OUTLINE GUIDELINES FOR THE BTS STANDARDS OF CARE COMMITTEE

GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF MYCOBACTERIUM TUBERCULOSIS INFECTION AND DISEASE IN PATIENTS WITH RENAL IMPAIRMENT

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Guidelines have been compiled by the Joint Tuberculosis Committee of the British Thoracic Society for the prevention and management of *Mycobacterium tuberculosis* infection and disease in patients with renal impairment. These guidelines are intended for use in patients with chronic kidney disease, those on dialysis and following renal transplantation. The risks of developing disease and the risks and benefits of treating latent infection are covered. These guidelines are intended to inform renal physicians and surgeons, respiratory physicians and infectious diseases physicians treating TB together with specialist nurses in those disciplines.

Abstracted bullet points

Evidence informing these guidelines is patchy. There is broad agreement on the following:

- Patients with chronic kidney disease (CKD), on dialysis and following transplantation are at significantly increased risk of tuberculosis (TB). **(B)**
- More than 50% of patients with renal disease have reduced skin test responsiveness to the tuberculin skin test. **(B)**
- Patients with CKD considered at risk for TB should have a history of prior TB or TB contact sought, any history of prior TB treatment checked, an appropriate clinical examination, a chest radiograph and, if appropriate, an interferon gamma release assay (IGRA) test specific for *Mycobacterium tuberculosis* antigens (see text). **(D)**
- Any patient with CKD with an abnormal chest radiograph consistent with past TB, or previous history of extra-pulmonary TB but who have previously received adequate treatment should be monitored regularly and considered for referral to and assessment by a specialist with an interest in TB. **(D)**
- Active TB should be excluded by appropriate investigations in patients with an abnormal CXR or a history of prior pulmonary or extra-pulmonary TB that has been either inadequately or not previously treated. Chemoprophylaxis should be given. **(A)**
- Any patient with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy agents, albeit with dose/dose interval modifications where appropriate (see text) and for standard duration as per the NICE Guidelines. **(A)**

- Close co-operation between renal physicians and specialists in the management of TB is strongly recommended. **(D)**

There is contention over the following:

- There is no evidence on when to screen for latent TB infection (LTBI), or which patients should receive chemoprophylaxis.
- Supporting evidence for methods of screening for LTBI is limited.
- There is disagreement over dosages, dose intervals and timing of doses for patients on dialysis.

On balance, the committee have agreed the following recommendations:

- Routine assessment of Stage V CKD patients with a TST or IGRA test is not recommended. Renal physicians may wish to assess individual patients at high risk of LTBI with an IGRA test. **(D)**
- Patients on the list for renal transplantation may be assessed with an IGRA test, giving the opportunity for chemoprophylaxis before transplantation. An individual risk assessment can be made using Tables 3-5. In general, all black African and Asian patients born outside the UK should be screened and considered for chemoprophylaxis prior to or after transplantation. **(D)**
- There is no evidence to support chemoprophylaxis for longer than six months for isoniazid or three months for isoniazid plus rifampicin. **(A)**
- Doses of anti-tuberculosis drugs should <u>not</u> be reduced as this leads to lower peak levels and possible development of drug resistance; **(D)**
- For patients on haemodialysis, dosing intervals should be increased to 3x weekly to reduce the risk of drug accumulation and toxicity; **(D)**

- Treatment can be given 4-6 hours before dialysis, avoiding the risk of having raised drug levels of ethambutol and pyrazinamide between dialysis sessions. This does, however, raise practical issues for those dialysing early in the morning and treatment given immediately after dialysis has the added advantage of ensuring adherence; **(D)**
- Peak and trough drug levels should be monitored, particularly for ethambutol and the aminoglycosides. **(D)**
- Treatment duration should follow the NICE Guidelines of 6 months for most cases of drug sensitive disease, with the exception of TB involving the CNS when treatment should be for one year. **(A)**
- Rifampicin in particular can interact with immunosuppressive regimens and steroid doses should be doubled. **(B)**

Patients with renal disease are at increased risk of tuberculosis (TB). This is true for all patients with chronic kidney disease (CKD), but particularly so for those from ethnic minority groups who are both at increased risk of developing active TB disease and in whom the prevalence of CKD is also substantially higher. Despite this increased risk, there are few guidelines for the investigation and treatment of TB disease in CKD (1). Although there is broad agreement over drug treatment and its' duration, there are problems with dosing. There are no randomised controlled trials into outcomes in patients with advanced CKD, and little information specifically dealing with issues of immunosuppression and transplantation. There is no evidence to guide protocols for active case finding (screening) and treatment of latent disease and there is variation in practice to approaches to prevent reactivation.

Evidence consists of small prospective studies of haemodialysis clearance, pharmacokinetic studies of therapy in renal failure, retrospective observational data, case reports and expert opinion. The objectives of these guidelines are to quantify the risks of developing active disease and to give advice where possible on the management of TB infection and disease in patients (a) with CKD; (b) on peritoneal dialysis and haemodialysis; and (c) with renal transplants. The risks and benefits of treatment for latent TB infection are covered. These guidelines are intended to inform renal physicians and surgeons, respiratory physicians and infectious diseases physicians treating TB together with specialist nurses in those disciplines.

