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A multicentre case-control study of nonsteroidal anti-inflammatory drugs as a risk factor for severe sepsis and septic shock

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Abstract

Introduction: We aimed to establish whether or not the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during evolving bacterial community-acquired infection in adults is associated with severe sepsis or septic shock.

Methods: We conducted a multicentre case-control study in eight intensive care units. Cases were all adult patients admitted for severe sepsis or septic shock due to a bacterial community-acquired infection. Controls were patients hospitalised with a mild community-acquired infection. Each case was matched to one control for age, presence of diabetes and site of infection.

Results: The main outcome measures were the proportions of cases and controls exposed to NSAIDs or aspirin during the observation period. In all, 152 matched pairs were analysed. The use of NSAIDs or aspirin during the observation period did not differ for cases and controls (27% versus 28, odds ratio (OR) 0.93, 95% confidence interval (CI) 0.52, 1.64). If aspirin was not considered, there was still no difference, and none if a distinction was made between acute and chronic drug treatment. However, for NSAID users, the median time to the prescription of effective antibiotic therapy was longer than for non-users (6 days, 95% CI 3.7 versus 3 days, 95% CI 2.3, $P = 0.02$).

Conclusions: In this study, the use of NSAIDs or aspirin during evolving bacterial infection was frequent and concerned one quarter of the patients with such infection. Although the use of NSAIDs by patients with severe sepsis or septic shock did not differ from their use by those with mild infection at the same infected site, we observed a longer median time to the prescription of effective antibiotic therapy for NSAID users.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin are widely used as antipyretic or analgesic drugs, even during evolving bacterial infections. Previous authors have described life-threatening infections associated with their use - mainly streptococcal infections and necrotizing fasciitis [1-4]. The involvement of NSAIDs in the aggravation of bacterial infection is a subject of controversy [5, 6]. A number of case reports concerning patients admitted to Intensive Care Units (ICUs) have suggested that the use of NSAIDs increases the severity of bacterial infections and might lead to shock and multiorgan failure [7-10]. In the present study, we aimed to investigate the question of whether exposure to NSAIDs or aspirin affects the evolution of bacterial infections.

Materials and methods

We carried out a multicentre case-control study in eight medical or polyvalent ICUs.

Study population

All the patients included were older than 15 and had a bacterial community-acquired infection. All the cases were patients admitted to an ICU with severe sepsis or septic shock [11, 12]. Patients with one or more of the following were excluded: chronic kidney failure (creatinine clearance < 30 ml/min), pregnancy, nosocomial infection, or congenital or acquired immunosuppression. Immunosuppression was defined as the presence of metastatic neoplasia, haemopathy, aplasia before the onset of sepsis, AIDS (independently of T4 cell counts), and the chronic administration of immunosuppressive treatments, involving, for instance, corticosteroids (equivalent of more than 30 days of prednisone at dosages exceeding 0.5 mg/kg/d), antineoplastic drugs or anti - tumour necrosis factor (TNF) drugs.

Controls were patients admitted to hospital for mild bacterial community-acquired infection, defined as infection without any signs of severe sepsis or septic shock from the onset of the disease to their discharge from the hospital. Each case was matched to one control for age (± 10 years), presence of diabetes mellitus and site of infection (lung, urinary tract, skin and soft tissue, abdomen, genital tract, joints, heart, central nervous system or primary bloodstream). Diabetes was chosen for the matching process because it is a frequent chronic condition which increases the risk of severe infection. The site of infection was chosen for the matching process because the use of NSAIDs might differ according to the site of infection. The type of micro-organism was not considered for the matching process because bacterial documentation was not always available during sepsis.

This study was observational and did not require any deviation from routine practice. Our regional ethics review board approved the study. Informed consent was not required.

