* N3 sepsis) or TI (meningococc* N3	Search modes -	25

	septic)	Boolean/Phrase	
S23	AB (septicemia or septicaemia or bacteremia or bacteraemia)	Search modes - Boolean/Phrase	1313
S22	TI (septicemia or septicaemia or bacteremia or bacteraemia)	Search modes - Boolean/Phrase	733
S21	TI (severe N2 sepsis) or AB (severe N2 sepsis)	Search modes - Boolean/Phrase	606
S20	MH NEONATAL SEPSIS	Search modes - Boolean/Phrase	284
S19	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S18	TI (sepsis N5 hypotension) or AB (sepsis N5 hypotension)	Search modes - Boolean/Phrase	29
S17	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046
S16	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15	Search modes - Boolean/Phrase	1770
S15	TI (paediatric* or pediatric*) or AB (paediatric* or pediatric*)	Search modes - Boolean/Phrase	29743
S14	AB (newborn*) or AB (neonate*)	Search modes - Boolean/Phrase	7636
S13	TI (newborn*) or TI (neonate*)	Search modes - Boolean/Phrase	5897
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55
S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004
S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes - Boolean/Phrase	10049
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes - Boolean/Phrase	82965
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_inotropes_septicaemia_embase_101008

EMBASE 1980 to 2008 Week 40

#	Searches	Results
1	exp CHILD/	619184
2	child$.tw.	481015
3	exp INFANT/	170905
4	infan$.tw.	169037
5	(baby or babies).tw.	27176
6	exp ADOLESCENT/	429426
7	teenag$.tw.	7893
8	adolescen$.tw.	82097
9	exp SCHOOLS/	36816
10	school$.tw.	73858
11	exp PUBERTY/	14156
12	pubescen$.tw.	642
13	NEWBORN/	177050
14	(newborn? or neonate?).ti,ab.	96311
15	(pediatric? or paediatric?).ti,ab.	108949
16	or/1-15	1259460
17	SEPTIC SHOCK/	12819
18	SEPTICEMIA/	8742
19	((septic or bacter?emic) adj shock).ti,ab.	8532
20	(sepsis adj5 hypotension).ti,ab.	256
21	BACTEREMIA/	14171
22	(severe adj2 sepsis).ti,ab.	2872
23	(septic?emia or bacter?emia).ti,ab.	21419
24	(meningococc$ adj3 (sepsis or septic)).ti,ab.	344
25	NEISSERIA MENINGITIDIS/	6788
26	(Neisseria meningitid$ or n meningitid$).ti,ab.	4314
27	MENINGOCOCCAL INFECTION/	2788
28	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	2356
29	meningococc?emi?.ti,ab.	423
30	(meningococcus or meningococci).ti,ab.	1459
31	MENINGOCOCCOSIS/	2788
32	MENINGOCOCCEMIA/	832
33	(blood adj2 poisoning).ti,ab.	61
34	SHOCK/	11352
35	shock.ti,ab.	72956
36	or/17-35	120022
37	INOTROPISM/	8844
38	exp CARDIOTONIC AGENT/	95524
39	(inotrope? or inotropic).ti,ab.	15142
40	(cardiotonic or cardio tonic or cardiotropic or cardio tropic).ti,ab.	1507

41	ADRENALIN/	48421
42	(Adrenalin$ or D-Adrenaline or D-Epifrin or D-Epinephrine or Epinefrin or Epinefrina or Epinephran or Epinephrine or Epinephrinum or L-Adrenalin or L-Adrenaline or L-Adrenaline Base or L-Epinephine or L-Epinephrine or L-Epirenamine or evoadrenaline or Levoepinephrine or Racepinefrina or Racepinefrine or Racepinefrinum or Racepinephrine).ti,ab.	30407
43	(ADROP or Adnephrine or Adrenal or Adrenalin-Medihaler or Adrenamine or Adrenan or Adrenapax or Adrenasol or Adrenatrate or Adrenine or Adrenodis or Adrenohorma or Adrenor or Adrenosan or Adrenutol or Adrin or Adrine or Aktamin or Ana-Guard or Antiasthmatique or Astminhal or Balmadren or Bernarenin or Biorenine or Bosmin or Brevirenin or Bronkaid or Chelafrin or Citanest Forte or Corisol or Drenamist or Duranest or Dylephrin or Epi EZ Pen Jr or Epifrin or Epiglaufrin or Epipen or Epirenamine or Epirenan or Epirenin or Epitrate or Eppy or Esphygmogenina or Exadrin or Glaucon or Glaucosan or Glauposine or Glycirenan or Haemostasin or Haemostatin or Hektalin or Hemisine or Hemostasin or Hemostatin or Hypernephrin or Hyporenin or IOP or Intranefrin or Iontocaine or Isoptoepinal or Kidoline or Levonor or Levorenen or Levorenin or Levorenine or Lidocaton or Lyophrin or Medihaler-Epi or Metanephrin or Micronefrin or Mucidrina or Myosthenine or Mytrate or Nephridine or Nephron or Nieraline or Nor-Epirenan or Norartrinal or Paranephrin or Primatene Mist or Renagladin or Renaglandin or Renaglandulin or Renaleptine or Renalina or Renoform or Renostypricin or Renostypticin or Renostyptin or Scurenaline or Septocaine or Simplene or Sindrenina or Soladren or Sphygmogenin or Stryptirenal or Styptirenal or Supracapsulin or Supradin or Supranefran or Supranephrane or Supranephrine or Supranol or Suprarenaline or Suprarenin or Suprel or Surenine or Surrenine or Sus-Phrine or Susphrine or Sympathin E or Sympathin I or Takamina or Takamine or Tokamina or Tolansin or Tolax or Tolcil or Tolhart or Tonogen or Twinject or Vaponefrin or Vasoconstrictine or Vasodrine or Vasoton or Vasotonin).ti,ab.	70533
44	NORADRENALIN/	64845
45	(Arterenol or L-Norepinephrine or L-noradrenaline or Noradrenaline or nor adrenaline or Nor epinephrine or Norepinephrine or levarterenol or levonorepinephrine or levophed).ti,ab.	59290
46	exp DOPAMINE RECEPTOR AFFECTING AGENT/	130568
47	(dopamine or dopaminergic).ti,ab.	85104
48	(dobutamine or Deoxyepinephrine or Dopamin or Dopamine HCl or Dophamine or Hydroxytyramin or Hydroxytyramine or Oxytyramine or dobucor or dobuject or dobutrex or Lilly 81929 or oxiken or posiject).ti,ab.	6245
49	VASOPRESSIN.hw.	24146
50	VASOTOCIN DERIVATIVE/	84
51	(3-Isoleucyl vasopressin or Arginine oxytocin or Arginine vasotocin or Argiprestocin Pitressin tannate or Vasopressin? or Vasotocin? or pitressin or pressyn or beta-Hypophamine).ti,ab.	22974
52	or/37-51	432468
53	and/16,36	18375
54	and/52-53	1140
55	CASE REPORT/	1008769
56	(letter or editorial or comment or historical article).pt.	643953

57 (case report or case study).ti.	99217
58 or/55-57	1572958
59 54 not 58	747
60 limit 59 to english language	623

MENG_inotropes_septicaemia_medline_101008

Ovid MEDLINE(R) 1950 to October Week 1 2008

#	Searches	Results
1	exp CHILD/	1292827
2	child$.ti,ab.	720904
3	exp INFANT/	801875
4	infan$.ti,ab.	255963
5	(baby or babies).ti,ab.	38012
6	toddler?.ti,ab.	3382
7	(neonat$ or newborn?).ti,ab.	223784
8	ADOLESCENT/	1297501
9	adolescen$.ti,ab.	108588
10	teen$.ti,ab.	14421
11	exp SCHOOLS/	60510
12	school$.ti,ab.	129712
13	exp PUBERTY/	13203
14	pubescen$.ti,ab.	821
15	(pediatric? or paediatric?).ti,ab.	131161
16	or/1-15	2696524
17	SHOCK, SEPTIC/	15214
18	SHOCK/	12074
19	(septic adj shock).ti,ab.	9479
20	shock.ti,ab.	95994
21	SEPSIS/	33748
22	BACTEREMIA/	12404
23	(septic?emi? or bacter?emi?).ti,ab.	29786
24	sepsis.ti,ab.	43425
25	MENINGOCOCCAL INFECTIONS/	4537
26	(meningococcal adj3 (septic or toxic or endotoxic or disease or infection?)).ti,ab.	3474
27	meningococc?emi?.ti,ab.	614
28	(Neisseria meningitid$ or n meningitid$).ti,ab.	5277
29	NEISSERIA MENINGITIDIS/	6120
30	(blood adj3 poisoning?).ti,ab.	179
31	(meningococcus or meningococci).ti,ab.	2089
32	or/17-31	192012
33	exp CARDIOTONIC AGENTS/	158724
34	(inotrope? or inotropic).ti,ab.	16823
35	(cardiotonic or cardio tonic or cardiotropic or cardio tropic).ti,ab.	1833
36	EPINEPHRINE/	47206
37	(Adrenalin$ or D-Adrenaline or D-Epifrin or D-Epinephrine or Epinefrin or Epinefrina or Epinephran or Epinephrine or Epinephrinum or L-Adrenalin or L-Adrenaline or L-Adrenaline Base or L-Epinephine or L-Epinephrine or L-Epirenamine or evoadrenaline or Levoepinephrine or Racepinefrina or	41189

	Racepinefrine or Racepinefrinum or Racepinephrine).ti,ab.	
38	(ADROP or Adnephrine or Adrenal or Adrenalin-Medihaler or Adrenamine or Adrenan or Adrenapax or Adrenasol or Adrenatrate or Adrenine or Adrenodis or Adrenohorma or Adrenor or Adrenosan or Adrenutol or Adrin or Adrine or Aktamin or Ana-Guard or Antiasthmatique or Astminhal or Balmadren or Bernarenin or Biorenine or Bosmin or Brevirenin or Bronkaid or Chelafrin or Citanest Forte or Corisol or Drenamist or Duranest or Dylephrin or Epi EZ Pen Jr or Epifrin or Epiglaufrin or Epipen or Epirenamine or Epirenan or Epirenin or Epitrate or Eppy or Esphygmogenina or Exadrin or Glaucon or Glaucosan or Glauposine or Glycirenan or Haemostasin or Haemostatin or Hektalin or Hemisine or Hemostasin or Hemostatin or Hypernephrin or Hyporenin or IOP or Intranefrin or Iontocaine or Isoptoepinal or Kidoline or Levonor or Levorenen or Levorenin or Levorenine or Lidocaton or Lyophrin or Medihaler-Epi or Metanephrin or Micronefrin or Mucidrina or Myosthenine or Mytrate or Nephridine or Nephron or Nieraline or Nor-Epirenan or Norartrinal or Paranephrin or Primatene Mist or Renagladin or Renaglandin or Renaglandulin or Renaleptine or Renalina or Renoform or Renostypricin or Renostypticin or Renostyptin or Scurenaline or Septocaine or Simplene or Sindrenina or Soladren or Sphygmogenin or Stryptirenal or Styptirenal or Supracapsulin or Supradin or Supranefran or Supranephrane or Supranephrine or Supranol or Suprarenaline or Suprarenin or Suprel or Surenine or Surrenine or Sus-Phrine or Susphrine or Sympathin E or Sympathin I or Takamina or Takamine or Tokamina or Tolansin or Tolax or Tolcil or Tolhart or Tonogen or Twinject or Vaponefrin or Vasoconstrictine or Vasodrine or Vasoton or Vasotonin).ti,ab.	95093
39	exp NOREPINEPHRINE/	78126
40	(Arterenol or L-Norepinephrine or L-noradrenaline or Noradrenaline or nor adrenaline or Nor epinephrine or Norepinephrine or levarterenol or levonorepinephrine or levophed).ti,ab.	73113
41	exp DOPAMINE AGENTS/	175283
42	DOPAMINE/	54022
43	(dopamine or dopaminergic).ti,ab.	93769
44	DOBUTAMINE/	4984
45	(dobutamine or Deoxyepinephrine or Dopamin or Dopamine HCl or Dophamine or Hydroxytyramin or Hydroxytyramine or Oxytyramine or dobucor or dobuject or dobutrex or Lilly 81929 or oxiken or posiject).ti,ab.	6365
46	VASOPRESSINS/	19413
47	VASOTOCIN/	1645
48	(3-Isoleucyl vasopressin or Arginine oxytocin or Arginine vasotocin or Argiprestocin Pitressin tannate or Vasopressin? or Vasotocin? or pitressin or pressyn or beta-Hypophamine).ti,ab.	27605
49	or/33-48	532771
50	and/16,32	42010
51	and/49-50	1015
52	CASE REPORTS/	1422404
53	(letter or editorial or comment or historical article).pt.	1184097
54	(case report or case study).ti.	123863
55	or/52-54	2488007

56 51 not 55	770
57 limit 56 to humans	680
58 limit 57 to english language	510

19 What type of intravenous fluid should be used to resuscitate children and young people with suspected meningococcal septicaemia?

MENG_fluids_sep_cctr_290408

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	exp CHILD/	37886
2	child$.tw.	31903
3	exp INFANT/	17078
4	infan$.tw.	11744
5	(baby or babies).tw.	1607
6	exp ADOLESCENT/	0
7	teenag$.tw.	303
8	adolescen$.tw.	4467
9	exp SCHOOLS/	471
10	school$.tw.	5857
11	exp PUBERTY/	202
12	pubescen$.tw.	10
13	or/1-12	58521
14	MENINGITIS/	99
15	exp MENINGITIS, BACTERIAL/	224
16	meningitis.tw.	480
17	meningoencephalitis.tw.	20
18	exp MENINGOCOCCAL INFECTIONS/	152
19	meningococc$.tw.	270
20	septic?emia.tw.	451
21	SEPSIS/	881
22	SHOCK, SEPTIC/ or SHOCK/ or HYPOTENSION/ or HYPOVOLEMIA/	1177
23	(shock or hypotension or hypovol?emia or low blood pressure).tw.	5470
24	or/14-23	7584
25	RESUSCITATION/	235
26	INFUSIONS, INTRAVENOUS/	6844
27	SALINE SOLUTION, HYPERTONIC/	246
28	REHYDRATION SOLUTIONS/	187
29	FLUID THERAPY/	758
30	exp ALBUMINS/	2463
31	POLYGELINE/	46
32	ISOTONIC SOLUTIONS/	445
33	COLLOIDS/ or SUSPENSIONS/	520
34	BLOOD VOLUME/ or PLASMA VOLUME/	784
35	PLASMA SUBSTITUTES/	365
36	(fluid$ adj3 (resuscitation or therap$ or intravenous$ or parenteral)).tw.	723

37 (saline adj3 (parenteral$ or intravenous$)).tw.	788
38 (albumin adj3 (parenteral$ or intravenous$)).tw.	98
39 (polygeline or gelofusine or haemaccel or thomaegelin).tw.	93
40 ringer's lactate.tw.	122
41 ((isotonic or hypertonic) adj3 solution).tw.	329
42 colloid$.tw.	875
43 crystalloid$.tw.	501
44 ((blood or plasma or intravascular) adj volume).tw.	1182
45 plasma substitute$.tw.	79
46 or/25-45	14571
47 13 and 24 and 46	136

MENG_fluids_sep_cdsrdare_290408

Cochrane Database of Systematic Reviews 1st Quarter 2008
Database of Abstracts of Reviews of Effects 1st Quarter 2008
CDSR, DARE

#	Searches	Results
1	child$.ti,ab,kw.	1751
2	infan$.ti,ab,kw.	878
3	(baby or babies).ti,ab,kw.	135
4	teenag$.ti,ab,kw.	7
5	adolescen$.ti,ab,kw.	699
6	(school$ or preschool$ or pre-school$).ti,ab,kw.	466
7	(nurser$ or kindergarten$).ti,ab,kw.	11
8	(puberty or pubscen$).ti,ab,kw.	1
9	or/1-8	2488
10	meningitis.ti,ab,kw.	29
11	meningoencephalitis.ti,ab,kw.	1
12	meningococc$.ti,ab,kw.	8
13	septic?emia.ti,ab,kw.	11
14	sepsis.ti,ab,kw.	107
15	(shock or hypotension or hypovol?emia or low blood pressure).ti,ab,kw.	101
16	or/10-15	227
17	resuscitation.ti,ab,kw.	53
18	(intravenous adj infusion$).ti,ab,kw.	15
19	saline solution.ti,ab,kw.	9
20	rehydration solution$.ti,ab,kw.	13
21	(fluid$ adj3 (therap$ or intravenous$ or parenteral)).ti,ab,kw.	55
22	(saline adj3 (parenteral$ or intravenous$)).ti,ab,kw.	2
23	(albumin adj3 (parenteral$ or intravenous$)).ti,ab,kw.	3
24	(polygeline or gelofusine or haemaccel or thomaegelin).ti,ab,kw.	0
25	ringer's lactate.ti,ab,kw.	0
26	((isotonic or hypertonic) adj3 solution).ti,ab,kw.	7
27	colloid$.ti,ab,kw.	30
28	crystalloid$.ti,ab,kw.	20
29	((blood or plasma or intravascular) adj volume).ti,ab,kw.	18
30	plasma substitute$.ti,ab,kw.	15
31	or/17-30	153
32	9 and 16 and 31	11

MENG_fluids_sep_RCTs_SRs_cinahl_290408_5

EBSCO Host Friday, July 31, 2009 10:13:27 AM

#	Query	Limiters/Expanders	Results
S57	S13 and S29 and S56	Search modes - Boolean/Phrase	0
S56	S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55	Search modes - Boolean/Phrase	255
S55	TI (plasma substitute) or AB (plasma substitute)	Search modes - Boolean/Phrase	1
S54	AB (blood volume) or AB (plasma volume) or AB (intravascular volume)	Search modes - Boolean/Phrase	787
S53	TI (blood volume) or TI (plasma volume) or TI (intravascular volume)	Search modes - Boolean/Phrase	140
S52	TI (crystalloid) or AB (crystalloid)	Search modes - Boolean/Phrase	208
S51	TI (colloid) or AB (colloid)	Search modes - Boolean/Phrase	214
S50	AB (isotonic N3 solution) or AB (hypertonic N3 solution)	Search modes - Boolean/Phrase	95
S49	TI (isotonic N3 solution) or TI (hypertonic N3 solution)	Search modes - Boolean/Phrase	32
S48	TI (ringer's lactate) or AB (ringer's lactate)	Search modes - Boolean/Phrase	43
S47	AB (polygeline or gelofusine or haemaccel or thomaegelin)	Search modes - Boolean/Phrase	15
S46	TI (polygeline or gelofusine or haemaccel or thomaegelin)	Search modes - Boolean/Phrase	8
S45	TI (albumin) or AB (albumin*)	Search modes - Boolean/Phrase	2772
S44	TI (saline*) or AB (saline*)	Search modes - Boolean/Phrase	3304
S43	TI (fluid*) or AB (fluid*)	Search modes - Boolean/Phrase	10251
S42	MH PLASMA SUBSTITUTES	Search modes - Boolean/Phrase	141
S41	MH PLASMA VOLUME	Search modes - Boolean/Phrase	221
S40	MH BLOOD VOLUME	Search modes - Boolean/Phrase	414
S39	MH SUSPENSIONS	Search modes - Boolean/Phrase	123
S38	MH COLLOIDS	Search modes - Boolean/Phrase	199
S37	MH ISOTONIC SOLUTIONS	Search modes - Boolean/Phrase	193
S36	MH POLYGELINE	Search modes - Boolean/Phrase	0

S35	MH ALBUMINS+	Search modes - Boolean/Phrase	4679
S34	MH FLUID THERAPY	Search modes - Boolean/Phrase	1576
S33	MH REHYDRATION SOLUTIONS	Search modes - Boolean/Phrase	126
S32	MH SALINE SOLUTION, HYPERTONIC	Search modes - Boolean/Phrase	231
S31	MH INFUSIONS, INTRAVENOUS	Search modes - Boolean/Phrase	2732
S30	MH RESUSCITATION	Search modes - Boolean/Phrase	2628
S29	S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28	Search modes - Boolean/Phrase	232
S28	AB (shock or hypotnensioni or hypovolemia or hypovolaemia or low blood pressure)	Search modes - Boolean/Phrase	3924
S27	TI (shock or hypotnensioni or hypovolemia or hypovolaemia or low blood pressure)	Search modes - Boolean/Phrase	2534
S26	MH HYPOVOLEMIA	Search modes - Boolean/Phrase	0
S25	MH HYPOTENSION	Search modes - Boolean/Phrase	1208
S24	MH SHOCK	Search modes - Boolean/Phrase	903
S23	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046
S22	MH SHOCK, SEPSIS	Search modes - Boolean/Phrase	0
S21	MH SEPSIS	Search modes - Boolean/Phrase	3327
S20	TI (septicaemia or septicemia) or AB (septicaemia or septicemia)	Search modes - Boolean/Phrase	477
S19	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S18	MH MENINGOCOCCAL INFECTIONS+	Search modes - Boolean/Phrase	793
S17	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110
S16	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S15	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S14	MH MENINGITIS	Search modes - Boolean/Phrase	927
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12	Search modes - Boolean/Phrase	1733
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55
S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004

S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes - Boolean/Phrase	10049
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes - Boolean/Phrase	82965
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_fluids_sep_RCTs_SRs_embase_290408

EMBASE 1980 to 2008 Week 17

#	Searches	Results
1	exp CHILD/	604854
2	child$.tw.	467323
3	exp INFANT/	167174
4	infan$.tw.	165265
5	(baby or babies).tw.	26427
6	exp ADOLESCENT/	417543
7	teenag$.tw.	7679
8	adolescen$.tw.	78995
9	exp SCHOOLS/	35497
10	school$.tw.	71252
11	exp PUBERTY/	13727
12	pubescen$.tw.	622
13	or/1-12	1099133
14	MENINGITIS/	13078
15	exp MENINGITIS, BACTERIAL/	7349
16	meningitis.tw.	21091
17	meningoencephalitis.tw.	2419
18	exp MENINGOCOCCAL INFECTIONS/	2694
19	meningococc$.tw.	5757
20	septic?emia.tw.	9223
21	SEPSIS/	38875
22	SHOCK, SEPTIC/ or SHOCK/ or HYPOTENSION/ or HYPOVOLEMIA/	65503
23	(shock or hypotension or hypovol?emia or low blood pressure).tw.	99015
24	or/14-23	204766
25	RESUSCITATION/	22826
26	INFUSIONS, INTRAVENOUS/	269627
27	SALINE SOLUTION, HYPERTONIC/	53333
28	REHYDRATION SOLUTIONS/	1399
29	FLUID THERAPY/	5937
30	exp ALBUMINS/	65840
31	POLYGELINE/	625
32	ISOTONIC SOLUTIONS/	936
33	COLLOIDS/ or SUSPENSIONS/	11072
34	BLOOD VOLUME/ or PLASMA VOLUME/	10673
35	PLASMA SUBSTITUTES/	1385
36	(fluid$ adj3 (resuscitation or therap$ or intravenous$ or parenteral)).tw.	5856
37	(saline adj3 (parenteral$ or intravenous$)).tw.	1920
38	(albumin adj3 (parenteral$ or intravenous$)).tw.	437
39	(polygeline or gelofusine or haemaccel or thomaegelin).tw.	541
40	ringer's lactate.tw.	778

41	((isotonic or hypertonic) adj3 solution).tw.	2290
42	colloid$.tw.	19006
43	crystalloid$.tw.	3105
44	((blood or plasma or intravascular) adj volume).tw.	14431
45	plasma substitute$.tw.	275
46	or/25-45	453463
47	CLINICAL TRIALS/	499549
48	(clinic$ adj5 trial$).ti,ab,sh.	117546
49	SINGLE BLIND PROCEDURE/	7500
50	DOUBLE BLIND PROCEDURE/	69004
51	RANDOM ALLOCATION/	25374
52	CROSSOVER PROCEDURE/	20190
53	PLACEBO/	112427
54	placebo$.ti,ab,sh.	162422
55	random$.ti,ab,sh.	405486
56	RANDOMIZED CONTROLLED TRIALS/	156880
57	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	89923
58	randomi?ed control$ trial$.tw.	29335
59	or/47-58	820359
60	META ANALYSIS/	33237
61	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	41642
62	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	24072
63	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1527
64	or/60-63	56842
65	review.pt.	868820
66	(medline or medlars or embase).ab.	20776
67	(scisearch or science citation index).ab.	604
68	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	6730
69	((hand or manual$) adj2 search$).tw.	2389
70	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	3841
71	(pooling or pooled or mantel haenszel).tw.	23229
72	(peto or dersimonian or "der simonian" or fixed effect).tw.	734
73	or/66-72	48125
74	65 and 73	16281
75	or/64,74	66141
76	case study.tw,sh.	21506
77	abstract report.tw,sh.	71203
78	note.tw,sh.	247558
79	short survey.tw,sh.	405246
80	letter.tw,sh.	400752
81	case report.tw,sh.	993058

82 editorial.tw,sh.	250567
83 or/76-82	2266023
84 59 not 83	728784
85 75 not 84	28575
86 or/84-85	757359
87 13 and 24 and 46 and 86	720
88 limit 87 to english language	650

MENG_fluids_sep_RCTs_SRs_medline_290408

Ovid MEDLINE(R) 1950 to April Week 3 2008

#	Searches	Results
1	exp CHILD/	1250165
2	child$.tw.	692089
3	exp INFANT/	776002
4	infan$.tw.	246735
5	(baby or babies).tw.	36533
6	exp ADOLESCENT/	1252358
7	teenag$.tw.	10181
8	adolescen$.tw.	103440
9	exp SCHOOLS/	58481
10	school$.tw.	124413
11	exp PUBERTY/	12802
12	pubescen$.tw.	784
13	or/1-12	2515661
14	MENINGITIS/	14717
15	exp MENINGITIS, BACTERIAL/	16660
16	meningitis.tw.	30685
17	meningoencephalitis.tw.	4031
18	exp MENINGOCOCCAL INFECTIONS/	8072
19	meningococc$.tw.	8106
20	septic?emia.tw.	12874
21	SEPSIS/	32548
22	SHOCK, SEPTIC/ or SHOCK/ or HYPOTENSION/ or HYPOVOLEMIA/	40581
23	(shock or hypotension or hypovol?emia or low blood pressure).tw.	125270
24	or/14-23	221591
25	RESUSCITATION/	18741
26	INFUSIONS, INTRAVENOUS/	38711
27	SALINE SOLUTION, HYPERTONIC/	3954
28	REHYDRATION SOLUTIONS/	970
29	FLUID THERAPY/	10736
30	exp ALBUMINS/	107833
31	POLYGELINE/	250
32	ISOTONIC SOLUTIONS/	6097
33	COLLOIDS/ or SUSPENSIONS/	12985
34	BLOOD VOLUME/ or PLASMA VOLUME/	22167
35	PLASMA SUBSTITUTES/	5484
36	(fluid$ adj3 (resuscitation or therap$ or intravenous$ or parenteral)).tw.	7252
37	(saline adj3 (parenteral$ or intravenous$)).tw.	2142
38	(albumin adj3 (parenteral$ or intravenous$)).tw.	492
39	(polygeline or gelofusine or haemaccel or thomaegelin).tw.	351

40	ringer's lactate.tw.	906
41	((isotonic or hypertonic) adj3 solution).tw.	3179
42	colloid$.tw.	20421
43	crystalloid$.tw.	3732
44	((blood or plasma or intravascular) adj volume).tw.	19601
45	plasma substitute$.tw.	715
46	or/25-45	250809
47	randomized controlled trial.pt.	255026
48	controlled clinical trial.pt.	78090
49	DOUBLE BLIND METHOD/	97243
50	SINGLE BLIND METHOD/	12002
51	RANDOM ALLOCATION/	60960
52	RANDOMIZED CONTROLLED TRIALS/	54047
53	or/47-52	430400
54	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	94753
55	clinical trial.pt.	449706
56	exp CLINICAL TRIAL/	543153
57	exp CLINICAL TRIALS AS TOPIC/	203842
58	(clinic$ adj5 trial$).tw,sh.	125995
59	PLACEBOS/	27246
60	placebo$.tw,sh.	122572
61	random$.tw,sh.	537946
62	or/54-61	946399
63	or/53,62	950904
64	META ANALYSIS/	18157
65	META ANALYSIS AS TOPIC/	8224
66	meta analysis.pt.	18157
67	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	32211
68	(systematic$ adj5 (review$ or overview$)).tw,sh.	16615
69	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1860
70	or/64-69	44768
71	review$.pt.	1374476
72	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	29219
73	((hand or manual$) adj2 search$).tw.	3274
74	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	4941
75	(pooling or pooled or mantel haenszel).tw,sh.	28547
76	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1287
77	or/72-76	59634
78	71 and 77	24871
79	or/70,78	59593
80	letter.pt.	623735

81 case report.tw.	133847
82 comment.pt.	355186
83 editorial.pt.	219277
84 historical article.pt.	250156
85 or/80-84	1265684
86 63 not 85	915808
87 79 not 85	56217
88 or/86-87	944432
89 13 and 24 and 46 and 88	424
90 limit 89 to (english language and humans)	374

20 Should fluid volume be restricted in children and young people with suspected/confirmed bacterial meningitis?

MENG_fluids_men_cctr_180408

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	MENINGITIS/	99
2	exp MENINGITIS, BACTERIAL/	224
3	meningitis.tw.	480
4	meningoencephalitis.tw.	20
5	or/1-4	570
6	RESUSCITATION/	235
7	FLUID THERAPY/	758
8	INFUSIONS, INTRAVENOUS/	6844
9	REHYDRATION SOLUTIONS/	187
10	BLOOD VOLUME/ or PLASMA VOLUME/	784
11	PLASMA SUBSTITUTES/	365
12	exp ALBUMINS/	2463
13	exp PLASMA/	206
14	POLYGELINE/	46
15	exp DEXTRANS/	421
16	exp STARCH/	679
17	(fluid$ adj3 (resuscitation or replacement or therap$ or intravenous$ or iv or parenteral or oral or nasogastric or restrict$ or limit$ or reduc$ or maint$ or manage$ or volume$ or regimen$)).tw.	2109
18	(volume adj replac$).tw.	140
19	((restrict$ or maint$) adj3 volume).tw.	139
20	((frozen or fresh or protein$) adj plasma).tw.	322
21	(plasma adj3 (volume or expan$)).tw.	816
22	human albumin$.tw.	193
23	(hypoalbumin$ or low albumin).tw.	94
24	(polygeline or gelofusine or haemaccel or hemaccel or thomaegelin).tw.	101
25	(dextran$ or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol).tw.	805
26	starch.tw.	902
27	hyponatr?emic solution$.tw.	0
28	or/6-27	15113
29	5 and 28	44

MENG_fluids_men_cdsrdare_180408

Cochrane Database of Systematic Reviews 1st Quarter 2008
Database of Abstracts of Reviews of Effects 1st Quarter 2008

#	Searches	Results
1	meningitis.ti,ab,kw.	29
2	meningoencephalitis.ti,ab,kw.	1
3	or/1-2	30
4	(intravenous adj infusion$).ti,ab,kw.	15
5	rehydration solution$.ti,ab,kw.	13
6	((blood or plasma or intravascular) adj volume).ti,ab,kw.	18
7	(albumin or hypoalbumin).ti,ab,kw.	36
8	plasma.ti,ab,kw.	107
9	(fluid$ adj3 (resuscitation or replacement or therap$ or intravenous$ or iv or parenteral or oral or nasogastric or restrict$ or limit$ or reduc$ or maint$ or manage$ or volume$ or regimen$)).ti,ab,kw.	82
10	(volume adj replac$).ti,ab,kw.	3
11	((restrict$ or maint$) adj3 volume).ti,ab,kw.	3
12	(polygeline or gelofusine or haemaccel or hemaccel or thomaegelin).ti,ab,kw.	0
13	(dextran$ or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol).ti,ab,kw.	10
14	starch.ti,ab,kw.	6
15	hyponatr?emic solution$.ti,ab,kw.	0
16	or/4-15	225
17	16 and 3	1

MENG_fluids_men_RCTs_SRs_cinahl_180408_3

EBSCO Host Friday, July 31, 2009 10:08:17 AM

#	Query	Limiters/Expanders	Results
S56	S24 and S55	Search modes - Boolean/Phrase	0
S55	S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54	Search modes - Boolean/Phrase	296
S54	AB (hyponatremic solution*) or AB (hyponaetremic solution*)	Search modes - Boolean/Phrase	0
S53	TI (hyponatremic solution*) or TI (hyponaetremic solution*)	Search modes - Boolean/Phrase	0
S52	AB (dextran* or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol)	Search modes - Boolean/Phrase	189
S51	TI (dextran* or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol)	Search modes - Boolean/Phrase	59
S50	AB (polygeline or gelofusine or haemaccel or hemaccel or thomagelin)	Search modes - Boolean/Phrase	18
S49	TI (polygeline or gelofusine or haemaccel or hemaccel or thomagelin)	Search modes - Boolean/Phrase	8
S48	TI (low albumin) or AB (low albumin)	Search modes - Boolean/Phrase	47
S47	TI (hypoalbumin*) or AB (hypoalbumin*)	Search modes - Boolean/Phrase	211
S46	TI (human albumin*) or AB (human albumin*)	Search modes - Boolean/Phrase	60
S45	AB (plasma N3 volume) or AB (plasma N3 expan*)	Search modes - Boolean/Phrase	316
S44	TI (plasma N3 volume) or TI (plasma N3 expan*)	Search modes - Boolean/Phrase	44
S43	AB (frozen plasma) or AB (fresh plasma) or AB (protein* plasma)	Search modes - Boolean/Phrase	203
S42	TI (frozen plasma) or TI (fresh plasma) or TI (protein* plasma)	Search modes - Boolean/Phrase	61
S41	AB (restrict* N3 volume) or AB (maint* N3 volume)	Search modes - Boolean/Phrase	131
S40	TI (restrict* N3 volume) or TI (maint* N3 volume)	Search modes - Boolean/Phrase	4
S39	TI (volume replac*) or AB (volume replac*)	Search modes - Boolean/Phrase	58
S38	TI (fluid*) or AB (fluid*)	Search modes - Boolean/Phrase	10251
S37	TI (starch) or AB (starch)	Search modes - Boolean/Phrase	358
S36	MH STARCH+	Search modes - Boolean/Phrase	0

S35	MH DEXTRANS+	Search modes - Boolean/Phrase	97
S34	MH POLYGELINE	Search modes - Boolean/Phrase	0
S33	MH PLASMA+	Search modes - Boolean/Phrase	718
S32	MH ALBUMINS+	Search modes - Boolean/Phrase	4679
S31	MH PLASMA SUBSTITUTES	Search modes - Boolean/Phrase	141
S30	MH PLASMA VOLUME	Search modes - Boolean/Phrase	221
S29	MH BLOOD VOLUME	Search modes - Boolean/Phrase	414
S28	MH REHYDRATION SOLUTIONS	Search modes - Boolean/Phrase	126
S27	MH INFUSIONS, INTRAVENOUS	Search modes - Boolean/Phrase	2732
S26	MH FLUID THERAPY	Search modes - Boolean/Phrase	1576
S25	MH RESUSCITATION	Search modes - Boolean/Phrase	2628
S24	(TI (meningoencephalitis) or AB (meningoencephalitis)) and (S20 or S21 or S22 or S23)	Search modes - Boolean/Phrase	0
S23	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110
S22	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S21	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S20	MH MENINGITIS	Search modes - Boolean/Phrase	927
S19	TI (fluid*) or AB (fluid*)	Search modes - Boolean/Phrase	10251
S18	TI (starch) or AB (starch)	Search modes - Boolean/Phrase	358
S17	MH STARCH+	Search modes - Boolean/Phrase	0
S16	MH DEXTRANS+	Search modes - Boolean/Phrase	97
S15	MH POLYGELINE	Search modes - Boolean/Phrase	0
S14	MH PLASMA+	Search modes - Boolean/Phrase	718
S13	MH ALBUMINS+	Search modes - Boolean/Phrase	4679
S12	MH PLASMA SUBSTITUTES	Search modes - Boolean/Phrase	141
S11	MH PLASMA VOLUME	Search modes - Boolean/Phrase	221

S10	MH BLOOD VOLUME	Search modes - Boolean/Phrase	414
S9	MH REHYDRATION SOLUTIONS	Search modes - Boolean/Phrase	126
S8	MH INFUSIONS, INTRAVENOUS	Search modes - Boolean/Phrase	2732
S7	MH FLUID THERAPY	Search modes - Boolean/Phrase	1576
S6	MH RESUSCITATION	Search modes - Boolean/Phrase	2628
S5	(TI (meningoencephalitis) or AB (meningoencephalitis)) and (S1 or S2 or S3 or S4)	Search modes - Boolean/Phrase	0
S4	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110
S3	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S2	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S1	MH MENINGITIS	Search modes - Boolean/Phrase	927

MENG_fluids_men_RCTs_SRs_embase_180408

EMBASE 1980 to 2008 Week 15

#	Searches	Results
1	MENINGITIS/	13054
2	exp MENINGITIS, BACTERIAL/	7328
3	meningitis.tw.	21052
4	meningoencephalitis.tw.	2411
5	or/1-4	29534
6	RESUSCITATION/	22752
7	FLUID THERAPY/	5899
8	INFUSIONS, INTRAVENOUS/	269627
9	REHYDRATION SOLUTIONS/	1398
10	BLOOD VOLUME/ or PLASMA VOLUME/	10633
11	PLASMA SUBSTITUTES/	1380
12	exp ALBUMINS/	65672
13	exp PLASMA/	31172
14	POLYGELINE/	624
15	exp DEXTRANS/	9515
16	exp STARCH/	6930
17	(fluid$ adj3 (resuscitation or replacement or therap$ or intravenous$ or iv or parenteral or oral or nasogastric or restrict$ or limit$ or reduc$ or maint$ or manage$ or volume$ or regimen$)).tw.	18289
18	(volume adj replac$).tw.	721
19	((restrict$ or maint$) adj3 volume).tw.	1425
20	((frozen or fresh or protein$) adj plasma).tw.	3239
21	(plasma adj3 (volume or expan$)).tw.	6116
22	human albumin$.tw.	1787
23	(hypoalbumin$ or low albumin).tw.	2686
24	(polygeline or gelofusine or haemaccel or hemaccel or thomaegelin).tw.	572
25	(dextran$ or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol).tw.	17892
26	starch.tw.	11129
27	hyponatr?emic solution$.tw.	3
28	or/6-27	448620
29	5 and 28	3153
30	CLINICAL TRIALS/	497844
31	(clinic$ adj5 trial$).ti,ab,sh.	117096
32	SINGLE BLIND PROCEDURE/	7468
33	DOUBLE BLIND PROCEDURE/	68835
34	RANDOM ALLOCATION/	25316
35	CROSSOVER PROCEDURE/	20140
36	PLACEBO/	111912

37	placebo$.ti,ab,sh.	161851
38	random$.ti,ab,sh.	404256
39	RANDOMIZED CONTROLLED TRIALS/	156348
40	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	89734
41	randomi?ed control$ trial$.tw.	29169
42	or/30-41	817852
43	META ANALYSIS/	33174
44	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	41510
45	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	23933
46	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1519
47	or/43-46	56626
48	review.pt.	866295
49	(medline or medlars or embase).ab.	20667
50	(scisearch or science citation index).ab.	601
51	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	6676
52	((hand or manual$) adj2 search$).tw.	2380
53	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	3817
54	(pooling or pooled or mantel haenszel).tw.	23160
55	(peto or dersimonian or "der simonian" or fixed effect).tw.	727
56	or/49-55	47927
57	48 and 56	16196
58	or/47,57	65882
59	case study.tw,sh.	21437
60	abstract report.tw,sh.	71203
61	note.tw,sh.	246859
62	short survey.tw,sh.	404673
63	letter.tw,sh.	399601
64	case report.tw,sh.	991284
65	editorial.tw,sh.	249786
66	or/59-65	2261268
67	42 not 66	726610
68	58 not 67	28471
69	or/67-68	755081
70	29 and 69	286
71	limit 70 to english language	241

MENG_fluids_men_RCTs_SRs_medline_180408

Ovid MEDLINE(R) 1950 to April Week 2 2008

#	Searches	Results
1	MENINGITIS/	14716
2	exp MENINGITIS, BACTERIAL/	16650
3	meningitis.tw.	30667
4	meningoencephalitis.tw.	4030
5	or/1-4	44396
6	RESUSCITATION/	18728
7	FLUID THERAPY/	10725
8	INFUSIONS, INTRAVENOUS/	38662
9	REHYDRATION SOLUTIONS/	969
10	BLOOD VOLUME/ or PLASMA VOLUME/	22162
11	PLASMA SUBSTITUTES/	5481
12	exp ALBUMINS/	107737
13	exp PLASMA/	11037
14	POLYGELINE/	250
15	exp DEXTRANS/	20903
16	exp STARCH/	22124
17	(fluid$ adj3 (resuscitation or replacement or therap$ or intravenous$ or iv or parenteral or oral or nasogastric or restrict$ or limit$ or reduc$ or maint$ or manage$ or volume$ or regimen$)).tw.	22514
18	(volume adj replac$).tw.	792
19	((restrict$ or maint$) adj3 volume).tw.	1635
20	((frozen or fresh or protein$) adj plasma).tw.	3731
21	(plasma adj3 (volume or expan$)).tw.	8202
22	human albumin$.tw.	2267
23	(hypoalbumin$ or low albumin).tw.	3300
24	(polygeline or gelofusine or haemaccel or hemaccel or thomaegelin).tw.	368
25	(dextran$ or haemodex or hemodex or hyskon or infukoll or macrodex or ploy glucin or promit or rheodextran or rheomacrodex or rheopolyglucin or rondex or saviosol).tw.	23107
26	starch.tw.	15389
27	hyponatr?emic solution$.tw.	3
28	or/6-27	290615
29	5 and 28	866
30	randomized controlled trial.pt.	254671
31	controlled clinical trial.pt.	78053
32	DOUBLE BLIND METHOD/	97156
33	SINGLE BLIND METHOD/	11987
34	RANDOM ALLOCATION/	60879
35	RANDOMIZED CONTROLLED TRIALS/	53828
36	or/30-35	429697

37	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	94669
38	clinical trial.pt.	449571
39	exp CLINICAL TRIAL/	542475
40	exp CLINICAL TRIALS AS TOPIC/	203502
41	(clinic$ adj5 trial$).tw,sh.	125725
42	PLACEBOS/	27235
43	placebo$.tw,sh.	122393
44	random$.tw,sh.	536972
45	or/37-44	944880
46	or/36,45	949377
47	META ANALYSIS/	18023
48	META ANALYSIS AS TOPIC/	8209
49	meta analysis.pt.	18023
50	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	32029
51	(systematic$ adj5 (review$ or overview$)).tw,sh.	16538
52	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1851
53	or/47-52	44536
54	review$.pt.	1372562
55	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	29012
56	((hand or manual$) adj2 search$).tw.	3260
57	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	4912
58	(pooling or pooled or mantel haenszel).tw,sh.	28466
59	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1271
60	or/55-59	59369
61	54 and 60	24655
62	or/53,61	59286
63	letter.pt.	623241
64	case report.tw.	133733
65	comment.pt.	354750
66	editorial.pt.	218994
67	historical article.pt.	249999
68	or/63-67	1264529
69	46 not 68	914323
70	62 not 68	55917
71	or/69-70	942867
72	29 and 71	98
73	limit 72 to (english language and humans)	76

21 What are the clinical indications for intubation in children and young people with suspected/confirmed meningococcal septicaemia?