1. INTRODUCTION

1.1 Structure of the recommendations

The format follows that used for other BTS guidelines. At the beginning there is a summary of the abstracted bullet points from each section. The recommendations are the revised Scottish Intercollegiate Guidelines Network (SIGN) grading system available at http://www.sign.ac.uk/guidelines/fulltext/50/section6.html (table 1). The primary source literature has been individually graded for its methodology (where appropriate) and the grading given alongside the reference using the revised SIGN levels of evidence (table 2).

Table 1: Revised SIGN grading system: grades of recommendation

A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; *or*
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating

Table 2: Revised SIGN grading system: levels 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

1.2 Methodology for the creation of the recommendations

The initial systematic literature search (Medline, DataStar Web) was carried out by two members of the committee (CS and SD) using tuberculosis, renal/kidney failure, renal transplant 1970-2008 as search criteria. A paper based exploration of the relevant literature was pursued from this core dataset. Only English language papers including all well formulated clinical case series were included. Abstracts were excluded.

After the appraisal of data, the guideline was initially drafted by HM with SD and PD, then discussed by the whole group, the evidence debated, and redrafted several times. The draft was based where possible on any published evidence, but this was combined with clinical expertise where necessary and where no evidence was available. The

manuscript was then reviewed by the BTS TB Specialist Advisory Group before being placed on the BTS website for consultation by the membership. It was also reviewed by the Renal Association. Following this, further amendments were made and the document reviewed by the Joint Tuberculosis and Standard of Care Committees of the BTS. After final approval from these committees, the guidelines were submitted for peer review prior to publication.

1.3 Conflict of interest

All members of the Guidelines Committee were asked to submit a written record of possible conflicts of interest to the Standards of Care Committee of the BTS.

1.4 Suggested review date

The Guidelines Committee suggest that the guidelines be reviewed in three years.

2. BACKGROUND

2.1 The Need for Recommendations

Advanced CKD is associated with an acquired immunodeficiency state as a result of functional abnormalities of neutrophils, reduced T- and B-cell function and compromised monocyte and natural killer cell function (2,3). 25-Hydroxyvitamin D insufficiency, common in stages 3-5 CKD, may also play an important role through impaired monocyte function, reducing production of cathelicidin, a peptide capable of destroying M. tuberculosis (4). The risk of developing TB is compounded further by associated comorbid conditions, immunosuppressive drugs and socio-economic factors (5-7). According to the NICE guidelines, the relative risk for developing active TB is 10-25 in patients with CKD or on haemodialysis, and 37 for renal transplant recipients (8) where

the normal inflammatory response to infection is attenuated by immunosuppressive therapy.

In clinical practice, there are still conflicting data relating to early identification of patients at risk, optimal prophylaxis and best forms of therapy for those with latent tuberculosis infection (LTBI). The American Thoracic Society / Centre for Disease Control committee on LTBI recommends targeted tuberculin skin testing for all patients with CKD, including transplant recipients (9). However, it is well known that this test lacks sensitivity, especially in patients on dialysis with reported anergy rates of up to 50% (10-13). Immunosuppressants used as treatment for kidney disease and in transplantation (including prednisolone, azathioprine, cyclophosphamide, ciclosporin, tacrolimus or mycophenolate mofetil and newer monocloncal antibodies) interfere with the accuracy of tuberculin skin testing (14). Chemoprophylaxis for LTBI itself carries a small risk of adverse events in patients with normal renal function, particularly of drug induced hepatitis which increases with age and is occasionally fatal. There is no equivalent data for patients with CKD. It is also important to exclude active TB disease before chemoprophylaxis is given, particularly as single agent chemoprophylaxis given when active disease is present could lead to the development of drug resistance.

Diagnosis of active TB is often delayed in renal patients as the clinical presentation may be uncharacteristic, especially in patients with extrapulmonary manifestations and non-specific symptoms (15). Finally, there is controversy about the optimal methods of delivering treatment for TB in patients with CKD. The majority of anti-tuberculosis drugs

are renally excreted and data on drug clearance during haemodialysis or peritoneal dialysis are scarce. These issues have led to many requests for advice.

2.2 Background Epidemiology

The magnitude of the problem of TB in patients with CKD has not been studied in detail, particularly in the UK. In the UK, CKD is four times more common in Asians and Blacks than in Whites (16) and it is in these former communities where TB is most prevalent. Of the several studies into the impact of CKD in areas of high background prevalence, a Chinese report of 1498 patients derived a relative risk of 31.4 for those with CKD (17). Retrospective studies of patients on maintenance haemodialysis have however led to estimates of a 10 to 25 fold higher risk of developing TB compared with the general population (6, 7, 18-20). TB prevalence studies in renal transplant recipients give rates ranging from 100 to 400 per 100,000 in Northern Europe and North America (21-27). A single centre experience from Belgium suggested a post-transplant prevalence of 0.36% (28). In a review of 756 transplanted patients in Taiwan, the incidence of TB was 3.8% (29). Studies from the Indian Subcontinent unsurprisingly suggest a much higher prevalence. Further studies show an increased risk of post transplant TB with increased duration of pre-transplant haemodialysis and number of post transplant rejection episodes (30). Immunosuppression with tacrolimus or mycophenylate mofetil is associated with the development of TB earlier in the post-transplant period and in younger patients (26).