Study design

For cases, the observation period began two days before the onset of infection, defined as the appearance of the first signs, and lasted until the beginning of severe sepsis or shock. Controls were observed for the same period (figure 1). Its duration varied from one case/control pair to another, but was identical for each case and matched control. NSAID use was quantified by careful listing of all the drugs taken during the observation period, and standard interviews were conducted by physicians. An exhaustive list of all oral and parenteral NSAIDs (including their International non-proprietary name and brand name) was provided to each investigator. All NSAIDs and aspirin were considered. However, when aspirin was taken as an antiplatelet aggregant for the prevention of cardiovascular diseases

(<350 mg/d), it was not taken into account. All types of oral and parenteral NSAID administration were considered (acute or chronic, prescribed or self-administered), whatever their duration and dosage. We defined acute administration of NSAIDs as their use for the observation period only, and chronic administration, as their use for a chronic disease before that period. As most of the cases could not be interviewed on their admission to the ICUs, the recording of their medical history required the help of their relatives and general practitioner, as well as reference to previous prescriptions. Antibiotic therapy was studied and was considered effective if it displayed appropriate *in vitro* activity and was appropriate against the pathogens isolated (or in the case of culture-negative bacterial infection, against the suspected pathogens according to international antibiotic therapy guidelines).

The main outcome measures of the study were the respective proportions of cases and controls who took prescribed or self-administered NSAIDs or aspirin during the observation period. We also compared, among the cases, the time from the first signs of infection to effective antibiotic therapy among NSAID users and non users.

Statistical analysis

The study was planned as an investigation of matched pairs (one-to-one). Assuming an NSAID use rate of 20% among the controls and an odds ratio of two, we planned to recruit 150 pairs (alpha and beta risks were respectively fixed at 5 and 20%). Odds ratios were estimated from discordant pairs, and exact 95% confidence intervals were computed from the tail probabilities of the binomial distribution [13]. Adjustments for parameters whose distribution among cases and controls differed significantly were made within the framework of conditional logistic regression. Lastly, the time to effective antibiotic therapy among cases was assessed by the Kaplan-

Meier method, and NSAID users and non users were compared using the log-rank test [14]. Data were analysed using SAS 9.1. Software.

Results

We recruited 152 cases from February 2004 to November 2005. They were matched to 152 controls. Table 1 shows the baseline characteristics of cases and controls. Diabetes was present in 20 pairs (13%). The sites of infection were the lung (n=71, 47%), urinary tract (n=30, 20%), skin or soft tissues (n=16, 11%), heart (n=11, 7%), abdomen (n=10, 7%), central nervous system (n=8, 5%), joints (n=4, 3%) and primary bloodstream (n=2, 1%). A higher percentage of cases than controls had pre-existing neoplastic disease, chronic hepatopathy, were smokers or had a higher McCabe disease severity score. A higher percentage of controls had rheumatic disease. The median observation period for which total consumption of NSAIDs was estimated was 6 days ([quartiles, 5-10], min and max, 3 and 32).

On inclusion, the characteristics of the 152 cases included severe sepsis (n=34, 22%) and septic shock (n=118, 78%). The mean Simplified Acute Physiology Score II (SAPS II) was 49 ± 20. The median length of stay in an ICU was 10 days [quartiles, 4-17]. During hospitalisation in an ICU, circulatory failure was present in 134 cases (88%), respiratory failure in 101 (67%), kidney failure in 79 (52%), and haematological failure in 37 (24%).

Bacteriological identification revealed the presence of one or more organisms in 123/152 cases. The main organisms were *Streptococcus pneumoniae* (n=34, 28%), *Escherichia coli* (n=29, 24%), *Staphylococcus aureus* (n=19, 15%) and *Streptococcus pyogenes* (n=7, 6%). Antibiotic therapy before admission to an ICU proved ineffective in 74 cases (33%). Treatments included mechanical ventilation in

124 cases (82%), vasopressive drugs in 128 (84%), dialysis in 35 (23%), corticosteroids in 107 (70%) and drotrecogin alpha in 33 (22%). Surgery was performed to treat the origin of sepsis in 40 (26%) of the cases. The mortality rate in ICUs was 24%.