MENG_intubation_septicaemia_all_ages_cctr_260608

EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2008

#	Searches	Results
1	exp CHILD/	38473
2	child$.ti,ab.	32312
3	exp INFANT/	17332
4	infan$.ti,ab.	11877
5	(baby or babies).ti,ab.	1645
6	toddler?.ti,ab.	240
7	ADOLESCENT/	54093
8	teen$.ti,ab.	464
9	adolescen$.ti,ab.	4499
10	exp SCHOOLS/	494
11	school$.ti,ab.	5850
12	exp PUBERTY/	205
13	pubescen$.ti,ab.	10
14	or/1-13	95068
15	shock.ti.	828
16	SHOCK/	96
17	SHOCK, SEPTIC/	252
18	(septic adj shock).ti,ab.	375
19	(sepsis adj5 hypotension).ti,ab.	17
20	BACTEREMIA/	380
21	(severe adj2 sepsis).ti,ab.	267
22	(septic?emi? or bacter?emi?).ti,ab.	1258
23	MENINGOCOCCAL INFECTIONS/	72
24	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	61
25	meningococc?emi?.ti,ab.	6
26	or/17-25	2040
27	or/15-16,26	2697
28	INTUBATION/	133
29	INTUBATION, INTRATRACHEAL/	2036
30	(oro?pharyn$ adj2 airway?).ti,ab.	81
31	(ET tube? or ETT).ti,ab.	157
32	((endo?tracheal or intra?tracheal or naso?tracheal or trachea?) adj3 tube?).ti,ab.	739
33	((endo?tracheal or intra?tracheal or naso?tracheal or trachea?) adj3 intubation?).ti,ab.	2028
34	LARYNGEAL MASKS/	546

35 ((larynx or laryngeal) adj3 mask$).ti,ab.	697
36 exp RESPIRATION, ARTIFICIAL/	2668
37 (respiration? adj3 (artificial$ or mechanical$)).ti,ab.	30
38 (ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	2304
39 (airway? adj2 management).ti,ab.	207
40 (CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	914
41 PPV.ti,ab.	175
42 (respirat$ adj3 support?).ti,ab.	164
43 ((early or late or pre?emptive$ or preventive$ or elective$) adj3 intubat$).ti,ab.	66
44 (ventilator? or respirator? or oxygenator?).ti,ab.	17653
45 exp OXYGEN INHALATION THERAPY/	752
46 RESPIRATORY THERAPY/	347
47 EXTRACORPOREAL MEMBRANE OXYGENATION/	105
48 exp OXYGENATORS/	99
49 (oxygen adj3 (extra?corporeal$ or inhalation or therap$ or treatment?)).ti,ab.	1012
50 oxygenation.ti,ab.	1621
51 RESPIRATORY INSUFFICIENCY/th, pc	336
52 or/28-51	24932
53 and/14,27	731
54 and/52-53	76
55 and/26,52	222
56 55 not 14	158

MENG_intubation_septicaemia_all_ages_medline_260608

Ovid MEDLINE(R) 1950 to June Week 3 2008

#	Searches	Results
1	exp CHILD/	1264719
2	child$.ti,ab.	702361
3	exp INFANT/	784538
4	infan$.ti,ab.	249935
5	(baby or babies).ti,ab.	36996
6	toddler?.ti,ab.	3259
7	exp ADOLESCENT/	1268046
8	teen$.ti,ab.	14075
9	adolescen$.ti,ab.	105376
10	exp SCHOOLS/	59032
11	school$.ti,ab.	126186
12	exp PUBERTY/	12929
13	pubescen$.ti,ab.	796
14	or/1-13	2545949
15	shock.ti.	41832
16	SHOCK/	11757
17	SHOCK, SEPTIC/	14922
18	(septic adj shock).ti,ab.	9238
19	(sepsis adj5 hypotension).ti,ab.	289
20	BACTEREMIA/	12047
21	(severe adj2 sepsis).ti,ab.	2881
22	(septic?emi? or bacter?emi?).ti,ab.	29111
23	MENINGOCOCCAL INFECTIONS/	4399
24	(meningococcal adj3 (sepsis or septic or toxic or endotoxic or disease or infection?)).ti,ab.	3514
25	meningococc?emi?.ti,ab.	601
26	or/17-25	58019
27	or/15-16,26	97158
28	INTUBATION/	4143
29	INTUBATION, INTRATRACHEAL/	23158
30	(oro?pharyn$ adj2 airway?).ti,ab.	262
31	(ET tube? or ETT).ti,ab.	774
32	((endo?tracheal or intra?tracheal or naso?tracheal or trachea?) adj3 tube?).ti,ab.	6852
33	((endo?tracheal or intra?tracheal or naso?tracheal or trachea?) adj3 intubation?).ti,ab.	9360
34	LARYNGEAL MASKS/	3136
35	((larynx or laryngeal) adj3 mask$).ti,ab.	2842
36	exp RESPIRATION, ARTIFICIAL/	45643
37	(respiration? adj3 (artificial$ or mechanical$)).ti,ab.	1678
38	(ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	26025

39 (airway? adj2 management).ti,ab.	2344
40 (CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	4595
41 PPV.ti,ab.	3576
42 (respirat$ adj3 support?).ti,ab.	1828
43 ((early or late or pre?emptive$ or preventive$ or elective$) adj3 intubat$).ti,ab.	370
44 (ventilator? or respirator? or oxygenator?).ti,ab.	243984
45 exp OXYGEN INHALATION THERAPY/	18012
46 RESPIRATORY THERAPY/	5087
47 EXTRACORPOREAL MEMBRANE OXYGENATION/	3214
48 exp OXYGENATORS/	2206
49 (oxygen adj3 (extra?corporeal$ or inhalation or therap$ or treatment?)).ti,ab.	8788
50 oxygenation.ti,ab.	23762
51 RESPIRATORY INSUFFICIENCY/th, pc	8501
52 or/28-51	345688
53 and/14,27	20122
54 and/52-53	2049
55 (letter or editorial or historical article or note).pt.	1096973
56 CASE REPORTS/	1391176
57 (case report or case study).ti.	120845
58 or/55-57	2372498
59 54 not 58	1692
60 limit 59 to (english language and humans)	1299
61 and/26,52	4903
62 limit 61 to "all adult (19 plus years)"	2355
63 (letter or editorial or historical article or note).pt.	1096973
64 CASE REPORTS/	1391176
65 (case report or case study).ti.	120845
66 or/63-65	2372498
67 62 not 66	1755
68 limit 67 to (english language and humans)	1459

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008
MENG_intubation_meningitis_cctr_301008

#	Searches	Results
1	meningoencephalitis.ti,ab.	18
2	MENINGOENCEPHALITIS/	10
3	meningitis.ti,ab.	478
4	exp MENINGITIS/	350
5	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
6	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	10
7	or/1-6	580
8	((rise or rais?? or elevat$ or increas$ or high) adj3 (ICP or intracranial pressure? or intra cranial pressure?)).ti,ab.	193
9	INTRACRANIAL HYPERTENSION/	49
10	or/8-9	220
11	exp CENTRAL NERVOUS SYSTEM INFECTIONS/	694
12	or/3,11	908
13	and/10,12	14
14	or/7,13	584
15	INTUBATION/	136
16	INTUBATION, INTRATRACHEAL/	2080
17	(oro?pharyn$ adj2 airway?).ti,ab.	82
18	(ET tube? or ETT).ti,ab.	160
19	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 tube?).ti,ab.	773
20	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 tube?).ti,ab.	303
21	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 intubation?).ti,ab.	2183
22	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 intubation?).ti,ab.	1382
23	LARYNGEAL MASKS/	560
24	((larynx or laryngeal) adj3 mask$).ti,ab.	715
25	exp RESPIRATION, ARTIFICIAL/	2889
26	(respiration? adj3 (artificial$ or mechanical$)).ti,ab.	29
27	(ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	2364
28	(airway? adj2 management).ti,ab.	216
29	(CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	973
30	PPV.ti,ab.	183
31	(respirat$ adj3 support?).ti,ab.	170
32	((early or late or preemptive$ or pre emptive$ or preventive$ or elective$ or emergency) adj3 intubat$).ti,ab.	91
33	(ventilator? or respirator? or oxygenator?).ti,ab.	18234
34	exp OXYGEN INHALATION THERAPY/	763
35	RESPIRATORY THERAPY/	350

36	EXTRACORPOREAL MEMBRANE OXYGENATION/	106
37	exp OXYGENATORS/	100
38	(oxygen adj3 (extra corporeal$ or extracorporeal$ or inhalation or therap$ or treatment?)).ti,ab.	1050
39	oxygenation.ti,ab.	1654
40	RESPIRATORY INSUFFICIENCY/th, pc	342
41	or/15-38	25035
42	and/14,41	26

MENG_intubation_meningitis_cdsrdare_301008

DARE, CDSR

#	Searches	Results
1	meningoencephalitis.ti,ab.	1
2	MENINGOENCEPHALITIS.kw.	1
3	meningitis.ti,ab.	31
4	MENINGITIS.kw.	21
5	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
6	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	0
7	or/1-6	34
8	((rise or rais?? or elevat$ or increas$ or high) adj3 (ICP or intracranial pressure? or intra cranial pressure?)).ti,ab.	10
9	INTRACRANIAL HYPERTENSION.kw.	8
10	or/8-9	14
11	CENTRAL NERVOUS SYSTEM INFECTION$.kw.	0
12	or/3,11	31
13	and/10,12	1
14	or/7,13	34
15	INTUBATION.kw.	52
16	INTUBATION, INTRATRACHEAL.kw.	41
17	(oro?pharyn$ adj2 airway?).ti,ab.	0
18	(ET tube? or ETT).ti,ab.	3
19	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 tube?).ti,ab.	16
20	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 tube?).ti,ab.	2
21	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 intubation?).ti,ab.	23
22	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 intubation?).ti,ab.	5
23	LARYNGEAL MASKS.kw.	4
24	((larynx or laryngeal) adj3 mask$).ti,ab.	4
25	RESPIRATION, ARTIFICIAL.kw.	90
26	(respiration? adj3 (artificial$ or mechanical$)).ti,ab.	0
27	(ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	100
28	(airway? adj2 management).ti,ab.	3
29	(CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	33
30	PPV.ti,ab.	5
31	(respirat$ adj3 support?).ti,ab.	26
32	((early or late or preemptive$ or pre emptive$ or preventive$ or elective$ or emergency) adj3 intubat$).ti,ab.	4
33	(ventilator? or respirator? or oxygenator?).ti,ab.	394
34	OXYGEN INHALATION THERAPY.kw.	30
35	RESPIRATORY THERAPY.kw.	18

36	EXTRACORPOREAL MEMBRANE OXYGENATION.kw.	1
37	OXYGENATOR$.kw.	0
38	(oxygen adj3 (extra corporeal$ or extracorporeal$ or inhalation or therap$ or treatment?)).ti,ab.	72
39	oxygenation.ti,ab.	35
40	RESPIRATORY INSUFFICIENCY.kw.	41
41	or/15-38	588
42	and/14,41	5

MENG_intubation_meningitis_cinahl_031108_8

EBSCO-Host July 30, 2009

#	Query	Limiters/Expanders	Results
S69	S34 and S67	Limiters - English Language Search modes - Boolean/Phrase	0
S68	S34 and S67	Search modes - Boolean/Phrase	0
S67	S46 or S66	Search modes - Boolean/Phrase	10
S66	S35 or S36 or S37 or S38 or S39 or S40 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65	Search modes - Boolean/Phrase	251
S65	TI (ventilator*) or AB (ventilator*)	Search modes - Boolean/Phrase	4895
S64	(MH "RESPIRATORY THERAPY EQUIPMENT and SUPPLIES+")	Search modes - Boolean/Phrase	4741
S63	TI (intubat*) or AB (intubat*)	Search modes - Boolean/Phrase	3240
S62	TI (respirat* N3 support*) or AB (respirat* N3 support*)	Search modes - Boolean/Phrase	383
S61	TI (PPV) or AB (PPV)	Search modes - Boolean/Phrase	346
S60	AB (CPAP or PAP ventilation or continuous positive airway pressure)	Search modes - Boolean/Phrase	683
S59	TI (CPAP or PAP ventilation or continuous positive airway pressure)	Search modes - Boolean/Phrase	549
S58	TI (airway* N2 management) or AB (airway* N2 management)	Search modes - Boolean/Phrase	740
S57	TI (ventilat* N3 mechanical) or AB (ventilat* N3 mechanical)	Search modes - Boolean/Phrase	3607
S56	TI (ventilat* N3 artificial) or AB (ventilat* N3 artificial)	Search modes - Boolean/Phrase	96
S55	TI (respiration* N3 mechanical) or AB (respiration* N3 mechanical)	Search modes - Boolean/Phrase	8
S54	TI (respiration* N3 artificial) or AB (respiration* N3 artificial)	Search modes - Boolean/Phrase	22
S53	TI (oxygen N3 mask*) or AB (oxygen N3 mask*)	Search modes - Boolean/Phrase	85
S52	TI (laryngeal N3 mask*) or AB (laryngeal N3 mask*)	Search modes - Boolean/Phrase	258
S51	TI (larynx N3 mask*) or AB (larynx N3 mask*)	Search modes - Boolean/Phrase	1
S50	MH OXYGEN MASK	Search modes - Boolean/Phrase	0
S49	MH RESPIRATION, ARTIFICIAL+	Search modes - Boolean/Phrase	8874
S48	MH VENTILATION, MECHANICAL+	Search modes -	0

		Boolean/Phrase	
S47	MH LARYNGEAL MASKS	Search modes - Boolean/Phrase	350
S46	S44 and S45	Search modes - Boolean/Phrase	0
S45	TI (tube* or intubation*) or AB (tube* or intubation*)	Search modes - Boolean/Phrase	13649
S44	S41 or S42 or S43	Search modes - Boolean/Phrase	16
S43	TI (intra tracheal) or AB (intra tracheal)	Search modes - Boolean/Phrase	1
S42	TI (oro tracheal or endo tracheal or intra tracheal naso tracheal or trachea*) or AB (oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea*)	Search modes - Boolean/Phrase	1445
S41	TI (orotracheal or endotracheal or nasotracheal or trachea*) or AB (orotracheal or endotracheal or nasotracheal or trachea*)	Search modes - Boolean/Phrase	3057
S40	TI (ETT) or AB (ETT)	Search modes - Boolean/Phrase	149
S39	TI (ET tube*) or AB (ET tube*)	Search modes - Boolean/Phrase	35
S38	TI (oro pharny* N2 airway*) or AB (oro pharny* N2 airway*)	Search modes - Boolean/Phrase	0
S37	TI (oropharny* N2 airway*) or AB (oropharny* N2 airway*)	Search modes - Boolean/Phrase	0
S36	MH INTUBATION, INTRATRACHEAL	Search modes - Boolean/Phrase	3106
S35	MH INTUBATION	Search modes - Boolean/Phrase	251
S34	S11 or S33	Search modes - Boolean/Phrase	30
S33	S30 AND S32	Search modes - Boolean/Phrase	1
S32	S3 or S31	Search modes - Boolean/Phrase	166
S31	MH CENTRAL NERVOUS SYSTEM INFECTIONS+	Search modes - Boolean/Phrase	6325
S30	S28 or S29	Search modes - Boolean/Phrase	18
S29	MH INTRACRANIAL PRESSURE, INCREASED	Search modes - Boolean/Phrase	600
S28	S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27	Search modes - Boolean/Phrase	254
S27	TI (high* N3 intra cranial pressure*) or AB (high* N3 intra cranial pressure*)	Search modes - Boolean/Phrase	0
S26	TI (increas* N3 intra cranial pressure*) or AB (increas* N3 intra cranial pressure*)	Search modes - Boolean/Phrase	1
S25	TI (elevat* N3 intra cranial pressure*) or AB (elevat* N3 intra cranial pressure*)	Search modes - Boolean/Phrase	0
S24	TI (rais* N3 intra cranial pressure*) or AB (rais* N3 intra	Search modes -	0

	cranial pressure*)	Boolean/Phrase	
S23	TI (rise N3 intra cranial pressure*) or AB (rise N3 intra cranial pressure*)	Search modes - Boolean/Phrase	0
S22	TI (intracranial pressure*) or AB (intracranial pressure*)	Search modes - Boolean/Phrase	701
S21	TI (high N3 intracranial) or AB (high* N3 intracranial)	Search modes - Boolean/Phrase	60
S20	TI (increas* N3 intracranial) or AB (increas* N3 intracranial)	Search modes - Boolean/Phrase	274
S19	TI (elevat* N3 intracranial) or AB (elevat* N3 intracranial)	Search modes - Boolean/Phrase	62
S18	TI (rais* adj3 intracranial) or AB (rais* adj3 intracranial)	Search modes - Boolean/Phrase	0
S17	TI (rise adj3 intracranial) or AB (rise adj3 intracranial)	Search modes - Boolean/Phrase	0
S16	TI (high* N3 ICP) or AB (high* N3 ICP)	Search modes - Boolean/Phrase	26
S15	TI (increas* N3 ICP) or AB (increas* N3 ICP)	Search modes - Boolean/Phrase	90
S14	TI (elevat* N3 ICP) or AB (elevat* N3 ICP)	Search modes - Boolean/Phrase	28
S13	TI (rais* N3 ICP) or AB (rais* N3 ICP)	Search modes - Boolean/Phrase	14
S12	TI (rise N3 ICP) or AB (rise N3 ICP)	Search modes - Boolean/Phrase	11
S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10	Search modes - Boolean/Phrase	1712
S10	TI (viral N3 meningitis) or AB (viral N3 meningitis)	Search modes - Boolean/Phrase	56
S9	TI (virus N3 meningitis) or AB (virus N3 meningitis)	Search modes - Boolean/Phrase	13
S8	TI (virus N3 meninges) or AB (virus N3 meninges)	Search modes - Boolean/Phrase	0
S7	TI (viral N3 meninges) or AB (viral N3 meninges)	Search modes - Boolean/Phrase	1
S6	TI (infect* N3 meninges) or AB (infect* N3 meninges)	Search modes - Boolean/Phrase	4
S5	TI (bacterial N3 meninges) or AB (bacterial N3 meninges)	Search modes - Boolean/Phrase	1
S4	MH MENINGITIS+	Search modes - Boolean/Phrase	1962
S3	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S2	MH MENINGOENCEPHALITIS	Search modes - Boolean/Phrase	88
S1	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110

MENG_intubation_meningitis_embase_031108

EMBASE 1980 to 2008 Week 43

#	Searches	Results
1	MENINGOENCEPHALITIS/	2921
2	MENINGITIS/	13449
3	((bacterial$ or infect$) adj3 meninges).ti,ab.	31
4	(infect$ adj3 (leptomeninges or subarachnoid space?)).ti,ab.	17
5	meningoencephalitis.ti,ab.	2486
6	meningitis.ti,ab.	21617
7	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	656
8	or/1-7	29953
9	((rise or rais?? or elevat$ or increas$ or high) adj3 (ICP or intracranial pressure? or intra cranial pressure?)).ti,ab.	5709
10	INTRACRANIAL HYPERTENSION/	5685
11	10 or 9	9712
12	exp CENTRAL NERVOUS SYSTEM INFECTION/	62500
13	6 or 12	66577
14	11 and 13	817
15	8 or 14	30219
16	ENDOTRACHEAL INTUBATION/	15480
17	ENDOBRONCHIAL INTUBATION/	466
18	INTUBATION/	6017
19	RESPIRATORY TRACT INTUBATION/	952
20	(ET tube? or ETT).ti,ab.	756
21	((intratracheal or intra tracheal or endotracheal or endo tracheal or intratracheal or orotracheal or oro tracheal or naso tracheal or nasotracheal or trachea?) adj3 tube?).ti,ab.	5952
22	((intratracheal or intra tracheal or orotracheal or oro tracheal or endotracheal or endo tracheal or nasotracheal or naso tracheal or trachea?) adj3 intubation?).ti,ab.	8980
23	(oro?pharyn$ adj2 airway?).ti,ab.	217
24	LARYNGEAL MASKS/	3645
25	OXYGEN MASK/	97
26	((larynx or laryngeal or oxygen$) adj3 mask$).ti,ab.	3178
27	exp ARTIFICIAL VENTILATION/	52398
28	(respiration? adj3 (artificial$ or mechanical$)).ti,ab.	589
29	(ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	23776
30	(airway? adj2 management).ti,ab.	2415
31	(CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	4276
32	PPV.ti,ab.	3397
33	(respirat$ adj3 support?).ti,ab.	1593
34	((early or late or preemptive$ or pre emptive$ or prevent??ive$ or elective$ or emergency) adj3 intubat$).ti,ab.	767
35	ventilator?.ti,ab.	25053
36	VENTILATOR/	4814

37 or/16-36	102627
38 and/15,37	380
39 limit 38 to english language	313
40 (letter or editorial).pt.	647289
41 39 not 40	294

MENG_intubation_meningitis_medline_301008

Ovid MEDLINE(R) 1950 to October Week 4 2008

#	Searches	Results
1	meningoencephalitis.ti,ab.	4183
2	MENINGOENCEPHALITIS/	4840
3	meningitis.ti,ab.	31905
4	exp MENINGITIS/	41796
5	((bacterial$ or infect$) adj3 meninges).ti,ab.	45
6	((viral or virus) adj3 (meninges or meningitis)).ti,ab.	958
7	or/1-6	51643
8	((rise or rais?? or elevat$ or increas$ or high) adj3 (ICP or intracranial pressure? or intra cranial pressure?)).ti,ab.	6888
9	INTRACRANIAL HYPERTENSION/	1918
10	or/8-9	8095
11	exp CENTRAL NERVOUS SYSTEM INFECTIONS/	113668
12	or/3,11	121545
13	and/10,12	630
14	or/7,13	51809
15	INTUBATION/	4200
16	INTUBATION, INTRATRACHEAL/	23700
17	(oro?pharyn$ adj2 airway?).ti,ab.	265
18	(ET tube? or ETT).ti,ab.	800
19	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 tube?).ti,ab.	7081
20	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 tube?).ti,ab.	1988
21	((orotracheal or endotracheal or intratracheal or nasotracheal or trachea?) adj3 intubation?).ti,ab.	10096
22	((oro tracheal or endo tracheal or intra tracheal or naso tracheal or trachea?) adj3 intubation?).ti,ab.	4417
23	LARYNGEAL MASKS/	3226
24	((larynx or laryngeal) adj3 mask$).ti,ab.	2923
25	exp RESPIRATION, ARTIFICIAL/	46941
26	(respiration? adj3 (artificial$ or mechanical$)).ti,ab.	1710
27	(ventilat$ adj3 (artificial$ or mechanical$)).ti,ab.	26811
28	(airway? adj2 management).ti,ab.	2431
29	(CPAP or PAP ventilation or continuous positive airway pressure).ti,ab.	4796
30	PPV.ti,ab.	3788
31	(respirat$ adj3 support?).ti,ab.	1881
32	((early or late or preemptive$ or pre emptive$ or preventive$ or elective$ or emergency) adj3 intubat$).ti,ab.	827
33	(ventilator? or respirator? or oxygenator?).ti,ab.	251191
34	exp OXYGEN INHALATION THERAPY/	18499
35	RESPIRATORY THERAPY/	5219

36	EXTRACORPOREAL MEMBRANE OXYGENATION/	3283
37	exp OXYGENATORS/	2221
38	(oxygen adj3 (extra corporeal$ or extracorporeal$ or inhalation or therap$ or treatment?)).ti,ab.	9096
39	oxygenation.ti,ab.	24331
40	RESPIRATORY INSUFFICIENCY/th, pc	8761
41	or/15-38	340905
42	and/14,41	1547
43	CASE REPORTS/	1425518
44	(case report or case study).ti.	124260
45	(letter or editorial).pt.	884907
46	or/43-45	2193879
47	42 not 46	1176
48	limit 47 to humans	1063
49	limit 48 to english language	755

22 Should corticosteroids be used in the treatment of children and young people with suspected/confirmed bacterial meningitis?

MENG_corticosteroids_cctr_060308

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	MENINGITIS/	99
2	exp MENINGITIS, BACTERIAL/	224
3	meningitis.tw.	480
4	meningoencephalitis.tw.	20
5	exp MENINGOCOCCAL INFECTIONS/	152
6	meningococc$.tw.	270
7	septic?emia.tw.	451
8	or/1-7	1180
9	exp ADRENAL CORTEX HORMONES/	7753
10	corticosteroid$.tw.	5478
11	adrenal cortex extract.tw.	3
12	(adrenal adj2 (hormone$ or steroid$)).tw.	150
13	corticoid$.tw.	219
14	17-ketosteroid$.tw.	9
15	glucocorticoid$.tw.	1231
16	hydroxycorticosteroid$.tw.	37
17	mineralocorticoid$.tw.	109
18	dehydroepiandrosterone.tw.	456
19	itrocinonide.tw.	0
20	aldosterone.tw.	1801
21	corticosterone.tw.	37
22	cortisone.tw.	175
23	deoxycorticosterone.tw.	20
24	hydrocortisone.tw.	1011
25	prednisolone.tw.	1896
26	beclomethasone.tw.	1342
27	betamethasone.tw.	878
28	clobetasol.tw.	230
29	desonide.tw.	32
30	desoxymethasone.tw.	17
31	dexamethasone.tw.	2375
32	diflucortolone.tw.	37
33	fluocinonide.tw.	80
34	fluocortolone.tw.	31
35	fluorometholone.tw.	53

36 flurandrenolone.tw.	7
37 halcinonide.tw.	43
38 methylprednisolone.tw.	1367
39 prednisone.tw.	2769
40 triamcinolone.tw.	639
41 alclometasone.tw.	23
42 clobetasone.tw.	53
43 deoxycortone.tw.	0
44 fluclorolone.tw.	7
45 flunisolide.tw.	162
46 fluticasone.tw.	1772
47 budesonide.tw.	1852
48 deflazacort.tw.	99
49 estrenol.tw.	0
50 fluadrenolide.tw.	0
51 desoxycorticosterone.tw.	7
52 fludrocortisone.tw.	56
53 flumethasone.tw.	21
54 fluprednisolone.tw.	1
55 methandriol.tw.	0
56 norethandrolone.tw.	5
57 oxandrolone.tw.	85
58 oxymetholone.tw.	17
59 paramethasone.tw.	7
60 fluocinolone.tw.	102
61 dichlorisone.tw.	0
62 hydrocortamate.tw.	0
63 dehydrocorticosterone.tw.	0
64 medrysone.tw.	7
65 tetrahydrocorticosterone.tw.	2
66 mometasone.tw.	293
67 rimexolone.tw.	18
68 ciclesonide.tw.	180
69 or/9-68	23605
70 8 and 69	99

MENG_corticosteroids_cdsrdare_060308

EBM Reviews - Cochrane Database of Systematic Reviews 4th Quarter 2007
EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2008

#	Searches	Results
1	meningitis.ti,ab,kw.	28
2	meningoencephalitis.ti,ab,kw.	1
3	meningococc$.ti,ab,kw.	8
4	septic?emia.ti,ab,kw.	10
5	or/1-4	40
6	adrenal cortex hormone?.ti,ab,kw.	136
7	corticosteroid$.ti,ab,kw.	310
8	adrenal cortex extract?.ti,ab,kw.	0
9	(adrenal adj2 (hormone$ or steroid$)).ti,ab,kw.	137
10	corticoid$.ti,ab,kw.	0
11	17-ketosteroid$.ti,ab,kw.	0
12	glucocorticoid$.ti,ab,kw.	119
13	hydroxycorticosteroid$.ti,ab,kw.	0
14	mineralocorticoid$.ti,ab,kw.	0
15	dehydroepiandrosterone.ti,ab,kw.	6
16	itrocinonide.ti,ab,kw.	0
17	aldosterone.ti,ab,kw.	5
18	corticosterone.ti,ab,kw.	0
19	cortisone.ti,ab,kw.	2
20	deoxycorticosterone.ti,ab,kw.	0
21	hydrocortisone.ti,ab,kw.	19
22	prednisolone.ti,ab,kw.	41
23	beclomethasone.ti,ab,kw.	25
24	betamethasone.ti,ab,kw.	9
25	clobetasol.ti,ab,kw.	1
26	desonide.ti,ab,kw.	0
27	desoxymethasone.ti,ab,kw.	0
28	dexamethasone.ti,ab,kw.	51
29	diflucortolone.ti,ab,kw.	0
30	fluocinonide.ti,ab,kw.	1
31	fluocortolone.ti,ab,kw.	0
32	fluorometholone.ti,ab,kw.	0
33	flurandrenolone.ti,ab,kw.	0
34	halcinonide.ti,ab,kw.	0
35	methylprednisolone.ti,ab,kw.	22
36	prednisone.ti,ab,kw.	55
37	triamcinolone.ti,ab,kw.	9
38	alclometasone.ti,ab,kw.	0
39	clobetasone.ti,ab,kw.	0

40 deoxycortone.ti,ab,kw.	0
41 fluclorolone.ti,ab,kw.	0
42 flunisolide.ti,ab,kw.	3
43 fluticasone.ti,ab,kw.	18
44 budesonide.ti,ab,kw.	34
45 deflazacort.ti,ab,kw.	3
46 estrenol.ti,ab,kw.	0
47 fluadrenolide.ti,ab,kw.	0
48 desoxycorticosterone.ti,ab,kw.	0
49 fludrocortisone.ti,ab,kw.	1
50 flumethasone.ti,ab,kw.	0
51 fluprednisolone.ti,ab,kw.	0
52 methandriol.ti,ab,kw.	0
53 norethandrolone.ti,ab,kw.	0
54 oxandrolone.ti,ab,kw.	0
55 oxymetholone.ti,ab,kw.	0
56 paramethasone.ti,ab,kw.	0
57 fluocinolone.ti,ab,kw.	2
58 dichlorisone.ti,ab,kw.	0
59 hydrocortamate.ti,ab,kw.	0
60 dehydrocorticosterone.ti,ab,kw.	0
61 medrysone.ti,ab,kw.	0
62 tetrahydrocorticosterone.ti,ab,kw.	0
63 mometasone.ti,ab,kw.	2
64 rimexolone.ti,ab,kw.	0
65 ciclesonide.ti,ab,kw.	2
66 or/6-65	497
67 5 and 66	5

MENG_corticosteroids_cinahl_060308_shortenedversion_2
EBSCO Host Friday, July 31, 2009 9:51:26 AM

#	Query	Limiters/Expanders	Results
		Limiters - English Language	
		Search modes - Boolean/Phrase	
S14	(S9 or S10) and (S8 and S11)		1
S13	(S9 or S10) and (S8 and S11)	Search modes - Boolean/Phrase	1

S12	(S9 or S10) and (S8 and S11)	Search modes - Boolean/Phrase	1
S11	S9 or S10	Search modes - Boolean/Phrase	75
S10	TI (corticoid* or corticosteroid*) or AB (corticoid* or corticosteroid*)	Search modes - Boolean/Phrase	4574
S9	MH ADRENAL CORTEX HORMONES+	Search modes - Boolean/Phrase	8420
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7	Search modes - Boolean/Phrase	1632
S7	TI (septicemi* or septicaemi*) or AB (septicemi* or septicaemi*)	Search modes - Boolean/Phrase	495
S6	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S5	MH MENINGOCOCCAL INFECTIONS+	Search modes - Boolean/Phrase	793
S4	TI (meningoencephalitis) or AB (meningoencephalitis)	Search modes - Boolean/Phrase	110
S3	TI (meningitis) or AB (meningitis)	Search modes - Boolean/Phrase	1700
S2	MH MENINGITIS, BACTERIAL+	Search modes - Boolean/Phrase	971
S1	MH MENINGITIS	Search modes - Boolean/Phrase	927

MENG_corticosteroids_embase_060308

EMBASE 1980 to 2008 Week 09

#	Searches	Results
1	exp CHILD/	600215
2	child$.tw.	463093
3	exp INFANT/	165955
4	infan$.tw.	164077
5	(baby or babies).tw.	26217
6	exp ADOLESCENT/	413580
7	teenag$.tw.	7600
8	adolescen$.tw.	78035
9	exp SCHOOLS/	35070
10	school$.tw.	70455
11	exp PUBERTY/	13593
12	pubescen$.tw.	613
13	or/1-12	1089676
14	MENINGITIS/	12981
15	exp MENINGITIS, BACTERIAL/	7268
16	meningitis.tw.	20928
17	meningoencephalitis.tw.	2400
18	exp MENINGOCOCCAL INFECTIONS/	2671
19	meningococc$.tw.	5730
20	septic?emia.tw.	9173
21	or/14-20	41780
22	exp ADRENAL CORTEX HORMONES/	362875
23	corticosteroid$.tw.	47323
24	adrenal cortex extract.tw.	8
25	(adrenal adj2 (hormone$ or steroid$)).tw.	3265
26	corticoid$.tw.	2479
27	17-ketosteroid$.tw.	414
28	glucocorticoid$.tw.	32695
29	hydroxycorticosteroid$.tw.	301
30	mineralocorticoid$.tw.	4568
31	dehydroepiandrosterone.tw.	6537
32	itrocinonide.tw.	0
33	aldosterone.tw.	17016
34	corticosterone.tw.	13357
35	cortisone.tw.	3055
36	deoxycorticosterone.tw.	2558
37	hydrocortisone.tw.	7693
38	prednisolone.tw.	12025
39	beclomethasone.tw.	2008

40 betamethasone.tw.	2671
41 clobetasol.tw.	551
42 desonide.tw.	59
43 desoxymethasone.tw.	24
44 dexamethasone.tw.	29814
45 diflucortolone.tw.	56
46 fluocinonide.tw.	93
47 fluocortolone.tw.	69
48 fluorometholone.tw.	147
49 flurandrenolone.tw.	5
50 halcinonide.tw.	46
51 methylprednisolone.tw.	7966
52 prednisone.tw.	13356
53 triamcinolone.tw.	3139
54 alclometasone.tw.	64
55 clobetasone.tw.	133
56 deoxycortone.tw.	2
57 fluclorolone.tw.	1
58 flunisolide.tw.	322
59 fluticasone.tw.	1790
60 budesonide.tw.	2893
61 deflazacort.tw.	348
62 estrenol.tw.	1
63 fluadrenolide.tw.	0
64 desoxycorticosterone.tw.	239
65 fludrocortisone.tw.	497
66 flumethasone.tw.	49
67 fluprednisolone.tw.	2
68 methandriol.tw.	6
69 norethandrolone.tw.	23
70 oxandrolone.tw.	257
71 oxymetholone.tw.	118
72 paramethasone.tw.	27
73 fluocinolone.tw.	213
74 dichlorisone.tw.	1
75 hydrocortamate.tw.	0
76 dehydrocorticosterone.tw.	274
77 medrysone.tw.	11
78 tetrahydrocorticosterone.tw.	23
79 mometasone.tw.	391
80 rimexolone.tw.	43
81 ciclesonide.tw.	167

82	or/22-81	396569
83	21 and 82	4199
84	limit 83 to english language	3254
85	84 and 13	1026
86	limit 84 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	823
87	85 or 86	1026

MENG_corticosteroids_medline_060308

Ovid MEDLINE(R) 1950 to February Week 4 2008

#	Searches	Results
1	exp CHILD/	1217391
2	child$.tw.	673967
3	exp INFANT/	754403
4	infan$.tw.	240148
5	(baby or babies).tw.	35643
6	exp ADOLESCENT/	1218782
7	teenag$.tw.	9894
8	adolescen$.tw.	100748
9	exp SCHOOLS/	57045
10	school$.tw.	121312
11	exp PUBERTY/	12530
12	pubescen$.tw.	759
13	or/1-12	2449550
14	MENINGITIS/	14398
15	exp MENINGITIS, BACTERIAL/	16342
16	meningitis.tw.	30049
17	meningoencephalitis.tw.	3945
18	exp MENINGOCOCCAL INFECTIONS/	7856
19	meningococc$.tw.	7889
20	septic?emia.tw.	12634
21	or/14-20	59918
22	exp ADRENAL CORTEX HORMONES/	275692
23	corticosteroid$.tw.	52845
24	adrenal cortex extract.tw.	34
25	(adrenal adj2 (hormone$ or steroid$)).tw.	4824
26	corticoid$.tw.	4400
27	17-ketosteroid$.tw.	2218
28	glucocorticoid$.tw.	37319
29	hydroxycorticosteroid$.tw.	1221
30	mineralocorticoid$.tw.	5237
31	dehydroepiandrosterone.tw.	7687
32	itrocinonide.tw.	0
33	aldosterone.tw.	22296
34	corticosterone.tw.	16636
35	cortisone.tw.	9472
36	deoxycorticosterone.tw.	3228
37	hydrocortisone.tw.	11486
38	prednisolone.tw.	14737
39	beclomethasone.tw.	2159
40	betamethasone.tw.	2958

41 clobetasol.tw.	497
42 desonide.tw.	60
43 desoxymethasone.tw.	24
44 dexamethasone.tw.	33715
45 diflucortolone.tw.	78
46 fluocinonide.tw.	147
47 fluocortolone.tw.	96
48 fluorometholone.tw.	152
49 flurandrenolone.tw.	40
50 halcinonide.tw.	59
51 methylprednisolone.tw.	8735
52 prednisone.tw.	15953
53 triamcinolone.tw.	3869
54 alclometasone.tw.	24
55 clobetasone.tw.	87
56 deoxycortone.tw.	19
57 fluclorolone.tw.	9
58 flunisolide.tw.	260
59 fluticasone.tw.	1641
60 budesonide.tw.	2564
61 deflazacort.tw.	271
62 estrenol.tw.	11
63 fluadrenolide.tw.	0
64 desoxycorticosterone.tw.	851
65 fludrocortisone.tw.	549
66 flumethasone.tw.	132
67 fluprednisolone.tw.	23
68 methandriol.tw.	7
69 norethandrolone.tw.	131
70 oxandrolone.tw.	296
71 oxymetholone.tw.	221
72 paramethasone.tw.	91
73 fluocinolone.tw.	398
74 dichlorisone.tw.	8
75 hydrocortamate.tw.	2
76 dehydrocorticosterone.tw.	323
77 medrysone.tw.	23
78 tetrahydrocorticosterone.tw.	47
79 mometasone.tw.	293
80 rimexolone.tw.	26
81 ciclesonide.tw.	128
82 or/22-81	342238

83 and/21,82	2527
84 limit 83 to humans	2130
85 limit 84 to english language	1417
86 85 and 13	676
87 limit 85 to "all child (0 to 18 years)"	648
88 86 or 87	676

23 What is the effect of experimental therapies in children and young people with suspected/confirmed meningococcal septicaemia?