The 2006 NICE guidelines give an overall relative risk following renal transplantation of 37 (8), based on a small series from 1983 (23). Refinements in immunosuppression, however, have led to marked reduction in rejection rates and a rise in infective

complications. It is likely that this risk has increased over time.

3. DIAGNOSIS OF LATENT TB INFECTION (LTBI)

3.1 Timing of Screening

For patients with CKD, there is no evidence on when or how to screen for LTBI. Screening all patients with advanced CKD or even only those on haemodialysis or peritoneal dialysis would be time consuming, expensive and unlikely to be cost effective, but in order to give guidance on this issue, data on the rates of active TB in these groups need to be collected. Some patients are more at risk than others, e.g., some ethnic minority groups and patients born abroad in areas of high prevalence (tables 3 & 4) and those on immunosuppression or due to start immunosuppression for transplantation. The relative risk of developing TB in patients with CKD is shown in Table 5, assuming an increased risk of 20-fold compared with the normal population.

The risk of developing active TB following renal transplant is particularly high (Table 5), and screening may be beneficial for this group. Chemoprophylaxis could be offered to those with LTBI prior to transplantation, precluding the need for post-transplant prophylaxis. Whether or not a screening and treatment programme has benefit over universal post-transplant prophylaxis with isoniazid in those most at risk is unknown. There are advantages in screening pre-transplant when compared with post-transplant when immunosuppression may affect the assays used and treating LTBI with rifampicin (with its potent interactions with immunosuppressive agents) offers substantial risk to the allograft.

3.2 Method of Screening

The tuberculin skin test (TST) is unreliable in patients with advanced CKD and in those on immunosuppressive agents. A positive test may be useful but a negative result cannot be assumed to be a true negative. The new interferon gamma release assays (IGRA tests) have not been fully evaluated in these groups of patients although studies are ongoing and planned across Europe (TBNET - Tuberculosis Network European Trials Group). There are two commercially available tests, the T-SPOT.*TB* assay (Oxford Immunotec, UK) and the QuantiFeron-TB Gold (Cellestis, Australia). While the QuantiFeron test is technically easier to perform, recent evidence suggests that the T-SPOT is the more sensitive of the two tests, especially in the immunosuppressed (31). A recent study compared the T-SPOT.*TB* with the TST and the opinions of an expert physician panel in 203 haemodialysis patients exposed to infectious TB. The T-SPOT.*TB* correlated more closely with surrogate markers of LTBI (radiographic changes, previous history of TB, born in a TB endemic country) than the TST, and with clinical judgement than with the TST (32). In a further study, both IGRA tests were compared with the TST in 100 renal dialysis patients exposed to a case of sputum smear positive TB. Positive IGRA results were more closely associated with recent exposure than were positive TST results (33). The limited evidence available to date suggests IGRA tests will be more useful as a screening tool in this patient group than the TST **(D)**. These should be interpreted in the light of radiographic changes, previous history of TB, foreign travel, ethnic and environmental background. The IGRA tests are not affected by previous BCG vaccination or infection with most environmental mycobacteria, but cannot distinguish between LTBI and active disease.

4. CHEMOPROPHYLAXIS

There are three potential chemoprophylaxis regimens: isoniazid for 6 months (6H), rifampicin plus isoniazid for 3 months (3RH) or rifampicin alone for 4-6 months (4-6R). Rifampicin and pyrazinamide for 2 months (2RZ) was a regimen used in the USA (34), but it had a very high rate of hepatitis (Table 5) with a number of fatalities reported (35, 36). Accordingly, the choice of regimen is between 6H, which has a lower hepatitis rate, and 3RH which may have advantages in terms of shorter duration and thus possibly better adherence (Table 5), and also less risk of drug resistance developing if active disease is present or 4-6R which can be well tolerated, although there is little published evidence to date (37). **(A)**

There are little data on chemoprophylaxis specifically in patients with CKD. One report of isoniazid prophylaxis for one year in 109 patients with CKD on haemodialysis showed reduced numbers developing TB with a risk ratio of 0.4 (38). Significant hepatitis, however, developed in 16.7% (most of these were either hepatitis B or C positive, emphasising the increased risk of treatment in those with known liver disease). One year of isoniazid prophylaxis post transplant reduced the incidence of TB by about 50% (39-41).

