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Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study

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***Objectives*: To determine the attributable mortality and excess length of stay (LOS) associated with the use of inadequate empirical antimicrobial therapy in patients with sepsis at admission to the intensive care unit (ICU).**

***Methods*: A retrospective matched cohort study was performed using a prospectively collected database at a 40 bed general ICU at a university public hospital. Patients who received inadequate antimicrobial therapy at admission to the ICU (exposed) were matched with controls (unexposed) on the basis of origin of sepsis, inflammatory response at admission, surgical or medical status, hospital- or community-acquired sepsis, APACHE II score (±2 points) and age (±10 years). Clinical outcome was assessed by in-hospital mortality, and this analysis was also performed in those pairs without nosocomial infection in the ICU.**

***Results*: Eighty-seven pairs were successfully matched. Fifty-nine exposed patients died [67.8% mortality (95% CI, 58.0–77.6%)] and 25 unexposed controls died [28.7% mortality (95% CI, 19.2–38.2%)] ($P < 0.001$). Excess in-hospital mortality was estimated to be 39.1%. The rate of nosocomial infection was significantly higher in patients with inadequate empirical therapy (16.1%) than in those treated empirically with adequate antibiotics (3.4%) ($P = 0.013$). Excess in-hospital mortality was 31.4% after excluding those 17 pairs that developed a nosocomial infection in the ICU. Inadequate antimicrobial therapy was associated with a significant increment in duration of hospitalization (15 days in surviving pairs).**

***Conclusions*: Inadequate antimicrobial therapy at admission to the ICU with sepsis is associated with excess mortality and increases LOS.**

Keywords: septic shock, mortality, length of stay, bacteraemia, initial antibiotic therapy

Introduction

A prompt institution of antimicrobial therapy that is active against the causative pathogen(s) is crucial in the treatment of patients with severe infections and sepsis. In fact, the Surviving Sepsis Campaign strongly recommends initiating antibiotic therapy within the first hour of recognition of severe sepsis, after suitable cultures have been obtained.[1]

We demonstrated in an observational study the protective effect on mortality of adequate initial therapy in critically ill septic patients after adjusting for confounding factors,[2] which has also been broached by others with similar results.[3,4] This has also been established for different types of infections and for specific pathogens.[5–7] Conversely, other studies with similar designs have questioned the benefits of adequate antibiotic therapy on survival of patients with bacteraemia and sepsis.[8–10]

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Diverse methodological issues (i.e. definition of inadequate antibiotic therapy, analysis of confounding variables, such as severity of illness and underlying diseases, and proper statistical power) should be carefully considered to analyse the association between adequacy of antibiotic therapy and survival in septic patients.[11,12]

This research question cannot be solved in randomized trials for obvious ethical reasons. Moreover, the exact magnitude of the empirical antimicrobial therapy has not been evaluated. Until now, little information is available in relation to the impact of inadequate antimicrobial therapy on the acquisition of nosocomial infections or the duration of hospitalization. On this topic, it is worth mentioning a recent study carried out in non-critically infected patients, which demonstrated that appropriate empirical antibiotic therapy shortened the length of hospital stay.[13] In this era of limited resources and expenditure containment, it is essential to determine whether the administration of inadequate therapy prolongs the length of stay (LOS) and is therefore associated with an increment in the costs.

To establish the clinical and economic consequences of inadequate empirical antimicrobial therapy, we carried out a matched cohort study including patients with the diagnosis of sepsis at admission to the intensive care unit (ICU). Our main objective was to determine whether the administration of inadequate antimicrobial therapy causes a significant attributable mortality. Our secondary objectives were to assess the excess length of ICU and hospital stays associated with the use of antimicrobials in the first 24 h in the ICU without microbiological activity against the causal pathogen(s).

Methods

Setting

This study was performed in the ICU of the Hospital Virgen del Rocío. This is a 40 bed medical-surgical unit in a large university public hospital. Since 1997, all patients meeting criteria for sepsis on admission to the ICU were included in a database and followed up until death or hospital discharge. Two previous studies have been published with this database.[2,14] Written consent for the present study was not required by the Ethics Committee of the Hospital, which approved this research. Management of these patients has been described elsewhere.[2]

Design

We conducted a retrospective matched cohort study using this prospectively collected database. All consecutive patients included up to December 2006 with microbiologically documented sepsis that received inadequate antimicrobial therapy at admission to the ICU were elected as exposed patients. Microbiologically documented sepsis was considered when a relevant microorganism from a suspected focus of infection was isolated and/or bacteraemia was present.[2] Therapy was considered inadequate when no effective drug against the isolated pathogen(s) was included in the empirical antibiotic treatment within the first 24 h of admission to the ICU or the doses and pattern of administration were not in accordance with current medical standards.

Every exposed patient was matched, by an investigator (J. G.-M.) blinded to the outcome, with another patient with adequate antimicrobial therapy, based on: (i) source of sepsis; (ii) inflammatory response at admission to the ICU (sepsis, severe sepsis or septic shock); (iii) surgical or medical status; (iv) hospital- or community-acquired sepsis; (v) severity of illness at admission (APACHE II score comprised severity index, age and chronic health status[15]) ($\pm$2 points); and (vi) age ($\pm$10 years). In the case of two or more potential unexposed subjects, selection was based on those subjects with the nearest date of ICU admission.