All controls had a mild bacterial community-acquired infection. The median length of their hospital stay was 7 days [quartiles 5-14]. None of them developed severe sepsis or septic shock, none was admitted to an ICU, and none died. Bacteriological identification revealed the presence of one or more micro-organisms in 75/152 controls (49%). The main organisms were *Escherichia coli* (n=29, 39%), *Staphylococcus aureus* (n=11, 15%) and *Streptococcus pneumoniae* (n=7, 9%). Only one *Streptococcus pyogenes* was identified.

The use of NSAIDs or aspirin during the observation period did not differ in cases and controls (27% vs 28, odds ratio 0.93, 95% confidence interval [CI] 0.52, 1.64, p=0.79 , table 2). If aspirin was not considered, there was still no difference, and no difference either when acute and chronic NSAID treatments were considered separately. Whether the duration of exposure taken into account was 1 day, >1 day or > 2 days, or whether the end of the observation period was defined as the day of hospital admission rather than the beginning of severe sepsis or shock, NSAID or aspirin ingestion did not differ for cases and controls (data not shown). Lastly, there was still no difference between the two groups after adjustment for pre-existing diseases or for treatment centre (data not shown). Few diabetic patients were included in the study (only 20 pairs). There was no difference between their NSAID or aspirin consumption and that of the rest of the population studied. However, more non diabetic controls than cases used aspirin (11 % vs 4, odds ratio 0.36, p =0.04). For the three main sites of infection (lung, urinary tract, and skin or soft tissue),

NSAID use varied, depending on the site: thus, twice as many cases and controls with urinary tract or skin and soft tissue infections as with lung infections used NSAIDs. We did not observe any difference between cases and controls for any of the sites studied.

Consequently, in the light of these findings, only the cases were studied. For NSAID users among the cases, the time from the first signs to the prescription of an effective antibiotic therapy was longer than for non users (median : 6 days, 95% CI 3, 7 vs 3 days, 95% CI 2, 3, p=0.02 [figure 2]). Among the cases, NSAID users had a mortality rate of 27%, and non users, of 23% (p=0.58).

Discussion

The present results failed to support the hypothesis that NSAID exposure during evolving bacterial infection is associated with an increased risk of severe sepsis or septic shock. However, we observed that in patients with severe sepsis or septic shock, NSAID use is associated with a longer time from the first signs of infection to the prescription of effective antibiotic therapy.

As stated in the introduction, several case reports for patients admitted to ICUs [7-9] have suggested that NSAID treatment might increase the severity of infection and lead to shock and multiorgan failure, because life-threatening infections - mainly streptococcal, especially necrotizing fasciitis - have been described following the use of NSAIDs [3, 5] and less frequently, infection by other organisms such as *Staphylococcus* sp or Gram negative bacilli [15]. However, unlike these case reports, case-control studies are designed to establish an association between an event and a risk factor and to quantify the risk involved. Most of the case-control studies relevant to the present investigation concerned the link between NSAID exposure of

children with varicella and skin or soft tissue infections [16-19]. A significant association, which persisted after adjustment for age, sex and infection by micro-organisms (i.e. streptococci and other germs), was found between ibuprofen use and necrotizing fasciitis [19]. This finding is particularly interesting, because the protopathic bias of the study was limited, as all the cases had necrotizing fasciitis, and all the controls, severe post-varicella skin or soft tissue infections. As far as we know our study is the first case-control investigation to concern adults with community-acquired bacterial infections. Because the incidence of skin and soft tissue infections in ICUs is lower than that of lung or urinary tract infections [20], we included patients with many kinds of severe bacterial infections generally admitted to ICUs. The main sites of infection were lung, for which fewer subjects were given NSAIDs than for other infected sites, followed by the urinary tract.