MENG_experimental_sep_cctr_280308

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	SHOCK/ or SHOCK, SEPTIC/	333
2	septic shock.tw. or shock.ti. or acute hypotension.ti.	971
3	exp MENINGOCOCCAL INFECTIONS/	152
4	meningococc$.tw.	270
5	SEPSIS/ or BACTEREMIA/	1239
6	(sepsis or septic?emia or bacter?emia).tw.	3110
7	or/1-6	4593
8	PROTEIN C/	150
9	(protein c or blood coagulation factor inhibitor or rhapc).tw.	318
10	(apc not (antigen presenting cells or adenomatous polyposis coli or anaphase promoting complex)).tw.	140
11	(Xigris or drotrecogin).tw.	34
12	(bactericidal permeability increasing adj (protein or factor)).tw.	21
13	bpi.tw.	53
14	(Neuprex or opebacan or rbpi21).tw.	13
15	or/8-14	510
16	7 and 15	64

MENG_experimental_sep_cdsrdare_280308

EBM Reviews - Cochrane Database of Systematic Reviews 1st Quarter 2008
EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2008

#	Searches	Results
1	(SHOCK or SHOCK, SEPTIC).kw.	28
2	septic shock.ti,ab. or shock.ti. or acute hypotension.ti.	26
3	MENINGOCOCCAL INFECTION$.kw.	3
4	meningococc$.ti,ab.	8
5	(SEPSIS or SEPTIC?EMIA or BACTER?EMIA).kw.	76
6	(sepsis or septic?emia or bacter?emia).ti,ab.	101
7	or/1-6	174
8	(PROTEIN C or ACTIVATED PROTEIN C).kw.	4
9	(protein c or blood coagulation factor inhibitor or rhapc).ti,ab.	2
10	(apc not (antigen presenting cells or adenomatous polyposis coli or anaphase promoting complex)).ti,ab.	2
11	(Xigris or drotrecogin).ti,ab.	1
12	(bactericidal permeability increasing adj (protein or factor)).ti,ab.	0
13	bpi.ti,ab.	0
14	(Neuprex or opebacan or rbpi21).ti,ab.	0
15	or/8-14	5
16	7 and 15	4

MENG_experimental_sep_cinahl_280308_2

EBSCO Host Friday, July 31, 2009 10:04:15 AM

#	Query	Limiters/Expanders	Results
S31	S26 NOT S30	Search modes - Boolean/Phrase	13
S30	S27 or S28 or S29	Search modes - Boolean/Phrase	26
S29	PT editorial	Search modes - Boolean/Phrase	103521
S28	PT commentary	Search modes - Boolean/Phrase	98964
S27	PT letter	Search modes - Boolean/Phrase	77534
S26	S12 and S25	Search modes - Boolean/Phrase	0
S25	S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24	Search modes - Boolean/Phrase	203
S24	AB (neuprex or opebacan or rbpi21)	Search modes - Boolean/Phrase	1
S23	TI (neuprex or opebacan or rbpi21)	Search modes - Boolean/Phrase	2
S22	TI (bpi) or AB (bpi)	Search modes - Boolean/Phrase	106
S21	AB (bactericidal permeability increasing N1 factor)	Search modes - Boolean/Phrase	0
S20	AB (bactericidal permeability increasing N1 protein)	Search modes - Boolean/Phrase	9
S19	TI (bactericidal permeability increasing N1 factor)	Search modes - Boolean/Phrase	0
S18	TI (bactericidal permeability increasing N1 protein)	Search modes - Boolean/Phrase	7
S17	TI (xigris or drotrecogin) or AB (xigris or drotrecogin)	Search modes - Boolean/Phrase	110

S16	TI (apc) or AB (apc)	Search modes - Boolean/Phrase	228
S15	AB (protein c OR blood coagulation factor inhibitor or rhapc)	Search modes - Boolean/Phrase	317
S14	TI (protein c OR blood coagulation factor inhibitor or rhapc)	Search modes - Boolean/Phrase	183
S13	MH PROTEIN C	Search modes - Boolean/Phrase	0
S12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11	Search modes - Boolean/Phrase	1722
S11	AB (sepsis or septicemia or septicaemia or bacteremia or bacteraemia)	Search modes - Boolean/Phrase	4075
S10	TI (sepsis or septicemia or septicaemia or bacteremia or bacteraemia)	Search modes - Boolean/Phrase	2416
S9	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S8	MH SEPSIS	Search modes - Boolean/Phrase	3327
S7	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S6	MH MENINGOCOCCAL INFECTIONS+	Search modes - Boolean/Phrase	793
S5	TI (acute hypotension)	Search modes - Boolean/Phrase	6
S4	TI (shock)	Search modes - Boolean/Phrase	2460
S3	TI (septic shock) or AB (septic shock)	Search modes - Boolean/Phrase	871
S2	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046
S1	MH SHOCK	Search modes - Boolean/Phrase	903

MENG_experimental_sep_embase_280308

EMBASE 1980 to 2008 Week 12

#	Searches	Results
1	SHOCK/ or SHOCK, SEPTIC/	22827
2	septic shock.tw. or shock.ti. or acute hypotension.ti.	31863
3	exp MENINGOCOCCAL INFECTIONS/	2680
4	meningococc$.tw.	5742
5	SEPSIS/ or BACTEREMIA/	50723
6	(sepsis or septic?emia or bacter?emia).tw.	54743
7	or/1-6	118104
8	PROTEIN C/	6630
9	(protein c or blood coagulation factor inhibitor or rhapc).tw.	9665
10	(apc not (antigen presenting cells or adenomatous polyposis coli or anaphase promoting complex)).tw.	6744
11	(Xigris or drotrecogin).tw.	578
12	(bactericidal permeability increasing adj (protein or factor)).tw.	442
13	bpi.tw.	704
14	(Neuprex or opebacan or rbpi21).tw.	65
15	or/8-14	18927
16	CLINICAL TRIALS/	496005
17	(clinic$ adj5 trial$).ti,ab,sh.	116591
18	SINGLE BLIND PROCEDURE/	7429
19	DOUBLE BLIND PROCEDURE/	68653
20	RANDOM ALLOCATION/	25236
21	CROSSOVER PROCEDURE/	20075
22	PLACEBO/	111315
23	placebo$.ti,ab,sh.	161175
24	random$.ti,ab,sh.	402742
25	RANDOMIZED CONTROLLED TRIALS/	155780
26	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	89526
27	randomi?ed control$ trial$.tw.	28976
28	or/16-27	814965
29	META ANALYSIS/	33101
30	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	41351
31	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	23790
32	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1512
33	or/29-32	56381
34	review.pt.	863292
35	(medline or medlars or embase).ab.	20552
36	(scisearch or science citation index).ab.	599
37	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	6633
38	((hand or manual$) adj2 search$).tw.	2366
39	(electronic database$ or bibliographic database$ or computeri?ed database$ or	3786

	online database$).tw.	
40	(pooling or pooled or mantel haenszel).tw.	23090
41	(peto or dersimonian or "der simonian" or fixed effect).tw.	721
42	or/35-41	47711
43	34 and 42	16098
44	or/33,43	65585
45	case study.tw,sh.	21347
46	abstract report.tw,sh.	71202
47	note.tw,sh.	246060
48	short survey.tw,sh.	404018
49	letter.tw,sh.	398121
50	case report.tw,sh.	988984
51	editorial.tw,sh.	248834
52	or/45-51	2255355
53	28 not 52	724037
54	44 not 53	28328
55	or/53-54	752365
56	7 and 15 and 55	483
57	limit 56 to english language	426

MENG_experimental_sep_medline_280308

Ovid MEDLINE(R) 1950 to March Week 3 2008

#	Searches	Results
1	SHOCK/ or SHOCK, SEPTIC/	25838
2	septic shock.tw. or shock.ti. or acute hypotension.ti.	46618
3	exp MENINGOCOCCAL INFECTIONS/	8039
4	meningococc$.tw.	8076
5	SEPSIS/ or BACTEREMIA/	43606
6	(sepsis or septic?emia or bacter?emia).tw.	65530
7	or/1-6	141532
8	PROTEIN C/	4745
9	(protein c or blood coagulation factor inhibitor or rhapc).tw.	10325
10	(apc not (antigen presenting cells or adenomatous polyposis coli or anaphase promoting complex)).tw.	7281
11	(Xigris or drotrecogin).tw.	327
12	(bactericidal permeability increasing adj (protein or factor)).tw.	470
13	bpi.tw.	703
14	(Neuprex or opebacan or rbpi21).tw.	41
15	or/8-14	17990
16	randomized controlled trial.pt.	252114
17	controlled clinical trial.pt.	77520
18	DOUBLE BLIND METHOD/	96269
19	SINGLE BLIND METHOD/	11828
20	RANDOM ALLOCATION/	60524
21	RANDOMIZED CONTROLLED TRIALS/	53211
22	or/16-21	425673
23	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	93748
24	clinical trial.pt.	446746
25	exp CLINICAL TRIAL/	533233
26	exp CLINICAL TRIALS AS TOPIC/	201934
27	(clinic$ adj5 trial$).tw,sh.	124320
28	PLACEBOS/	27011
29	placebo$.tw,sh.	121322
30	random$.tw,sh.	531156
31	or/23-30	934360
32	or/22,31	939298
33	META ANALYSIS/	17590
34	META ANALYSIS AS TOPIC/	8109
35	meta analysis.pt.	17757
36	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	31519
37	(systematic$ adj5 (review$ or overview$)).tw,sh.	16211
38	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1835
39	or/33-38	43846

40	review$.pt.	1363872
41	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	28600
42	((hand or manual$) adj2 search$).tw.	3189
43	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	4825
44	(pooling or pooled or mantel haenszel).tw,sh.	28226
45	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1257
46	or/41-45	58658
47	40 and 46	24266
48	or/39,47	58394
49	letter.pt.	615918
50	case report.tw.	132753
51	comment.pt.	350904
52	editorial.pt.	216549
53	historical article.pt.	248161
54	or/49-53	1251585
55	32 not 54	904792
56	48 not 54	55076
57	or/55-56	932900
58	7 and 15 and 57	355
59	limit 58 to (english language and humans)	292

24 Should corticosteroids be used in the treatment of children and young people with suspected/confirmed meningococcal septicaemia?

MENG_corticosteroids_sep_cctr_010508

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2008

#	Searches	Results
1	SHOCK/ or SHOCK, SEPTIC/	333
2	septic shock.ti,ab. or shock.ti. or acute hypotension.ti.	971
3	exp MENINGOCOCCAL INFECTIONS/	152
4	meningococc$.ti,ab.	270
5	SEPSIS/ or BACTEREMIA/	1239
6	(sepsis or septic?emia or bacter?emia).ti,ab.	3110
7	or/1-6	4593
8	exp ADRENAL CORTEX HORMONES/	7753
9	corticosteroid$.ti,ab.	5478
10	adrenal cortex extract.ti,ab.	3
11	(adrenal adj2 (hormone$ or steroid$)).ti,ab.	150
12	corticoid$.ti,ab.	219
13	17-ketosteroid$.ti,ab.	9
14	glucocorticoid$.ti,ab.	1231
15	hydroxycorticosteroid$.ti,ab.	37
16	mineralocorticoid$.ti,ab.	109
17	dehydroepiandrosterone.ti,ab.	456
18	itrocinonide.ti,ab.	0
19	aldosterone.ti,ab.	1801
20	corticosterone.ti,ab.	37
21	cortisone.ti,ab.	175
22	deoxycorticosterone.ti,ab.	20
23	hydrocortisone.ti,ab.	1011
24	prednisolone.ti,ab.	1896
25	beclomethasone.ti,ab.	1342
26	betamethasone.ti,ab.	878
27	clobetasol.ti,ab.	230
28	desonide.ti,ab.	32
29	desoxymethasone.ti,ab.	17
30	dexamethasone.ti,ab.	2375
31	diflucortolone.ti,ab.	37
32	fluocinonide.ti,ab.	80
33	fluocortolone.ti,ab.	31
34	fluorometholone.ti,ab.	53
35	flurandrenolone.ti,ab.	7
36	halcinonide.ti,ab.	43

37 methylprednisolone.ti,ab.	1367
38 prednisone.ti,ab.	2769
39 triamcinolone.ti,ab.	639
40 alclometasone.ti,ab.	23
41 clobetasone.ti,ab.	53
42 deoxycortone.ti,ab.	0
43 fluclorolone.ti,ab.	7
44 flunisolide.ti,ab.	162
45 fluticasone.ti,ab.	1772
46 budesonide.ti,ab.	1852
47 deflazacort.ti,ab.	99
48 estrenol.ti,ab.	0
49 fluadrenolide.ti,ab.	0
50 desoxycorticosterone.ti,ab.	7
51 fludrocortisone.ti,ab.	56
52 flumethasone.ti,ab.	21
53 fluprednisolone.ti,ab.	1
54 methandriol.ti,ab.	0
55 norethandrolone.ti,ab.	5
56 oxandrolone.ti,ab.	85
57 oxymetholone.ti,ab.	17
58 paramethasone.ti,ab.	7
59 fluocinolone.ti,ab.	102
60 dichlorisone.ti,ab.	0
61 hydrocortamate.ti,ab.	0
62 dehydrocorticosterone.ti,ab.	0
63 medrysone.ti,ab.	7
64 tetrahydrocorticosterone.ti,ab.	2
65 mometasone.ti,ab.	293
66 rimexolone.ti,ab.	18
67 ciclesonide.ti,ab.	180
68 or/8-67	23605
69 7 and 68	205

MENG_corticosteroids_sep_cdsrdare_010508

Cochrane Database of Systematic Reviews 1st Quarter 2008
Database of Abstracts of Reviews of Effects 1st Quarter 2008
CDSR, DARE

#	Searches	Results
1	(SHOCK or SHOCK, SEPTIC).kw.	29
2	septic shock.ti,ab. or shock.ti. or acute hypotension.ti.	28
3	MENINGOCOCCAL INFECTION$.kw.	4
4	meningococc$.ti,ab.	9
5	(SEPSIS or SEPTIC?EMIA or BACTER?EMIA).kw.	82
6	(sepsis or septic?emia or bacter?emia).ti,ab.	104
7	or/1-6	182
8	(ADRENAL CORTEX HORMONE$ or CORTICOSTEROID$).kw.	215
9	corticosteroid$.ti,ab.	299
10	adrenal cortex extract.ti,ab.	0
11	(adrenal adj2 (hormone$ or steroid$)).ti,ab.	1
12	corticoid$.ti,ab.	0
13	17-ketosteroid$.ti,ab.	0
14	glucocorticoid$.ti,ab.	26
15	hydroxycorticosteroid$.ti,ab.	0
16	mineralocorticoid$.ti,ab.	0
17	dehydroepiandrosterone.ti,ab.	5
18	itrocinonide.ti,ab.	0
19	aldosterone.ti,ab.	5
20	corticosterone.ti,ab.	0
21	cortisone.ti,ab.	2
22	deoxycorticosterone.ti,ab.	0
23	hydrocortisone.ti,ab.	11
24	prednisolone.ti,ab.	32
25	beclomethasone.ti,ab.	15
26	betamethasone.ti,ab.	8
27	clobetasol.ti,ab.	1
28	desonide.ti,ab.	0
29	desoxymethasone.ti,ab.	0
30	dexamethasone.ti,ab.	41
31	diflucortolone.ti,ab.	0
32	fluocinonide.ti,ab.	1
33	fluocortolone.ti,ab.	0
34	fluorometholone.ti,ab.	0
35	flurandrenolone.ti,ab.	0
36	halcinonide.ti,ab.	0
37	methylprednisolone.ti,ab.	15
38	prednisone.ti,ab.	30

39 triamcinolone.ti,ab.	7
40 alclometasone.ti,ab.	0
41 clobetasone.ti,ab.	0
42 deoxycortone.ti,ab.	0
43 fluclorolone.ti,ab.	0
44 flunisolide.ti,ab.	3
45 fluticasone.ti,ab.	19
46 budesonide.ti,ab.	25
47 deflazacort.ti,ab.	3
48 estrenol.ti,ab.	0
49 fluadrenolide.ti,ab.	0
50 desoxycorticosterone.ti,ab.	0
51 fludrocortisone.ti,ab.	1
52 flumethasone.ti,ab.	0
53 fluprednisolone.ti,ab.	0
54 methandriol.ti,ab.	0
55 norethandrolone.ti,ab.	0
56 oxandrolone.ti,ab.	0
57 oxymetholone.ti,ab.	0
58 paramethasone.ti,ab.	0
59 fluocinolone.ti,ab.	1
60 dichlorisone.ti,ab.	0
61 hydrocortamate.ti,ab.	0
62 dehydrocorticosterone.ti,ab.	0
63 medrysone.ti,ab.	0
64 tetrahydrocorticosterone.ti,ab.	0
65 mometasone.ti,ab.	2
66 rimexolone.ti,ab.	0
67 ciclesonide.ti,ab.	2
68 or/8-67	481
69 7 and 68	15

MENG_corticosteroids_sep_cinahl_010508_2
EBSCO Host Friday, July 31, 2009 9:58:19 AM

#	Query	Limiters/Expanders	Results
		Limiters - English Language	
S34	S13 and S24 and S31	Search modes - Boolean/Phrase	0
S33	S13 and S24 and S31	Search modes - Boolean/Phrase	0
S32	S13 and S24 and S31	Search modes - Boolean/Phrase	0
S31	S25 or S26 or S27 or S28 or S29 or S30	Search modes - Boolean/Phrase	103
S30	TI (corticoid*) or AB (corticoid*)	Search modes - Boolean/Phrase	36
S29	AB (adrenal N2 hormone*) or AB (adrenal N2 steroid*)	Search modes - Boolean/Phrase	53
S28	TI (adrenal N2 hormone*) or TI (adrenal N2 steroid*)	Search modes - Boolean/Phrase	10
S27	TI (adrenal cortex extract) or AB (adrenal cortex extract)	Search modes - Boolean/Phrase	1
S26	TI (corticosteroid*) or AB (corticosteroid*)	Search modes - Boolean/Phrase	4539
S25	MH ADRENAL CORTEX HORMONES+	Search modes - Boolean/Phrase	8420
S24	S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23	Search modes - Boolean/Phrase	174
S23	AB (sepsis or septicaemia or septicemia or bacteraemia or bacteremia)	Search modes - Boolean/Phrase	4075
S22	TI (sepsis or septicaemia or septicemia or bacteraemia or bacteremia)	Search modes - Boolean/Phrase	2416
S21	MH BACTEREMIA	Search modes -	1700

		Boolean/Phrase	
S20	MH SEPSIS	Search modes - Boolean/Phrase	3327
S19	TI (meningococc*) or AB (meningococc*)	Search modes - Boolean/Phrase	627
S18	TI (acute hypotension)	Search modes - Boolean/Phrase	6
S17	TI shock	Search modes - Boolean/Phrase	2460
S16	TI (septic shock) or AB (septic shock)	Search modes - Boolean/Phrase	871
S15	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046
S14	MH SHOCK	Search modes - Boolean/Phrase	903
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12	Search modes - Boolean/Phrase	1733
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55
S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004
S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes -	10049

		Boolean/Phrase	
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes - Boolean/Phrase	82965
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_corticosteroids_sep_embase_010508

EMBASE 1980 to 2008 Week 17

#	Searches	Results
1	exp CHILD/	604854
2	child$.tw.	467323
3	exp INFANT/	167174
4	infan$.tw.	165265
5	(baby or babies).tw.	26427
6	exp ADOLESCENT/	417543
7	teenag$.tw.	7679
8	adolescen$.tw.	78995
9	exp SCHOOLS/	35497
10	school$.tw.	71252
11	exp PUBERTY/	13727
12	pubescen$.tw.	622
13	or/1-12	1099133
14	*SHOCK/ or *SHOCK, SEPTIC/	10500
15	septic shock.tw. or shock.ti. or acute hypotension.ti.	32025
16	exp MENINGOCOCCAL INFECTIONS/	2694
17	meningococc$.tw.	5757
18	*SEPSIS/ or *BACTEREMIA/	22378
19	(sepsis or septic?emia or bacter?emia).ti.	18032
20	or/14-19	65918
21	exp ADRENAL CORTEX HORMONES/	366495
22	corticosteroid$.tw.	47739
23	adrenal cortex extract.tw.	8
24	(adrenal adj2 (hormone$ or steroid$)).tw.	3276
25	corticoid$.tw.	2498
26	17-ketosteroid$.tw.	415
27	glucocorticoid$.tw.	32957
28	hydroxycorticosteroid$.tw.	301
29	mineralocorticoid$.tw.	4608
30	dehydroepiandrosterone.tw.	6586
31	itrocinonide.tw.	0
32	aldosterone.tw.	17115
33	corticosterone.tw.	13448
34	cortisone.tw.	3069
35	deoxycorticosterone.tw.	2568
36	hydrocortisone.tw.	7722
37	prednisolone.tw.	12116
38	beclomethasone.tw.	2012
39	betamethasone.tw.	2681

40 clobetasol.tw.	554
41 desonide.tw.	60
42 desoxymethasone.tw.	24
43 dexamethasone.tw.	29997
44 diflucortolone.tw.	56
45 fluocinonide.tw.	93
46 fluocortolone.tw.	69
47 fluorometholone.tw.	149
48 flurandrenolone.tw.	5
49 halcinonide.tw.	46
50 methylprednisolone.tw.	8022
51 prednisone.tw.	13434
52 triamcinolone.tw.	3191
53 alclometasone.tw.	64
54 clobetasone.tw.	133
55 deoxycortone.tw.	2
56 fluclorolone.tw.	1
57 flunisolide.tw.	322
58 fluticasone.tw.	1814
59 budesonide.tw.	2912
60 deflazacort.tw.	350
61 estrenol.tw.	1
62 fluadrenolide.tw.	0
63 desoxycorticosterone.tw.	240
64 fludrocortisone.tw.	503
65 flumethasone.tw.	49
66 fluprednisolone.tw.	2
67 methandriol.tw.	6
68 norethandrolone.tw.	23
69 oxandrolone.tw.	258
70 oxymetholone.tw.	118
71 paramethasone.tw.	27
72 fluocinolone.tw.	214
73 dichlorisone.tw.	1
74 hydrocortamate.tw.	0
75 dehydrocorticosterone.tw.	277
76 medrysone.tw.	11
77 tetrahydrocorticosterone.tw.	23
78 mometasone.tw.	396
79 rimexolone.tw.	43
80 ciclesonide.tw.	171
81 or/21-80	400360

82 13 and 20 and 81	619
83 limit 82 to english language	468

MENG_corticosteroids_sep_medline_010508

Ovid MEDLINE(R) 1950 to April Week 4 2008

#	Searches	Results
1	exp CHILD/	1250986
2	child$.tw.	692675
3	exp INFANT/	776469
4	infan$.tw.	246906
5	(baby or babies).tw.	36562
6	exp ADOLESCENT/	1253283
7	teenag$.tw.	10195
8	adolescen$.tw.	103566
9	exp SCHOOLS/	58538
10	school$.tw.	124564
11	exp PUBERTY/	12809
12	pubescen$.tw.	786
13	or/1-12	2517465
14	SHOCK/ or SHOCK, SEPTIC/	25975
15	septic shock.tw. or shock.ti. or acute hypotension.ti.	46888
16	exp MENINGOCOCCAL INFECTIONS/	8075
17	meningococc$.tw.	8109
18	SEPSIS/ or BACTEREMIA/	43974
19	(sepsis or septic?emia or bacter?emia).tw.	66041
20	or/14-19	142472
21	exp ADRENAL CORTEX HORMONES/	281235
22	corticosteroid$.tw.	54097
23	adrenal cortex extract.tw.	35
24	(adrenal adj2 (hormone$ or steroid$)).tw.	4896
25	corticoid$.tw.	4479
26	17-ketosteroid$.tw.	2257
27	glucocorticoid$.tw.	37821
28	hydroxycorticosteroid$.tw.	1241
29	mineralocorticoid$.tw.	5334
30	dehydroepiandrosterone.tw.	7804
31	itrocinonide.tw.	0
32	aldosterone.tw.	22718
33	corticosterone.tw.	16835
34	cortisone.tw.	9653
35	deoxycorticosterone.tw.	3301
36	hydrocortisone.tw.	11659
37	prednisolone.tw.	15015
38	beclomethasone.tw.	2198
39	betamethasone.tw.	3030
40	clobetasol.tw.	517

41 desonide.tw.	64
42 desoxymethasone.tw.	24
43 dexamethasone.tw.	34145
44 diflucortolone.tw.	78
45 fluocinonide.tw.	160
46 fluocortolone.tw.	97
47 fluorometholone.tw.	158
48 flurandrenolone.tw.	46
49 halcinonide.tw.	63
50 methylprednisolone.tw.	8867
51 prednisone.tw.	16290
52 triamcinolone.tw.	4056
53 alclometasone.tw.	25
54 clobetasone.tw.	87
55 deoxycortone.tw.	31
56 fluclorolone.tw.	9
57 flunisolide.tw.	262
58 fluticasone.tw.	1678
59 budesonide.tw.	2613
60 deflazacort.tw.	273
61 estrenol.tw.	13
62 fluadrenolide.tw.	0
63 desoxycorticosterone.tw.	862
64 fludrocortisone.tw.	562
65 flumethasone.tw.	139
66 fluprednisolone.tw.	23
67 methandriol.tw.	7
68 norethandrolone.tw.	133
69 oxandrolone.tw.	302
70 oxymetholone.tw.	222
71 paramethasone.tw.	94
72 fluocinolone.tw.	419
73 dichlorisone.tw.	8
74 hydrocortamate.tw.	2
75 dehydrocorticosterone.tw.	326
76 medrysone.tw.	23
77 tetrahydrocorticosterone.tw.	47
78 mometasone.tw.	297
79 rimexolone.tw.	26
80 ciclesonide.tw.	131
81 or/21-80	349140
82 13 and 20 and 81	1188

83 limit 82 to (english language and humans)	878

25 What is the effect on outcomes of using scoring systems in children and young people with suspected/confirmed meningococcal septicaemia?

MENG_scoring_systems_septicaemia_cctr_250608

EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2008

#	Searches	Results
1	exp CHILD/	38473
2	child$.ti,ab.	32312
3	exp INFANT/	17332
4	infan$.ti,ab.	11877
5	(baby or babies).ti,ab.	1645
6	toddler?.ti,ab.	240
7	ADOLESCENT/	54093
8	teen$.ti,ab.	464
9	adolescen$.ti,ab.	4499
10	exp SCHOOLS/	494
11	school$.ti,ab.	5850
12	exp PUBERTY/	205
13	pubescen$.ti,ab.	10
14	or/1-13	95068
15	SHOCK, SEPTIC/	252
16	SHOCK/	96
17	shock.ti.	828
18	(septic adj shock).ti,ab.	375
19	(sepsis adj5 hypotension).ti,ab.	17
20	BACTEREMIA/	380
21	(severe adj2 sepsis).ti,ab.	267
22	(septic?emi? or bacter?emi?).ti,ab.	1258
23	(meningococc$ adj3 (disease or infection? or sepsis or septic or toxic or endotoxic)).ti,ab.	62
24	MENINGOCOCCAL INFECTIONS/	72
25	or/15-24	2697
26	"SEVERITY OF ILLNESS INDEX"/	7518
27	((scoring or rating) adj3 (system? or scale?)).ti,ab.	7398
28	((score? or scoring or scale? or criteria or criterion or rating? or algorithm? or tool? or indices or index$) adj3 (prognos?s or prognostic$ or predict$ or severity or symptom?)).ti,ab.	10685
29	(bedside adj2 predict$).ti,ab.	1
30	((assess$ or predict$) adj3 severity).ti,ab.	1364
31	GMSPS.ti,ab.	0
32	Glasgow meningococcal septic?emia prognostic.ti,ab.	1
33	((Lewis or Ansari or Istanbul or Bjark or Kahn or Leclerc or Niklasson or Damrosch or Stokland) adj3 (scale? or score? or rating? or index)).ti,ab.	5

34 (Gedde Dahl$ or PRISM III or PRISM 3).ti,ab.	2
35 (pediatric risk of mortality score? or paediatric risk of mortality score?).ti,ab.	6
36 (paediatric index of mortality or PIM2).ti,ab.	1
37 (Malley adj3 score?).ti,ab.	0
38 or/26-37	23208
39 and/14,25	732
40 and/38-39	40

MENG_scoring_systems_septicaemia_cdsrdare_250608

CDSR, DARE

#	Searches	Results
1	CHILD.kw.	1140
2	child$.ti,ab.	1418
3	INFANT.kw.	802
4	infan$.ti,ab.	529
5	(baby or babies).ti,ab.	134
6	toddler?.ti,ab.	5
7	ADOLESCENT.kw.	733
8	teen$.ti,ab.	10
9	adolescen$.ti,ab.	209
10	SCHOOLS.kw.	21
11	school$.ti,ab.	115
12	PUBERTY.kw.	0
13	pubescen$.ti,ab.	0
14	or/1-13	2670
15	SEPTIC SHOCK.kw.	0
16	SHOCK.kw.	30
17	shock.ti.	27
18	(septic adj shock).ti,ab.	9
19	(sepsis adj5 hypotension).ti,ab.	1
20	(BACTEREMIA or SEPTICEMIA).kw.	29
21	(severe adj2 sepsis).ti,ab.	12
22	(septic?emi? or bacter?emi?).ti,ab.	23
23	(meningococc$ adj3 (disease or infection? or sepsis or septic or toxic or endotoxic)).ti,ab.	6
24	MENINGOCOCCAL INFECTION$.kw.	4
25	or/15-24	99
26	(SCORING SYSTEM$ or RATING SCALE$ or SEVERITY OF ILLNESS INDEX or PREDICTOR?).kw.	198
27	((scoring or rating) adj3 (system? or scale?)).ti,ab.	90
28	((score? or scoring or scale? or criteria or criterion or rating? or algorithm? or tool? or indices or index$) adj3 (prognos?s or prognostic$ or predict$ or severity or symptom?)).ti,ab.	108
29	(bedside adj2 predict$).ti,ab.	0
30	((assess$ or predict$) adj3 severity).ti,ab.	15
31	GMSPS.ti,ab.	0
32	Glasgow meningococcal septic?emia prognostic.ti,ab.	0
33	((Lewis or Ansari or Istanbul or Bjark or Kahn or Leclerc or Niklasson or Damrosch or Stokland) adj3 (scale? or score? or rating? or index)).ti,ab.	0
34	(Gedde Dahl$ or PRISM III or PRISM 3).ti,ab.	0
35	(pediatric risk of mortality score? or paediatric risk of mortality score?).ti,ab.	0

36 (paediatric index of mortality or PIM2).ti,ab.	0
37 (Malley adj3 score?).ti,ab.	0
38 or/26-37	398
39 and/14,25	25
40 and/38-39	0

MENG_scoring_systems_septicaemia_cinahl_250608_5
EBSCO Host Friday, July 31, 2009 5:59:00 AM

#	Query	Limiters/Expanders	Results
S54	S15 and S36 and S53	Search modes - Boolean/Phrase	0
S53	S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52	Search modes - Boolean/Phrase	160
S52	TI (clinical assessment tool*) or AB (clinical assessment tool*)	Search modes - Boolean/Phrase	64
S51	TI (paediatric index of mortality) or AB (paediatric index of mortality)	Search modes - Boolean/Phrase	5
S50	TI (pediatric index of mortality) or AB (pediatric index of mortality)	Search modes - Boolean/Phrase	3
S49	AB (glasgow meningococcal septicemia prognostic)	Search modes - Boolean/Phrase	0
S48	TI (glasgow meningococcal septicemia prognostic)	Search modes - Boolean/Phrase	0
S47	AB (glasgow meningococcal septicaemia prognostic)	Search modes - Boolean/Phrase	0
S46	TI (glasgow meningococcal septicaemia prognostic)	Search modes - Boolean/Phrase	0
S45	AB (glascow meningococcal septicaemia prognostic)	Search modes - Boolean/Phrase	0
S44	TI (glascow meningococcal septicaemia prognostic)	Search modes - Boolean/Phrase	0
S43	TI (GMSPS) or AB (GMSPS)	Search modes - Boolean/Phrase	0
S42	AB (assess* N3 severity) or AB (predict* N3 severity)	Search modes - Boolean/Phrase	1530
S41	TI (assess* N3 severity) or TI (predict* N3 severity)	Search modes - Boolean/Phrase	236
S40	TI (bedside N2 predict*) or AB (bedside N2 predict*)	Search modes - Boolean/Phrase	21
S39	AB (scoring N3 scale*) or AB (scoring N3 system*) or AB (rating N3 system*) or AB (rating N3 scale*)	Search modes - Boolean/Phrase	5740
S38	TI (scoring N3 scale*) or TI (scoring N3 system*) or TI (rating N3 system*) or TI (rating N3 scale*)	Search modes - Boolean/Phrase	737
S37	MH CLINICAL ASSESSMENT TOOLS+	Search modes - Boolean/Phrase	55201