No chemoprophylaxis regimen is wholly effective; protective efficacies of 60-65% have been reported for 6H (42) and of 50% for 3RH (43). There is strong evidence that regimens longer than 6H have only very minimal additional advantage and, furthermore, increase the risk of hepatitis (42). **(A)**

5. RISKS OF TUBERCULOSIS AND OF DRUG INDUCED HEPATITIS FROM CHEMOPROPHYLAXIS

5.1 Risks of TB

The risk of developing active TB has been reported in earlier BTS Guidelines and have been reproduced here (44). The incidence of TB in the population of the United Kingdom (UK) varies markedly according to a number of factors (45, 46): age, ethnic group and, for those not born in the UK, the length of time since first entry. Where possible, data on the current annual risk of TB have been updated from those derived from continuous enhanced surveillance (Tables 4).

Calculation of the risk of TB is as follows:

- If white and UK born use Table 3.
- If Indian subcontinent (ISC) use Table 4.
- If black African use Table 3 (similar data to Table 4 not yet available).
- If either white non-UK born or other ethnic group, use "all patient rate" in table 3B.
- If in doubt or in special circumstances, consult the lead clinician for TB, usually the local thoracic physician.

5.2 Risks of Drug Induced Hepatitis from TB Chemoprophylaxis

The rates of drug induced hepatitis from various TB chemoprophylaxis regimens have been given in earlier BTS Guidelines (44). These were based on a database search (Medline and Embase) on the reported hepatotoxicity of antituberculous chemoprophylaxis from 1966 to 2002 in adults. A further database search to 2006 has not altered the rates given in reference 41 and reproduced here. Children were excluded as they have a very low rate of drug reactions, and studies in HIV positive patients were

also excluded because such individuals have a higher than normal drug reaction profile (47). The hepatitis rates for various regimens are shown in Table 5.

Only hepatitis sufficient to stop treatment (symptomatic) or grade 3 (alanine transferase [ALT] 5-20 times normal) or grade 4 (ALT >20 times normal) hepatitis is reported here. This guidance does not apply to patients co-infected with HIV, hepatitis B or C.

6. RECOMMENDATIONS FOR MANAGEMENT OF LTBI

6.1 Assessment

- All patients should have any history of prior TB treatment checked, a clinical examination, and a chest radiograph. **(D)**
- Any patient with an abnormal chest radiograph or previous history of TB or TB treatment should be monitored regularly and considered for referral to a specialist with an interest in TB, either a thoracic or infectious disease physician. **(D)**
- Routine assessment of patients with CKD or those on haemodialysis or peritoneal dialysis with a TST or IGRA test is not recommended. Renal physicians may wish to assess individual patients at high risk of LTBI with an IGRA test and discuss the results with a TB specialist, usually a respiratory or infectious diseases physician. **(D)**
- Patients on the waiting list for renal transplantation may be assessed with an IGRA test, giving the opportunity for chemoprophylaxis before transplantation. The current practice in most renal units is to give prophylaxis to all at risk transplant patients without assessment. A significant proportion of patients will be receiving prophylaxis without evidence of LTBI.

6.2 Chemoprophylaxis

From tables 3B and 4 it can be seen that all non-white patients and those born abroad and living in the UK for <5 years are at greater risk of reactivating TB than of hepatitis from chemoprophylaxis.

- In general, isoniazid and rifampicin can be used in normal doses in renal impairment, during dialysis and following transplantation (*vide infra).* **(D)**

- For chemoprophylaxis use 6 months of isoniazid 300mg daily (or 5mg/kg for children, maximum 300mg/day) plus pyridoxine 10-25mg* daily; or isoniazid plus rifampicin (as Rifinah) plus pyridoxine for 3 months; or rifampicin 450mg daily for adults <50kg or 600mg daily for adults >50kg (or 10mg/kg for children, maximum 600mg/day) for 4-6 months. Any of these regimens is adequate for chemoprophylaxis. Long term use of isoniazid is not recommended (42). **(A)**

*Footnote: Only 50mg tablets of pyridoxine are available in some pharmacies but note that pyridoxine antgonises isoniazid on a mg for mg basis, effectively reducing the dose.

- There is NO evidence to support use of lower doses. These are inadequate for treatment of LTBI and may encourage the development of drug resistance. **(D)**
- The decision on chemoprophylaxis regimen should be made by the thoracic or infectious disease physician with informal discussion with both the patient and renal team. **(D)**
- If patients who have had chemoprophylaxis develop symptoms suggestive of clinical TB, they should be promptly and appropriately investigated. **(D)**

7. ANTI-TUBERCULOSIS DRUGS IN RENAL IMPAIRMENT

The pharmacological properties of anti tuberculosis drugs determine how their levels are likely to be influenced by renal failure, clearance during dialysis and also their interaction with immunosuppressive drugs used in patients with renal transplantation. These have been extensively reviewed (48-50) but considerable confusion still surrounds dosing of antituberculous chemotherapy, dosage schedule, therapeutic drug monitoring, exact timing of administration in relation to dialysis and regarding concomitant use of immunosuppressive drugs following renal transplantation. Treatment duration should, however, follow the NICE Guidelines of 6 months for most cases of fully sensitive disease, with the exception of TB involving the CNS when treatment should be for one year. **(A)**

7.1 Pharmacokinetics and Toxicity of First line Therapy

Overall, in renal patients the incidence of adverse effects attributable to their antituberculous chemotherapy was significantly higher than that reported in patients with normal renal function (51).