Several possible explanations can be suggested for the present failure to find a link between NSAID use and an increased risk of sepsis during bacterial infection. Firstly, the sites of infection and micro-organisms involved, especially the low incidence of skin and soft tissue infections and consequently of streptococcal infections, were the ones most frequently involved in studies whose authors found a link between NSAID and sepsis. Here, however, we included various kinds of bacterial community-acquired infections, and among the 16 case/control pairs of subjects with skin and soft tissue infections, *Streptococcus pyogenes* was only identified in seven cases and one control. Secondly, more microbiological documentation was available for cases than controls. However, this was not surprising, because the incidence of bacteraemia was usually higher in severe sepsis and septic shock, and because lung samples are more frequently available in patients with mechanical ventilation than in those without. The resulting high rate of undocumented infection in the control group

may have biased the results of the study. Thirdly, as regards the underestimation of NSAID use among the cases, we assumed that more cases than controls took NSAIDs because the cases were more severely ill, and that NSAIDs were prescribed or self-administered against pain or fever. The underestimation may have been due to the greater difficulty of assessing drug use in severely ill patients than in controls with mild infection, whose interviews provided more accurate information. Family questioning and analysis of initial prescriptions were mostly used for cases, and direct questioning, for controls. Other possible explanations for our negative results are that the study may have been underpowered (overestimation of the use of NSAIDs in cases), that there may have been a sampling bias if the true population using NSAIDs was not representative of either the cases or the controls, and that the patients with the most severe septic shock might have had no time to use NSAIDs.

Although the patients in our study were suffering from ongoing infection, many had started taking NSAIDs before the beginning of effective antibiotic therapy. Among the cases, the median time from the first signs of infection to effectiveness was twice as long for NSAID users as for non users (figure 2). This was in agreement with the observations reported by Zerr et al., who found a longer duration of secondary symptoms before hospitalisation in NSAID-exposed than unexposed patients [19]. These results suggest that NSAIDs probably delay the prescription of effective antibiotic therapy because they might mask the progression of disease by suppressing the inflammatory response induced by the infection [21, 22]. This is a very important consideration, because delay in diagnosis and consequently in the administration of effective antibiotic therapy was recently shown to be one of the main risk factors for mortality [23].

The potentially harmful effect of NSAIDs might vary, depending on whether or not patients receive effective antibiotic therapy. Although this was not taken into account in our study, we observed higher but not significant mortality in NSAID-exposed patients. Certain other authors aimed to demonstrate, on the contrary, that NSAIDs have a beneficial effect during sepsis, as observed in animals, and that the inhibition of cyclo-oxygenase activity improves survival and reduces the physiological abnormalities caused by sepsis [22]. In adults given effective antibiotic therapy for sepsis, some authors failed to find any difference between the clinical outcome of NSAID users and non users, despite a decrease in prostacyclin metabolites in users [24-26]. However, the latter results do not rule out the possibility that NSAIDs might be harmful for patients given ineffective antibiotic therapy. In any case, these drugs may predispose to severe bacterial infections because they inhibit leukocyte adherence, phagocytosis and bactericidal activity in vitro [22]. In addition, as NSAIDs have been found to increase inflammatory cytokine production in animal and human studies [24, 27, 28], and as the mortality rate for sepsis correlates with high Interleukin 6 and TNFα levels, the use of prostaglandin inhibitors in sepsis may be harmful. From this point of view, it might be useful to study infections more directly linked to the impairment of granulocyte function, such as fasciitis, extensive abscesses or collections of bacteria from different sites, rather than severe sepsis or septic shock, which are mainly the consequence of the systemic inflammatory reaction.

Conclusions

In conclusion, the prescribed or self-administered use of NSAIDs is frequent during evolving bacterial infection, but here it did not differ in patients with mild community

acquired-infection and those with severe sepsis or septic shock. Our results therefore failed to support the hypothesis that during bacterial community-acquired infection, NSAIDs increase the risk of severe sepsis or septic shock. Nevertheless, NSAID use was associated with delayed prescription of effective antibiotic therapy. Further studies are needed to establish 1) the effects of NSAIDs on patients whose antibiotic therapy is not effective, and 2) whether or not NSAID use increases the morbidity of bacterial infections such as fasciitis or extensive abscesses, rather than the frequency of severe sepsis and septic shock.

Key messages

- More than one quarter of the patients who developed bacterial community-acquired infection were exposed to NSAIDs.
- For the patients with severe sepsis or septic shock who were given NSAIDs, the median interval between the first signs and the prescription of effective antibiotic therapy was longer than for those not given NSAIDs.