S36	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35	Search modes - Boolean/Phrase	286
S35	TI shock*	Search modes - Boolean/Phrase	2862
S34	MH SHOCK	Search modes - Boolean/Phrase	903
S33	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S32	TI (septicemi* or bacteremi*) or AB (septicemi* or bacteremi*)	Search modes - Boolean/Phrase	1340
S31	TI (septicaemi* or bacteraemi*) or AB (septicaemi* or bacteraemi*)	Search modes - Boolean/Phrase	485
S30	TI (meningococc* N3 endotoxic) or AB (meningococc* N3 endotoxic)	Search modes - Boolean/Phrase	1
S29	TI (meningococc* N3 toxic) or AB (meningococc* N3 toxic)	Search modes - Boolean/Phrase	0
S28	TI (meningococc* N3 septic) or AB (meningococc* N3 septic)	Search modes - Boolean/Phrase	18
S27	TI (meningococc* N3 sepsis) or AB (meningococc* N3 sepsis)	Search modes - Boolean/Phrase	20
S26	TI (meningococc* N3 infection*) or AB (meningococc* N3 infection*)	Search modes - Boolean/Phrase	49
S25	TI (meningococc* N3 disease) or AB (meningococc* N3 disease)	Search modes - Boolean/Phrase	265
S24	TI (bacteraemi* shock) or AB (bacteraemi* shock)	Search modes - Boolean/Phrase	0
S23	TI (bacteremi* shock) or AB (bacteremi* shock)	Search modes - Boolean/Phrase	0
S22	TI (bacteremic shock) or AB (bacteremic shock)	Search modes - Boolean/Phrase	0
S21	TI (septic shock) or AB (septic shock)	Search modes - Boolean/Phrase	871
S20	TI (severe N2 sepsis) or AB (severe N2 sepsis)	Search modes - Boolean/Phrase	606
S19	MH NEONATAL SEPSIS	Search modes - Boolean/Phrase	284
S18	MH BACTEREMIA	Search modes - Boolean/Phrase	1700
S17	TI (sepsis N5 hypotension) or AB (sepsis N5 hypotension)	Search modes - Boolean/Phrase	29

S16	MH SHOCK, SEPTIC	Search modes - Boolean/Phrase	1046
S15	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14	Search modes - Boolean/Phrase	1757
S14	AB (newborn*) or AB (neonate*)	Search modes - Boolean/Phrase	7636
S13	TI (newborn*) or TI (neonate*)	Search modes - Boolean/Phrase	5897
S12	TI (pubescen*) or AB (pubescen*)	Search modes - Boolean/Phrase	55
S11	MH PUBERTY+	Search modes - Boolean/Phrase	1004
S10	TI (school*) or AB (school*)	Search modes - Boolean/Phrase	38329
S9	MH SCHOOLS+	Search modes - Boolean/Phrase	21736
S8	TI (adolescen*) or AB (adolescen*)	Search modes - Boolean/Phrase	28859
S7	TI (teenag*) or AB (teenag*)	Search modes - Boolean/Phrase	3515
S6	MH ADOLESCENCE+	Search modes - Boolean/Phrase	128199
S5	TI (baby or babies) or AB (baby or babies)	Search modes - Boolean/Phrase	10049
S4	TI (infan*) or AB (infan*)	Search modes - Boolean/Phrase	28358
S3	MH INFANT+	Search modes - Boolean/Phrase	82965
S2	TI (child*) or AB (child*)	Search modes - Boolean/Phrase	117798
S1	MH CHILD+	Search modes - Boolean/Phrase	199308

MENG_scoring_systems_septicaemia_embase_250608

EMBASE 1980 to 2008 Week 25

#	Searches	Results
1	exp CHILD/	609746
2	child$.tw.	471837
3	exp INFANT/	168438
4	infan$.tw.	166476
5	(baby or babies).tw.	26678
6	exp ADOLESCENT/	421627
7	teenag$.tw.	7743
8	adolescen$.tw.	80067
9	exp SCHOOLS/	35942
10	school$.tw.	72107
11	exp PUBERTY/	13877
12	pubescen$.tw.	628
13	NEWBORN/	175189
14	(newborn? or neonate?).ti,ab.	94943
15	or/1-14	1219366
16	SEPTIC SHOCK/	12493
17	SEPTICEMIA/	8583
18	((septic or bacter?emic) adj shock).ti,ab.	8349
19	(sepsis adj5 hypotension).ti,ab.	252
20	BACTEREMIA/	13869
21	(severe adj2 sepsis).ti,ab.	2778
22	(septic?emi? or bacter?emi?).ti,ab.	22608
23	(meningococc$ adj3 (sepsis or septic or disease or infection? or toxic or endotoxic)).ti,ab.	2539
24	SHOCK/	11176
25	shock.ti.	27256
26	or/16-25	77904
27	SCORING SYSTEM/	94746
28	RATING SCALE/	50992
29	((scoring or rating) adj3 (system? or scale?)).ti,ab.	31518
30	PREDICTION/	122296
31	((assess$ or predict$) adj3 severity).ti,ab.	8189
32	((score? or scoring or scale? or criteria or criterion or rating? or algorithm? or indices or index$ or tool?) adj3 (prognos?s or prognostic$ or predict$ or severity or symptom?)).ti,ab.	50391
33	(bedside adj2 predict$).ti,ab.	42
34	GMSPS.ti,ab.	18
35	Glasgow meningococcal septic?emia prognostic.ti,ab.	26
36	((Lewis or Ansari or Istanbul or Bjark or Kahn or Leclerc or Niklasson or Damrosch or Stokland) adj3 (scale? or score? or rating? or index)).ti,ab.	50

37 (Gedde Dahl$ or PRISM III or PRISM 3).ti,ab.	38
38 (pediatric risk of mortality score? or paediatric risk of mortality score?).ti,ab.	113
39 paediatric index of mortality.ti,ab.	21
40 (Malley adj3 score?).ti,ab.	1
41 or/27-40	295642
42 and/15,26	13238
43 and/41-42	539
44 (letter or editorial or note).pt,sh.	891990
45 CASE REPORT/	994402
46 (case report or case study).ti.	96935
47 or/44-46	1796889
48 43 not 47	510
49 limit 48 to (human and english language)	461

MENG_scoring_systems_septicaemia_medline_250608

Ovid MEDLINE(R) 1950 to June Week 2 2008

#	Searches	Results
1	exp CHILD/	1263775
2	child$.ti,ab.	701617
3	exp INFANT/	784019
4	infan$.ti,ab.	249731
5	(baby or babies).ti,ab.	36967
6	toddler?.ti,ab.	3251
7	exp ADOLESCENT/	1266935
8	teen$.ti,ab.	14060
9	adolescen$.ti,ab.	105214
10	exp SCHOOLS/	58956
11	school$.ti,ab.	126010
12	exp PUBERTY/	12917
13	pubescen$.ti,ab.	795
14	or/1-13	2543898
15	SHOCK, SEPTIC/	14893
16	SHOCK/	11751
17	shock.ti.	41793
18	(septic adj shock).ti,ab.	9214
19	(sepsis adj5 hypotension).ti,ab.	288
20	BACTEREMIA/	12031
21	(severe adj2 sepsis).ti,ab.	2872
22	(septic?emi? or bacter?emi?).ti,ab.	29092
23	(meningococc$ adj3 (disease or infection? or sepsis or septic or toxic or endotoxic)).ti,ab.	3610
24	MENINGOCOCCAL INFECTIONS/	4396
25	or/15-24	96992
26	"SEVERITY OF ILLNESS INDEX"/	96948
27	((scoring or rating) adj3 (system? or scale?)).ti,ab.	34270
28	((score? or scoring or scale? or criteria or criterion or rating? or algorithm? or tool? or indices or index$) adj3 (prognos?s or prognostic$ or predict$ or severity or symptom?)).ti,ab.	55269
29	(bedside adj2 predict$).ti,ab.	42
30	((assess$ or predict$) adj3 severity).ti,ab.	9078
31	GMSPS.ti,ab.	21
32	Glasgow meningococcal septic?emia prognostic.ti,ab.	27
33	((Lewis or Ansari or Istanbul or Bjark or Kahn or Leclerc or Niklasson or Damrosch or Stokland) adj3 (scale? or score? or rating? or index)).ti,ab.	63
34	(Gedde Dahl$ or PRISM III or PRISM 3).ti,ab.	47
35	(pediatric risk of mortality score? or paediatric risk of mortality score?).ti,ab.	127
36	(paediatric index of mortality or PIM2).ti,ab.	122

37 (Malley adj3 score?).ti,ab.	1
38 or/26-37	175682
39 and/14,25	20057
40 and/38-39	720
41 (letter or editorial or note).pt.	854496
42 CASE REPORTS/	1390155
43 (case report or case study).ti.	120711
44 or/41-43	2130736
45 40 not 44	638
46 limit 45 to (english language and humans)	565

26 Do specialist transport teams improve outcomes and/or reduce adverse incidents during the transfer of children with meningococcal disease?

MENG_sptransport_cctr_050509

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2009

#	Searches	Results
1	exp CHILD/	30320
2	child$.ti,ab.	33908
3	exp INFANT/	17921
4	infan$.ti,ab.	12323
5	(baby or babies).ti,ab.	1696
6	toddler?.ti,ab.	261
7	(neonat$ or newborn?).ti,ab.	6928
8	ADOLESCENT/	56381
9	adolescen$.ti,ab.	4994
10	teen$.ti,ab.	510
11	exp SCHOOLS/	580
12	school$.ti,ab.	6316
13	exp PUBERTY/	218
14	pubescen$.ti,ab.	12
15	(pediatric? or paediatric?).ti,ab.	6479
16	or/1-15	102480
17	MENINGITIS, MENINGOCOCCAL/	90
18	MENINGOCOCCAL INFECTIONS/	74
19	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	81
20	meningococc?emi$.ti,ab.	5
21	NEISSERIA MENINGITIDIS/	124
22	(neisseria meningitid$ or n meningitid$).ti,ab.	140
23	(meningococcus or meningococci$).ti,ab.	54
24	SEPSIS/	915
25	(sepsis or septic or septic?emi$ or shock$ or endotoxic$ or collaps$).ti,ab.	5603
26	SHOCK, SEPTIC/	263
27	SHOCK, TOXIC/	263
28	SHOCK, ENDOTOXIC/	263
29	or/17-28	6186
30	INTENSIVE CARE UNITS/ or exp INTENSIVE CARE UNITS, PEDIATRIC/	1129
31	PICU.ti,ab.	43
32	PMICU.ti,ab.	0
33	HOSPITALS, SPECIAL/ or HOSPITAL, PEDIATRIC/	23
34	((intensive or tertiary) adj3 care).ti,ab.	5489
35	or/30-34	5828
36	TRANSPORTATION OF PATIENTS/	59

37 exp PATIENT CARE TEAM/	729
38 PATIENT TRANSFER/	55
39 mobile intensive care.ti,ab.	25
40 ((dedicated or p?ediatric) adj retrieval team$).ti,ab.	0
41 MOBILE HEALTH UNITS/	32
42 specialist transport team$.ti,ab.	0
43 (specialist adj2 transfer$).ti,ab.	0
44 intensivist$.ti,ab.	21
45 (interhospital adj2 (transport$ or transfer$)).ti,ab.	12
46 or/36-45	914
47 and/16,29,35,46	1

MENG_sptransport_cdsrdare_050509

DARE, CDSR

#	Searches	Results
1	CHILD.kw.	1293
2	child$.tw,tx.	4116
3	INFANT.kw.	878
4	infan$.tw,tx.	1626
5	(baby or babies).tw,tx.	803
6	toddler?.tw,tx.	76
7	(neonat$ or newborn?).tw,tx.	1364
8	ADOLESCENT.kw.	848
9	adolescen$.tw,tx.	1442
10	teen$.tw,tx.	197
11	SCHOOLS.kw.	29
12	school$.tw,tx.	2513
13	PUBERTY.kw.	0
14	pubescen$.tw,tx.	16
15	(pediatric? or paediatric?).tw,tx.	1355
16	or/1-15	6029
17	MENINGITIS, MENINGOCOCCAL.kw.	4
18	MENINGOCOCCAL INFECTIONS.kw.	5
19	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).tw,tx.	12
20	meningococc?emi$.tw,tx.	2
21	NEISSERIA MENINGITIDIS.kw.	4
22	(neisseria meningitid$ or n meningitid$).tw,tx.	6
23	(meningococcus or meningococci$).tw,tx.	8
24	SEPSIS.kw.	63
25	(sepsis or septic or septic?emi$ or shock$ or endotoxic$ or collaps$).tw,tx.	1066
26	SHOCK, SEPTIC.kw.	16
27	SHOCK, TOXIC.kw.	0
28	SHOCK, ENDOTOXIC.kw.	0
29	or/17-28	1072
30	(INTENSIVE CARE UNITS or INTENSIVE CARE UNITS, PEDIATRIC).kw.	53
31	PICU.tw,tx.	7
32	PMICU.tw,tx.	0
33	(HOSPITALS, SPECIAL or HOSPITAL, PEDIATRIC).kw.	4
34	((intensive or tertiary) adj3 care).tw,tx.	1032
35	or/30-34	1035
36	TRANSPORTATION OF PATIENTS.kw.	4
37	PATIENT CARE TEAM.kw.	46
38	PATIENT TRANSFER.kw.	3
39	mobile intensive care.tw,tx.	1
40	((dedicated or p?ediatric) adj retrieval team$).tw,tx.	0

41 MOBILE HEALTH UNITS.kw.	1
42 specialist transport team$.tw,tx.	0
43 (specialist adj2 transfer$).tw,tx.	2
44 intensivist$.tw,tx.	7
45 (interhospital adj2 (transport$ or transfer$)).tw,tx.	0
46 or/36-45	62
47 and/16,29,35,46	0

MENG_sptransport_cinahl_240409_6
EBSCO Host Friday, July 31, 2009 8:34:23 AM

Friday, July 31, 2009 8:34:23 AM

#	Query	Limiters/Expanders	Results
S63	S17 and S32 and S42 and S62	Search modes - Boolean/Phrase	0
S62	S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61	Search modes - Boolean/Phrase	177
S61	AB (interhospital N2 transfer*)	Search modes - Boolean/Phrase	52
S60	AB (interhospital N2 transport*)	Search modes - Boolean/Phrase	30
S59	TI (interhospital N2 transfer*)	Search modes - Boolean/Phrase	38
S58	TI (interhospital N2 transport*)	Search modes - Boolean/Phrase	28
S57	TI (intensivist*) or AB (intensivist*)	Search modes - Boolean/Phrase	288
S56	AB (specialist N2 transfer*)	Search modes - Boolean/Phrase	16
S55	TI (specialist N2 transfer*)	Search modes - Boolean/Phrase	1
S54	AB specialist transport team*	Search modes - Boolean/Phrase	0
S53	AB specialist transport team*	Search modes - Boolean/Phrase	0
S52	TI specialist transport team*	Search modes - Boolean/Phrase	0
S51	MH MOBILE HEALTH UNITS	Search modes - Boolean/Phrase	746
S50	AB (pediatric* N3 retrieval team*) or AB (paediatric* N3 retrieval team*)	Search modes - Boolean/Phrase	1
S49	TI (pediatric* N3 retrieval team*) or TI (paediatric* N3 retrieval team*)	Search modes - Boolean/Phrase	1
S48	AB (dedicated N3 retrieval team*)	Search modes - Boolean/Phrase	2
S47	TI (dedicated N3 retrieval team*)	Search modes - Boolean/Phrase	1
S46	AB mobile intensive care	Search modes -	26

		Boolean/Phrase	
S45	TI mobile intensive care	Search modes - Boolean/Phrase	14
S44	MH TRANSFER, DISCHARGE	Search modes - Boolean/Phrase	1873
S43	MH TRANSPORTATION OF PATIENTS	Search modes - Boolean/Phrase	2038
S42	S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41	Search modes - Boolean/Phrase	92
S41	TI (tertiary N3 care*) or AB (tertiary N3 care*)	Search modes - Boolean/Phrase	3470
S40	TI (intensive N3 care*) or AB (intensive N3 care*)	Search modes - Boolean/Phrase	14383
S39	MH HOSPITALS, PEDIATRIC	Search modes - Boolean/Phrase	2886
S38	MH HOSPITALS, SPECIAL	Search modes - Boolean/Phrase	1148
S37	TI (PMICU) or AB (PMICU)	Search modes - Boolean/Phrase	0
S36	TI (PICU) or AB (PICU)	Search modes - Boolean/Phrase	463
S35	MH PEDIATRIC UNITS	Search modes - Boolean/Phrase	339
S34	MH INTENSIVE CARE UNITS, PEDIATRIC	Search modes - Boolean/Phrase	1099
S33	MH INTENSIVE CARE UNITS	Search modes - Boolean/Phrase	8853
S32	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31	Search modes - Boolean/Phrase	226
S31	AB (sepsis or septic or septic*)	Search modes - Boolean/Phrase	3987
S30	TI (sepsis or septic or septic*)	Search modes - Boolean/Phrase	2576
S29	MH SEPSIS+	Search modes - Boolean/Phrase	6082
S28	TI (n meningitid*) or AB (n meningitid*)	Search modes - Boolean/Phrase	31
S27	TI (neisseria meningitid*) or AB (neisseria meningitid*)	Search modes - Boolean/Phrase	119
S26	MH NEISSERIA	Search modes - Boolean/Phrase	192
S25	TI (meningococcaemi* or meningococcemi*) or AB (meningococcaemi* or meningococcemi*)	Search modes - Boolean/Phrase	46
S24	TI (meningococcal N3 infection*) or AB (meningococcal N3 infection*)	Search modes - Boolean/Phrase	48
S23	TI (meningococcal N3 meningitis) or AB (meningococcal N3 meningitis)	Search modes - Boolean/Phrase	64
S22	TI (meningococcal N3 septicemi*) or AB (meningococcal N3 septicemi*)	Search modes - Boolean/Phrase	6
S21	TI (meningococcal N3 septicaemi*) or AB	Search modes -	29

	(meningococcal N3 septicaemi*)	Boolean/Phrase	
S20	TI (meningococcal N3 disease*) or AB (meningococcal N3 disease*)	Search modes - Boolean/Phrase	264
S19	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S18	MH MENINGITIS, MENINGOCOCCAL	Search modes - Boolean/Phrase	200
S17	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Search modes - Boolean/Phrase	1778
S16	TI (pediatric* or paediatric*) or AB (pediatric* or paediatric*)	Search modes - Boolean/Phrase	29743
S15	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	55
S14	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	55
S13	(MH "PUBERTY+")	Search modes - Boolean/Phrase	1004
S12	(TI "school*") or (AB "school*")	Search modes - Boolean/Phrase	38329
S11	(MH "SCHOOLS+")	Search modes - Boolean/Phrase	21736
S10	(TI "teen*") or (AB "teen*")	Search modes - Boolean/Phrase	6332
S9	(TI "adolescen*") or (AB "adolescen*")	Search modes - Boolean/Phrase	28859
S8	(MH "ADOLESCENCE+")	Search modes - Boolean/Phrase	128199
S7	(TI "neonat*" or "newborn?") or (AB "neonat*" or "newborn?")	Search modes - Boolean/Phrase	16412
S6	(TI "toddler*") or (AB "toddler*")	Search modes - Boolean/Phrase	1632
S5	(TI "baby" or "babies") or (AB "baby" or "babies")	Search modes - Boolean/Phrase	10049
S4	(TI "infant*") or (AB "infant*")	Search modes - Boolean/Phrase	27020
S3	(MH "INFANT+")	Search modes - Boolean/Phrase	82965
S2	(TI "child*") or (AB "child*")	Search modes - Boolean/Phrase	117798
S1	(MH "CHILD+")	Search modes - Boolean/Phrase	199308

MENG_sptransport_embase_050509

EMBASE 1980 to 2009 Week 18

#	Searches	Results
1	exp CHILD/	637726
2	child$.ti,ab.	497873
3	exp INFANT/	176270
4	infan$.ti,ab.	173819
5	(baby or babies).ti,ab.	27999
6	exp ADOLESCENT/	444339
7	teenag$.ti,ab.	8158
8	adolescen$.ti,ab.	85879
9	exp SCHOOLS/	38222
10	school$.ti,ab.	76633
11	exp PUBERTY/	14694
12	pubescen$.ti,ab.	671
13	NEWBORN/	180848
14	(newborn? or neonate?).ti,ab.	99160
15	(pediatric? or paediatric?).ti,ab.	115223
16	or/1-15	1299689
17	MENINGITIS/ or BACTERIAL MENINGITIS/	21004
18	NEISSERIA MENINGITIDIS/	7009
19	MENINGOCOCCOSIS/	2915
20	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	3189
21	meningococc?emi$.ti,ab.	431
22	(meningococcus or meningococci$).ti,ab.	1526
23	SEPTICEMIA/	9010
24	SEPSIS/	42213
25	SEPTIC SHOCK/	13396
26	(sepsis or septic or septi?emi$ or shock$ or endotoxic$ or collaps$).ti,ab.	146641
27	or/17-26	194065
28	INTENSIVE CARE UNIT/	29439
29	p?ediatric$ intensive care.tw.	2873
30	PICU.tw.	863
31	PMICU.tw.	1
32	((intensive or tertiary) adj3 care).ti,ab.	63447
33	or/28-32	75075
34	PATIENT TRANSPORT/	7034
35	PATIENT CARE/	84243
36	patient care team$.tw.	62
37	mobile intensive care.tw.	178
38	((dedicated or p?ediatric) adj retrieval team$).tw.	5
39	specialist transport team$.tw.	2
40	(specialist adj2 transfer$).ti,ab.	34

41 intensivist$.ti,ab.	1121
42 (interhospital adj2 (transport$ or transfer$)).ti,ab.	335
43 or/34-42	91616
44 and/16,27,33,43	90

MENG_sptransport_medline_050509

Ovid MEDLINE(R) 1950 to April Week 4 2009

#	Searches	Results
1	exp CHILD/	1277013
2	child$.ti,ab.	730652
3	exp INFANT/	781597
4	infan$.ti,ab.	256869
5	(baby or babies).ti,ab.	39347
6	toddler?.ti,ab.	3475
7	(neonat$ or newborn?).ti,ab.	222996
8	ADOLESCENT/	1284920
9	adolescen$.ti,ab.	110930
10	teen$.ti,ab.	15419
11	exp SCHOOLS/	60310
12	school$.ti,ab.	134121
13	exp PUBERTY/	13084
14	pubescen$.ti,ab.	845
15	(pediatric? or paediatric?).ti,ab.	134194
16	or/1-15	2679205
17	MENINGITIS, MENINGOCOCCAL/	3923
18	MENINGOCOCCAL INFECTIONS/	4425
19	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	4473
20	meningococc?emi$.ti,ab.	611
21	NEISSERIA MENINGITIDIS/	6010
22	(neisseria meningitid$ or n meningitid$).ti,ab.	5284
23	(meningococcus or meningococci$).ti,ab.	2154
24	SEPSIS/	33727
25	(sepsis or septic or septic?emi$ or shock$ or endotoxic$ or collaps$).ti,ab.	187629
26	SHOCK, SEPTIC/	15180
27	SHOCK, TOXIC/	15180
28	SHOCK, ENDOTOXIC/	15180
29	or/17-28	214481
30	INTENSIVE CARE UNITS/ or exp INTENSIVE CARE UNITS, PEDIATRIC/	33627
31	PICU.ti,ab.	999
32	PMICU.ti,ab.	1
33	HOSPITALS, SPECIAL/ or HOSPITAL, PEDIATRIC/	14567
34	((intensive or tertiary) adj3 care).ti,ab.	71600
35	or/30-34	98693
36	TRANSPORTATION OF PATIENTS/	7290
37	exp PATIENT CARE TEAM/	42774
38	PATIENT TRANSFER/	4074
39	mobile intensive care.ti,ab.	225
40	((dedicated or p?ediatric) adj retrieval team$).ti,ab.	10

41 MOBILE HEALTH UNITS/	2590
42 specialist transport team$.ti,ab.	2
43 (specialist adj2 transfer$).ti,ab.	35
44 intensivist$.ti,ab.	1012
45 (interhospital adj2 (transport$ or transfer$)).ti,ab.	364
46 or/36-45	56993
47 and/16,29,35,46	58

27 What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008
MENG_children_bacterial_morbidity_cctr_230109

#	Searches	Results
1	exp CHILD/	29922
2	child$.ti,ab.	33306
3	exp INFANT/	17712
4	infan$.ti,ab.	12147
5	(baby or babies).ti,ab.	1673
6	toddler?.ti,ab.	252
7	(neonat$ or newborn?).ti,ab.	6827
8	ADOLESCENT/	55610
9	adolescen$.ti,ab.	4812
10	teen$.ti,ab.	497
11	exp SCHOOLS/	562
12	school$.ti,ab.	6141
13	exp PUBERTY/	215
14	pubescen$.ti,ab.	11
15	(pediatric? or paediatric?).ti,ab.	6289
16	or/1-15	100848
17	meningoencephalitis.ti,ab.	18
18	MENINGOENCEPHALITIS/	10
19	meningitis.ti,ab.	478
20	MENINGITIS, BACTERIAL/	74
21	MENINGITIS, ESCHERICHIA COLI/	0
22	MENINGITIS, HAEMOPHILUS/	60
23	MENINGITIS, LISTERIA/	0
24	exp MENINGITIS, MENINGOCOCCAL/	90
25	MENINGITIS, PNEUMOCOCCAL/	43
26	((bacterial$ or infect$) adj3 meninges).ti,ab.	2
27	STREPTOCOCCUS AGALACTIAE/	65
28	(group b adj3 strep$).ti,ab.	163
29	or/17-28	726
30	exp VISION DISORDERS/	700
31	(vision$ or eyesight$).tw.	2413
32	exp HEARING LOSS/	480
33	(hear$ adj3 (impair$ or loss$)).tw.	843
34	deaf$.tw.	314
35	exp *MENTAL DISORDERS DIAGNOSED IN CHILDHOOD/	2561

36 CHILD BEHAVIOR DISORDERS/	442
37 exp COMMUNICATION DISORDERS/	725
38 DEVELOPMENTAL DISABILITIES/	236
39 exp LEARNING DISORDERS/	340
40 exp MENTAL RETARDATION/	650
41 MOTOR SKILLS DISORDERS/	49
42 exp MOOD DISORDERS/	5722
43 (behaviour$ or behavior$).tw.	19983
44 MOBILITY LIMITATION/	28
45 mobil$.tw.	3838
46 ((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	152
47 exp DYSLEXIA/	144
48 exp MEMORY DISORDERS/	622
49 exp PERCEPTUAL DISORDERS/	412
50 exp PSYCHOMOTOR DISORDERS/	409
51 (learning adj2 (difficult$ or impair$)).tw.	187
52 ((academic$ or education$ or school$) adj2 achieve$).tw.	202
53 exp SPEECH DISORDERS/	275
54 speech$.tw.	1319
55 WALKING/	1218
56 (ambulation or disabil$ or walk$).tw.	9102
57 exp COGNITION DISORDERS/	1445
58 cognition.tw.	1407
59 "QUALITY OF LIFE"/	6883
60 (quality of life or life quality).tw.	11016
61 ((learning or intellec$) adj2 (difficult$ or impair$)).tw.	228
62 exp HYDROCEPHALUS/	90
63 hydroceph$.tw.	135
64 exp EPILEPSY/	1503
65 epileps$.tw.	2140
66 (sequelae$ or morbid$).tw.	9854
67 exp MENINGITIS, BACTERIAL/co [Complications]	28
68 SEIZURES/	297
69 seizure$.tw.	2035
70 exp NEUROLOGIC MANIFESTATIONS/	19673
71 exp NEUROBEHAVIORAL MANIFESTATIONS/	3283
72 exp LANGUAGE DISORDERS/	518
73 LANGUAGE DEVELOPMENT DISORDERS/	69
74 CEREBRAL PALSY/	310
75 (cere$ adj2 pal$).tw.	481
76 PAIN/	6718
77 or/30-76	80008

78 and/16,29,77	141
79 limit 78 to yr="1995 - 2009"	75

MENG_children_bacterial_morbidity_cdsrdare_230109

DARE, CDSR

#	Searches	Results
1	CHILD.kw.	1243
2	child$.ti,ab.	1507
3	INFANT.kw.	858
4	infan$.ti,ab.	558
5	(baby or babies).ti,ab.	138
6	toddler?.ti,ab.	5
7	(neonat$ or newborn?).ti,ab.	522
8	ADOLESCENT.kw.	811
9	adolescen$.ti,ab.	235
10	teen$.ti,ab.	10
11	SCHOOLS.kw.	27
12	school$.ti,ab.	125
13	PUBERTY.kw.	0
14	pubescen$.ti,ab.	0
15	(pediatric? or paediatric?).ti,ab.	219
16	or/1-15	2889
17	meningoencephalitis.ti,ab.	1
18	MENINGOENCEPHALITIS.kw.	1
19	meningitis.ti,ab.	31
20	MENINGITIS, BACTERIAL.kw.	13
21	MENINGITIS, ESCHERICHIA COLI.kw.	0
22	MENINGITIS, HAEMOPHILUS.kw.	1
23	MENINGITIS, LISTERIA.kw.	0
24	MENINGITIS, MENINGOCOCCAL.kw.	4
25	MENINGITIS, PNEUMOCOCCAL.kw.	2
26	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
27	STREPTOCOCCUS AGALACTIAE.kw.	7
28	(group b adj3 strep$).ti,ab.	8
29	or/17-28	41
30	VISION DISORDERS.kw.	13
31	(vision$ or eyesight$).tw.	388
32	HEARING LOSS.kw.	30
33	(hear$ adj3 (impair$ or loss$)).tw.	202
34	deaf$.tw.	122
35	MENTAL DISORDERS DIAGNOSED IN CHILDHOOD.kw.	0
36	CHILD BEHAVIOR DISORDERS.kw.	27
37	COMMUNICATION DISORDERS.kw.	4
38	DEVELOPMENTAL DISABILITIES.kw.	20
39	LEARNING DISORDERS.kw.	12

40 MENTAL RETARDATION.kw.	23
41 MOTOR SKILLS DISORDERS.kw.	5
42 MOOD DISORDERS.kw.	19
43 (behaviour$ or behavior$).tw.	2553
44 MOBILITY LIMITATION.kw.	1
45 mobil$.tw.	729
46 ((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	97
47 DYSLEXIA.kw.	1
48 MEMORY DISORDERS.kw.	9
49 PERCEPTUAL DISORDERS.kw.	4
50 PSYCHOMOTOR DISORDERS.kw.	9
51 (learning adj2 (difficult$ or impair$)).tw.	56
52 ((academic$ or education$ or school$) adj2 achieve$).tw.	64
53 SPEECH DISORDERS.kw.	5
54 speech$.tw.	262
55 WALKING.kw.	49
56 (ambulation or disabil$ or walk$).tw.	2070
57 COGNITION DISORDERS.kw.	81
58 cognition.tw.	309
59 "QUALITY OF LIFE".kw.	327
60 (quality of life or life quality).tw.	3295
61 ((learning or intellec$) adj2 (difficult$ or impair$)).tw.	102
62 HYDROCEPHALUS.kw.	5
63 hydroceph$.tw.	47
64 EPILEPSY.kw.	93
65 epileps$.tw.	218
66 (sequelae$ or morbid$).tw.	2993
67 SEIZURES.kw.	37
68 seizure$.tw.	455
69 NEUROLOGIC MANIFESTATIONS.kw.	0
70 NEUROBEHAVIORAL MANIFESTATIONS.kw.	0
71 LANGUAGE DISORDERS.kw.	5
72 LANGUAGE DEVELOPMENT DISORDERS.kw.	11
73 CEREBRAL PALSY.kw.	49
74 (cere$ adj2 pal$).tw.	276
75 PAIN.kw.	855
76 or/30-75	7970
77 and/16,29,76	19

MENG_children_bacterial_morbidity_cinahl_260109

EBSCO-Host

#	Query	Limiters/Expanders	Results
S26	(S16 and S24)	Limiters - Published Date from: 199501-200901; Peer Reviewed; Exclude MEDLINE records; Publication Type: Journal Article; Language: English Search modes - Boolean/Phrase	653
S25	(S16 and S24)	Search modes - Boolean/Phrase	2580
S24	(S17 or S18 or S19 or S20 or S21 or S22 or S23)	Search modes - Boolean/Phrase	7725
S23	(TI "group b" N3 "strep*") or (AB "group b" N3 "strep*")	Search modes - Boolean/Phrase	415
S22	(TI "bacterial*" or "infect*" N3 "meninges") or (AB "bacterial*" or "infect*" N3 "meninges")	Search modes - Boolean/Phrase	5776
S21	(MH "MENINGITIS, MENINGOCOCCAL")	Search modes - Boolean/Phrase	190
S20	(MH "MENINGITIS, BACTERIAL")	Search modes - Boolean/Phrase	692
S19	(TI "meningitis") or (AB "meningitis")	Search modes - Boolean/Phrase	1599
S18	(MH "MENINGOENCEPHALITIS")	Search modes - Boolean/Phrase	79
S17	(TI "meningoencephalitis") or (AB "meningoencephalitis")	Search modes - Boolean/Phrase	103
S16	(S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1)	Search modes - Boolean/Phrase	315679
S15	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	49
S14	(TI "pubescen*") or (AB "pubescen*")	Search modes - Boolean/Phrase	49
S13	(MH "PUBERTY+")	Search modes - Boolean/Phrase	939
S12	(TI "school*") or (AB "school*")	Search modes - Boolean/Phrase	36159
S11	(MH "SCHOOLS+")	Search modes - Boolean/Phrase	20201
S10	(TI "teen*") or (AB "teen*")	Search modes - Boolean/Phrase	6013

S9	(TI "adolescen*") or (AB "adolescen*")	Search modes - Boolean/Phrase	27011
S8	(MH "ADOLESCENCE+")	Search modes - Boolean/Phrase	119290
S7	(TI "neonat*" or "newborn?") or (AB "neonat*" or "newborn?")	Search modes - Boolean/Phrase	15337
S6	(TI "toddler*") or (AB "toddler*")	Search modes - Boolean/Phrase	1548
S5	(TI "baby" or "babies") or (AB "baby" or "babies")	Search modes - Boolean/Phrase	9516
S4	(TI "infant*") or (AB "infant*")	Search modes - Boolean/Phrase	25491
S3	(MH "INFANT+")	Search modes - Boolean/Phrase	78322
S2	(TI "child*") or (AB "child*")	Search modes - Boolean/Phrase	110849
S1	(MH "CHILD+")	Search modes - Boolean/Phrase	187105

MENG_children_bacterial_morbidity_embase_230109

EMBASE 1980 to 2009 Week 03

#	Searches	Results
1	exp CHILD/	627359
2	child$.tw.	488737
3	exp INFANT/	173163
4	infan$.tw.	171256
5	(baby or babies).tw.	27584
6	exp ADOLESCENT/	436439
7	teenag$.tw.	8018
8	adolescen$.tw.	83876
9	exp SCHOOLS/	37578
10	school$.tw.	75378
11	exp PUBERTY/	14401
12	pubescen$.tw.	660
13	NEWBORN/	178767
14	(newborn? or neonate?).ti,ab.	97569
15	(pediatric? or paediatric?).ti,ab.	111346
16	or/1-15	1278231
17	meningoencephalitis.ti,ab.	2517
18	MENINGOENCEPHALITIS/	2974
19	meningitis.ti,ab.	21833
20	BACTERIAL MENINGITIS/	7704
21	EPIDEMIC MENINGITIS/	877
22	((bacterial$ or infect$) adj3 meninges).ti,ab.	32
23	STREPTOCOCCUS AGALACTIAE/	5136
24	(group b adj3 strep$).ti,ab.	4081
25	or/17-24	32185
26	exp VISION DISORDER/	77738
27	(vision$ or eyesight$).tw.	40489
28	HEARING LOSS/	12705
29	(hear$ adj3 (impair$ or loss$)).tw.	24426
30	deaf$.tw.	15568
31	exp *MENTAL DISEASE/	495231
32	exp BEHAVIOR DISORDER/	181552
33	exp COMMUNICATION DISORDER/	20211
34	DEVELOPMENTAL DISORDER/	12925
35	exp LEARNING DISORDER/	11182
36	exp MENTAL DEFICIENCY/	53858
37	exp PSYCHOMOTOR DISORDER/	25410
38	MOOD DISORDER/	10447
39	(behaviour$ or behavior$).tw.	385034

40 WALKING DIFFICULTY/	798
41 mobil$.tw.	125518
42 ((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	3440
43 DYSLEXIA/	3464
44 exp MEMORY DISORDER/	24125
45 exp PERCEPTION DISORDER/	7732
46 exp PSYCHOMOTOR DISORDER/	25410
47 (learning adj2 (difficult$ or impair$)).tw.	3753
48 ((academic$ or education$ or school$) adj2 achieve$).tw.	2117
49 exp SPEECH DISORDER/	24504
50 speech$.tw.	28363
51 WALKING/	14716
52 (ambulation or disabil$ or walk$).tw.	92749
53 COGNITIVE DEFECT/	38571
54 cognition.tw.	14825
55 exp "QUALITY OF LIFE"/	98505
56 (quality of life or life quality).tw.	72281
57 ((learning or intellec$) adj2 (difficult$ or impair$)).tw.	4725
58 exp HYDROCEPHALUS/	15578
59 hydroceph$.tw.	11614
60 exp EPILEPSY/	77287
61 epileps$.tw.	44003
62 (sequelae$ or morbid$).tw.	171571
63 BACTERIAL MENINGITIS/co [Complication]	594
64 SEIZURE/	44257
65 seizure$.tw.	57900
66 exp *NEUROLOGIC DISEASE/	782248
67 COGNITION/	70104
68 exp LANGUAGE DISABILITY/	18859
69 CEREBRAL PALSY/	9804
70 (cere$ adj2 pal$).tw.	8288
71 PAIN/	69934
72 or/26-71	2118160
73 and/16,25,72	8827
74 letter.pt.	435251
75 editorial.pt.	222742
76 CASE REPORT/	1021500
77 (case report or case study).ti.	100911
78 or/74-77	1598238
79 73 not 78	6019
80 limit 79 to english language	4792
81 limit 80 to yr="1995 - 2009"	2973

MENG_children_bacterial_morbidity_medline_230109

Ovid MEDLINE 1950 to January Week 2 2009

#	Searches	Results
1	exp CHILD/	1251902
2	child$.ti,ab.	712096
3	exp INFANT/	774121
4	infan$.ti,ab.	251846
5	(baby or babies).ti,ab.	38468
6	toddler?.ti,ab.	3336
7	(neonat$ or newborn?).ti,ab.	218966
8	ADOLESCENT/	1256192
9	adolescen$.ti,ab.	107147
10	teen$.ti,ab.	14984
11	exp SCHOOLS/	59325
12	school$.ti,ab.	130125
13	exp PUBERTY/	12836
14	pubescen$.ti,ab.	818
15	(pediatric? or paediatric?).ti,ab.	129543
16	or/1-15	2624778
17	meningoencephalitis.ti,ab.	4073
18	MENINGOENCEPHALITIS/	4699
19	meningitis.ti,ab.	31317
20	MENINGITIS, BACTERIAL/	4097
21	MENINGITIS, ESCHERICHIA COLI/	81
22	MENINGITIS, HAEMOPHILUS/	2109
23	MENINGITIS, LISTERIA/	630
24	exp MENINGITIS, MENINGOCOCCAL/	4234
25	MENINGITIS, PNEUMOCOCCAL/	2444
26	((bacterial$ or infect$) adj3 meninges).ti,ab.	43
27	STREPTOCOCCUS AGALACTIAE/	5519
28	(group b adj3 strep$).ti,ab.	4948
29	or/17-28	46047
30	exp VISION DISORDERS/	46956
31	(vision$ or eyesight$).tw.	49212
32	exp HEARING LOSS/	42215
33	(hear$ adj3 (impair$ or loss$)).tw.	27365
34	deaf$.tw.	22769
35	exp *MENTAL DISORDERS DIAGNOSED IN CHILDHOOD/	84215
36	CHILD BEHAVIOR DISORDERS/	15396
37	exp COMMUNICATION DISORDERS/	42834
38	DEVELOPMENTAL DISABILITIES/	10052
39	exp LEARNING DISORDERS/	15452

40 exp MENTAL RETARDATION/	68740
41 MOTOR SKILLS DISORDERS/	1201
42 exp MOOD DISORDERS/	83856
43 (behaviour$ or behavior$).tw.	460522
44 MOBILITY LIMITATION/	570
45 mobil$.tw.	138429
46 ((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	3332
47 exp DYSLEXIA/	5632
48 exp MEMORY DISORDERS/	15405
49 exp PERCEPTUAL DISORDERS/	17781
50 exp PSYCHOMOTOR DISORDERS/	8620
51 (learning adj2 (difficult$ or impair$)).tw.	4007
52 ((academic$ or education$ or school$) adj2 achieve$).tw.	3216
53 exp SPEECH DISORDERS/	21514
54 speech$.tw.	36980
55 WALKING/	10041
56 (ambulation or disabil$ or walk$).tw.	107802
57 exp COGNITION DISORDERS/	37158
58 cognition.tw.	15005
59 "QUALITY OF LIFE"/	70925
60 (quality of life or life quality).tw.	75758
61 ((learning or intellec$) adj2 (difficult$ or impair$)).tw.	5061
62 exp HYDROCEPHALUS/	16720
63 hydroceph$.tw.	15148
64 exp EPILEPSY/	102858
65 epileps$.tw.	48968
66 (sequelae$ or morbid$).tw.	194729
67 exp MENINGITIS, BACTERIAL/co [Complications]	2797
68 SEIZURES/	33029
69 seizure$.tw.	60253
70 exp NEUROLOGIC MANIFESTATIONS/	620390
71 exp NEUROBEHAVIORAL MANIFESTATIONS/	180782
72 exp LANGUAGE DISORDERS/	32671
73 LANGUAGE DEVELOPMENT DISORDERS/	3266
74 CEREBRAL PALSY/	11702
75 (cere$ adj2 pal$).tw.	10432
76 PAIN/	89005
77 or/30-76	1778475
78 and/16,29,77	5762
79 letter.pt.	634687
80 editorial.pt.	228019
81 CASE REPORTS/	1381910

82 (case report or case study).ti.	122402
83 or/79-82	2131716
84 78 not 83	4112
85 limit 84 to humans	3913
86 limit 85 to english language	2922
87 limit 86 to yr="1995 - 2009"	1622

MENG_children_bacterial_morbidity_psycinfo_230109

PsycINFO 1967 to January Week 3 2009

#	Searches	Results
1	meningoencephalitis.ti,ab.	79
2	meningitis.ti,ab.	421
3	BACTERIAL MENINGITIS/	50
4	((bacterial$ or infect$) adj3 meninges).ti,ab.	0
5	(group b adj3 strep$).ti,ab.	10
6	or/1-5	501
7	limit 6 to (100 childhood or 200 adolescence)	156
8	limit 7 to english language	137
9	limit 8 to yr="1995 - 2009"	92

28 What proportion of children and young people with meningococcal septicaemia develop physical and psychological morbidity?