Isoniazid(H):

Isoniazid is metabolised by the liver into less active compounds, which are then excreted by the kidneys. The most recent evidence available suggests that isoniazid is dialyzable in only very small amounts and most clearance occurs from hepatic metabolism (52).

Isoniazid has been administered at a doubled dose three times a week along with dialysis sessions; however, this may result in increased risk of neurotoxicity due to very high peak concentrations and so cannot be routinely recommended. There are no clear data on isoniazid elimination during peritoneal dialysis.

There was an unusually high incidence (46%; 11 patients) of neuropsychiatric

disturbance in one series of 24 patients with CKD treated for TB (53). Nine of the affected eleven patients were receiving haemodialysis. Symptoms usually developed within the first few weeks of therapy and included grand mal seizures (with no prior history), depressive psychosis, confusion, nightmares, hallucinations, peripheral neuropathy, twitching and dizziness. Neuropsychiatric side effects due to isoniazid have been reported in patients on dialysis elsewhere in the literature as case reports (53-56). A quarter of those receiving dialysis also experienced significant gastrointestinal adverse effects – jaundice, nausea and vomiting.

Ototoxicity has been described over a 10 year period in 7 patients with CKD receiving isoniazid (57). In 2 patients this reversed upon withdrawal of isoniazid. Rarely, renal failure itself may be associated with hearing loss due to the underlying disease (eg Alport Syndrome, Wegener's Granulomatosis) and by a variety of mechanisms such as axonal uraemic neuropathy (58) and the increased susceptibility to ototoxins (59, 60),

Pharmacokinetic studies of isoniazid in renal failure, however, suggest that even though the half-life of isoniazid is increased by about 45% in slow acetylators, this does not lead to significant adverse events necessitating dosage reduction, and therapeutic drug monitoring is not thought to be necessary (61). Furthermore, there is evidence to suggest that administering isoniazid in reduced doses may lead to reduced potency and risk the development of resistance (62).

Rifampicin (R):

Rifampicin is also metabolised by the liver. Its inactive metabolite formylrifampicin is excreted in the urine and its major metabolite, desacetyl-rifampicin, is excreted in bile.

Urinary excretion accounts for very little of its elimination from the body, with only about 10% of a given dose being found unchanged in the urine (52). Rifampicin does not appear in significant amounts in dialysate (63). Reported side effects for rifampicin do not appear to occur with significantly increased frequency in patients with CKD or on dialysis although rifampicin has been cited as a rare cause of acute renal failure (64). As such, there is widespread agreement that the dose of rifampicin need not be altered in renal impairment (62) and that drug levels need not be monitored.

Pyrazinamide (Z):

Pyrazinamide is metabolised in the liver. Only 3-4% is renally excreted in unaltered form (65, 66). Although the pharmacokinetics of the drug are unaltered initially in patients with renal failure, one study of its elimination found much higher levels detectable for up to 48 hours after administration (67). Due to its effect on uric acid retention, this may lead to hyperuricaemia and gout. Pyrazinamide and its metabolites can be eliminated from the body by haemodialysis (68). No data are available for peritoneal dialysis. Due to possible delayed elimination of the drug and its metabolite the dosage interval should be altered in CKD.

Ethambutol (E):

Around 80% of ethambutol is excreted unchanged by the kidneys (69-71). In patients with renal failure, excretion of ethambutol was significantly reduced following the usual dose of 15mg/kg (72). Ethambutol is renally excreted and ocular toxicity is largely dose-dependent (73). Ethambutol has been detected in dialysate.

It has improved efficacy when administered in high doses less often, than in a lower dose daily (61). Serum monitoring may be done and trough levels should be less than 1.0 micrograms/ml at 24 hours post-dose without dialysis.

Aminoglycosides:

Around 80% of streptomycin, kanamycin, amikacin and capreomycin are excreted unchanged in the urine without having undergone significant metabolism (61). Streptomycin causes significant vestibular toxicity but less nephrotoxicity compared with the other aminoglycosides. There is an increase in elimination time with increasing age and declining renal function (74). Approximately 40% of streptomycin, amikacin, capreomycin and kanamycin are removed by haemodialysis when these drugs are given just before haemodialysis (75). There is no available data on peritoneal dialysis. As with ethambutol and pyrazinamide, the dosing interval should be increased rather than the dose decreased as the drugs exhibit concentration-dependent bactericidal action, and lower doses may reduce drug efficacy (76). The American Thoracic Society recommend 12-15 mg/kg/dose two or three times per week for all of these drugs (1). Drug levels should be monitored.

8. RECOMMENDATIONS FOR THE TREATMENT OF ACTIVE TB

8.1 CKD, not on dialysis:

In general Isoniazid, Rifampicin and Pyrazinamide can be used in normal doses in renal impairment. Controlled clinical trials have shown three times weekly treatment with Pyrazinamide is therapeutically more effective than daily administration (1, 61, 77).