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
CI	Confident Interval
ICU	Intensive Care Unit
NSAID	Nonsteroidal Anti-Inflammatory Drug
OR	Odds Ratio
SAPS II	Simplified Acute Physiology Score II
TNF	Tumour Necrosis Factor

Competing interests:

The authors declare that they have no competing interests.

Authors' Contributions:

AL, BG, APJB and EAL participated in the design of the study, and drafted the manuscript. AL, CC, BF, IR, AK, AV, JT and DV helped to collect study data. BG performed the statistical analysis. All authors read and approved the final manuscript.

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Figure Legends

Figure 1. Observation period. The observation period for both cases and controls began 2 days before the onset of infection and for the cases, lasted until the beginning of severe sepsis or septic shock.

Figure 2. Comparison of the times from the first signs of infection to effective antibiotic therapy for cases using nonsteroidal anti-inflammatory drugs (NSAIDs) versus cases not using these drugs (Log-rank test : p=0.02).

Table 1 Baseline characteristics of the 152 pairs of matched cases and controls (n = pairs)

Characteristics	**Cases (n = 152)**	**Controls (n =152)**	***P* Value**
Sex M, n (%)	90 (59)	87 (57)	0.73
Age (yrs), mean (SD) *	60 (15)	61 (16)	0.67
Body mass index (Kg/m²), mean (SD)	26 (6)	26 (5)	0.91
Current smoking, n (%)	57 (37)	38 (25)	0.02
Pre-existing disease, n (%)	54 (35)	62 (41)	0.34
Chronic respiratory failure	22 (14)	15 (10)	0.22
Chronic heart failure	12 (8)	14 (9)	0.68
Moderate chronic kidney failure (Cl > 30 ml/min)	6 (4)	4 (3)	0.52
Chronic hepatopathy	12 (8)	4 (3)	0.04
Pre-existing neoplastic disease	12 (8)	2 (1)	0.01
Chronic rheumatic disease	13 (9)	30 (20)	0.01
McCabe disease severity score, n (%)			
1	125 (82)	149 (98)	<0.001
2	27 (18)	3 (2)	
3	0	0	

* Although age was a matching factor, a statistical test was performed because the matching window was fixed at ± 10 years

Table 2. Comparison of NSAID and Aspirin use by cases vs controls (n = number of pairs)

	NSAID users (%)		Odds ratio	95%CI	*P* Value
	Cases	Controls			
Global analysis (n = 152)					
NSAIDs and Aspirin	27	28	0.93	(0.52, 1.64)	0.79
NSAIDs	24	21	1.18	(0.64, 2.19)	0.56
Chronic treatment	4	5	0.86	(0.24, 2.98)	0.78
Acute treatment	20	16	1.40	(0.69, 2.92)	0.32
Aspirin	5	10	0.47	(0.16, 1.22)	0.09
Sub-group analysis					
Diabetes (n = 20)					
NSAIDs	20	5	4.00	(0.40, 196.99)	0.18
Aspirin	10	5	2.00	(0.40, 196.99)	0.56
No diabetes (n = 132)					
NSAIDs	24	23	1.05	(0.55, 2.00)	0.88
Aspirin	4	11	0.36	(0.10, 1.05)	0.04*
Site of infection					
Lung (n = 71)					
NSAIDs	14	15	0.90	(0.32, 2.46)	0.82
Aspirin	7	11	0.63	(0.16, 2.17)	0.40
Urinary tract (n = 30)					
NSAIDs	27	30	0.83	(0.02, 3.28)	0.76
Aspirin	3	7	0.50	(0.01, 9.60)	0.56
Skin and soft tissue (n = 16)					
NSAIDs	31	31	1.00	(0.07, 13.80)	1.00
Aspirin	0	6	-	-	-
Others (n = 35)					
NSAIDs	37	20	2.50	(0.72, 10.92)	0.11
Aspirin	3	11	0.25	(0.01, 2.53)	0.18

CI, confidence interval; NSAIDs: Nonsteroidal anti-inflammatory drugs.
* The apparent discordance between the confidence interval [CI] and statistical test results is due to the use of different but asymptotically equivalent statistical methods.