MENG_physical_pyscho_morbid_cinahl_130109

EBSCO Host Friday, July 31, 2009 6:57:13 AM

#	Query	Limiters/Expanders	Results
S63	S31 and S62	Search modes - Boolean/Phrase	0
S62	S61 or S60 or S59 or S58 or S57 or S56 or S55 or S54 or S53 or S52 or S51 or S50 or S49 or S48 or S47 or S46 or S45 or S44 or S43 or S42 or S41 or S40 or S39 or S38 or S37 or S36 or S35 or S34 or S33 or S32	Search modes - Boolean/Phrase	270
S61	TI ("ABG" or "VBG") or AB ("ABG" or "VBG")	Search modes - Boolean/Phrase	124
S60	(MH "CARBON DIOXIDE/BL")	Search modes - Boolean/Phrase	249
S59	(MH "OXYGEN/BL")	Search modes - Boolean/Phrase	524
S58	(TI "oxymetr*") or (AB "oxymetr*")	Search modes - Boolean/Phrase	19
S57	(TI "blood" N3 "carbon dioxide") or (AB "blood" N3 "carbon dioxide")	Search modes - Boolean/Phrase	31
S56	(TI "blood" N3 "oxygen*") or (AB "blood" N3 "oxygen*")	Search modes - Boolean/Phrase	716
S55	TI ("blood" N3 "gas*") or AB ("blood" N3 "gas*")	Search modes - Boolean/Phrase	1547
S54	TI (differential count*) or AB (differential count*)	Search modes - Boolean/Phrase	48
S53	MH BLOOD GAS ANALYSIS+	Search modes - Boolean/Phrase	3356
S52	(TI "WCC") or (AB "WCC")	Search modes - Boolean/Phrase	23
S51	(TI "lymphocytosis") or (AB "lymphocytosis")	Search modes - Boolean/Phrase	69
S50	(TI "leucocytosis") or (AB "leucocytosis")	Search modes - Boolean/Phrase	26
S49	(TI "leukocytosis") or (AB "leukocytosis")	Search modes - Boolean/Phrase	190
S48	MH NEUTROPENIA	Search modes - Boolean/Phrase	981
S47	MH NEUTROPHILS	Search modes - Boolean/Phrase	1092
S46	MH LYMPHOCYTES	Search modes - Boolean/Phrase	814
S45	MH LEUKOCYTES	Search modes - Boolean/Phrase	1081
S44	(TI "neutrophil*" N2 "count*") or (AB "neutrophil*" N2 "count*")	Search modes - Boolean/Phrase	353
S43	(TI "WBC" N2 "count*") or (AB "WBC" N2 "count*")	Search modes -	236

		Boolean/Phrase	
S42	(TI "white" N2 "count*") or (AB "white" N2 "count*")	Search modes - Boolean/Phrase	769
S41	(TI "white blood cell*" N3 "count*") or (AB "white blood cell*" N3 "count*")	Search modes - Boolean/Phrase	583
S40	(TI "lymphocyt*" N3 "count*") or (AB "lymphocyt*" N3 "count*")	Search modes - Boolean/Phrase	430
S39	(TI "leucocyt*" N3 "count*") or (AB "leucocyt*" N3 "count*")	Search modes - Boolean/Phrase	52
S38	(TI "leukocyt*" N3 "count*") or (AB "leukocyt*" N3 "count*")	Search modes - Boolean/Phrase	273
S37	MH LEUKOCYTE COUNT+	Search modes - Boolean/Phrase	2557
S36	(TI "ALC") or (AB "ALC")	Search modes - Boolean/Phrase	69
S35	(TI "reactive c protein*") or (AB "reactive c protein*")	Search modes - Boolean/Phrase	1
S34	(TI "CRP") or (AB "CRP")	Search modes - Boolean/Phrase	1261
S33	(TI "c reactive" N3 "protein*") or (AB "c reactive" N3 "protein*")	Search modes - Boolean/Phrase	2721
S32	MH C-REACTIVE PROTEIN	Search modes - Boolean/Phrase	3151
S31	S30 or S29 or S28 or S27 or S26 or S25 or S24 or S23 or S22 or S21 or S20 or S19 or S18 or S17 or S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1	Search modes - Boolean/Phrase	1971
S30	(MH MENINGITIS, MENINGOCOCCAL)	Search modes - Boolean/Phrase	200
S29	TI (bacteremia or bacteraemia) or AB (bacteremia or bacteraemia)	Search modes - Boolean/Phrase	1241
S28	(MH BACTEREMIA)	Search modes - Boolean/Phrase	1700
S27	TI (Henoch or Schoenlein or fulminans) or AB (Henoch or Schoenlein or fulminans)	Search modes - Boolean/Phrase	162
S26	TI (hemorrhag* N3 purpur*) or AB (hemorrhag* N3 purpur*)	Search modes - Boolean/Phrase	8
S25	TI (haemorrhag* N3 purpur*) or AB (haemorrhag* N3 purpur*)	Search modes - Boolean/Phrase	0
S24	TI (haemorrhag* N3 rash*) or AB (haemorrhag* N3 rash*)	Search modes - Boolean/Phrase	3
S23	TI (hemorrhag* N3 rash*) or AB (hemorrhag* N3 rash*)	Search modes - Boolean/Phrase	4
S22	(TI "meningococci") or (AB "meningococci")	Search modes - Boolean/Phrase	14
S21	(TI "meningococcus") or (AB "meningococcus")	Search modes - Boolean/Phrase	22
S20	MH NEISSERIA	Search modes - Boolean/Phrase	192
S19	(TI "n meningitid*") or (AB "n meningitid*")	Search modes -	31

		Boolean/Phrase	
S18	(TI "neisseria meningitid*") or (AB "neisseria meningitid*")	Search modes - Boolean/Phrase	119
S17	(TI "meningococcaemi*") or (AB "meningococcaemi*")	Search modes - Boolean/Phrase	6
S16	(TI "meningococcemi*") or (AB "meningococcemi*")	Search modes - Boolean/Phrase	40
S15	(TI "meningococc*" N3 "infection*") or (AB "meningococc*" N3 "infection*")	Search modes - Boolean/Phrase	49
S14	(TI "meningococc*" N3 "disease*") or (AB "meningococc*" N3 "disease*")	Search modes - Boolean/Phrase	265
S13	(TI "meningococc*" N3 "endotoxi*") or (AB "meningococc*" N3 "endotoxi*")	Search modes - Boolean/Phrase	1
S12	(TI "meningococc*" N3 "toxic") or (AB "meningococc*" N3 "toxic")	Search modes - Boolean/Phrase	0
S11	(TI "meningococc*" N3 "septic") or (AB "meningococc*" N3 "septic")	Search modes - Boolean/Phrase	18
S10	MH MENINGOCOCCAL INFECTIONS	Search modes - Boolean/Phrase	615
S9	(TI "septicaemi*") or (AB "septicaemi*")	Search modes - Boolean/Phrase	198
S8	(TI "septicemi*") or (AB "septicemi*")	Search modes - Boolean/Phrase	297
S7	MH PURPURA+	Search modes - Boolean/Phrase	770
S6	(TI "petechiae") or (AB "petechiae")	Search modes - Boolean/Phrase	79
S5	(TI "nonblanch*") or (AB "nonblanch*")	Search modes - Boolean/Phrase	11
S4	(TI "blanch*" N3 "rash*") or (AB "blanch*" N3 "rash*")	Search modes - Boolean/Phrase	3
S3	(TI "non blanch*" N3 "rash*") or (AB "non blanch*" N3 "rash*")	Search modes - Boolean/Phrase	1
S2	(TI "purpur*" N3 "rash*") or (AB "purpur*" N3 "rash*")	Search modes - Boolean/Phrase	20
S1	(TI "petechia*" N3 "rash*") or (AB "petechia*" N3 "rash*")	Search modes - Boolean/Phrase	22

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MENG_physical_pyscho_morbid_cctr_130109

#	Searches	Results
1	exp MENINGOCOCCAL INFECTIONS/	158
2	(meningoc$ or meningit$).tw.	749
3	exp NEISSERIA MENINGITIDIS/	145
4	(neisseria meningitid$ or n meningitid$).tw.	138
5	exp MENINGITIS, BACTERIAL/	230
6	exp MENINGOCOCCAL VACCINES/	144
7	or/1-6	804
8	SOCIAL SUPPORT/	1221
9	exp ADAPTATION, PSYCHOLOGICAL/	2259
10	STRESS, PSYCHOLOGICAL/	2022
11	exp COUNSELING/	1548
12	counsel$.tw.	3706
13	exp *ANXIETY/	1420
14	(patient adj3 (anxiety or stress)).tw.	350
15	STRESS DISORDERS, POST-TRAUMATIC/	433
16	DEPRESSION/	2970
17	PATIENT EDUCATION AS TOPIC/	3615
18	PREOPERATIVE CARE/	2329
19	POSTOPERATIVE CARE/	2744
20	(patient adj3 (recov$ or inform$ or care or educat$)).tw.	3146
21	*PROFESSIONAL-PATIENT RELATIONS/	0
22	*NURSE-PATIENT RELATIONS/	0
23	*PHYSICIAN-PATIENT RELATIONS/	0
24	(leaflet$ or booklet$ or pamphlet$ or tape$ or video$).tw.	6154
25	exp COMMUNICATION/	4738
26	PAMPHLETS/	386
27	PATIENT PARTICIPATION/	464
28	patient literature.tw.	3
29	exp PATIENT CARE TEAM/	717
30	information.tw.	11942
31	or/8-30	40042
32	exp PSYCHOTHERAPY, GROUP/	1393
33	FAMILY THERAPY/	383
34	"COST OF ILLNESS"/	324
35	CAREGIVERS/	535
36	PARENTS/	831
37	SIBLINGS/	47
38	exp FAMILY RELATIONS/	950
39	(family or parent$ or mother$ or father$ or brother$ or sister$ or sibling$).tw.	17741
40	(carer$ or caregiver$ or care-giver$).tw.	1580

41	(psycholog$ or social$ or psychosocial$).tw.	14583
42	or/32-41	32273
43	(organ adj3 (dysfunction$ or impair$ or failure$)).tw.	610
44	exp KIDNEY FAILURE/	2752
45	((kidney$ or renal$) adj3 (insuffic$ or failure$ or impair$ or dysfunc$)).tw.	4225
46	exp VISION DISORDERS/	700
47	(vision$ or eyesight$).tw.	2413
48	exp HEARING LOSS/	480
49	(hear$ adj3 (impair$ or loss$)).tw.	843
50	deaf$.tw.	314
51	exp *MENTAL DISORDERS DIAGNOSED IN CHILDHOOD/	2561
52	CHILD BEHAVIOR DISORDERS/	442
53	exp COMMUNICATION DISORDERS/	725
54	DEVELOPMENTAL DISABILITIES/	236
55	exp LEARNING DISORDERS/	340
56	exp MENTAL RETARDATION/	650
57	MOTOR SKILLS DISORDERS/	49
58	exp MOOD DISORDERS/	5722
59	(behaviour$ or behavior$).tw.	19983
60	MOBILITY LIMITATION/	28
61	mobil$.tw.	3838
62	((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	152
63	exp DYSLEXIA/	144
64	exp MEMORY DISORDERS/	622
65	exp PERCEPTUAL DISORDERS/	412
66	exp PSYCHOMOTOR DISORDERS/	409
67	(learning adj2 (difficult$ or impair$)).tw.	187
68	((academic$ or education$ or school$) adj2 achieve$).tw.	202
69	exp SPEECH DISORDERS/	275
70	speech$.tw.	1319
71	WALKING/	1218
72	(ambulation or disabil$ or walk$).tw.	9102
73	exp COGNITION DISORDERS/	1445
74	cognition.tw.	1407
75	"QUALITY OF LIFE"/	6883
76	(quality of life or life quality).tw.	11016
77	((learning or intellec$) adj2 (difficult$ or impair$)).tw.	228
78	exp HEMATOLOGIC DISEASES/	6531
79	((haematolog$ or hematolog$) adj2 (disease$ or disabilit$)).tw.	76
80	exp HYDROCEPHALUS/	90
81	hydroceph$.tw.	135
82	exp EPILEPSY/	1503

83	epileps$.tw.	2140
84	(sequelae$ or morbid$).tw.	9854
85	exp MENINGITIS, BACTERIAL/co [Complications]	28
86	SEIZURES/	297
87	seizure$.tw.	2035
88	exp NEUROLOGIC MANIFESTATIONS/	19673
89	exp NEUROBEHAVIORAL MANIFESTATIONS/	3283
90	exp LANGUAGE DISORDERS/	518
91	LANGUAGE DEVELOPMENT DISORDERS/	69
92	or/43-91	90672
93	CEREBRAL PALSY/	310
94	(cere$ adj2 pal$).tw.	481
95	exp RESPIRATORY TRACT DISEASES/	27596
96	exp RESPIRATION DISORDERS/	4613
97	exp RESPIRATORY INSUFFICIENCY/	1201
98	((resp$ or breath$) adj2 (insuff$ or probl$ or compl$ or abnorma$ or infect$ or disord$)).tw.	8582
99	PURPURA, SCHOENLEIN-HENOCH/	16
100	purpura$.tw.	274
101	exp SKIN DISEASES/	16151
102	(skin adj3 (involve$ or comp$ or abnorm$ or sequ$ or morbid$)).tw.	1346
103	or/93-102	50673
104	exp INTENSIVE CARE UNITS, PEDIATRIC/	350
105	((paed$ or neon$ or child$) adj2 inten$).tw.	770
106	picu.tw.	42
107	CRITICAL ILLNESS/	538
108	((critic$ or acut$) adj2 ill$).tw.	1871
109	or/104-108	2902
110	or/31,42,92,103,109	172137
111	and/7,110	293
112	limit 111 to yr="2006 - 2008"	34

MENG_physical_pyscho_morbid_cdsrdare_130109

DARE, CDSR

#	Searches	Results
1	MENINGOCOCCAL INFECTIONS.kw.	5
2	(meningoc$ or meningit$).tw.	159
3	NEISSERIA MENINGITIDIS.kw.	4
4	(neisseria meningitid$ or n meningitid$).tw.	6
5	MENINGITIS, BACTERIAL.kw.	13
6	MENINGOCOCCAL VACCINES.kw.	2
7	or/1-6	159
8	SOCIAL SUPPORT.kw.	86
9	ADAPTATION, PSYCHOLOGICAL.kw.	58
10	STRESS, PSYCHOLOGICAL.kw.	60
11	COUNSELING.kw.	104
12	counsel$.tw.	879
13	ANXIETY.kw.	195
14	(patient adj3 (anxiety or stress)).tw.	67
15	STRESS DISORDERS, POST-TRAUMATIC.kw.	25
16	DEPRESSION.kw.	183
17	PATIENT EDUCATION.kw.	247
18	PREOPERATIVE CARE.kw.	66
19	POSTOPERATIVE CARE.kw.	54
20	(patient adj3 (recov$ or inform$ or care or educat$)).tw.	1348
21	PROFESSIONAL-PATIENT RELATIONS.kw.	20
22	NURSE-PATIENT RELATIONS.kw.	6
23	PHYSICIAN-PATIENT RELATIONS.kw.	35
24	(leaflet$ or booklet$ or pamphlet$ or tape$ or video$).tw.	783
25	COMMUNICATION.kw.	82
26	PAMPHLETS.kw.	5
27	PATIENT PARTICIPATION.kw.	29
28	patient literature.tw.	0
29	PATIENT CARE TEAM.kw.	45
30	information.tw.	13201
31	or/8-30	13351
32	PSYCHOTHERAPY, GROUP.kw.	45
33	FAMILY THERAPY.kw.	35
34	"COST OF ILLNESS".kw.	19
35	CAREGIVERS.kw.	58
36	PARENTS.kw.	34
37	SIBLINGS.kw.	0
38	FAMILY RELATIONS.kw.	9
39	(family or parent$ or mother$ or father$ or brother$ or sister$ or sibling$).tw.	2947

40	(carer$ or caregiver$ or care-giver$).tw.	1204
41	(psycholog$ or social$ or psychosocial$).tw.	3541
42	or/32-41	5392
43	(organ adj3 (dysfunction$ or impair$ or failure$)).tw.	148
44	KIDNEY FAILURE.kw.	91
45	((kidney$ or renal$) adj3 (insuffic$ or failure$ or impair$ or dysfunc$)).tw.	735
46	VISION DISORDERS.kw.	13
47	(vision$ or eyesight$).tw.	388
48	HEARING LOSS.kw.	30
49	(hear$ adj3 (impair$ or loss$)).tw.	202
50	deaf$.tw.	122
51	MENTAL DISORDERS DIAGNOSED IN CHILDHOOD.kw.	0
52	CHILD BEHAVIOR DISORDERS.kw.	27
53	COMMUNICATION DISORDERS.kw.	4
54	DEVELOPMENTAL DISABILITIES.kw.	20
55	LEARNING DISORDERS.kw.	12
56	MENTAL RETARDATION.kw.	23
57	MOTOR SKILLS DISORDERS.kw.	5
58	MOOD DISORDERS.kw.	19
59	(behaviour$ or behavior$).tw.	2553
60	MOBILITY LIMITATION.kw.	1
61	mobil$.tw.	729
62	((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	97
63	DYSLEXIA.kw.	1
64	MEMORY DISORDERS.kw.	9
65	PERCEPTUAL DISORDERS.kw.	4
66	PSYCHOMOTOR DISORDERS.kw.	9
67	(learning adj2 (difficult$ or impair$)).tw.	56
68	((academic$ or education$ or school$) adj2 achieve$).tw.	64
69	SPEECH DISORDERS.kw.	5
70	speech$.tw.	262
71	WALKING.kw.	49
72	(ambulation or disabil$ or walk$).tw.	2070
73	COGNITION DISORDERS.kw.	81
74	cognition.tw.	309
75	"QUALITY OF LIFE".kw.	327
76	(quality of life or life quality).tw.	3295
77	((learning or intellec$) adj2 (difficult$ or impair$)).tw.	102
78	HEMATOLOGIC DISEASES.kw.	5
79	((haematolog$ or hematolog$) adj2 (disease$ or disabilit$)).tw.	28
80	HYDROCEPHALUS.kw.	5
81	hydroceph$.tw.	47

82	EPILEPSY.kw.	93
83	epileps$.tw.	218
84	(sequelae$ or morbid$).tw.	2993
85	SEIZURES.kw.	37
86	seizure$.tw.	455
87	NEUROLOGIC MANIFESTATIONS.kw.	0
88	NEUROBEHAVIORAL MANIFESTATIONS.kw.	0
89	LANGUAGE DISORDERS.kw.	5
90	LANGUAGE DEVELOPMENT DISORDERS.kw.	11
91	or/43-90	7708
92	CEREBRAL PALSY.kw.	49
93	(cere$ adj2 pal$).tw.	276
94	RESPIRATORY TRACT DISEASES.kw.	3
95	RESPIRATION DISORDERS.kw.	9
96	RESPIRATORY INSUFFICIENCY.kw.	42
97	((resp$ or breath$) adj2 (insuff$ or probl$ or compl$ or abnorma$ or infect$ or disord$)).tw.	1204
98	PURPURA, SCHOENLEIN-HENOCH.kw.	5
99	purpura$.tw.	45
100	SKIN DISEASES.kw.	23
101	(skin adj3 (involve$ or comp$ or abnorm$ or sequ$ or morbid$)).tw.	188
102	or/92-101	1614
103	INTENSIVE CARE UNITS, PEDIATRIC.kw.	3
104	((paed$ or neon$ or child$) adj2 inten$).tw.	407
105	picu.tw.	7
106	CRITICAL ILLNESS.kw.	71
107	((critic$ or acut$) adj2 ill$).tw.	418
108	or/103-107	805
109	or/31,42,91,102,108	13941
110	and/7,109	156

MENG_physical_pyscho_morbid_cinahl_130109

#	Query	Limiters/Expanders	Results
S28	(S19 and S26)	Limiters - Published Date from: 200601-200901 Search modes - Boolean/Phrase	155
S27	(S19 and S26)	Search modes - Boolean/Phrase	379
S26	(S20 or S21 or S22 or S23 or S24 or S25)	Search modes - Boolean/Phrase	2580
S25	(MH MENINGITIS, BACTERIAL+)	Search modes - Boolean/Phrase	894
S24	(TI neisseria meningitid*) or (AB neisseria meningitid*)	Search modes - Boolean/Phrase	104
S23	(MH NEISSERIA INFECTIONS)	Search modes - Boolean/Phrase	50
S22	(TI meningit*) or (AB meningit*)	Search modes - Boolean/Phrase	1668
S21	(TI meningoc*) or (AB meningoc*)	Search modes - Boolean/Phrase	623
S20	(MH MENINGOCOCCAL INFECTIONS)	Search modes - Boolean/Phrase	592
S19	(S10 or S18)	Search modes - Boolean/Phrase	226588
S18	(S11 or S12 or S13 or S14 or S15 or S16 or S17)	Search modes - Boolean/Phrase	137051
S17	(TI observation* N1 stud*) or (AB observation* N1 stud*)	Search modes - Boolean/Phrase	5261
S16	(TI cohort N1 stud*) or (AB cohort N1 stud*)	Search modes - Boolean/Phrase	10041
S15	(MH CROSS SECTIONAL STUDIES)	Search modes - Boolean/Phrase	29107
S14	(MH NONCONCURRENT PROSPECTIVE STUDIES)	Search modes - Boolean/Phrase	29
S13	(MH CORRELATIONAL STUDIES+)	Search modes - Boolean/Phrase	8965
S12	(MH CASE CONTROL STUDIES+)	Search modes - Boolean/Phrase	18220
S11	(MH PROSPECTIVE STUDIES)	Search modes - Boolean/Phrase	84817
S10	(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9)	Search modes - Boolean/Phrase	107250
S9	(MH QUANTITATIVE STUDIES)	Search modes - Boolean/Phrase	4441
S8	(TI placebo*) or (AB placebo*)	Search modes - Boolean/Phrase	13239
S7	(MH PLACEBOS)	Search modes - Boolean/Phrase	4879
S6	(TI random* allocat*) or (AB random* allocat*)	Search modes - Boolean/Phrase	1453
S5	(MH RANDOM ASSIGNMENT)	Search modes - Boolean/Phrase	20153
S4	(TI randomi* control* trial*) or (AB randomi* control* trial*)	Search modes - Boolean/Phrase	13627
S3	(TI singl* or doubl* or trebl* or tripl*)	Search modes - Boolean/Phrase	27480
S2	(TI clinic* N1 trial*) or (AB clinic* N1 trial*)	Search modes - Boolean/Phrase	16813

S1	(MH CLINICAL TRIALS+)	Search modes - Boolean/Phrase	69547

EMBASE 1980 to 2009 Week 02

MENG_physical_pyscho_morbid_embase_130109

#	Searches	Results
1	CLINICAL TRIALS/	526401
2	(clinic$ adj5 trial$).ti,ab,sh.	124734
3	SINGLE BLIND PROCEDURE/	7897
4	DOUBLE BLIND PROCEDURE/	70979
5	RANDOM ALLOCATION/	26420
6	CROSSOVER PROCEDURE/	20854
7	PLACEBO/	121858
8	placebo$.ti,ab,sh.	172733
9	random$.ti,ab,sh.	427454
10	RANDOMIZED CONTROLLED TRIALS/	164469
11	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.	92354
12	randomi?ed control$ trial$.tw.	32767
13	or/1-12	863344
14	META ANALYSIS/	34521
15	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.	44447
16	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.	27299
17	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.	1645
18	or/14-17	61694
19	review.pt.	914438
20	(medline or medlars or embase).ab.	23608
21	(scisearch or science citation index).ab.	734
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.	8737
23	((hand or manual$) adj2 search$).tw.	2703
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.	4375
25	(pooling or pooled or mantel haenszel).tw.	24763
26	(peto or dersimonian or "der simonian" or fixed effect).tw.	896
27	or/20-26	52832
28	and/19,27	18865
29	or/18,28	72125
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.	1728347
31	13 not 30	738573
32	29 not 31	33674
33	or/31-32	772247
34	CLINICAL STUDY/	17621
35	CASE CONTROL STUDY/	19388

36	FAMILY STUDY/	7991
37	LONGITUDINAL STUDY/	18996
38	RETROSPECTIVE STUDY/	96328
39	PROSPECTIVE STUDY/	79243
40	RANDOMIZED CONTROLLED TRIALS/	164469
41	39 not 40	69178
42	COHORT ANALYSIS/	52433
43	(cohort adj (study or studies)).mp.	35258
44	(case control adj (study or studies)).tw.	33781
45	(follow up adj (study or studies)).tw.	22449
46	(observational adj (study or studies)).tw.	17861
47	(epidemiologic$ adj (study or studies)).tw.	34711
48	(cross sectional adj (study or studies)).tw.	25212
49	or/34-38,41-48	371616
50	or/33,49	1083090
51	MENINGOCOCCOSIS/	2839
52	(meningoc$ or meningit$).tw.	29120
53	NEISSERIA MENINGITIDIS/	6891
54	(neisseria meningitid$ or n meningitid$).tw.	4379
55	BACTERIAL MENINGITIS/	7698
56	MENINGOCOCCUS VACCINE/	2598
57	or/51-56	32633
58	SOCIAL SUPPORT/	16411
59	ADAPTIVE BEHAVIOR/	2875
60	MENTAL STRESS/	12220
61	exp COUNSELING/	46660
62	counsel$.tw.	36383
63	*ANXIETY/	18173
64	(patient adj3 (anxiety or stress)).tw.	1482
65	POSTTRAUMATIC STRESS DISORDER/	14221
66	exp DEPRESSION/	153690
67	PATIENT EDUCATION/	26855
68	PREOPERATIVE CARE/	7582
69	POSTOPERATIVE CARE/	23680
70	(patient adj3 (recov$ or inform$ or care or educat$)).tw.	40751
71	HUMAN RELATION/	14157
72	NURSE PATIENT RELATIONSHIP/	1024
73	DOCTOR PATIENT RELATIONSHIP/	28451
74	(leaflet$ or booklet$ or pamphlet$ or tape$ or video$).tw.	65025
75	exp INTERPERSONAL COMMUNICATION/	125031
76	PUBLICATION/	53843
77	PATIENT PARTICIPATION/	2707

78	patient literature.tw.	21
79	PATIENT CARE/	81991
80	information.tw.	381302
81	or/58-80	964076
82	GROUP THERAPY/	7391
83	FAMILY THERAPY/	4685
84	"COST OF ILLNESS"/	4831
85	CAREGIVER/	13696
86	exp PARENT/	38006
87	SIBLING/	11450
88	exp FAMILY RELATION/	24057
89	(family or parent$ or mother$ or father$ or brother$ or sister$ or sibling$).tw.	522564
90	(carer$ or caregiver$ or care-giver$).tw.	16380
91	(psycholog$ or social$ or psychosocial$).tw.	235801
92	or/82-91	752820
93	(organ adj3 (dysfunction$ or impair$ or failure$)).tw.	12062
94	exp KIDNEY FAILURE/	99811
95	((kidney$ or renal$) adj3 (insuffic$ or failure$ or impair$ or dysfunc$)).tw.	74533
96	exp VISION DISORDER/	77649
97	(vision$ or eyesight$).tw.	40438
98	HEARING LOSS/	12676
99	(hear$ adj3 (impair$ or loss$)).tw.	24384
100	deaf$.tw.	15554
101	exp *MENTAL DISEASE/	494775
102	exp BEHAVIOR DISORDER/	181357
103	exp COMMUNICATION DISORDER/	20191
104	DEVELOPMENTAL DISORDER/	12911
105	exp LEARNING DISORDER/	11162
106	exp MENTAL DEFICIENCY/	53810
107	exp PSYCHOMOTOR DISORDER/	25386
108	MOOD DISORDER/	10417
109	(behaviour$ or behavior$).tw.	384657
110	WALKING DIFFICULTY/	785
111	mobil$.tw.	125389
112	((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	3437
113	DYSLEXIA/	3461
114	exp MEMORY DISORDER/	24095
115	exp PERCEPTION DISORDER/	7725
116	exp PSYCHOMOTOR DISORDER/	25386
117	(learning adj2 (difficult$ or impair$)).tw.	3748
118	((academic$ or education$ or school$) adj2 achieve$).tw.	2117
119	exp SPEECH DISORDER/	24468

120	speech$.tw.	28331
121	WALKING/	14695
122	(ambulation or disabil$ or walk$).tw.	92635
123	COGNITIVE DEFECT/	38518
124	cognition.tw.	14807
125	exp "QUALITY OF LIFE"/	98318
126	(quality of life or life quality).tw.	72165
127	((learning or intellec$) adj2 (difficult$ or impair$)).tw.	4718
128	exp HEMATOLOGIC DISEASE/	720890
129	((haematolog$ or hematolog$) adj2 (disease$ or disabilit$)).tw.	2561
130	exp HYDROCEPHALUS/	15562
131	hydroceph$.tw.	11609
132	exp EPILEPSY/	77217
133	epileps$.tw.	43964
134	(sequelae$ or morbid$).tw.	171375
135	BACTERIAL MENINGITIS/co [Complication]	593
136	SEIZURE/	44208
137	seizure$.tw.	57851
138	exp *NEUROLOGIC DISEASE/	781560
139	COGNITION/	70037
140	exp LANGUAGE DISABILITY/	18840
141	or/93-140	2773294
142	CEREBRAL PALSY/	9790
143	(cere$ adj2 pal$).tw.	8278
144	exp RESPIRATORY TRACT DISEASE/	731403
145	exp BREATHING DISORDER/	79647
146	((resp$ or breath$) adj2 (insuff$ or probl$ or compl$ or abnorma$ or infect$ or disord$)).tw.	81437
147	ANAPHYLACTOID PURPURA/	2390
148	purpura$.tw.	11528
149	exp SKIN DISEASE/	514125
150	(skin adj3 (involve$ or comp$ or abnorm$ or sequ$ or morbid$)).tw.	14081
151	or/142-150	1234754
152	exp INTENSIVE CARE/	197700
153	((paed$ or neon$ or child$) adj2 inten$).tw.	7624
154	picu.tw.	828
155	CRITICAL ILLNESS/	12863
156	((critic$ or acut$) adj2 ill$).tw.	21991
157	or/152-156	217159
158	or/81,92,141,151,157	4548995
159	and/50,57,158	3182
160	limit 159 to yr="2006 - 2009"	862

MENG_physical_pyscho_morbid_medline_130109

Ovid MEDLINE 1950 to November Week 3 2008

#	Searches	Results
1	randomized controlled trial.pt.	269477
2	controlled clinical trial.pt.	80776
3	DOUBLE BLIND METHOD/	101566
4	SINGLE BLIND METHOD/	12762
5	RANDOM ALLOCATION/	63710
6	RANDOMIZED CONTROLLED TRIALS/	58509
7	or/1-6	454816
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	99256
9	clinical trial.pt.	460981
10	exp CLINICAL TRIAL/	572702
11	exp CLINICAL TRIALS AS TOPIC/	215116
12	(clinic$ adj5 trial$).tw,sh.	135508
13	PLACEBOS/	28390
14	placebo$.tw,sh.	128873
15	random$.tw,sh.	573052
16	or/8-15	1005126
17	or/7,16	1009800
18	META ANALYSIS/	20263
19	META ANALYSIS AS TOPIC/	8898
20	meta analysis.pt.	20263
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	35783
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	19221
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	1997
24	or/18-23	50110
25	review$.pt.	1444767
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	32669
27	((hand or manual$) adj2 search$).tw.	3600
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	5576
29	(pooling or pooled or mantel haenszel).tw,sh.	30507
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1441
31	or/26-30	65217
32	25 and 31	27917
33	or/24,32	66312
34	letter.pt.	654713
35	case report.tw.	140604
36	comment.pt.	376142
37	editorial.pt.	234908
38	historical article.pt.	258893

39	or/34-38	1331435
40	17 not 39	972374
41	33 not 39	62622
42	or/40-41	1004300
43	EPIDEMIOLOGIC STUDIES/	4335
44	exp CASE CONTROL STUDIES/	417270
45	exp COHORT STUDIES/	709364
46	case control.tw.	44486
47	(cohort adj (study or studies)).tw.	38894
48	cohort analy$.tw.	1917
49	(follow up adj (study or studies)).tw.	29041
50	(observational adj (study or studies)).tw.	18458
51	longitudinal.tw.	84451
52	retrospective.tw.	157290
53	cross sectional.tw.	84279
54	CROSS-SECTIONAL STUDIES/	95990
55	or/43-54	1244020
56	or/42,55	2027253
57	exp MENINGOCOCCAL INFECTIONS/	8435
58	(meningoc$ or meningit$).tw.	42351
59	exp NEISSERIA MENINGITIDIS/	6604
60	(neisseria meningitid$ or n meningitid$).tw.	5327
61	exp MENINGITIS, BACTERIAL/	17435
62	exp MENINGOCOCCAL VACCINES/	1653
63	or/57-62	47288
64	SOCIAL SUPPORT/	34452
65	exp ADAPTATION, PSYCHOLOGICAL/	76799
66	STRESS, PSYCHOLOGICAL/	61953
67	exp COUNSELING/	26136
68	counsel$.tw.	44851
69	exp *ANXIETY/	18710
70	(patient adj3 (anxiety or stress)).tw.	1879
71	STRESS DISORDERS, POST-TRAUMATIC/	13471
72	DEPRESSION/	52340
73	PATIENT EDUCATION AS TOPIC/	54361
74	PREOPERATIVE CARE/	42098
75	POSTOPERATIVE CARE/	45973
76	(patient adj3 (recov$ or inform$ or care or educat$)).tw.	60186
77	*PROFESSIONAL-PATIENT RELATIONS/	6163
78	*NURSE-PATIENT RELATIONS/	12582
79	*PHYSICIAN-PATIENT RELATIONS/	22387
80	(leaflet$ or booklet$ or pamphlet$ or tape$ or video$).tw.	82204