Pyridoxine supplementation should be given with isoniazid to prevent the development of peripheral neuropathy. In severe renal impairment (without dialysis) some authors advocate reducing the dose of Isoniazid to 200 milligrams once daily but there is no evidence to support this. Ethambutol is also predominantly removed by the kidney and dose reduction or increasing the dose interval with therapeutic drug monitoring is mandatory. Recommended drug doses with creatinine clearance are shown in Table 6. The fourth drug is needed because of the rising rate of isoniazid resistance (7% in England and Wales) and the disproportionate number of ethnic minority cases with CKD. Ethambutol and the aminoglycosides have the disadvantage of renal clearance, the need for reduced dosage and drug monitoring. Recent data have shown that gatifloxacin and moxifloxacin are at least equivalent, and possibly superior to ethambutol as the fourth drug in treatment (78, 79). An alternative to the usual induction regimen of daily RHZE for the first two months of treatment would be daily RHZMoxi for the first two months. If there is culture confirmation of fully sensitive TB before two months, then the fourth drug (ethambutol or moxifloxacin) may be stopped early. This regimen using moxifloxacin instead of ethambutol is only suitable for daily treatment and cannot be used for a three times weekly regimen. It should also be noted that there have been reports of liver dysfunction and long QT interval with moxifloxacin, dysglycaemia with gatifloxacin and connective tissue problems with the quinolone group.

8.2 Haemodialysis:

Both rifampicin and isoniazid may be given in their usual daily doses. Haemodialysis removes a significant amount of Pyrazinamide and the primary metabolite of Pyrazinamide, Pyrazinoic acid, accumulates in patients with renal failure (52). Advice

varies over whether reduction or spacing of the dose of Pryazinamide is best for patients on haemodialysis. Variable doses of 25 to 30 milligrams per kilogram 3 times weekly (52) or 40 milligrams per kilogram 3 times weekly (61) have been recommended. The American Guidelines generally recommend a change in dose frequency rather than dose level as, although toxicity may be avoided by reducing the dose, the peak serum concentrations may be too low, leading to suboptimal treatment (1). Pyrazinamide should be administered immediately after haemodialysis or 4-6 hours beforehand. Ethambutol can be given at a dose of 15 to 25 milligrams per kilogram 3 times weeks for patients on regular haemodialysis. Some authorities recommended dosing 4 to 6 hours before haemodialysis (61). Others recommend post dialysis treatment using doses as above and in Table 6 (1, 52, 80).

8.3 Peritoneal Dialysis

Mechanisms for drug removal differ between haemodialysis and peritoneal dialysis so it cannot be assumed that recommendations for haemodialysis also apply to peritoneal dialysis. Such patients may require careful monitoring including measurement of drug levels.

8.4 Critically Ill Patients on Continuous Renal Replacement Therapy

There are no studies on the management of critically ill patients with TB and renal failure on continuous renal replacement therapy (continuous venovenous haemodialysis or continuous venovenous haemo(dia)filtration). In principle, the treatment should follow the NICE guidelines (8) but exact choice of drugs and dosing will depend on associated comorbidities and interaction with other drugs. Close collaboration between critical care pharmacists, respiratory (and/or infectious diseases physicians) and the renal team is

essential. Monitiring of drug levels (where possible) is strongly recommended.

8.5 Renal Transplantation

Renal function usually improves after transplantation but can vary. Dose modifications may be necessary depending on level of transplant function (Table 6) and additional drugs, and levels should be monitored.

Anti tuberculosis drug interactions with immunosuppressive drugs are important. Rifampicin is the drug most likely to interfere with immunosuppressive treatment by induction of liver enzymes. Daily corticosteroid dosage should be increased to one and a half to twice the baseline dosage in patients taking Rifampicin. Rifampicin also lowers ciclosporin blood levels which should be monitored and the dose adjusted. Information on the extent, duration, and potency of the rifampin-tacrolimus interaction is limited. There is one case report describing a renal transplant recipient who demonstrated an increase in tacrolimus metabolism as a result of rifampicin administration (81). Once rifampicin has been stopped, liver enzyme induction usually takes two weeks to return to normal.

Azathioprine sometimes causes hepato-toxicity which has to be differentiated from the hepato-toxicity due to anti tuberculous drugs.

In summary:

- In renal patients, doses of anti-tuberculous drugs should not be reduced as this leads to lower peak levels and possible development of drug resistance; **(D)**
- For patients on three times weekly haemodialysis, dosing intervals should be increased to 3x weekly to reduce the risk of drug accumulation and toxicity; **(D)**
- There is no consensus on whether treatment should be given 4 to 6 hours before

dialysis or immediately after haemodialysis. The majority of the committee concluded, however, that immediately after dialysis had the added advantage of ensuring adherence; **(D)**

- Peak and trough drug levels should be monitored, particularly for ethambutol and the aminoglycosides, especially if there is concern regarding over and under dosing. **(D)**
- Treatment duration should follow the NICE Guidelines of 6 months for most cases of fully sensitive disease, with the exception of TB involving the CNS when treatment should be for one year. **(A)**
- Rifampicin in particular can interact with immunosuppressive regimens and steroid doses should be doubled in regimens including rifampicin. **(B)**