Figure 1

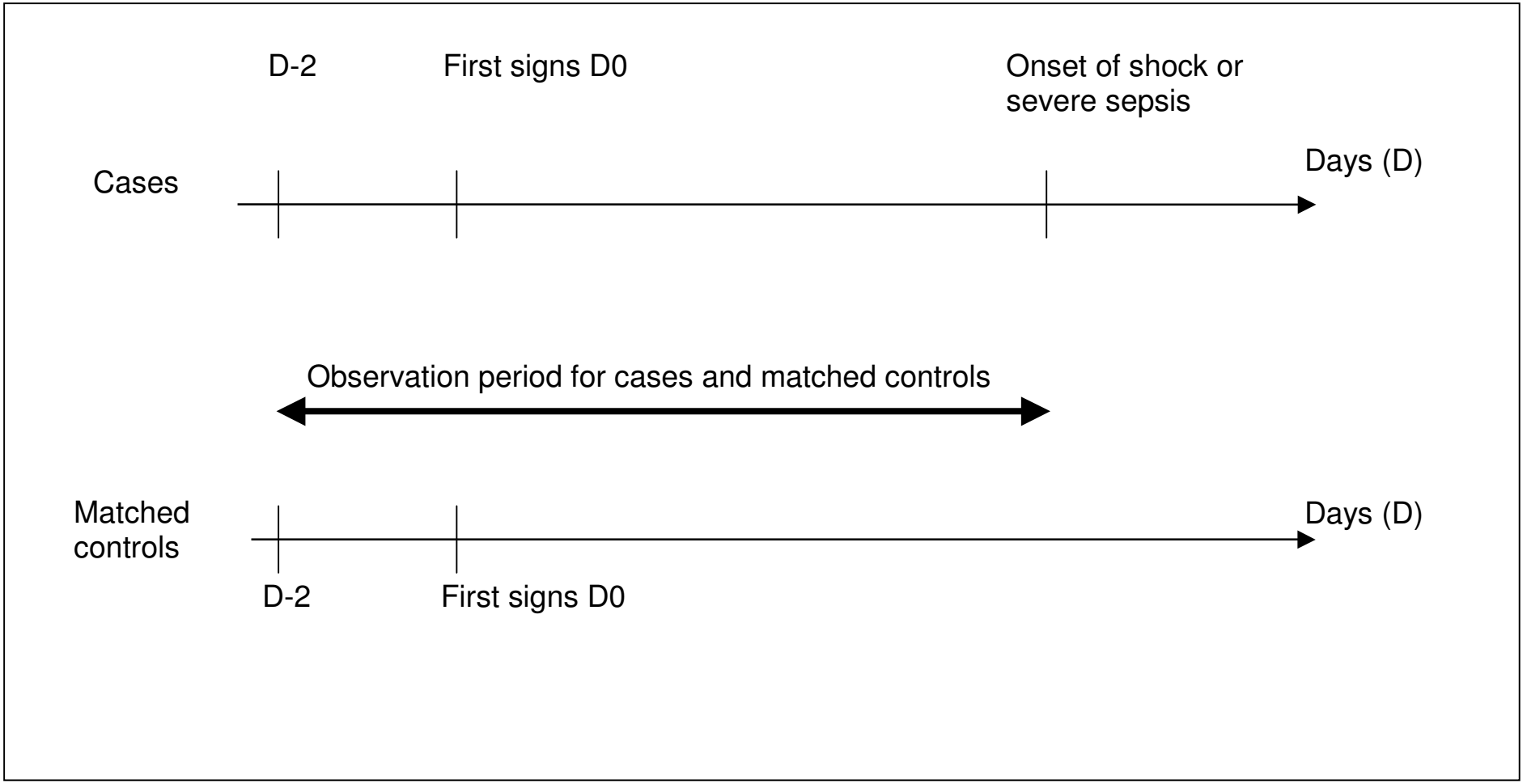
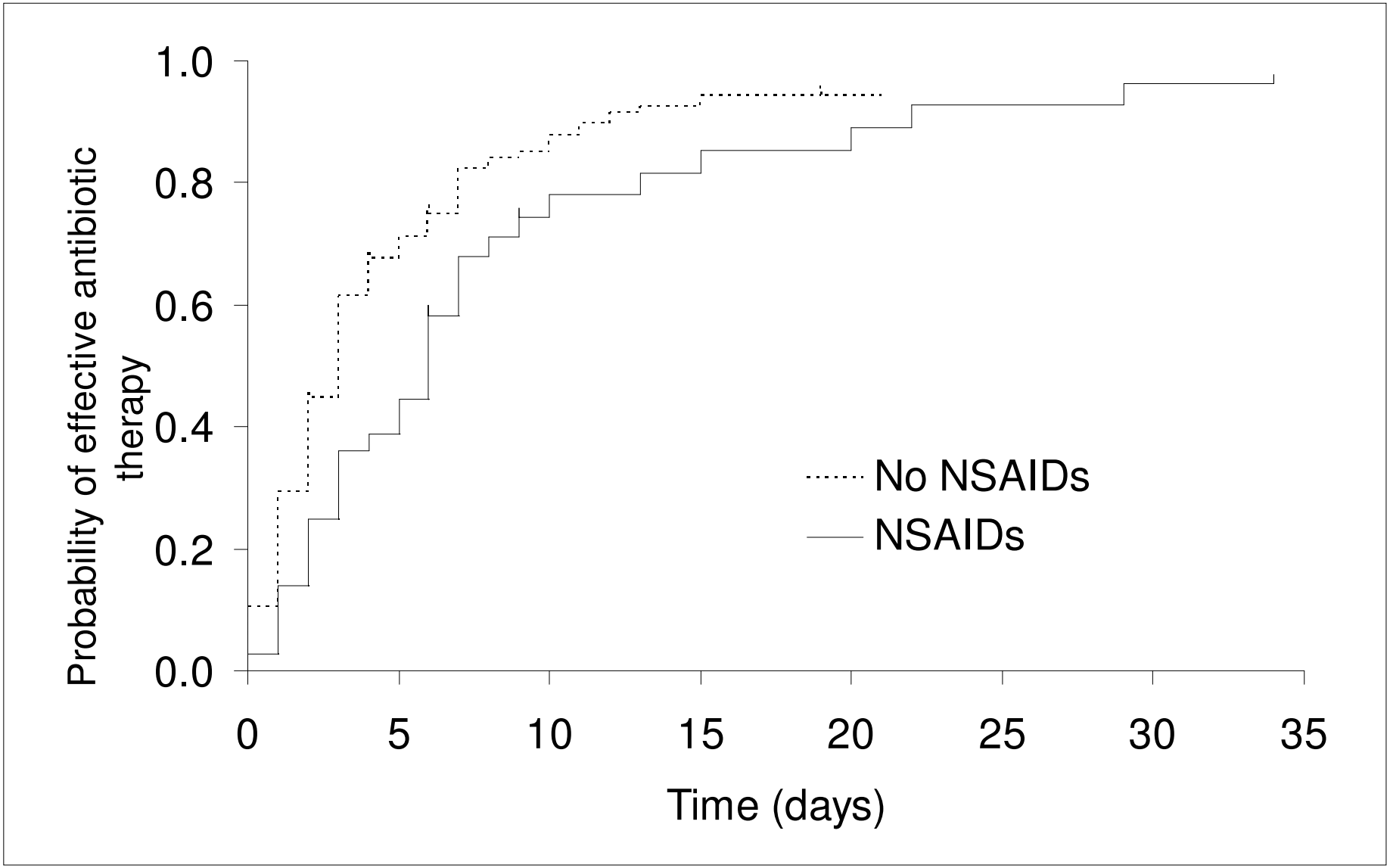

D-2
First signs D0
Onset of shock or severe sepsis
Days (D)
Cases
Observation period for cases and matched controls
Matched controls
Days (D)
D-2
First signs D0

Figure 2


Probability of effective antibiotic therapy
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
Time (days)
No NSAIDs
NSAIDs