81	exp COMMUNICATION/	269175
82	PAMPHLETS/	2500
83	PATIENT PARTICIPATION/	13085
84	patient literature.tw.	29
85	exp PATIENT CARE TEAM/	43600
86	information.tw.	464096
87	or/64-86	1227343
88	exp PSYCHOTHERAPY, GROUP/	19797
89	FAMILY THERAPY/	6683
90	"COST OF ILLNESS"/	11286
91	CAREGIVERS/	12914
92	PARENTS/	30074
93	SIBLINGS/	3377
94	exp FAMILY RELATIONS/	54743
95	(family or parent$ or mother$ or father$ or brother$ or sister$ or sibling$).tw.	671026
96	(carer$ or caregiver$ or care-giver$).tw.	22389
97	(psycholog$ or social$ or psychosocial$).tw.	313995
98	or/88-97	992681
99	(organ adj3 (dysfunction$ or impair$ or failure$)).tw.	12956
100	exp KIDNEY FAILURE/	95056
101	((kidney$ or renal$) adj3 (insuffic$ or failure$ or impair$ or dysfunc$)).tw.	93765
102	exp VISION DISORDERS/	49960
103	(vision$ or eyesight$).tw.	51564
104	exp HEARING LOSS/	44591
105	(hear$ adj3 (impair$ or loss$)).tw.	28758
106	deaf$.tw.	23924
107	exp *MENTAL DISORDERS DIAGNOSED IN CHILDHOOD/	86842
108	CHILD BEHAVIOR DISORDERS/	15786
109	exp COMMUNICATION DISORDERS/	44167
110	DEVELOPMENTAL DISABILITIES/	10506
111	exp LEARNING DISORDERS/	15845
112	exp MENTAL RETARDATION/	71036
113	MOTOR SKILLS DISORDERS/	1259
114	exp MOOD DISORDERS/	88259
115	(behaviour$ or behavior$).tw.	472480
116	MOBILITY LIMITATION/	606
117	mobil$.tw.	141233
118	((post-traumatic or post traumatic) adj2 (stress$ or neuroses$)).tw.	3461
119	exp DYSLEXIA/	5788
120	exp MEMORY DISORDERS/	16237
121	exp PERCEPTUAL DISORDERS/	18561
122	exp PSYCHOMOTOR DISORDERS/	9015

123	(learning adj2 (difficult$ or impair$)).tw.	4144
124	((academic$ or education$ or school$) adj2 achieve$).tw.	3266
125	exp SPEECH DISORDERS/	22217
126	speech$.tw.	38256
127	WALKING/	10568
128	(ambulation or disabil$ or walk$).tw.	110912
129	exp COGNITION DISORDERS/	39425
130	cognition.tw.	15705
131	"QUALITY OF LIFE"/	72989
132	(quality of life or life quality).tw.	77464
133	((learning or intellec$) adj2 (difficult$ or impair$)).tw.	5224
134	exp HEMATOLOGIC DISEASES/	383893
135	((haematolog$ or hematolog$) adj2 (disease$ or disabilit$)).tw.	3477
136	exp HYDROCEPHALUS/	17320
137	hydroceph$.tw.	15709
138	exp EPILEPSY/	107503
139	epileps$.tw.	51026
140	(sequelae$ or morbid$).tw.	200026
141	exp MENINGITIS, BACTERIAL/co [Complications]	2864
142	SEIZURES/	34360
143	seizure$.tw.	62347
144	exp NEUROLOGIC MANIFESTATIONS/	646636
145	exp NEUROBEHAVIORAL MANIFESTATIONS/	187511
146	exp LANGUAGE DISORDERS/	33760
147	LANGUAGE DEVELOPMENT DISORDERS/	3386
148	or/99-147	2316558
149	CEREBRAL PALSY/	12222
150	(cere$ adj2 pal$).tw.	10870
151	exp RESPIRATORY TRACT DISEASES/	865349
152	exp RESPIRATION DISORDERS/	119219
153	exp RESPIRATORY INSUFFICIENCY/	43934
154	((resp$ or breath$) adj2 (insuff$ or probl$ or compl$ or abnorma$ or infect$ or disord$)).tw.	95499
155	PURPURA, SCHOENLEIN-HENOCH/	2974
156	purpura$.tw.	16100
157	exp SKIN DISEASES/	674209
158	(skin adj3 (involve$ or comp$ or abnorm$ or sequ$ or morbid$)).tw.	15507
159	or/149-158	1596549
160	exp INTENSIVE CARE UNITS, PEDIATRIC/	9309
161	((paed$ or neon$ or child$) adj2 inten$).tw.	9312
162	picu.tw.	954
163	CRITICAL ILLNESS/	9388

164 ((critic$ or acut$) adj2 ill$).tw.	25222
165 or/160-164	42886
166 or/87,98,148,159,165	5150802
167 and/56,63,166	3770
168 limit 167 to yr="2006 - 2009"	633

MENG_physical_pyscho_morbid_psycinfo_130109

PsycINFO 1967 to January Week 1 2009

#	Searches	Results
1	LITERATURE REVIEW/	21991
2	BETWEEN GROUPS DESIGN/	97
3	EXPERIMENTAL DESIGN/	6940
4	RANDOM SAMPLING/	402
5	EXPERIMENT CONTROLS/	491
6	META-ANALYSIS/	2842
7	random$.tw.	74961
8	(meta-analys#s or metaanalys#s).ti.	3906
9	(systematic$ adj (review$ or overview$)).ti.	1586
10	((single or double or triple) adj (blind$ or mask$)).ti.	3109
11	rct.tw.	607
12	LONGITUDINAL STUDIES/	14445
13	RETROSPECTIVE STUDIES/	290
14	PROSPECTIVE STUDIES/	305
15	FOLLOWUP STUDIES/	12492
16	(comparative adj5 study).tw.	7846
17	(case control adj5 (study or studies)).tw.	2194
18	(retrospectiv$ adj5 (study or studies)).tw.	4588
19	(prospectiv$ adj5 (study or studies)).tw.	11469
20	(case$ adj2 series).ti,ab.	1432
21	(case$ adj2 control$).ti,ab.	3668
22	or/1-21	160217
23	exp MENINGITIS/	197
24	(meningoc$ or meningit$).tw.	492
25	(neisseria meningitid$ or n meningitid$).tw.	9
26	or/23-25	516
27	and/22,26	58
28	limit 27 to yr="2006 - 2009"	15

29 What is the prevalence of primary immunodeficiency in children and young people with meningococcal disease?

MENG_incidence_immunodeficiency_medline_161208

Ovid MEDLINE 1950 to November Week 3 2008

#	Searches	Results
1	MENINGITIS, MENINGOCOCCAL/	4049
2	MENINGOCOCCAL INFECTIONS/	4559
3	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	4587
4	meningococc?emi$.ti,ab.	620
5	NEISSERIA MENINGITIDIS/	6159
6	(neisseria meningitid$ or n meningitid$).ti,ab.	5327
7	(meningococcus or meningococci$).ti,ab.	2229
8	or/1-7	13075
9	(immunodeficien$ or immuno deficien$).ti,ab.	87173
10	immune deficien$.ti,ab.	8644
11	IMMUNOCOMPROMISED HOST/	10306
12	(immunocompromised or immuno compromised).ti,ab.	13964
13	immune compromised.ti,ab.	352
14	IMMUNITY/	18407
15	complement.ti,ab.	78364
16	COMPLEMENT SYSTEM PROTEINS/	23222
17	COMPLEMENT HEMOLYTIC ACTIVITY ASSAY/	492
18	(ch50 or ch 50).ti,ab.	1148
19	PROPERDIN/	1500
20	properdin.ti,ab.	1462
21	(total adj3 (haemolytic$ or hemolytic$)).ti,ab.	577
22	ANTIBODIES/	77950
23	antibod$.ti.	169622
24	IMMUNOGLOBULINS/	37320
25	(immunoglobulin$ or immuno globulin$).ti,ab.	101583
26	IMMUNOGLOBULIN A/	27481
27	IMMUNOGLOBULIN D/	2539
28	IMMUNOGLOBULIN E/	28941
29	IMMUNOGLOBULIN G/	95473
30	IMMUNOGLOBULIN M/	43404
31	or/9-30	581413
32	and/8,31	1669
33	letter.pt.	654713
34	editorial.pt.	234908
35	CASE REPORTS/	1432649
36	(case report or case study).ti.	125291

37 or/33-36	2205298
38 32 not 37	1440
39 limit 38 to humans	1070
40 limit 39 to english language	916

MENG_incidence_immunodeficiency_cctr_161208

EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2008

#	Searches	Results
1	MENINGITIS, MENINGOCOCCAL/	90
2	MENINGOCOCCAL INFECTIONS/	73
3	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	82
4	meningococc?emi$.ti,ab.	5
5	NEISSERIA MENINGITIDIS/	124
6	(neisseria meningitid$ or n meningitid$).ti,ab.	138
7	(meningococcus or meningococci$).ti,ab.	54
8	or/1-7	311
9	(immunodeficien$ or immuno deficien$).ti,ab.	2059
10	immune deficien$.ti,ab.	135
11	IMMUNOCOMPROMISED HOST/	117
12	(immunocompromised or immuno compromised).ti,ab.	226
13	immune compromised.ti,ab.	4
14	IMMUNITY/	198
15	complement.ti,ab.	1091
16	COMPLEMENT SYSTEM PROTEINS/	110
17	COMPLEMENT HEMOLYTIC ACTIVITY ASSAY/	9
18	(ch50 or ch 50).ti,ab.	37
19	PROPERDIN/	4
20	properdin.ti,ab.	5
21	(total adj3 (haemolytic$ or hemolytic$)).ti,ab.	20
22	ANTIBODIES/	491
23	antibod$.ti.	2230
24	IMMUNOGLOBULINS/	475
25	(immunoglobulin$ or immuno globulin$).ti,ab.	2195
26	IMMUNOGLOBULIN A/	490
27	IMMUNOGLOBULIN D/	9
28	IMMUNOGLOBULIN E/	841
29	IMMUNOGLOBULIN G/	1600
30	IMMUNOGLOBULIN M/	429
31	or/9-30	9732
32	and/8,31	62

MENG_incidence_immunodeficiency_cdsrdare_161208

DARE, CDSR

#	Searches	Results
1	MENINGITIS, MENINGOCOCCAL.kw.	4
2	MENINGOCOCCAL INFECTIONS.kw.	5
3	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	8
4	meningococc?emi$.ti,ab.	0
5	NEISSERIA MENINGITIDIS.kw.	4
6	(neisseria meningitid$ or n meningitid$).ti,ab.	0
7	(meningococcus or meningococci$).ti,ab.	0
8	or/1-7	9
9	(immunodeficien$ or immuno deficien$).ti,ab.	25
10	immune deficien$.ti,ab.	2
11	IMMUNOCOMPROMISED HOST.kw.	16
12	(immunocompromised or immuno compromised).ti,ab.	7
13	immune compromised.ti,ab.	1
14	IMMUNITY.kw.	5
15	complement.ti,ab.	6
16	COMPLEMENT SYSTEM PROTEINS.kw.	0
17	COMPLEMENT HEMOLYTIC ACTIVITY ASSAY.kw.	0
18	(ch50 or ch 50).ti,ab.	0
19	PROPERDIN.kw.	0
20	properdin.ti,ab.	0
21	(total adj3 (haemolytic$ or hemolytic$)).ti,ab.	1
22	ANTIBODIES.kw.	90
23	antibod$.ti.	31
24	IMMUNOGLOBULINS.kw.	50
25	(immunoglobulin$ or immuno globulin$).ti,ab.	65
26	IMMUNOGLOBULIN A.kw.	50
27	IMMUNOGLOBULIN D.kw.	0
28	IMMUNOGLOBULIN E.kw.	3
29	IMMUNOGLOBULIN G.kw.	21
30	IMMUNOGLOBULIN M.kw.	6
31	or/9-30	228
32	and/8,31	0

MENG_incidence_immunodeficiency_cinahl_161208

#	Query	Limiters/Expanders	Results
S31	(S13 and S30)	Search modes - Boolean/Phrase	40
S30	(S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29)	Search modes - Boolean/Phrase	16426
S29	(TI immunoglobulin* or immuno globulin*) or (AB immunoglobulin* or immuno globulin*)	Search modes - Boolean/Phrase	1814
S28	(MH IMMUNOGLOBULINS)	Search modes - Boolean/Phrase	3008
S27	(TI antibod*)	Search modes - Boolean/Phrase	2081
S26	(MH ANTIBODIES)	Search modes - Boolean/Phrase	1683
S25	(TI total N3 hemolytic*) or (AB total N3 hemolytic*)	Search modes - Boolean/Phrase	8
S24	(TI total N3 haemolytic*) or (AB total N3 haemolytic*)	Search modes - Boolean/Phrase	4
S23	(TI properdin) or (AB properdin)	Search modes - Boolean/Phrase	3
S22	(TI ch50 or ch 50) or (AB ch50 or ch 50)	Search modes - Boolean/Phrase	17
S21	(TI complement) or (AB complement)	Search modes - Boolean/Phrase	1776
S20	(MH COMPLEMENT)	Search modes - Boolean/Phrase	289
S19	(MH IMMUNITY)	Search modes - Boolean/Phrase	1706
S18	(TI immune compromised) or (AB immune compromised)	Search modes - Boolean/Phrase	26
S17	(TI immunocompromised or immuno compromised) or (AB immunocompromised or immuno compromised)	Search modes - Boolean/Phrase	883
S16	(MH IMMUNOCOMPROMISED HOST)	Search modes - Boolean/Phrase	1171
S15	(TI immune deficien*) or (AB immune deficien*)	Search modes - Boolean/Phrase	590
S14	(TI immunodeficien* or immuno deficien*) or (AB immunodeficien* or immuno deficien*)	Search modes - Boolean/Phrase	4858
S13	(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12)	Search modes - Boolean/Phrase	913
S12	(TI meningococci*) or (AB meningococci*)	Search modes -	18

		Boolean/Phrase	
S11	(TI meningococcus) or (AB meningococcus)	Search modes - Boolean/Phrase	20
S10	(TI neisseria meningitid*) or (AB neisseria meningitid*)	Search modes - Boolean/Phrase	103
S9	(MH NEISSERIA INFECTIONS)	Search modes - Boolean/Phrase	50
S8	(TI meningococcemi*) or (AB meningococcemi*)	Search modes - Boolean/Phrase	40
S7	(TI meningococcaemi*) or (AB meningococcaemi*)	Search modes - Boolean/Phrase	6
S6	(TI meningococcal N3 infection*) or (AB meningococcal N3 infection*)	Search modes - Boolean/Phrase	44
S5	(TI meningococcal N3 meningitis) or (AB meningococcal N3 meningitis)	Search modes - Boolean/Phrase	63
S4	(TI meningococcal N3 septic?emi*) or (AB meningococcal N3 septic?emi*)	Search modes - Boolean/Phrase	28
S3	(TI meningococcal N3 disease*) or (AB meningococcal N3 disease*)	Search modes - Boolean/Phrase	258
S2	(MH MENINGOCOCCAL INFECTIONS)	Search modes - Boolean/Phrase	583
S1	(MH MENINGITIS, MENINGOCOCCAL)	Search modes - Boolean/Phrase	184

MENG_incidence_immunodeficiency_embase_161208

EMBASE 1980 to 2008 Week 50

#	Searches	Results
1	EPIDEMIC MENINGITIS/	877
2	MENINGOCOCCOSIS/	2831
3	MENINGOCOCCEMIA/	841
4	(meningococcal adj3 (disease$ or septic?emi$ or meningitis or infection?)).ti,ab.	3127
5	meningococc?emi$.ti,ab.	430
6	NEISSERIA MENINGITIDIS/	6868
7	(neisseria meningitid$ or n meningitid$).ti,ab.	4365
8	(meningococcus or meningococci$).ti,ab.	1503
9	or/1-8	10231
10	IMMUNE DEFICIENCY/	33538
11	(immunodeficien$ or immuno deficien$).ti,ab.	75755
12	immune deficien$.ti,ab.	7254
13	IMMUNOCOMPROMISED PATIENT/	903
14	(immunocompromised or immuno compromised).ti,ab.	13088
15	immune compromised.ti,ab.	332
16	IMMUNITY/	21514
17	COMPLEMENT/	8488
18	complement.ti,ab.	57085
19	(ch50 or ch 50).ti,ab.	869
20	PROPERDIN/	332
21	properdin.ti,ab.	573
22	(total adj3 (haemolytic$ or hemolytic$)).ti,ab.	400
23	ANTIBODY/	39314
24	antibod$.ti.	117675
25	IMMUNOGLOBULIN/	40642
26	(immunoglobulin$ or immuno globulin$).ti,ab.	77081
27	exp IMMUNOGLOBULIN ANTIBODY/	24201
28	or/10-27	412279
29	and/9,28	1565
30	letter.pt.	432931
31	editorial.pt.	221160
32	CASE REPORT/	1017866
33	(case report or case study).ti.	100427
34	or/30-33	1591053
35	29 not 34	1335
36	limit 35 to english language	1228

National Institute for Health and Clinical Excellence

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Bacterial meningitis and meningococcal septicaemia

Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

NICE clinical guideline 102
Developed by the National Collaborating Centre for Women's and Children's Health

NICE clinical guideline 102
Bacterial meningitis and meningococcal septicaemia

Ordering information
You can download the following documents from www.nice.org.uk/guidance/CG102

- The NICE guideline (this document) – all the recommendations.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2201 (quick reference guide)
- N2202 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Introduction

Bacterial meningitis is an infection of the surface of the brain (meninges) by bacteria that have usually travelled there from mucosal surfaces via the bloodstream. In children and young people aged 3 months or older, the most frequent causes of bacterial meningitis include *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib). These organisms occur normally in the upper respiratory tract and can cause invasive disease when acquired by a susceptible person. In neonates (children younger than 28 days), the most common causative organisms are *Streptococcus agalactiae* (Group B streptococcus), *Escherichia coli*, *S pneumoniae* and *Listeria monocytogenes*.

Most *N meningitidis* colonisations are asymptomatic, but occasionally the organism invades the bloodstream to cause disease. Meningococcal disease most commonly presents as bacterial meningitis (15% of cases) or septicaemia (25% of cases), or as a combination of the two syndromes (60% of cases). Meningococcal disease is the leading infectious cause of death in early childhood, making its control a priority for clinical management (as well as public health surveillance and control).

The epidemiology of bacterial meningitis in the UK has changed dramatically in the past two decades following the introduction of vaccines to control Hib, serogroup C meningococcus and some types of pneumococcus. As no vaccine is currently licensed against serogroup B meningococcus, this pathogen is now the most common cause of bacterial meningitis (and septicaemia) in children and young people aged 3 months or older.

This guideline does not consider meningitis associated with tuberculosis (TB), because tuberculous meningitis (or meningeal TB) is covered in ‘Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control’ (NICE clinical guideline 33). However, some features of the presentation of tuberculous meningitis are indistinguishable from bacterial meningitis.

Under the Health Protection (Notification) Regulations 2010, registered medical practitioners in England have a legal requirement to notify the proper officer of the local authority urgently when they have reasonable grounds for suspecting that a patient has meningitis or meningococcal septicaemia.

Where the evidence supported it, the Guideline Development Group made separate recommendations for the management of different conditions (bacterial meningitis, meningococcal septicaemia, and in some cases, meningococcal disease). Unless otherwise specified, the recommendations refer to all children and young people aged under 16 years. The Guideline Development Group also used the term ‘neonate’ in some recommendations.

The guideline will assume that prescribers will use a drug’s summary of product characteristics (SPC) to inform their decisions for individual patients.

Patient-centred care

This guideline offers best practice advice on the care of children and young people younger than 16 years with bacterial meningitis and meningococcal septicaemia.

Treatment and care should take into account the child's or young person's needs and preferences, as well as those of their parents or carers. Children and young people with bacterial meningitis and meningococcal septicaemia should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals, but this depends on their age and capacity to make decisions. Where a child or young person is not old enough or does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Healthcare professionals should follow the guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Sometimes if a child or young person appears to have a serious illness that could indicate the need for urgent treatment, the medical staff may not have time to fully discuss what is involved in that treatment beforehand.

In an emergency if the person with parental responsibility cannot be contacted, healthcare professionals may give treatment immediately when it is in the child's or young person's best interests.

Good communication between healthcare professionals and children and young people, and their parents and carers, is essential. It should be supported by evidence-based written information tailored to their specific needs. Treatment and care, and information given about it, should be culturally appropriate. Information should also be accessible to people with

additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in ‘Transition: getting it right for young people’ (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with bacterial meningitis and meningococcal septicaemia. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Key priorities for implementation

Symptoms and signs of bacterial meningitis and meningococcal septicaemia

- Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 1.
  - Be aware that:
    - ◊ some children and young people will present with mostly non-specific symptoms or signs and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
    - ◊ children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia and the symptoms and signs may become more severe and more specific over time.
  - Recognise shock (see table 1) and manage urgently in secondary care.
- Healthcare professionals should be trained in the recognition and management of meningococcal disease.

Management in the pre-hospital setting

- Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Diagnosis in secondary care

Investigation and management in children and young people with petechial rash

- Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):
  - petechiae start to spread
  - the rash becomes purpuric
  - there are signs of bacterial meningitis (see table 1)
  - there are signs of meningococcal septicaemia (see table 1)
  - the child or young person appears ill to a healthcare professional.

Polymerase chain reaction

- Perform whole blood real-time polymerase chain reaction testing (EDTA[1] sample) for *N meningitidis* to confirm a diagnosis of meningococcal disease.

Lumbar puncture

- In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:
  - signs suggesting raised intracranial pressure
    - ◊ reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
    - ◊ relative bradycardia and hypertension
    - ◊ focal neurological signs
    - ◊ abnormal posture or posturing
    - ◊ unequal, dilated or poorly responsive pupils
    - ◊ papilloedema
    - ◊ abnormal ‘doll’s eye’ movements
  - shock (see table 1)
  - extensive or spreading purpura
  - after convulsions until stabilised
  - coagulation abnormalities
    - ◊ coagulation results (if obtained) outside the normal range
    - ◊ platelet count below 100 x 10^9/litre
    - ◊ receiving anticoagulant therapy
  - local superficial infection at the lumbar puncture site
  - respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

[1] Ethylenediaminetetraacetic acid.

Management in secondary care

Fluids for bacterial meningitis

- Do not restrict fluids unless there is evidence of:
  - raised intracranial pressure, **or**
  - increased antidiuretic hormone secretion[2].

Intravenous fluid resuscitation in meningococcal septicaemia

- In children and young people with suspected or confirmed meningococcal septicaemia:
  - if there are signs of shock give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards
  - if the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - if the signs of shock still persist after the first 40 ml/kg:
    - ◊ immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
    - ◊ call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
    - ◊ start treatment with vasoactive drugs
    - ◊ be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume
    - ◊ consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes
  - discuss further management with a paediatric intensivist.

[2] See National Patient Safety Agency (2207) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk

Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

- Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' [NICE technology appraisal 166]).
- Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate services. The following morbidities should be specifically considered:
  - hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)
  - orthopaedic complications (damage to bones and joints)
  - skin complications (including scarring from necrosis)
  - psychosocial problems
  - neurological and developmental problems
  - renal failure.

1 Guidance

The following guidance is based on the best available evidence. The full guideline (www.nice.org.uk/guidance/CG102/Guidance/pdf) gives details of the methods and the evidence used to develop the guidance.

This guideline assumes that fever in children younger than 5 years will be managed according to ‘Feverish illness in children’ (NICE clinical guideline 47) until bacterial meningitis or meningococcal septicaemia is suspected.

1.1 Bacterial meningitis and meningococcal septicaemia in children and young people – symptoms, signs and initial assessment

1.1.1 Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 1.

- Be aware that:
  - some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
  - children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia, and the symptoms and signs may become more severe and more specific over time.
- Recognise shock (see table 1) and manage urgently in secondary care.

Table 1 Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Symptom/sign	Bacterial meningitis (meningococcal meningitis and meningitis caused by other bacteria)	Meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia)	Meningococcal septicaemia	Notes
Common non-specific symptoms/signs				
Fever	✓	✓	✓	Not always present, especially in neonates
Vomiting/nausea	✓	✓	✓	
Lethargy	✓	✓	✓	
Irritable/unsettled	✓	✓	✓	
Ill appearance	✓	✓	✓	
Refusing food/drink	✓	✓	✓	
Headache	✓	✓	✓	
Muscle ache/joint pain	✓	✓	✓	
Respiratory symptoms/signs or breathing difficulty	✓	✓	✓	
Less common non-specific symptoms/signs				
Chills/shivering	✓	✓	✓	
Diarrhoea, abdominal pain/distension	✓	✓	NK	
Sore throat/coryza or other ear, nose and throat symptoms/signs	✓	✓	NK	
More specific symptoms/signs				
Non-blanching rash	✓	✓	✓	Be aware that a rash may be less visible in darker skin tones – check soles of feet, palms of hands and conjunctivae
Stiff neck	✓	✓	NK	
Altered mental state	✓	✓	✓	Includes confusion, delirium and drowsiness, and impaired

				consciousness
Capillary refill time more than 2 seconds	NK	✓	✓	
Unusual skin colour	NK	✓	✓	
Shock	✓	✓	✓	
Hypotension	NK	✓	✓	
Leg pain	NK	✓	✓	
Cold hands/feet	NK	✓	✓	
Back rigidity	✓	✓	NK	
Bulging fontanelle	✓	✓	NK	Only relevant in children aged under 2 years
Photophobia	✓	✓	X	
Kernig's sign	✓	✓	X	
Brudzinski's sign	✓	✓	X	
Unconsciousness	✓	✓	✓	
Toxic/moribund state	✓	✓	✓	
Paresis	✓	✓	X	
Focal neurological deficit including cranial nerve involvement and abnormal pupils	✓	✓	X	
Seizures	✓	✓	X	

Signs of shock

- Capillary refill time more than 2 seconds
- Unusual skin colour
- Tachycardia and/or hypotension
- Respiratory symptoms or breathing difficulty
- Leg pain
- Cold hands/feet
- Toxic/moribund state
- Altered mental state/decreased conscious level
- Poor urine output

✓ symptom/sign present
X symptom/sign not present
NK not known if a symptom/sign is present (not reported in the evidence)

1.1.2 Be alert to the possibility of bacterial meningitis or meningococcal septicaemia when assessing children or young people with acute febrile illness.

1.1.3 Healthcare professionals should be aware that classical signs of meningitis (neck stiffness, bulging fontanelle, high-pitched cry) are often absent in infants with bacterial meningitis[3].

1.1.4 Be aware that children and young people with bacterial meningitis commonly present with non-specific symptoms and signs, including fever, vomiting, irritability, and upper respiratory tract symptoms. Some children with bacterial meningitis present with seizures[4].

1.1.5 Consider other non-specific features of the child's or young person's presentation, such as:

- the level of parental or carer concern (particularly compared with previous illness in the child or young person or their family),
- how quickly the illness is progressing, **and**
- clinical judgement of the overall severity of the illness.

1.1.6 In children and young people with suspected bacterial meningitis or meningococcal septicaemia, undertake and record physiological observations of heart rate, respiratory rate, oxygen saturations, blood pressure, temperature, perfusion (capillary refill) and neurological assessment (for example the Alert, Voice, Pain, Unresponsive [AVPU] scale) at least hourly.

1.1.7 Healthcare professionals should be trained in the recognition and management of meningococcal disease.

1.1.8 Notify a proper officer of the local authority urgently on suspicion of meningitis or meningococcal septicaemia. This is a legal

[3] This recommendation is from 'Feverish illness in children' (NICE clinical guideline 47) (www.nice.org.uk/guidance/CG47).
[4] See table 2 in 'Feverish illness in children' (NICE clinical guideline 47) (www.nice.org.uk/guidance/CG47).

requirement under the Health Protection (Notification) Regulations 2010[5,6].

1.1.9 Be aware of 'Guidance for Public Health Management of Meningococcal Disease in the UK' (Health Protection Agency Meningococcus Forum, 2006)[7].

1.2 Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

1.2.1 Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Suspected bacterial meningitis without non-blanching rash

1.2.2 Transfer children and young people with suspected bacterial meningitis without non-blanching rash directly to secondary care without giving parenteral antibiotics.

1.2.3 If urgent transfer to hospital is not possible (for example, in remote locations or adverse weather conditions), administer antibiotics to children and young people with suspected bacterial meningitis.

Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia)

1.2.4 Give parenteral antibiotics (intramuscular or intravenous benzylpenicillin) at the earliest opportunity, either in primary or secondary care, but do not delay urgent transfer to hospital to give the parenteral antibiotics.

[5] See www.opsi.gov.uk
[6] The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health protection legislation guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510
[7] See www.hpa.org.uk

1.2.5 Withhold benzylpenicillin only in children and young people who have a clear history of anaphylaxis after a previous dose; a history of a rash following penicillin is not a contraindication.

1.3 Diagnosis in secondary care

1.3.1 Perform a very careful examination for signs of meningitis or septicaemia in children and young people presenting with petechial rashes (see table 1).

Investigation and management in children and young people with petechial rash

1.3.2 Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):

- petechiae start to spread
- the rash becomes purpuric
- there are signs of bacterial meningitis (see table 1)
- there are signs of meningococcal septicaemia (see table 1)
- the child or young person appears ill to a healthcare professional.

1.3.3 If a child or young person has an unexplained petechial rash and fever (or history of fever) carry out the following investigations:

- full blood count
- C-reactive protein (CRP)
- coagulation screen
- blood culture
- whole-blood polymerase chain reaction (PCR) for *N meningitidis*
- blood glucose
- blood gas.

1.3.4 In a child or young person with an unexplained petechial rash and fever (or history of fever) but none of the high-risk clinical manifestations (see table 1):

- Treat with intravenous ceftriaxone immediately if the CRP and/or white blood cell count (especially neutrophil count) is raised, as this indicates an increased risk of having meningococcal disease.
- Be aware that while a normal CRP and normal white blood cell count mean meningococcal disease is less likely, they do not rule it out. The CRP may be normal and the white blood cell count normal or low even in severe meningococcal disease.
- Assess clinical progress by monitoring vital signs (respiratory rate, heart rate, blood pressure, conscious level [Glasgow Coma Scale and/or APVU], temperature), capillary refill time, and oxygen saturations. Carry out observations at least hourly over the next 4–6 hours.
- If doubt remains, treat with antibiotics and admit to hospital.

1.3.5 If the child or young person is assessed as being at low risk of meningococcal disease and is discharged after initial observation, advise parents or carers to return to hospital if the child or young person appears ill to them.

1.3.6 Be aware that in children and young people who present with a non-spreading petechial rash without fever (or history of fever) who do not appear ill to a healthcare professional, meningococcal disease is unlikely, especially if the rash has been present for more than 24 hours. In such cases consider:

- other possible diagnoses
- performing a full blood count and coagulation screen.

Investigation and management in children and young people with suspected bacterial meningitis

1.3.7 In children and young people with suspected bacterial meningitis, perform a CRP and white blood cell count:

- If the CRP and/or white blood cell count is raised and there is a non-specifically abnormal cerebrospinal fluid (CSF) (for example consistent with viral meningitis), treat as bacterial meningitis.
- Be aware that a normal CRP and white blood cell count does not rule out bacterial meningitis.
- Regardless of the CRP and white blood cell count, if no CSF is available for examination or if the CSF findings are uninterpretable, manage as if the diagnosis of meningitis is confirmed.

Polymerase chain reaction (PCR) tests for bacterial meningitis and meningococcal disease

1.3.8 Perform whole blood real-time PCR testing (EDTA[8] sample) for *N meningitidis* to confirm a diagnosis of meningococcal disease.

1.3.9 The PCR blood sample should be taken as soon as possible because early samples are more likely to be positive.

1.3.10 Use PCR testing of blood samples from other hospital laboratories if available, to avoid repeating the test.

1.3.11 Be aware that a negative blood PCR test result for *N meningitidis* does not rule out meningococcal disease.

1.3.12 Submit CSF to the laboratory to hold for PCR testing for *N meningitidis* and *S pneumoniae,* but only perform the PCR testing if the CSF culture is negative.

[8] Ethylenediaminetetraacetic acid.

1.3.13 Be aware that CSF samples taken up to 96 hours after admission to hospital may give useful results.

Skin samples and throat swabs for meningococcal disease

1.3.14 Do not use any of the following techniques when investigating for possible meningococcal disease: skin scrapings, skin biopsies, petechial or purpuric lesion aspirates (obtained with a needle and syringe), or throat swabs.

Performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis

1.3.15 Perform a lumbar puncture as a primary investigation unless this is contraindicated.

1.3.16 Do not allow lumbar puncture to delay the administration of parenteral antibiotics.

1.3.17 CSF examination should include white blood cell count and examination, total protein and glucose concentrations, Gram stain and microbiological culture. A corresponding laboratory-determined blood glucose concentration should be measured.

1.3.18 In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:

- signs suggesting raised intracranial pressure
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - relative bradycardia and hypertension
  - focal neurological signs
  - abnormal posture or posturing
  - unequal, dilated or poorly responsive pupils
  - papilloedema
  - abnormal ‘doll’s eye’ movements
- shock (see table 1)

- extensive or spreading purpura
- after convulsions until stabilised
- coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 109/litre
  - receiving anticoagulant therapy
- local superficial infection at the lumbar puncture site
- respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

1.3.19 In children and young people with suspected bacterial meningitis, if contraindications to lumbar puncture exist at presentation consider delaying lumbar puncture until there are no longer contraindications. Delayed lumbar puncture is especially worthwhile if there is diagnostic uncertainty or unsatisfactory clinical progress.

1.3.20 CSF white blood cell counts, total protein and glucose concentrations should be made available within 4 hours to support the decision regarding adjunctive steroid therapy.

1.3.21 Start antibiotic treatment for bacterial meningitis if the CSF white blood cell count is abnormal:

- in neonates at least 20 cells/microlitre (be aware that even if fewer than 20 cells/microlitre, bacterial meningitis should still be considered if other symptoms and signs are present – see table 1)
- in older children and young people more than 5 cells/microlitre or more than 1 neutrophil/microlitre, regardless of other CSF variables.

1.3.22 In children and young people with suspected bacterial meningitis, consider alternative diagnoses if the child or young person is

significantly ill and has CSF variables within the accepted normal ranges.

1.3.23 Consider herpes simplex encephalitis as an alternative diagnosis.

1.3.24 If CSF white cell count is increased and there is a history suggesting a risk of tuberculous meningitis, evaluate for the diagnosis of tuberculous meningitis in line with ‘Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control’ (NICE clinical guideline 33).

1.3.25 Perform a repeat lumbar puncture in neonates with:

- persistent or re-emergent fever
- deterioration in clinical condition
- new clinical findings (especially neurological findings) or
- persistently abnormal inflammatory markers.

1.3.26 Do not perform a repeat lumbar puncture in neonates:

- who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery
- before stopping antibiotic therapy if they are clinically well.

Cranial computed tomography in suspected bacterial meningitis

1.3.27 Use clinical assessment and not cranial computed tomography (CT), to decide whether it is safe to perform a lumbar puncture. CT is unreliable for identifying raised intracranial pressure.

1.3.28 If a CT scan has been performed, do not perform a lumbar puncture if the CT scan shows radiological evidence of raised intracranial pressure.

1.3.29 In children and young people with a reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more) or with focal neurological signs, perform a CT scan to detect alternative intracranial pathology.

1.3.30 Do not delay treatment to undertake a CT scan.

1.3.31 Clinically stabilise children and young people before CT scanning.

1.3.32 If performing a CT scan consult an anaesthetist, paediatrician or intensivist.

1.4 Management in secondary care

Antibiotics for suspected bacterial meningitis or meningococcal disease

1.4.1 Treat children and young people aged 3 months or older with suspected bacterial meningitis without delay using intravenous ceftriaxone.

1.4.2 Treat children younger than 3 months with suspected bacterial meningitis without delay using intravenous cefotaxime plus either amoxicillin or ampicillin.

1.4.3 Treat suspected meningococcal disease without delay using intravenous ceftriaxone.

1.4.4 Treat children and young people with suspected bacterial meningitis who have recently travelled outside the UK or have had prolonged or multiple exposure to antibiotics (within the past 3 months) with vancomycin in addition to the above antibiotics.

1.4.5 Where ceftriaxone is used, do not administer it at the same time as calcium-containing infusions. Instead, use cefotaxime[9].

1.4.6 In children younger than 3 months, ceftriaxone may be used as an alternative to cefotaxime (with or without ampicillin or amoxicillin), but be aware that ceftriaxone should not be used in premature babies or in babies with jaundice, hypoalbuminaemia or acidosis as it may exacerbate hyperbilirubinaemia.

[9] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update: Vol. 3 Issue 3. Available from www.mhra.gov.uk

1.4.7 If tuberculous meningitis is part of the differential diagnosis use antibiotic treatment appropriate for tuberculous meningitis in line with ‘Tuberculosis’ (NICE clinical guideline 33).

1.4.8 If herpes simplex meningoencephalitis is part of the differential diagnosis give appropriate antiviral treatment.

Treatment for specific infections in confirmed bacterial meningitis

Children and young people aged 3 months or older

1.4.9 Treat *H influenzae* type b meningitis with intravenous ceftriaxone for 10 days in total unless directed otherwise by the results of antibiotic sensitivities.

1.4.10 Treat *S pneumoniae* meningitis with intravenous ceftriaxone for 14 days in total unless directed otherwise by the results of antibiotic sensitivities.

Children younger than 3 months

1.4.11 Treat Group B streptococcal meningitis with intravenous cefotaxime for at least 14 days. If the clinical course is complicated[10] consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

1.4.12 Treat bacterial meningitis due to *L monocytogenes* with intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first 7 days.

1.4.13 Treat bacterial meningitis due to Gram-negative bacilli with intravenous cefotaxime for at least 21 days unless directed otherwise by the results of antibiotic sensitivities. If the clinical course is complicated[11] consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

[10] For example, if there is poor response to antibiotic therapy, effusion or abscess, or concomitant intraventricular haemorrhage in a premature baby.

[11] For example, if there is poor response to antibiotic therapy, effusion or abscess, or concomitant intraventricular haemorrhage in a premature baby.

Treatment of unconfirmed bacterial meningitis

1.4.14 In children and young people aged 3 months or older with unconfirmed, uncomplicated but clinically suspected bacterial meningitis, treat with intravenous ceftriaxone for at least 10 days depending on symptoms and signs and course of the illness.

1.4.15 In children younger than 3 months with unconfirmed but clinically suspected bacterial meningitis, treat with cefotaxime plus either ampicillin or amoxicillin for at least 14 days. If the clinical course is complicated[12], consider extending the duration of treatment and consulting an expert in paediatric infectious diseases.

Meningococcal disease

1.4.16 In children and young people with confirmed meningococcal disease, treat with intravenous ceftriaxone for 7 days in total unless directed otherwise by the results of antibiotic sensitivities.

1.4.17 In children and young people with unconfirmed but clinically suspected meningococcal disease, treat with intravenous ceftriaxone for 7 days in total.