9. SUGGESTED AUDIT CRITERIA

Suggested audit criteria are as follows:

- History of previous TB or contact checked? (Y/N)
- If at risk for TB, has a CXR (and IGRA test if appropriate) been performed? (Y/N)
- If chest radiograph abnormal, has active TB been excluded? (Y/N)
- If active or latent disease, has patient been referred to a TB specialist? (Y/N)
- Chemoprophylaxis given at the correct dose for the appropriate time for latent disease? (Y/N)
- Full treatment given with appropriate dose/interval modifications given for active disease? (Y/N)
- Peak and trough drug levels monitored where appropriate? (Y/N)

TABLE 3 ANNUAL RISK OF TUBERCULOSIS DISEASE/100000 IN ENGLAND AND WALES

(A) Effect of Age (to the nearest whole number)

Age(years)	White	Black-African
0-14	1	47
15-34	2	314
35-54	4	168
55-74	7	204
>75	11	not available

(B) Effect of Place of birth/Duration in England and Wales

Age	Place of birth	Years after first entry	All patient Rate	ISC* ethnic Rate
0-14	UK		3	21
	Abroad		31	88
15 and over	UK		4	59
15-34	Abroad	0-4	180	540
		5 years and over	53	87
35 and over	Abroad	0-4	146	593
		5 years and over	39	108

Population figures from the Office of National Statistics Labour Force Survey 2000
TB data from case reports to Enhanced TB Surveillance 2000 Health Protection Agency
*ISC= Indian Subcontinent

How to use
If white UK born use data from Table 3A
If Indian subcontinent (ISC) use Table 3B
If Black-African use Table 3A (similar data to Table 3B not yet available)
If either white non-UK born or other ethnic group use All patient rate Table 1B

If in doubt or in special circumstances consult local thoracic physician

Taken from reference 41 with permission.

TABLE 4 Sample Calculations based on Tables 3A and 3B (adapted from ref 41)

The weighted average risk for prophylaxis with 6H is 278/100000 which is used for these calculations. That for 3RH is higher at 1766/100000 but may need to be considered if a shorter duration of chemoprophylaxis is needed on clinical grounds (see 6.2)

Case Type calculation	Annual disease disease/100000	Effect of CKD x20	Effect of renal tx x37	Risks of prophylaxis /100000 (Table 5)	Risk/benefit
White UK born					
Age 35-54	4	80	148	278	Observation
Age 55-74	7	140	259		
Indian sub Continent Age >35 In UK 3 years	593	11,860	17,790	278	Prophylaxis
Black-African Age 35-54	168	3,360	6,216	278	Prophylaxis
Other ethnic Age 35 or over In UK >5 years	39	780	1,443	278	Prophylaxis

TABLE 5 HEPATIC RISKS OF CHEMOPROPHYLAXIS

Reference	N=	Hepatitis/100000*	% Completion	Comments
Regimen 6H				
IUALTD(80)	6,965	480	78	65% protective efficacy (1 death from 6H)
Jasmer(83)	282	1000	59	
Nolan(84)	11,141	100	-	Female OR 3.3 (0.87-12.45) White OR 2.60 (0.75-8.95) Increase with age Chi^2 5.22 (P=0.02)
Bailey(85)	427	1170		
Weighted average	**18,815**	**278**		
Regimen 3RH				
HK TB Service	170	**1766**	-	50% protective efficacy in silicosis
Regimen 2RZ				
Lee(86)	148	9459	57	Female OR 4.1 (1.2-14.3) Recent conversion OR 14.3 (1.8-115)
Jasmer(83)	307	7700	61	Age>35 OR 12.2 (1.49-100.3) OR 8.46 x isoniazid (1.9-76.5)
Stout(87)	114	5300	67.5	
Weighted average	569	**6648**		

*Symptomatic or Grade3/4 hepatitis
H=isoniazid R=Rifampicin Z=Pyrazinamide

Taken from Ref 41 with permission.

Table 6.

Recommended doses of first line drugs in chronic kidney disease.

	Stage 1 to 3 chronic kidney disease	***Stage 4 and 5 chronic kidney disease***	***Renal transplant recipients***
Isoniazid^{+}	300mg daily	300mg daily or 15mg/kg max 900mg 3x/week	300mg daily
Rifampicin^{++}	<50kg: 450mg daily >50kg: 600mg daily	<50kg: 450mg daily >50kg: 600mg daily	<50kg: 450mg daily >50kg: 600mg daily
Pyrizinamide*	<50kg: 1.5g daily >50kg: 2g daily	25-30mg/kg three times weekly	<50kg: 1.5g daily >50kg: 2g daily
Ethambutol**	15mg/kg daily	15-25mg/kg three times weekly max 2.5gm	15mg/kg daily
Moxifloxacin	400mg daily	Not suitable for 3x weekly regimen	400mg daily

Stage 1 CKD: Normal creatinine clearance and function but urinary tract abnormality, eg., polycystic kidney, structural abnormality.
Stage 2 CKD: Creatinine clearance 60-90mls/min
Stage 3 CKD: " " 30-60mls/min
Stage 4 CKD: " " 15-30mls/min
Stage 5 CKD: " " <15mls/min with or without dialysis.

+For children, use 5mg/kg to max 300mg. Pyridoxine supplementation 10-25mg/day essential in renal failure.
++ For children, use 10mg/kg to max 600mg
*Check uric acid and monitor for gout
**Monitor colour vision and visual acuity. Check peak and trough drug levels. Isoniazid and rifampicin may be given intravenously where absorption is compromised. Dose: Isoniazid 300mg as single daily dose; Rifampicin 450mg or 600mg depending on weight by infusion over 2-3 hours.

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APPENDIX 1

Second Line Drugs

Patients developing drug resistant disease will need treatment with second line drugs. This medication must be prescribed with the full involvement of a specialist with experience in the management of drug resistant tuberculosis.

Fluoroquinolones:

Both ofloxacin and ciprofloxacin are also dependent on renal clearance and doses should be reduced accordingly. Other fluoroqinolones undergo some degree of renal clearance that varies from drug to drug. Levofloxacin undergoes greater renal clearance than moxifloxacin (A1).

Fluroquinolones decrease the metabolism of ciclosporin A and displace it from the bound form thus increasing its toxicity.

Cycloserine:

Up to 70% of Cycloserine is excreted by the kidney and 56% removed by haemodialysis (A2-4). Given that dose-related neurological and psychiatric side effects of cycloserine have been reported in up to 50% patients (A5), dose adjustment in the setting of renal failure is recommended. There are no specific data related to peritoneal dialysis.

The ATS recommend increasing the dose interval and suggest 250mg once daily or 500mg three times per week. Again, it should be given after haemodialysis to avoid

under-dosing and monitored for neurotoxicity.

Para-amino salicylic acid:

A modest amount of PAS (6.3%) is cleared by haemodialysis but its metabolite, acetyl-PAS, is substantially removed. 4mg twice daily should be adequate (A6).

Ethionamide:

Ethionamide is not cleared by the kidneys nor is it removed by haemodialysis so no adjustment to dosing is needed (A4).

Other suggestions shown below have been drawn up from Drug Prescribing in Renal Failure 4th edition (A7) and are approved by the FDA.

The ATS use a creatinine clearance of <30 ml/min as their cut off below which changes need to be made. There are insufficient data in patients with a reduced creatinine clearance but >30ml/min. In these patients, standard doses can be given but measurement of serum levels is recommended where possible to avoid toxicity.

Renal Impairment

Drug	GFRml/min	Dose	Dialysis
Streptomycin[+]	20-50	50-100% daily (7.5-15mg/kg every 24hrs)	HD as for GFR<10 CAVH as for GFR 10-20
	10-20	50-100% every 24-72 hrs (7.5-15mg/kg every 24-72hrs)	
	<10	50-100% every 72-96 hrs (7.5-15mg/kg every 72-96hrs)	
PAS (manufacturer states Avoid in severe RF) Peritoneal:as<10ml/min	>50ml/min	100%	HD: give after HD
	10-50	50-75%*	
	<10	50%*	CAVH: ditto
Ethionamide[++]	>50	no change	no changes in HD
	10-50	" "	
	<10	50%	
Capreomycin[**] (adjust dose to give Steady state concns Of 10mcg/ml)	>50	24hr dose interval	HD: give after HD
	10-50	24hr dose interval	Peritoneal: no change
	<10	48hrs dose interval	CAVH: dose as 10-50ml/min
Cycloserine[***] (blood monitoring - Levels <30mg/l)	>50	12hrs dose interval	HD: no change
	10-50	12-24hrs	Peritoneal:no change
	<10	24hrs	CAVH: dose as 10-50 ml/min

[+] intramuscular: 15mg/kg (max 1g daily). Dose is reduced in <50kg and >40years to max 500-750mg daily

Children and infants aged 1 month to 18 years with TB may be given streptomycin 20-40mg/kg daily to a max of 1gm daily.

Peak plasma concentrations should be between 15 and 40 micrograms/ml and trough concentrations <3-5micrograms/ml or <1microgram/ml in CKD or those >50years.

*caution when reducing dose PAS – may become subtherapeutic.

Usual adult dose 4g tds. Dosage recommended for paediatric patients is 200-300mg/kg daily in 2-4 divided doses. Granules should be administered in acidic food or drink with a pH<5, eg fruit juice, and should be swallowed without chewing.

[++]Adults 15-20mg/kg/day in single or divided doses (usul dose 500-1gm daily). Children 10-20mg/kg/day in single or divided doses.

[**] Adults 1gm im every 24 hours (not to exceed 20mg/kg/day). Do therapeutic drug monitoring. Chilren – no data.

[***]Usual adult dose 500mg-1gm daily in divided doses, monitored by TDM. The initial adult dosage most frequently given is 250mg bd at 12 hour intervals for the first

two weeks. A daily dosage of 1gm should not be exceeded.

Appendix 1 References

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