Other aspects of management in bacterial meningitis and meningococcal septicaemia

Metabolic disturbances

1.4.18 In children and young people with suspected or confirmed meningococcal septicaemia, anticipate, monitor and correct the following metabolic disturbances using local or national protocols:

- hypoglycaemia
- acidosis
- hypokalaemia
- hypocalcaemia
- hypomagnesaemia
- anaemia

[12] For example, if there is poor response to antibiotic therapy, effusion or abscess, or concomitant intraventricular haemorrhage in a premature baby.

- coagulopathy.

Seizures

1.4.19 Use local or national protocols for management of seizures in children and young people with suspected bacterial meningitis or meningococcal septicaemia.

Raised intracranial pressure

1.4.20 Use local or national protocols to treat raised intracranial pressure.

Fluid management in suspected or confirmed bacterial meningitis

1.4.21 Assess for all of the following:

- signs of shock (see table 1)
- raised intracranial pressure
- signs of dehydration.

Refer to 'Diarrhoea and vomiting in children' (NICE clinical guideline 84) for assessment of shock and dehydration.

1.4.22 If present, correct dehydration using enteral fluids or feeds, or intravenous isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with dextrose 5%).

1.4.23 Do not restrict fluids unless there is evidence of:

- raised intracranial pressure, **or**
- increased antidiuretic hormone secretion[13].

1.4.24 Give full-volume maintenance fluids to avoid hypoglycaemia and maintain electrolyte balance.

1.4.25 Use enteral feeds as maintenance fluid if tolerated.

1.4.26 If intravenous maintenance fluid is required, use isotonic fluids (for example, sodium chloride 0.9% with glucose 5% or sodium chloride

[13] See National Patient Safety Agency (2207) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk

0.9% with dextrose 5%). In neonates, use glucose 10% and added sodium chloride for maintenance.

1.4.27 Monitor fluid administration and urine output to ensure adequate hydration and avoid overhydration.

1.4.28 Monitor electrolytes and blood glucose regularly (at least daily while the child or young person is receiving intravenous fluids).

1.4.29 If there are signs of raised intracranial pressure or evidence of shock, initiate emergency management for these conditions and discuss ongoing fluid management with a paediatric intensivist.

Intravenous fluid resuscitation in meningococcal septicaemia

1.4.30 In children and young people with suspected or confirmed meningococcal septicaemia:

- If there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards.
- If the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes.
- If the signs of shock still persist after the first 40 ml/kg:
  - immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
  - start treatment with vasoactive drugs
  - be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume

  - consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes.
- Discuss further management with a paediatric intensivist.

Vasoactive therapy for shock in meningococcal septicaemia

1.4.31 If shock persists despite fluid resuscitation (more than 40 ml/kg) and treatment with either intravenous adrenaline or intravenous noradrenaline, or both, consider potential reasons (such as persistent acidosis, incorrect dilution, extravasation) and discuss further management options with a paediatric intensivist.

1.4.32 Use local or national protocols for the administration of vasoactive agents in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

Respiratory support in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia

1.4.33 In self-ventilating children and young people with signs of respiratory distress, administer 15-litre face mask oxygen via a reservoir rebreathing mask.

1.4.34 If there is a threatened loss of airway patency, implement airway-opening manoeuvres, and start bag–valve mask ventilation in preparation for tracheal intubation.

1.4.35 A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

1.4.36 Be aware that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are very ill and at grave risk of sudden deterioration during intubation. Anticipate aspiration, pulmonary oedema or worsening shock

during intubation. Ensure that they are nil by mouth from admission to hospital and that the following are available before intubation:

- facilities to administer fluid boluses
- appropriate vasoactive drugs
- access to a healthcare professional experienced in the management of critically ill children.

1.4.37 Undertake tracheal intubation and mechanical ventilation for the following indications:

- threatened (for example, loss of gag reflex), or actual loss of airway patency
- the need for any form of assisted ventilation, for example bag–mask ventilation
- clinical observation of increasing work of breathing
- hypoventilation or apnoea
- features of respiratory failure, including:
  - irregular respiration (for example, Cheyne–Stokes breathing)
  - hypoxia (PaO2 less than 13 kPa or 97.5 mmHg) or decreased oxygen saturations in air
  - hypercapnia (PaCO2 greater than 6 kPa or 45 mmHg)
- continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- signs of raised intracranial pressure
- impaired mental status:
  - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - moribund state
- control of intractable seizures
- need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit or another hospital.

1.4.38 Use local or national protocols for intubation.

Corticosteroids

Bacterial meningitis

1.4.39 Do not use corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis.

1.4.40 Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[14] for suspected or confirmed bacterial meningitis as soon as possible if lumbar puncture reveals any of the following:

- frankly purulent CSF
- CSF white blood cell count greater than 1000/microlitre
- raised CSF white blood cell count with protein concentration greater than 1 g/litre
- bacteria on Gram stain.

1.4.41 If tuberculous meningitis is in the differential diagnosis, refer to 'Tuberculosis' (NICE clinical guideline 33) before administering steroids, because steroids may be harmful if given without antituberculous therapy.

1.4.42 If dexamethasone was not given before or with the first dose of antibiotics, but was indicated, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics.

1.4.43 After the first dose of dexamethasone discuss the decision to continue dexamethasone with a senior paediatrician.

[14] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice (see the full guideline for further details). The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Dexamethasone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

Meningococcal septicaemia

1.4.44 Do not treat with high-dose corticosteroids (defined as dexamethasone 0.6 mg/kg/day or an equivalent dose of other corticosteroids).

1.4.45 In children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 0.25 mg/m^2 four times daily)[15] should be used only when directed by a paediatric intensivist.

Adjunctive therapies

1.4.46 Do not use activated protein C or recombinant bacterial permeability-increasing protein in children and young people with meningococcal septicaemia.

Monitoring for deterioration for meningococcal disease

1.4.47 Monitor children and young people closely after admission to hospital for signs of deterioration (monitor respiration, pulse, blood pressure, oxygen saturation and Glasgow Coma Scale score).

1.4.48 Be aware that children and young people with meningococcal disease can deteriorate rapidly, regardless of the results of any initial assessment of severity.

Retrieval and transfer to tertiary care

1.4.49 Children and young people who need resuscitation should be discussed with a paediatric intensivist as soon as possible.

1.4.50 Transfer of children and young people to tertiary care should be undertaken by an experienced paediatric intensive care retrieval team comprising medical and nursing staff.

[15] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice (see the full guideline for further details). The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Hydrocortisone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

1.5 Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

1.5.1 Before discharging children and young people from hospital:

- consider their requirements for follow-up, taking into account potential sensory, neurological, psychosocial, orthopaedic, cutaneous and renal morbidities, **and**
- discuss potential long-term effects of their condition and likely patterns of recovery with the child or young person and their parents or carers, and provide them with opportunities to discuss issues and ask questions.

1.5.2 Offer children and young people and their parents or carers:

- information about and access to further care immediately after discharge, **and**
- contact details of patient support organisations including meningitis charities that can offer support, befriending, in-depth information, advocacy, counselling, and written information to signpost families to further help, **and**
- advice on accessing future care.

1.5.3 Offer a formal audiological assessment as soon as possible, preferably before discharge, within 4 weeks of being fit to test.

1.5.4 Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness ' [NICE technology appraisal 166]).

1.5.5 Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and

offered referral to the appropriate services. The following morbidities should be specifically considered:

- hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)
- orthopaedic complications (damage to bones and joints)
- skin complications (including scarring from necrosis)
- psychosocial problems
- neurological and developmental problems
- renal failure.

1.5.6 Inform the child's or young person's GP, health visitor and school nurse (for school-age children and young people) about their bacterial meningitis or meningococcal septicaemia.

1.5.7 Healthcare professionals with responsibility for monitoring the child's or young person's health should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects of bacterial meningitis and meningococcal septicaemia.

Immune testing

1.5.8 Test children and young people for complement deficiency if they have had either:

- more than one episode of meningococcal disease, **or**
- one episode of meningococcal disease caused by serogroups other than B (for example A, C, Y W135, X, 29E), **or**
- meningococcal disease caused by any serogroup and a history of other recurrent or serious bacterial infections.

1.5.9 Children and young people with recurrent episodes of meningococcal disease should be assessed by a specialist in infectious disease or immunology.

1.5.10 Do not test children and young people for complement deficiency who have had either:

- a single episode of meningococcal disease caused by serogroup B meningococcus, **or**
- unconfirmed meningococcal disease.

1.5.11 Discuss appropriate testing for complement deficiency with local immunology laboratory staff.

1.5.12 If a child or young person who has had meningococcal disease has a family history of meningococcal disease or complement deficiency, test the child or young person for complement deficiency.

1.5.13 If a child or young person who has had meningococcal disease is found to have complement deficiency, test their parents and siblings for complement deficiency.

1.5.14 Refer children and young people with complement deficiency to a healthcare professional with expertise in the management of the condition.

1.5.15 Do not test children and young people for immunoglobulin deficiency if they have had meningococcal disease, unless they have a history suggestive of an immunodeficiency (that is, a history of serious, persistent, unusual, or recurrent infections).

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/guidance/CG102

How this guideline was developed

NICE commissioned the National Collaborating Centre for Women's and Children's Health to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B).

There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/guidelinesprocess). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

3 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG102).

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline (see section 5).

4.1 Symptoms and signs of bacterial meningitis and meningococcal disease

What are the symptoms and signs of bacterial meningitis and meningococcal disease in children and young people aged under 16 years that differentiate between these conditions and minor self-limiting infections (including those characterised by fever)?

Why this is important

Research is needed from primary and secondary care settings on the diagnostic accuracy of symptoms and signs suggestive of bacterial meningitis and meningococcal disease in children and young people. The research should focus on identifying individual symptoms and signs, or groups of symptoms and signs that are effective as predictors of bacterial meningitis and meningococcal disease. These symptoms and signs should also differentiate effectively between these conditions and minor self-limiting infections. The research should include consideration of the effectiveness of symptoms and signs of acute feverish illness as predictors of meningococcal disease. Consideration should also be given to the age of the child or young person (in terms of the relevance of particular symptoms and signs) and the clinical setting at presentation. Suitable study designs would include diagnostic accuracy studies as well as observational studies (such as case–control studies), and the research could include a systematic review of studies that have already been published.

4.2 Predictive value of blood test results and CSF findings

What are the normal ranges for blood and CSF parameters in children and young people in the UK?

Why this is important

Bacterial meningitis is a rare disease that is not easily distinguishable clinically from aseptic meningitis. It is, however, important to recognise those children who are most likely to have bacterial meningitis to direct appropriate management of the condition and to avoid inappropriate treatment of aseptic

meningitis. Since the introduction of vaccines to protect against Hib, meningococcus serogroup C and pneumococcus, no high-quality studies involving previously healthy children and young people have been conducted in the UK to determine normal ranges for blood test results or CSF findings in bacterial and aseptic meningitis. Such studies are needed to provide reference values to help interpret blood test results and CSF findings in children (especially neonates) and young people with suspected bacterial meningitis.

4.3 Albumin and crystalloid solutions for fluid resuscitation

How effective is albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock?

Why this is important

There are theoretical reasons why albumin solution may be more effective than crystalloid solution in children and young people with septic shock. However, no clinical studies have evaluated the effectiveness of albumin solution in children and young people with meningococcal disease. Concerns about the safety of colloids such as albumin solution led to a widespread change in clinical practice in the 1990s to using crystalloid solutions, despite a lack of evidence of equivalent effectiveness. Although albumin solution is considerably more expensive than crystalloid solution, a small additional benefit of albumin over crystalloid (one death prevented in more than 14,000 treated cases) would make the use of albumin solution cost effective. Randomised controlled trials are therefore needed to compare the effectiveness of albumin and crystalloid solutions in children and young people with septic shock.

4.4 Adjunctive corticosteroid treatment

What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis?

Why this is important

Neonatal bacterial meningitis is associated with high morbidity, despite the availability of antibiotics that are highly effective against the leading causes of bacterial meningitis in this age group. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms. Corticosteroids are effective as an adjunct to antibiotic treatment in older children with meningitis caused by Hib, and in adults with bacterial meningitis. However, there is insufficient evidence to support a recommendation for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the spectrum of organisms causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same. A large-scale randomised controlled trial is therefore needed to compare the effectiveness of antibiotic treatment plus corticosteroids with antibiotic treatment alone in neonates with suspected or confirmed bacterial meningitis.

4.5 Steroid replacement treatment

How effective is steroid replacement treatment in children and young people with vasopressor-unresponsive shock caused by septicaemia, including meningococcal septicaemia?

Why this is important

Well-conducted but relatively small randomised controlled trials involving adults only suggest that low-dose corticosteroid replacement treatment may ameliorate haemodynamic failure and inflammatory dysregulation associated with severe sepsis. Such treatment may also improve outcomes following septic shock. Severe sepsis in children and young people differs from that in adults, in that multiple-organ dysfunction is less common in children and young people, and mortality is lower. A randomised controlled trial involving children and young people is needed to evaluate the effectiveness of corticosteroid replacement treatment. Studies involving adults suggest that those with normal adrenal function have worse outcomes if they receive steroids than those with adrenal dysfunction, and so the proposed trial should

consider whether testing for adrenal dysfunction before starting steroid replacement treatment improves outcomes.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, 'Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care' contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Women's and Children's Health, and is available from www.ncc-wch.org.uk and our website (www.nice.org.uk/guidance/CG102/FullGuidance).

5.2 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG102QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2201).

5.3 'Understanding NICE guidance'

A summary for patients and their parents and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG102PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2202).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about bacterial meningitis and meningococcal disease.

6 Related NICE guidance

Published

Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. NICE clinical guideline 84 (2009). Available from www.nice.org.uk/guidance/CG84

Feverish illness in children. Assessment and initial management in children younger than 5 years. NICE clinical guideline 47 (2007). Available from www.nice.org.uk/guidance/CG47

Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE clinical guideline 33 (2006). Available from www.nice.org.uk/guidance/CG33

Cochlear implants for children and adults with severe to profound deafness. NICE technology appraisal 166 (2009). Available from www.nice.org.uk/guidance/TA166

7 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

Appendix A: The Guideline Development Group

National Collaborating Centre and NICE project team

Guideline Development Group

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Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

Aomesh Bhatt
Industry representative

Peter Robb (Chair)
Consultant ENT surgeon, Epsom and St Helier University Hospitals Trust and The Royal Surrey County NHS Trusts

Christine Hine
Consultant in public health, Bristol and South Gloucestershire PCT

John Seddon
Lay representative, Chairman, V.O.I.C.E.S.

Greg Rogers
Primary care representative, Kent

Appendix C: The algorithms

For the algorithms see the quick reference guide at
www.nice.org.uk/guidance/CG102/quickrefguide

NHS
National Institute for Health and Clinical Excellence

Quick reference guide

Issue date: June 2010

Bacterial meningitis and meningococcal septicaemia

Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

NICE clinical guideline 102
Developed by the National Collaborating Centre for Women's and Children's Health

About this booklet

This is a quick reference guide that summarises the recommendations NICE has made to the NHS in 'Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care' (NICE clinical guideline 102).

Who should read this booklet?

This quick reference guide is for healthcare professionals and other staff who care for people who have or who are suspected of having bacterial meningitis or meningococcal septicaemia.

Who wrote the guideline?

The guideline was developed by the National Collaborating Centre for Women's and Children's Health, which is linked with the Royal College of Obstetricians and Gynaecologists. The Collaborating Centre worked with a group of healthcare professionals (including consultants, GPs and nurses), patient members and carers, and technical staff, who reviewed the evidence and drafted the recommendations. The recommendations were finalised after public consultation.

For more information on how NICE clinical guidelines are developed, go to **www.nice.org.uk**

Where can I get more information about the guideline?

The NICE website has the recommendations in full, reviews of the evidence they are based on, a summary of the guideline for patients and carers, and tools to support implementation (see inside back cover for more details).

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NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Contents

Key to terms used

CRP C-reactive protein

CSF Cerebrospinal fluid

CT Computed tomography

EDTA Ethylenediaminetetraacetic acid

H influenzae *Haemophilus influenzae*

L monocytogenes *Listeria monocytogenes*

N meningitidis *Neisseria meningitidis*

PCR Polymerase chain reaction

SPC Summary of product characteristics

S pneumoniae *Streptococcus pneumoniae*

WBC White blood cell

Introduction

- Meningococcal disease is the leading infectious cause of death in early childhood. It most commonly presents as bacterial meningitis (15% of cases of *N meningitidis*) or septicaemia (25% of cases), or as a combination of the two presentations (60% of cases).
- The epidemiology of bacterial meningitis in the UK has changed dramatically in the past two decades following the introduction of vaccines to control *H influenzae* type b, serogroup C meningococcus and pneumococcal disease. However, no vaccine is currently licensed against serogroup B meningococcus, and this pathogen is now the most common cause of bacterial meningitis (and septicaemia) in children and young people aged 3 months or older.
- The control of meningococcal disease is therefore a priority for clinical management (as well as public health surveillance and control).
- Bacterial meningitis and meningococcal septicaemia are managed in different ways, therefore it is important that healthcare professionals are able to recognise them and manage them accordingly.

Patient-centred care

Bacterial meningitis and meningococcal septicaemia are life-threatening conditions that require urgent medical treatment. Nevertheless, treatment and care should take into account the child's or young person's individual needs and preferences, as well as those of their parents or carers, where possible. In an emergency, if the person with parental responsibility cannot be contacted, healthcare professionals may give treatment immediately when it is in the child's or young person's best interests.

Good communication between healthcare professionals and children and young people, and their parents and carers, is essential. It should be supported by evidence-based information to allow children and young people, and their parents and carers, to reach informed decisions about their care. Follow advice on seeking consent from the Department of Health or Welsh Assembly Government if needed. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Key priorities for implementation

Symptoms and signs of bacterial meningitis and meningococcal septicaemia

- Consider bacterial meningitis and meningococcal septicaemia in children and young people who present with the symptoms and signs in table 1.
  - Be aware that:
    - some children and young people will present with mostly non-specific symptoms or signs and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way
    - children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia and the symptoms and signs may become more severe and more specific over time.
  - Recognise shock (see table 1) and manage urgently in secondary care.
- Healthcare professionals should be trained in the recognition and management of meningococcal disease.

Management in the pre-hospital setting

- Primary care healthcare professionals should transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning 999.

Diagnosis in secondary care

Investigation and management in children and young people with petechial rash

- Give intravenous ceftriaxone immediately to children and young people with a petechial rash if any of the following occur at any point during the assessment (these children are at high risk of having meningococcal disease):
  - petechiae start to spread
  - the rash becomes purpuric
  - there are signs of bacterial meningitis (see table 1)
  - there are signs of meningococcal septicaemia (see table 1)
  - the child or young person appears ill to a healthcare professional.

Polymerase chain reaction

- Perform whole blood real-time PCR testing (EDTA sample) for *N meningitidis* to confirm a diagnosis of meningococcal disease.

Lumbar puncture

- In children and young people with suspected meningitis or suspected meningococcal disease, perform a lumbar puncture unless any of the following contraindications are present:
  - signs suggesting raised intracranial pressure
    - reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
    - relative bradycardia and hypertension
    - focal neurological signs
    - abnormal posture or posturing
    - unequal, dilated or poorly responsive pupils
    - papilloedema
    - abnormal 'doll's eye' movements
  - shock (see table 1)
  - extensive or spreading purpura
  - after convulsions until stabilised
  - coagulation abnormalities
    - coagulation results (if obtained) outside the normal range
    - platelet count below 100 x 10^9/litre
    - receiving anticoagulant therapy
  - local superficial infection at the lumbar puncture site
  - respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency).

Management in secondary care

Fluids for bacterial meningitis

- Do not restrict fluids unless there is evidence of:
  - raised intracranial pressure, **or**
  - increased antidiuretic hormone secretion[1].

Intravenous fluid resuscitation in meningococcal septicaemia

- In children and young people with suspected or confirmed meningococcal septicaemia:
  - if there are signs of shock give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the child or young person immediately afterwards

[1] See National Patient Safety Agency (2007) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk

- if the signs of shock persist, immediately give a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
- if the signs of shock still persist after the first 40 ml/kg:
  - immediately give a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes
  - call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation
  - start treatment with vasoactive drugs
  - be aware that some children and young people may require large volumes of fluid over a short period of time to restore their circulating volume
  - consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes
- discuss further management with a paediatric intensivist.

Long-term management

Long-term effects of bacterial meningitis and meningococcal septicaemia

- Offer children and young people with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing (further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' [NICE technology appraisal 166]).
- Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate services. The following morbidities should be specifically considered:
  - hearing loss (with the child or young person having undergone an urgent assessment for cochlear implants as soon as they are fit)
  - orthopaedic complications (damage to bones and joints)
  - skin complications (including scarring from necrosis)
  - psychosocial problems
  - neurological and developmental problems
  - renal failure.

Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Table 1 Symptoms and signs of bacterial meningitis and meningococcal septicaemia

Symptom/sign	Bacterial meningitis (meningococcal meningitis and meningitis caused by other bacteria)	Meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia)	Meningococcal septicaemia	Notes
Common non-specific symptoms/signs				
Fever	✓	✓	✓	Not always present, especially in neonates
Vomiting/nausea	✓	✓	✓	
Lethargy	✓	✓	✓	
Irritable/unsettled	✓	✓	✓	
Ill appearance	✓	✓	✓	
Refusing food/drink	✓	✓	✓	
Headache	✓	✓	✓	
Muscle ache/joint pain	✓	✓	✓	
Respiratory symptoms/ signs or breathing difficulty	✓	✓	✓	
Less common non-specific symptoms/signs				
Chills/shivering	✓	✓	✓	
Diarrhoea, abdominal pain/distension	✓	✓	NK	
Sore throat/coryza or other ear, nose and throat symptoms/signs	✓	✓	NK	
More specific symptoms/signs				
Non-blanching rash	✓	✓	✓	Be aware that a rash may be less visible in darker skin tones – check soles of feet, palms of hands and conjunctivae

✓ symptom/sign present ✗ symptom/sign not present NK: not known if a symptom/sign is present (not reported in the evidence)

Table 1 Symptoms and signs of bacterial meningitis and meningococcal septicaemia (continued)

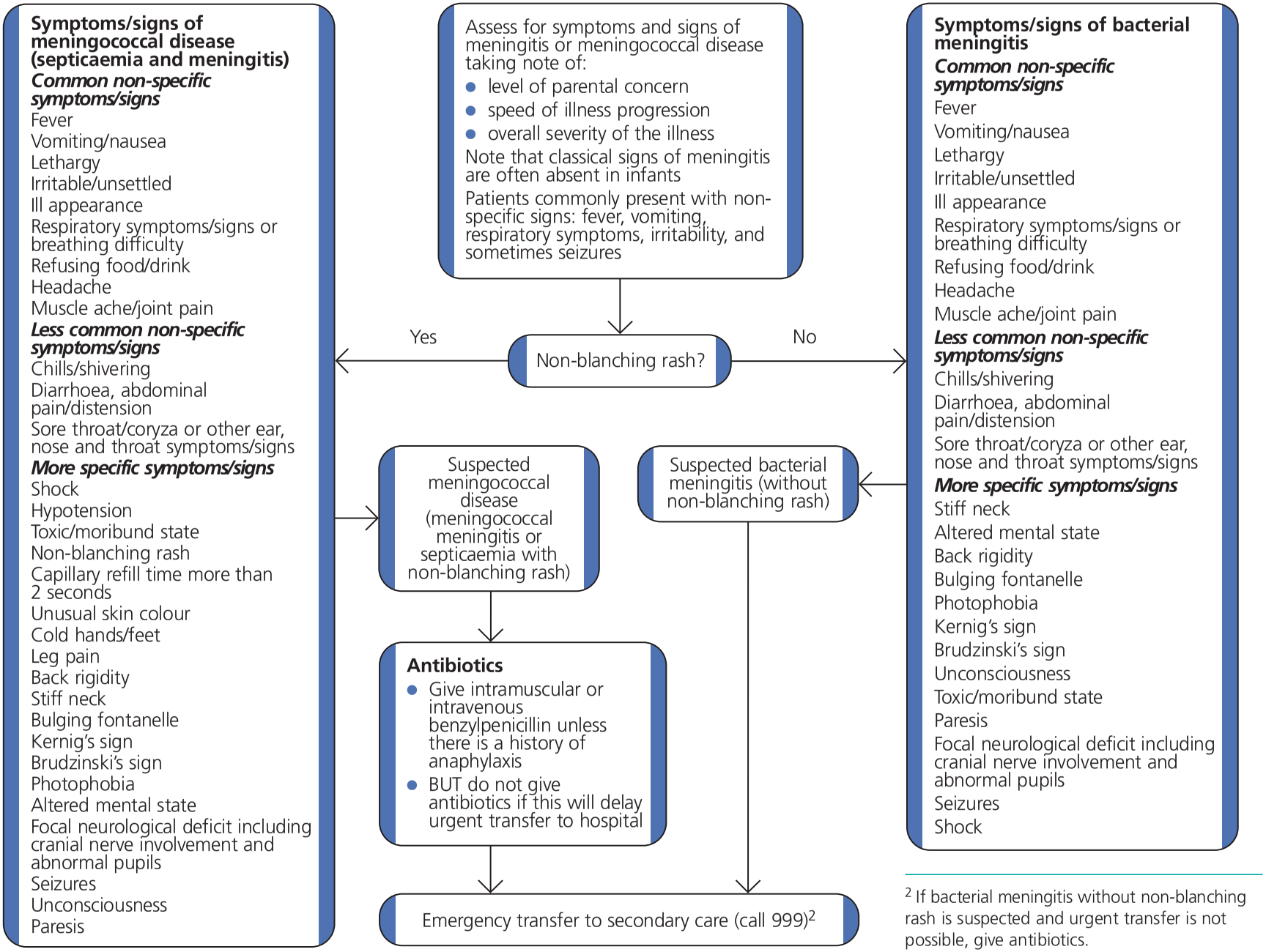
Symptom/sign	Bacterial meningitis (meningococcal meningitis and meningitis caused by other bacteria)	Meningococcal disease (meningococcal meningitis and/or meningococcal septicaemia)	Meningococcal septicaemia	Notes
Stiff neck	✓	✓	NK	
Altered mental state	✓	✓	✓	Includes confusion, delirium and drowsiness, and impaired consciousness
Capillary refill time more than 2 seconds	NK	✓	✓	
Unusual skin colour	NK	✓	✓	
Shock	✓	✓	✓	
Hypotension	NK	✓	✓	
Leg pain	NK	✓	✓	
Cold hands/feet	NK	✓	✓	
Back rigidity	✓	✓	NK	
Bulging fontanelle	✓	✓	NK	Only relevant in children under 2 years
Photophobia	✓	✓	✗	
Kernig's sign	✓	✓	✗	
Brudzinski's sign	✓	✓	✗	
Unconsciousness	✓	✓	✓	
Toxic/moribund state	✓	✓	✓	
Paresis	✓	✓	✗	
Focal neurological deficit including cranial nerve involvement and abnormal pupils	✓	✓	✗	
Seizures	✓	✓	✗	

Signs of shock

- Capillary refill time more than 2 seconds
- Unusual skin colour
- Tachycardia and/or hypotension
- Respiratory symptoms or breathing difficulty
- Leg pain
- Cold hands/feet
- Toxic/moribund state
- Altered mental state/decreased conscious level
- Poor urine output

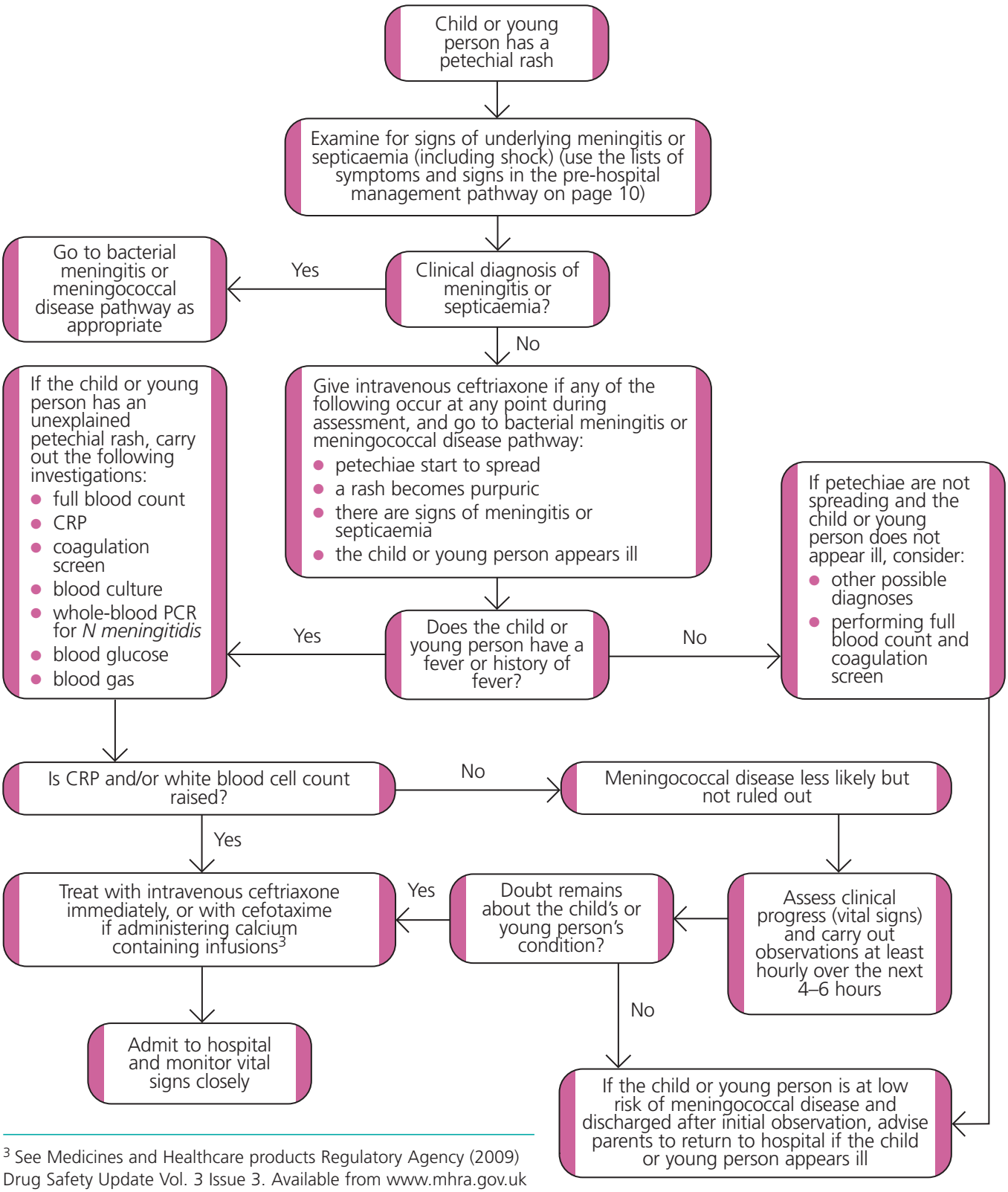
✓ symptom/sign present ✗ symptom/sign not present NK: not known if a symptom/sign is present (not reported in the evidence)

Pre-hospital management – meningococcal disease and bacterial meningitis



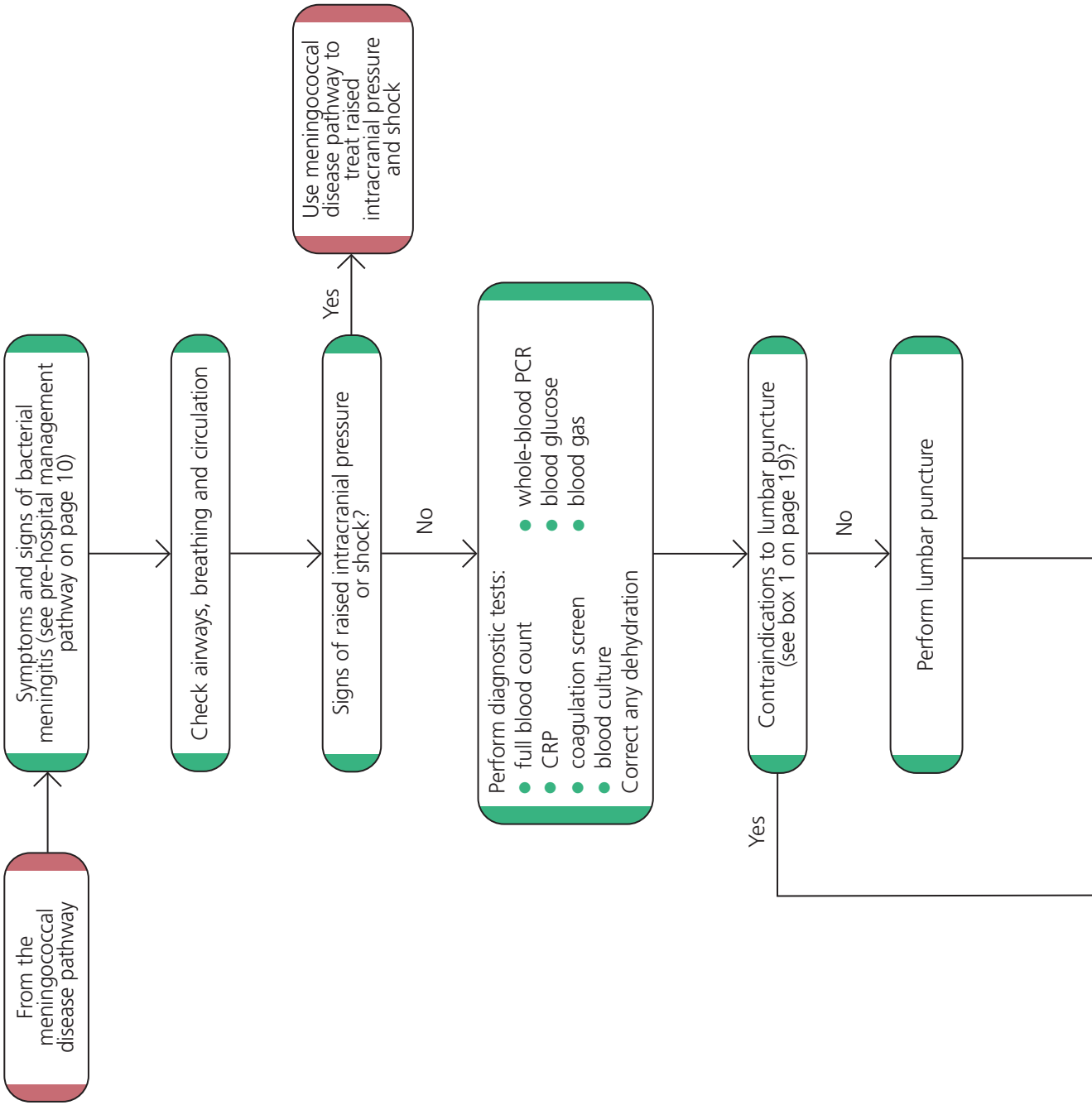
[2] If bacterial meningitis without non-blanching rash is suspected and urgent transfer is not possible, give antibiotics.

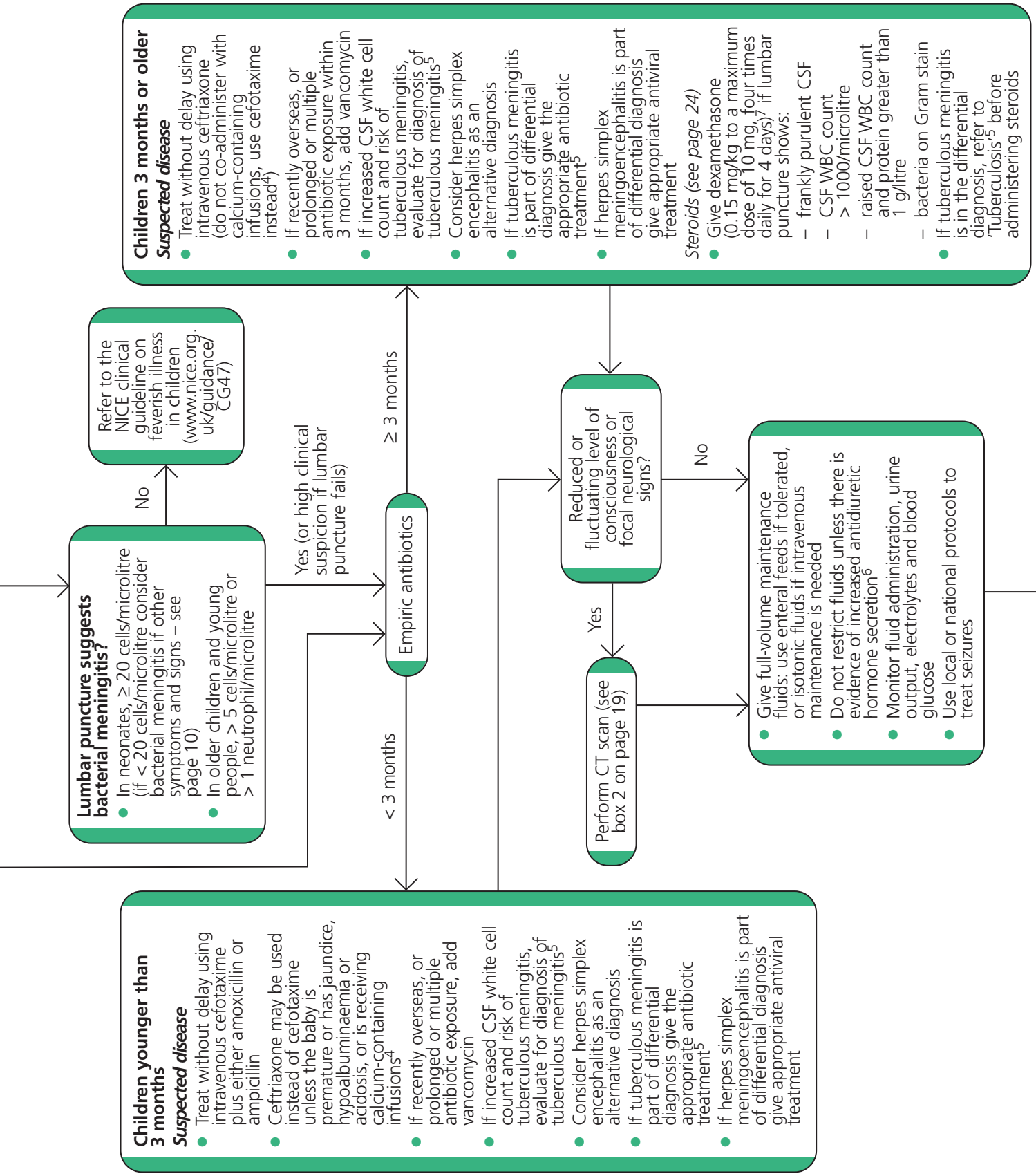
Management of petechial rash

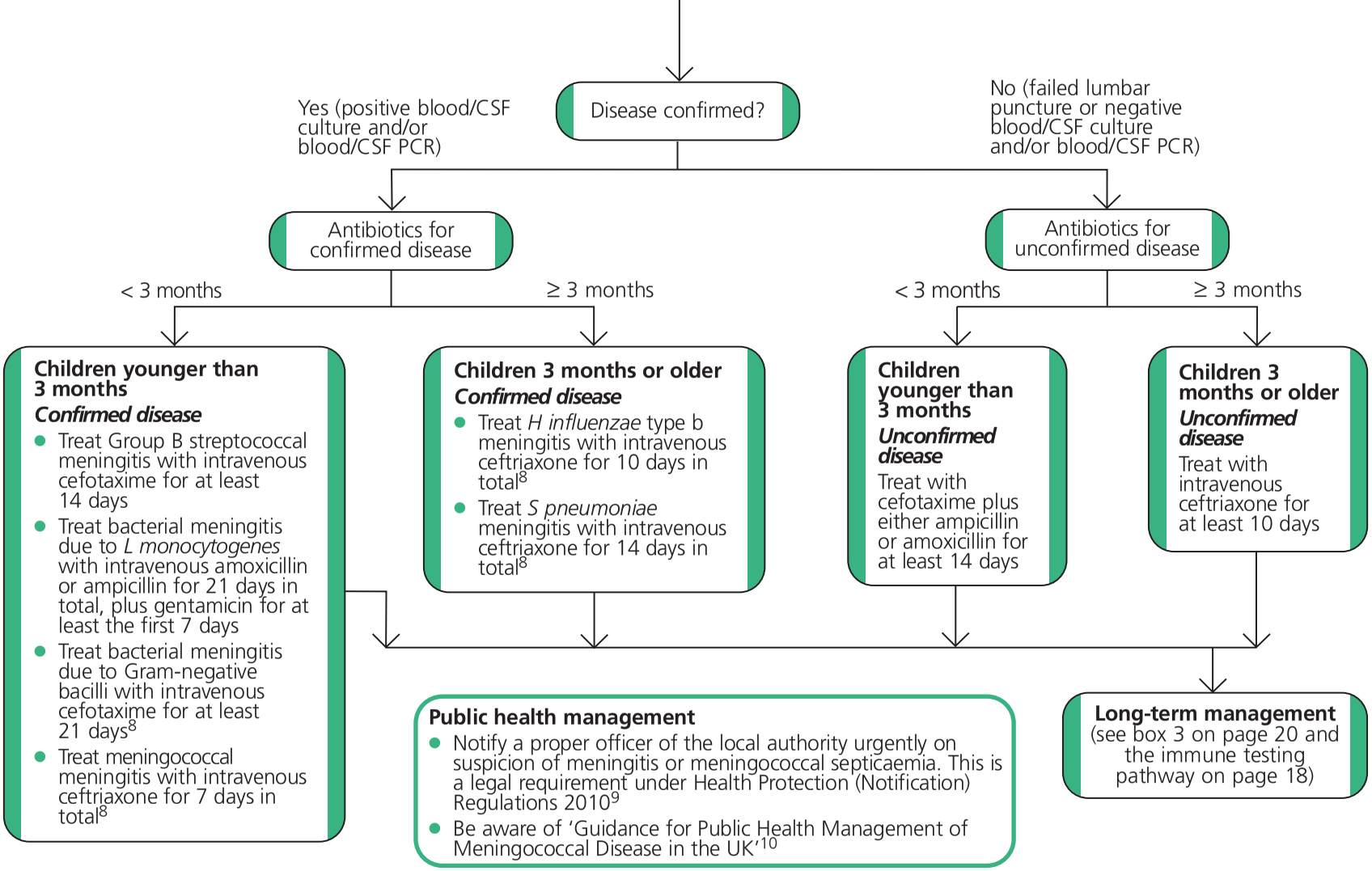


[3] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk

Bacterial meningitis pathway



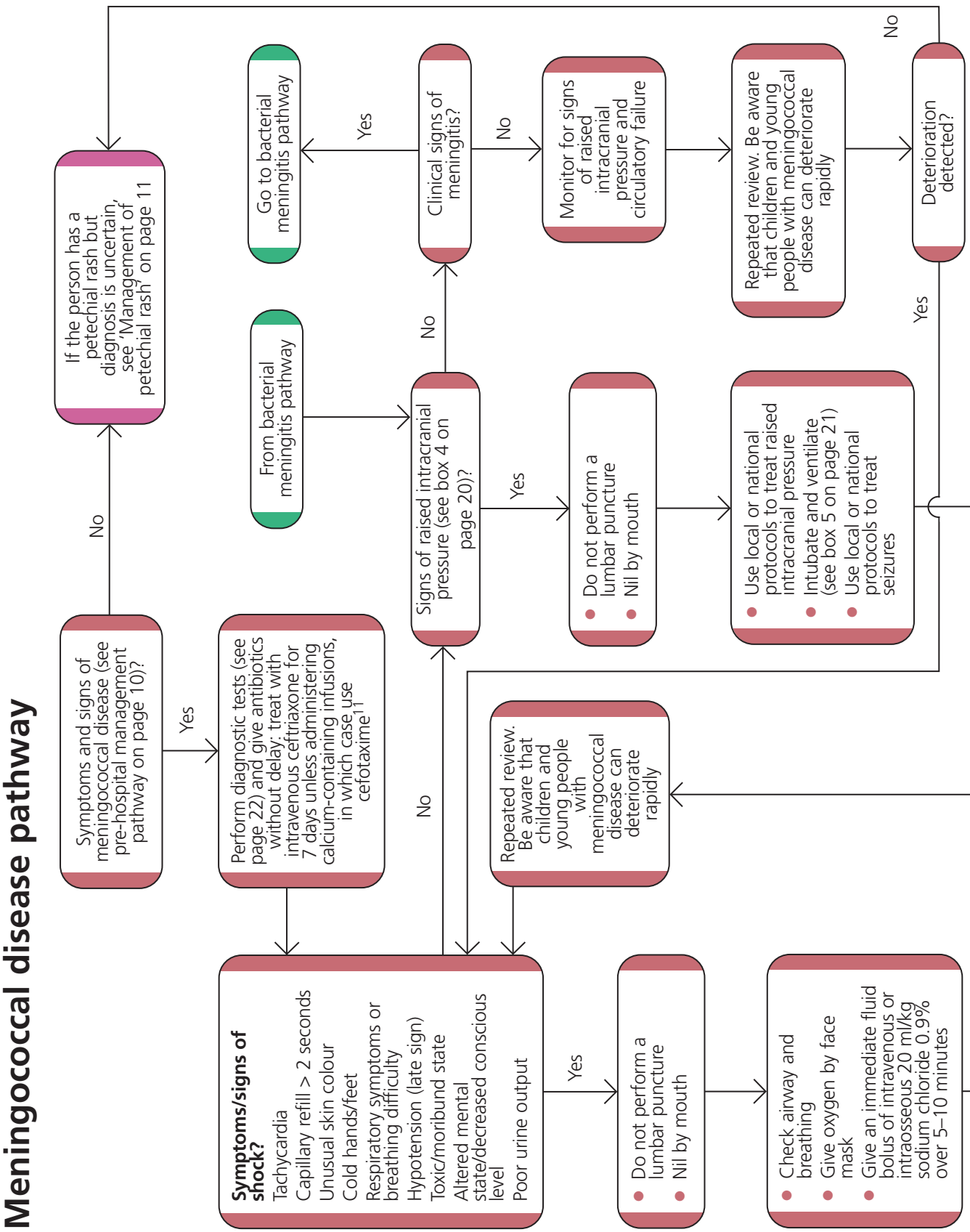

Children younger than 3 months
Suspected disease
Treat without delay using intravenous cefotaxime plus either amoxicillin or ampicillin
Ceftriaxone may be used instead of cefotaxime unless the baby is premature or has jaundice, hypoalbuminaemia or acidosis, or is receiving calcium-containing infusions[4]
If recently overseas, or prolonged or multiple antibiotic exposure, add vancomycin
If increased CSF white cell count and risk of tuberculous meningitis, evaluate for diagnosis of tuberculous meningitis[5]
Consider herpes simplex encephalitis as an alternative diagnosis
If tuberculous meningitis is part of differential diagnosis give the appropriate antibiotic treatment[5]
If herpes simplex meningoencephalitis is part of differential diagnosis give appropriate antiviral treatment
< 3 months
Lumbar puncture suggests bacterial meningitis?
In neonates, ≥ 20 cells/microlitre (if < 20 cells/microlitre consider bacterial meningitis if other symptoms and signs – see page 10)
In older children and young people, > 5 cells/microlitre or > 1 neutrophil/microlitre
No
Refer to the NICE clinical guideline on feverish illness in children (www.nice.org.uk/guidance/CG47)
Yes (or high clinical suspicion if lumbar puncture fails)
Empiric antibiotics
≥ 3 months
Children 3 months or older
Suspected disease
Treat without delay using intravenous ceftriaxone (do not co-administer with calcium-containing infusions, use cefotaxime instead[4])
If recently overseas, or prolonged or multiple antibiotic exposure within 3 months, add vancomycin
If increased CSF white cell count and risk of tuberculous meningitis, evaluate for diagnosis of tuberculous meningitis[5]
Consider herpes simplex encephalitis as an alternative diagnosis
If tuberculous meningitis is part of differential diagnosis give the appropriate antibiotic treatment[5]
If herpes simplex meningoencephalitis is part of differential diagnosis give appropriate antiviral treatment
Steroids (see page 24)
Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[7] if lumbar puncture shows:
– frankly purulent CSF
– CSF WBC count > 1000/microlitre
– raised CSF WBC count and protein greater than 1 g/litre
– bacteria on Gram stain
If tuberculous meningitis is in the differential diagnosis, refer to 'Tuberculosis'[5] before administering steroids
Reduced or fluctuating level of consciousness or focal neurological signs?
Yes
No
Perform CT scan (see box 2 on page 19)
Give full-volume maintenance fluids: use enteral feeds if tolerated, or isotonic fluids if intravenous maintenance is needed
Do not restrict fluids unless there is evidence of increased antidiuretic hormone secretion[6]
Monitor fluid administration, urine output, electrolytes and blood glucose
Use local or national protocols to treat seizures



[4] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk
[5] See 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control'. Available from www.nice.org.uk/guidance/CG33
[6] See National Patient Safety Agency (2007) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk
[7] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice (see the full guideline for further details). The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Dexamethasone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.
[8] Unless directed otherwise by the results of antibiotic sensitivities.
[9] www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health protection legislation guidance 2010' at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114510
[10] Health Protection Agency Meningococcus Forum, 2006; see www.hpa.org.uk

Fold out this page to view the bacterial meningitis pathway

Meningococcal disease pathway



Reassess immediately

If signs of shock persist, immediately give a second bolus of intravenous or intraosseous 20 ml/kg sodium chloride 0.9% **or** human albumin 4.5% solution over 5–10 minutes

If signs of shock remain after a total of 40 ml/kg fluid:

- immediately give a third bolus of intravenous or intraosseous 20 ml/kg sodium chloride 0.9% **or** human albumin 4.5% solution over 5–10 minutes
- call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation (use local or national protocols for intubation)
- start treatment with vasoactive drugs (use local or national protocols)
- consult with paediatric intensivist
- anticipate aspiration and pulmonary oedema

Anticipate, monitor and correct glucose, acid/base and electrolyte disturbances, and anaemia and coagulopathy using local or national protocols

Do not restrict fluids unless there is evidence of:

- raised intracranial pressure, **or**
- increased antidiuretic hormone secretion[12]

Discuss transfer to intensive care with a paediatric intensivist (see bacterial meningitis pathway for antibiotic treatment of unconfirmed or confirmed disease)

- Transfer to tertiary care should be undertaken by an experienced paediatric intensive care retrieval team

Long-term management (see box 3 on page 20 and the immune testing pathway on page 18)

Public health management

- Notify a proper officer of the local authority urgently on suspicion of meningitis or meningococcal septicaemia. This is a legal requirement under Health Protection (Notification) Regulations 2010[13]
- Be aware of 'Guidance for Public Health Management of Meningococcal Disease in the UK'[14]

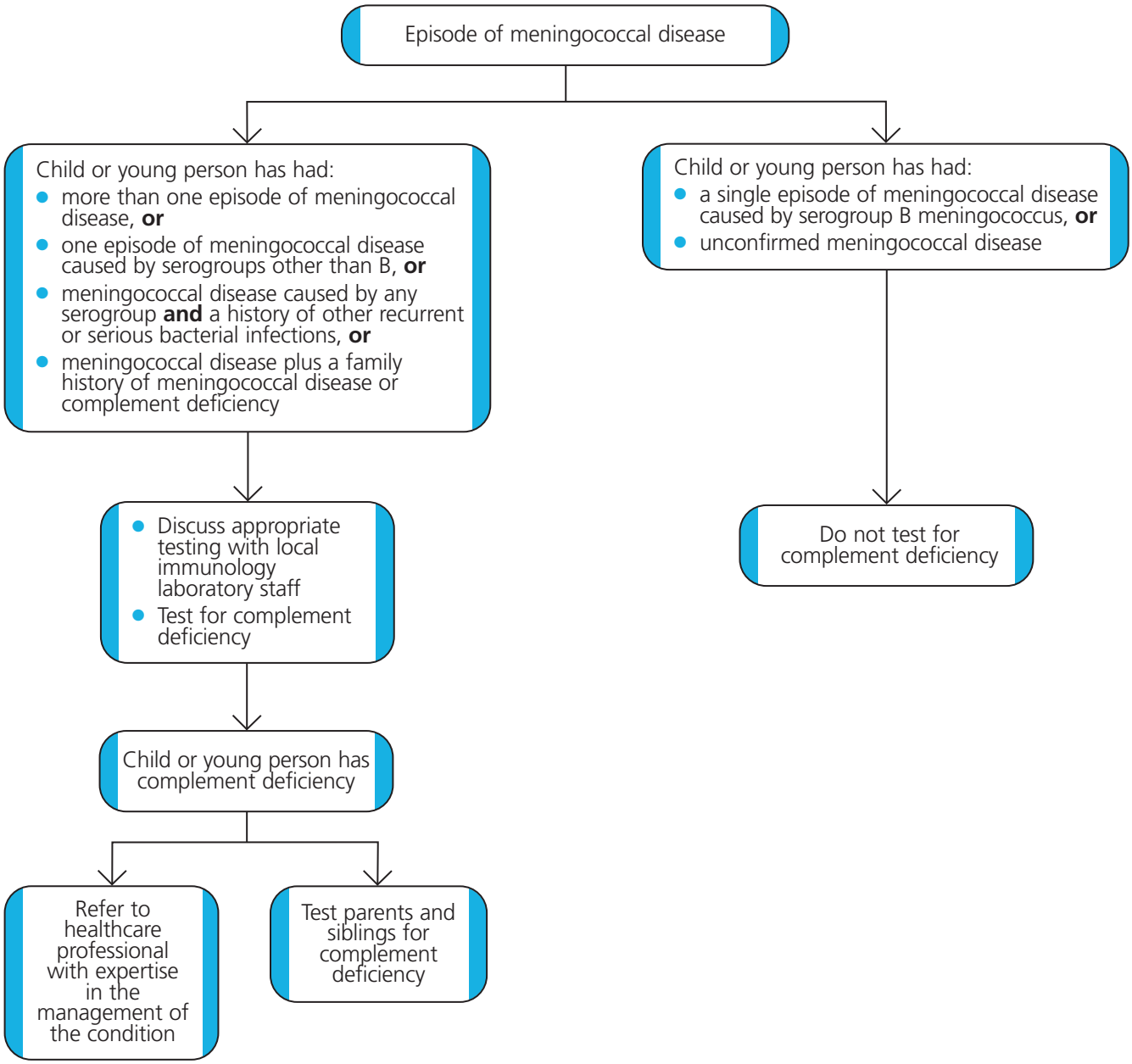
[11] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk

[12] See National Patient Safety Agency (2007) Patient safety alert 22: Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available from www.nrls.npsa.nhs.uk

[13] www.opsi.gov.uk. The Department of Health has issued guidance on health protection legislation which explains the notification requirements. See 'Health protection legislation guidance 2010' at www.dh.gov.uk/en/PublicationsandstatisticsPublications/PublicationsPolicyAndGuidance/DH_114510

[14] Health Protection Agency Meningococcus Forum, 2006; see www.hpa.org.uk

Immune testing in children and young people who have had meningococcal disease



- Children and young people with recurrent episodes of meningococcal disease should be assessed by a specialist in infectious disease or immunology.
- Do not test children and young people for immunoglobulin deficiency if they have had meningococcal disease, unless they have a history suggestive of an immunodeficiency.

Information for bacterial meningitis and meningococcal disease pathways

See the bacterial meningitis pathway and the meningococcal disease pathway on pages 12–17.

Box 1 Contraindications to lumbar puncture

- Signs suggesting raised intracranial pressure (see box 4)
- Shock
- Extensive or spreading purpura
- After convulsions until stabilised
- Coagulation abnormalities
  - coagulation results (if obtained) outside the normal range
  - platelet count below 100 x 10^9/litre
  - receiving anticoagulant therapy
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency (lumbar puncture is considered to have a high risk of precipitating respiratory failure in the presence of respiratory insufficiency)
- Radiological evidence of raised intracranial pressure

Box 2 Cranial CT scanning

- Perform a CT scan to detect alternative intracranial pathology if consciousness is reduced or fluctuating, or there are focal neurological signs.
- Do not delay treatment to undertake a CT scan.
- Clinically stabilise children and young people before CT scanning.
- If performing a CT scan consult an anaesthetist, paediatrician or intensivist.

Box 3 Long-term management

- Consider requirements for follow-up before discharge.
- Discuss likely patterns of recovery and potential long-term effects with the child or young person and their parents or carers.
- Offer information about further care and contact details of patient support organisations.
- Inform the child's or young person's GP, health visitor and school nurse about their bacterial meningitis.
- Healthcare professionals should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects.
- Offer a formal audiological assessment as soon as possible, within 4 weeks of being fit to test.
- Offer children and young people with severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing[15].
- Children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after hospital discharge to discuss morbidities associated with their condition and offered referral to the appropriate services.

Box 4 Signs suggesting raised intracranial pressure

- Reduced or fluctuating level of consciousness
- Relative bradycardia and hypertension
- Focal neurological signs
- Abnormal posture or posturing
- Unequal, dilated or poorly responsive pupils
- Papilloedema
- Abnormal 'doll's eye' movements

[15] Further guidance on the use of cochlear implants for severe to profound deafness can be found in 'Cochlear implants for children and adults with severe to profound deafness' (NICE technology appraisal 166)

Box 5 Intubation and ventilation

A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

Indications for tracheal intubation and mechanical ventilation

- Threatened or actual loss of airway patency
- Need for any form of assisted ventilation
- Clinical observation of increasing work of breathing
- Hypoventilation or apnoea
- Features of respiratory failure
- Continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- Signs of raised intracranial pressure
- Impaired mental status
- Control of intractable seizures
- Need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit/another hospital

Preparation for intubation

Ensure that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are nil by mouth from admission to hospital and that the following are available before intubation:

- facilities to administer fluid boluses
- appropriate vasoactive drugs
- access to a healthcare professional experienced in the management of critically ill children.

Healthcare professionals should be trained in the recognition and management of meningococcal disease

Diagnosis in secondary care

See the bacterial meningitis pathway on pages 12–14 and the meningococcal disease pathway on pages 16–17.

Tests for suspected bacterial meningitis

- In suspected bacterial meningitis perform a CRP and white blood cell count.
  - If there is a raised CRP and/or white blood cell count and an abnormal CSF, treat as bacterial meningitis.
  - Do not rule out bacterial meningitis if CRP and white blood cell count are normal.
  - If no CSF is available or the CSF findings are uninterpretable, manage as confirmed meningitis.

PCR tests for bacterial meningitis and meningococcal disease

- Perform whole blood real-time PCR testing (EDTA sample) for *N meningitidis* to confirm a diagnosis of meningococcal disease.
- Take the PCR blood sample as soon as possible.
- Use PCR testing of blood samples from other hospital laboratories if available, to avoid repeating the test.
- Do not rule out meningococcal disease if a blood PCR test result for *N meningitidis* is negative.

Lumbar puncture and CSF investigations

- Perform a lumbar puncture as a primary investigation unless this is contraindicated.
- If there are contraindications, consider delaying lumbar puncture until there are no longer contraindications.
- Do not allow lumbar puncture to delay the administration of parenteral antibiotics.
- Submit CSF to the laboratory to hold for PCR testing for *N meningitidis* and *S pneumoniae*, but only perform the PCR testing if the CSF culture is negative.
- Be aware that CSF samples taken up to 96 hours after admission to hospital may give useful PCR results.
- CSF examination should include white blood cell count and examination, total protein and glucose concentrations, Gram stain and microbiological culture. A corresponding laboratory-determined blood glucose concentration should be measured.
- CSF white blood cell counts, total protein and glucose concentrations should be made available within 4 hours to support the decision regarding adjunctive steroid therapy.
- In suspected bacterial meningitis, consider alternative diagnoses if the child or young person is significantly ill and has CSF variables within the accepted normal ranges.
- Consider herpes simplex encephalitis as an alternative diagnosis.

Repeat lumbar puncture in neonates

- Perform a repeat lumbar puncture in neonates with:
  - persistent or re-emergent fever
  - deterioration in clinical condition
  - new clinical findings (especially neurological findings) or
  - persistently abnormal inflammatory markers.
- Do not perform a repeat lumbar puncture in neonates:
  - who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery
  - before stopping antibiotic therapy if they are clinically well.

Skin samples and throat swabs for meningococcal disease

- Do not use any of the following techniques when investigating for possible meningococcal disease: skin scrapings, skin biopsies, petechial or purpuric lesion aspirates (obtained with a needle and syringe), or throat swabs.

Management in secondary care

See the bacterial meningitis pathway on pages 12–14 and the meningococcal disease pathway on pages 16–17.

Corticosteroids

Bacterial meningitis

- Do not use corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis.
- If dexamethasone was not given before or with the first dose of antibiotics, but was indicated, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics.
- After the first dose of dexamethasone discuss the decision to continue dexamethasone with a senior paediatrician.

Meningococcal septicaemia

- Do not treat meningococcal septicaemia with high-dose corticosteroids (defined as dexamethasone 0.6 mg/kg/day or an equivalent dose of other corticosteroids).
- In children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 0.25 mg/m^2 four times daily)[16] should be used only when directed by a paediatric intensivist.

Adjunctive therapies

- Do not use activated protein C or recombinant bacterial permeability-increasing protein in children and young people with meningococcal septicaemia.

[16] The dosage given in the recommendation is based on high-quality evidence and is consistent with established clinical practice (see the full guideline for further details). The guideline will assume that prescribers will use a drug's SPC to inform their decisions for individual patients. Hydrocortisone does not have UK marketing authorisation for use at the dose specified in the recommendation. Such use is an off-label use. Informed consent should be obtained and documented in line with normal standards in emergency care.

Further information

Ordering information

You can download the following documents from **www.nice.org.uk/guidance/CG102**

- The NICE guideline – all the recommendations.
- A quick reference guide (this document) – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2201 (quick reference guide)
- N2202 ('Understanding NICE guidance').

Implementation tools

NICE has developed tools to help organisations implement this guidance (see **www.nice.org.uk/guidance/CG102**).

Related NICE guidance

For information about NICE guidance that has been issued or is in development, see **www.nice.org.uk**

Published

- Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. NICE clinical guideline 84 (2009). Available from **www.nice.org.uk/guidance/CG84**
- Feverish illness in children. Assessment and initial management in children younger than 5 years. NICE clinical guideline 47 (2007). Available from **www.nice.org.uk/guidance/CG47**
- Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE clinical guideline 33 (2006). Available from **www.nice.org.uk/guidance/CG33**
- Cochlear implants for children and adults with severe to profound deafness. NICE technology appraisal 166 (2009). Available from **www.nice.org.uk/guidance/TA166**

Updating the guideline

This guideline will be updated as needed, and information about the progress of any update will be available at **www.nice.org.uk/guidance/CG102**

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NHS
National Institute for Health and Clinical Excellence

Understanding NICE guidance

Information for people who use NHS services

Bacterial meningitis and meningococcal septicaemia in children and young people

NICE 'clinical guidelines' advise the NHS on caring for people with specific conditions or diseases and the treatments they should receive.

This booklet is about the care and treatment of children and young people under 16 years with bacterial meningitis or meningococcal septicaemia in the NHS in England and Wales, including urgent treatment where appropriate and longer term care. It explains guidance (advice) from NICE (the National Institute for Health and Clinical Excellence). It is written for the parents and carers of children and young people with bacterial meningitis or meningococcal septicaemia, but it may also be useful for children and young people themselves or anyone with an interest in the conditions.

The booklet is to help you understand the care and treatment that should be available in the NHS. It does not describe bacterial meningitis or meningococcal septicaemia or the tests or treatments for them in detail. Your child's doctor should discuss these with you. There are examples of questions you could ask throughout this booklet to help you with this. You can get more information from the organisations listed on page 11.

Information about NICE clinical guideline 102
Issue date: June 2010

Contents

The advice in the NICE guideline covers:

- all children and young people under 16 years of age who have or who are suspected of having bacterial meningitis or meningococcal septicaemia.

It does not specifically look at:

- children and young people with known immunodeficiency (problems with the immune system's ability to fight infections)
- children and young people with brain tumours, existing hydrocephalus (also known as 'water on the brain') or who are having fluid drained from around their brain
- newborn babies already receiving care in neonatal units.

Various aspects of wider management including complications are not dealt with.

For the remainder of this booklet the term 'child' will be used to describe a child or young person under 16 years.

Your child's care

Meningitis and meningococcal septicaemia are life-threatening diseases that require urgent, emergency treatment.

Treatment and care should take into account the child's needs and preferences, as well as those of their parents or carers, and you have the right to be fully informed and to make decisions in partnership with your child's healthcare team. In some cases, children can give consent for themselves, depending on their age and how well they understand their condition and the treatment. Sometimes you will be asked to give consent for them as their parent or the person with parental responsibility. If you need more information on consent you could look at the following booklets available from the Department of Health (**www.dh.gov.uk/consent**):

- Consent: a guide for children and young people.
- Consent – what you have a right to expect: a guide for parents.

Sometimes if a child appears to have a serious illness that could indicate the need for urgent treatment, the medical staff may not have time to fully discuss what is involved in that treatment beforehand. In these circumstances, detailed discussions and explanations may have to wait.

In an emergency, if the person with parental responsibility cannot be contacted, healthcare professionals may give treatment immediately when it is in the child's best interests.

All healthcare professionals should treat you and your child with respect, sensitivity and understanding. The information you get from your child's healthcare team should include details of the possible benefits and risks of particular treatments, and you should be offered clear and simple explanations of bacterial meningitis and meningococcal septicaemia. You and your child (where appropriate) can raise questions and discuss options for treatment. You can change your mind as your child's treatment progresses, or your child's condition or your own circumstances change.

Your child's treatment and care, and the information you are given about it, should take account of any religious, ethnic or cultural needs your family may have. It should also take into account any additional factors, such as physical or learning disabilities, sight or hearing problems, or difficulties with reading or speaking English. Your child's healthcare team should be able to arrange an interpreter and/or an advocate (someone who supports you in putting across your views) if you need them.

If you think that your child's care does not match what is described in this booklet, please talk to a member of your child's healthcare team.

Bacterial meningitis and meningococcal septicaemia

Bacterial meningitis and meningococcal septicaemia are not very common, but when they happen, they can be very serious and can quickly lead to complications such as brain damage, skin damage and amputations, and even death. However, most children and young people make a full recovery if they are treated early.

Bacterial meningitis occurs when bacteria infect the lining of the brain (the meninges) and the spinal cord. Meningococcal septicaemia – or blood poisoning – occurs when the bacteria in the blood multiply uncontrollably. Meningococcal disease can appear as meningococcal meningitis or meningococcal septicaemia, or a combination of both.

For the remainder of this booklet, bacterial meningitis and meningococcal septicaemia will be referred to as meningitis and septicaemia respectively.

Symptoms and signs

If you visit your GP with your unwell child, your GP should assess them to try and find out what is wrong. Your GP should also consider how concerned you are about your child's illness, how quickly the illness is progressing and how severe the illness is.

If your child has certain symptoms or signs (see boxes 1 and 2), your GP may suspect that they have meningitis or septicaemia, or both of these conditions. If your child has suspected meningococcal disease and a non-blanching rash (that is, the rash doesn't fade when a glass is pressed firmly against the skin; this is known as the 'tumbler test') your child should be transferred to hospital as a 999 emergency and given antibiotics at the earliest possible opportunity.

If your GP suspects meningitis and your child doesn't have a non-blanching rash, your child should be transferred to hospital as a 999 emergency. If this isn't possible (for example if the hospital is far away) your child should be given antibiotics before being transferred to hospital.

Box 1 Symptoms and signs of bacterial meningitis

- Fever/vomiting
- Headache
- Stiff neck
- Dislike of bright lights
- Very sleepy/vacant/difficult to wake
- Confused/delirious
- Non-blanching rash (but in some kinds of meningitis there is no rash)
- Seizures

Babies may also refuse feeds, be irritable with a high-pitched cry, have a stiff body and have a bulging soft spot on the top of their head.

Not everyone gets all of these symptoms. If you think your child is ill enough to need medical help, then trust your instincts.

Box 2 Symptoms and signs of meningococcal septicaemia

- Non-blanching rash plus:
  - fever
  - vomiting/nausea
  - lethargy
  - muscle ache/joint pain
  - cold hands/feet
  - leg pain
  - pale/mottled skin
  - rapid breathing/breathlessness
  - confusion
  - very sleepy/vacant/difficult to wake.

Not everyone gets all of these symptoms. In the early stages, there may not be a rash, or the rash may fade on pressure (blanch). If you think your child is ill enough to need medical help, then trust your instincts.

At the hospital – diagnosis and treatment

Rash

If your child has a rash, the doctor will do a very careful assessment to see whether the child is likely to have meningitis, septicaemia or a combination of both. In particular, the doctor will look to see whether the rash is spreading and whether it is non-blanching.

If your child has a non-blanching rash, they should be given antibiotics immediately if they look unwell or they have other symptoms and signs of meningitis or septicaemia (see boxes 1 and 2).

If your child has a non-blanching rash and fever (or has previously had a fever) they may need to have a blood test. If results of the blood tests are not normal, your child should be given antibiotics and admitted to hospital. If the blood tests are normal your child's condition should be monitored for several hours, and if the doctor thinks there is a possibility they may have meningitis or septicaemia, they should be given antibiotics and admitted to hospital.

After assessing your child, the doctor may conclude that they probably don't have septicaemia or meningitis and they may be discharged after initial observation. However, you should return to hospital immediately if your child looks unwell.

If your child has a non-blanching rash but no fever, and they don't look unwell, they probably don't have meningitis or septicaemia, so the doctor may want to consider a different diagnosis.

Diagnostic tests

Once your child has arrived at the hospital, the doctors should carefully examine them. If the doctors suspect meningitis or septicaemia, they should do some tests to confirm the diagnosis. Your child should be kept under observation and their condition monitored carefully.

Meningitis

Your child should have a blood test if meningitis is suspected.

Almost all children with suspected meningitis will need to have a lumbar puncture to confirm the diagnosis. This is a routine test in paediatrics and should not alarm you. During this procedure, a sample of cerebrospinal fluid (the fluid surrounding the brain and spinal cord) is taken from the lower part of the spinal canal using a hollow needle. Any fluid taken is then tested in a laboratory.

If the blood tests or lumbar puncture tests are abnormal and indicate a bacterial infection, your child will need antibiotics. The tests may also show which types of bacteria are causing any infection, and the doctor will use this information to decide which type of antibiotic to use.

Babies will sometimes need to have a second lumbar puncture during the course of treatment if they have a persistent fever or a fever that has returned, their condition gets worse, they have new symptoms or there is evidence of continuing infection on blood tests.

If your child is having problems staying conscious, or they have signs of brain injury or brain inflammation (these are known as focal neurological signs), your child might have a brain scan (also known as a computed tomography scan or a CT scan) to see if there is an underlying problem.

Septicaemia

Your child will normally have a blood test if septicaemia is suspected. If the blood tests are abnormal, this may indicate a bacterial infection and your child will usually be given antibiotics.

Questions you might like to ask your child's healthcare team when you arrive at the hospital

- Please tell me what you are going to do and why.
- How serious is this illness?
- Please tell me what the treatment will involve.
- How long will it take for the treatment to have an effect?
- How will you know the treatment is working?
- Does my child need to be transferred to another hospital for ongoing or intensive care?
- Can I check that I've understood what you've said?

Emergency care

The doctor will check your child for specific signs if he or she thinks your child has meningitis or septicaemia. Some of the signs described below can occur in either condition.

Meningitis

If meningitis is suspected or has been confirmed, the doctor should look for signs of raised pressure in the brain and signs of dehydration.

If your child is dehydrated, they should be given fluids. The fluids may be given intravenously, through a needle or thin tube inserted directly into a vein. Alternatively, the fluids can be given directly into the stomach or small intestine using a thin tube, which is usually inserted through the nose. Your child's condition should be monitored to make sure their body is getting the right amount of fluid.

Depending on the results of the lumbar puncture (see page 6), your child may be given drugs called corticosteroids to reduce the inflammation in the brain.

Septicaemia

If your child is suspected of having septicaemia the doctor should look for signs of shock. Clinical shock is when the blood doesn't circulate around the body properly, which means that the body's tissues and organs cannot function correctly. If your child is in shock they should be treated with fluids and then immediately reassessed. Severe shock eventually causes low blood pressure, so they may need drugs urgently to help improve the circulation quickly and stabilise their condition.

If your child has suspected or confirmed septicaemia they may need some help to breathe. This may involve using a special face mask or a machine called a ventilator to help them breathe in more oxygen. If your child needs to be put on a ventilator, or their condition is very serious, they may need to be transferred to a paediatric intensive care unit.

Questions you might like to ask your child's healthcare team once their condition has stabilised

- Please tell me more about meningitis and/or septicaemia.
- Is there some written information (like a leaflet) that I can have?
- Are there any support organisations in my local area?

Information, support and follow-up

Before your child is discharged from hospital their doctor should consider what their needs might be after they've left hospital. Most children recover well, but for some it will take a while to return to normal. The doctor should discuss with you and your child what the long-term effects of the disease might be, as well as likely patterns of recovery, and give opportunities to ask questions.

The circumstances will be different for each child but after-effects of meningitis might include emotional and psychological problems or minor learning difficulties, which may require extra help or support at school. Very severe cases can cause hearing loss, and damage to the brain or other parts of the nervous system, perhaps causing learning impairment, epilepsy, and problems with movement and coordination. Septicaemia can cause scarring to the skin, and could lead to amputations and other damage to bones. The kidneys may be affected. These problems should be obvious very early in the course of the illness.

You should be offered information about further care and how to access it, and contact details of patient support organisations (some of these are given on page 11).

If your child has had meningitis or septicaemia they should be offered a hearing test, if possible before they are discharged from hospital. If they are severely or profoundly deaf, they should be offered an urgent assessment for cochlear implants (small devices that help with hearing by stimulating the auditory nerve, which carries 'hearing information' to the brain in the form of electrical impulses) as soon as they are fit to be tested. About 4–6 weeks after the hearing test, a paediatrician should discuss with you and your child the results of the test and any conditions they may have as a result of having meningitis or septicaemia.

Your child's doctor should let their GP, health visitor and school nurse know about your child's meningitis or septicaemia. Healthcare professionals monitoring your child should be alert for any late complications that may develop, including sensory, nerve, bone, or emotional or psychological problems.

If you have talked to your healthcare team, and you think that a treatment is suitable for your child but it is not available, you can contact your local patient advice and liaison service ('PALS').

Other tests

Some children with meningitis or septicaemia can have an abnormality of the immune system that has made them susceptible to these diseases. This is very rare but occasionally needs to be investigated. If this is the case, your child might later be tested for a condition called 'complement deficiency', depending on their own medical history and that of their immediate family. This will check whether your child has a problem with their immune system, such as a pre-existing genetic defect, that could increase the risk of developing infections.

If your child is found to have complement deficiency, then you and/or the child's biological parents, and their brothers and sisters should also be tested for it. Your child should also be referred to a healthcare professional who has expertise in managing the condition.

If your child has meningococcal disease that keeps returning, they should be assessed by a specialist in immunology and infections.

More information

The organisations below can provide more information and support for people with meningitis or septicaemia. NICE is not responsible for the quality or accuracy of any information or advice provided by these organisations.

- The Meningitis Trust, 0800 028 1828 (24-hour freephone helpline), **www.meningitis-trust.org**
- Meningitis Research Foundation, 0808 800 3344 (24-hour freephone helpline), **www.meningitis.org**

NHS Choices (**www.nhs.uk**) may be a good place to find out more. Your local patient advice and liaison service (usually known as 'PALS') may be able to give you more information and support. You should also contact PALS if you are unhappy with the treatment you are offered, but you should talk about your care with a member of your healthcare team first. If your local PALS is not able to help you, they should refer you to your local independent complaints advocacy service. If you live in Wales you should speak to NHS Direct Wales for information on who to contact.

About NICE

NICE produces guidance (advice) for the NHS about preventing, diagnosing and treating medical conditions. The guidance is written by independent experts including healthcare professionals and people representing patients and carers. They consider the evidence on the disease and treatments, the views of patients and carers and the experiences of doctors, nurses and other healthcare professionals. Staff working in the NHS are expected to follow this guidance.

To find out more about NICE, its work and how it reaches decisions, see **www.nice.org.uk/AboutGuidance**

This booklet and other versions of the guideline aimed at healthcare professionals are available at **www.nice.org.uk/guidance/CG102**. *The versions for healthcare professionals contain more detailed information on the care and treatment your child should be offered.*

You can order printed copies of this booklet from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N2202). The NICE website has a screen reader service called Browsealoud, which allows you to listen to our guidance. Click on the Browsealoud logo on the NICE website to use this service.

We encourage NHS and voluntary organisations to use text from this booklet in their own information about bacterial meningitis and meningococcal septicaemia.

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