As expected, mortality can be derived from the APACHE II system (APACHE II score and diagnostic category) measured at ICU admission; this matching procedure results in an equal expected mortality for both groups: exposed and unexposed. The mortality attributable to inadequate empirical antimicrobial therapy was determined by subtracting the crude mortality of the exposed patients from the crude mortality of the unexposed patients. The excess stay attributable to inadequate empirical antimicrobial therapy was defined as the difference in the LOS between exposed and unexposed in surviving pairs.

Failure of organs and severity of multiple organ dysfunction syndrome were evaluated by the Sequential Organ Failure Assessment (SOFA) scale on admission and during the subsequent clinical course.[16] The worsening of the clinical situation was evaluated calculating the delta-SOFA: worst SOFA score during the ICU stay minus SOFA score in the first 24 h.[17] Development of nosocomial infections in the ICU, ventilator-associated pneumonia (VAP), catheter-related bloodstream infection (CRBSI) and primary bacteraemia was also recorded following previous definitions.[18]

Statistical analysis

All patients were followed up until hospital discharge. Descriptive statistical analysis was performed. Continuous variables were compared using the paired Student's *t*-test or the Wilcoxon test, as appropriate. LOSs were summarized as median and interquartile range (IQR) 25% to 75% and compared using the Wilcoxon test. Categorical variables including mortality were analysed by McNemar's test. All *P* values were two-tailed. Data were collected and analysed with the SPSS 14.0 software package.

Results

A total of 919 patients were admitted to the ICU with the diagnosis of sepsis during the study period. Microbiological documentation of sepsis was achieved in 73.3% of these subjects. Ninety-one patients received inadequate empirical therapy and were therefore elected as exposed subjects.

Eighty-seven of them were successfully matched to unexposed subjects and were enrolled in the study. No match was found in four patients with inadequate empirical antibiotic therapy (three of them died). The demographic data of exposed and unexposed patients are shown in Table 1. The severity of illness at admission measured by APACHE II score was similar in both matched groups. Source of infection was identical in all pairs: abdomen 36, lung 18, urinary tract 11, unknown origin 10, soft tissue 6, catheter 5 and CNS 1. At admission to the ICU, sepsis was present in 3 pairs, severe sepsis in 30 pairs and septic shock in 54 pairs. Sepsis was community-acquired in 45 pairs and hospital-acquired in 42 pairs. Length of previous hospitalization (median) in patients with hospital-acquired sepsis was not

Table 1. Clinical characteristics of exposed patients (inadequate empirical antimicrobial therapy) and their unexposed controls (adequate empirical antimicrobial therapy)

Characteristic	Exposed ($n = 87$), *n* (%)	Unexposed ($n = 87$), *n* (%)	*P* value
Age (years)[a]	62 (11.6)	63.8 (11.3)	0.22
Gender (male)	53 (60.9)	58 (66.6)	0.48
APACHE II[a]	19.7 (6.2)	19.7 (6.0)	0.87
SOFA[a]	8.4 (4.3)	8.2 (4.1)	0.69
Diabetes mellitus	20 (23.0)	19 (21.8)	1
Immunosuppression	15 (17.2)	13 (14.9)	0.82
Hepatic cirrhosis	4 (4.6)	4 (4.6)	1
ESRD	9 (10.3)	4 (4.6)	0.18
Chronic heart failure	2 (2.3)	6 (6.9)	0.28
COPD	8 (9.2)	8 (9.2)	1
Cancer	7 (8.1)	15 (17.2)	0.13
ICU mortality	51 (58.6)	24 (27.6)	<0.0001
In-hospital mortality	59 (67.8)	25 (28.7)	<0.0001

[a]Results are expressed as mean (SD).
APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Table 2. Pathogens isolated in blood and the source of sepsis in exposed and unexposed patients (number of isolations in blood cultures is shown in parentheses)

Pathogen	Exposed	Unexposed
Acinetobacter spp.	9 (6)	1 (1)
Aeromonas hydrophila	3 (3)	1 (1)
Aspergillus spp.	1	0
Bacteroides fragilis	0	1 (1)
Brucella melitensis	1 (1)	0
Candida spp.	15 (10)	3 (3)
Clostridium spp.	0	2 (2)
Escherichia coli	24 (17)	26 (17)
Enterobacter spp.	1	8 (3)
Enterococcus spp.	4 (2)	6 (6)
Hemophilus spp.	0	1 (1)
Klebsiella spp.	2 (2)	17 (8)
Nocardia spp.	1	0
Morganella spp.	1	1 (1)
Pneumocystis jiroveci	1	0
Prevotella spp.	1 (1)	0
Proteus spp.	5	2 (1)
Pseudomonas aeruginosa	12 (4)	4 (2)
Serratia spp.	0	2 (2)
Staphylococcus aureus	5 (4)	2 (1)
Staphylococcus epidermidis	2 (2)	1 (1)
Stenotrophomonas maltophilia	2	0
Streptococcus pneumoniae	3 (1)	10 (4)
Streptococcus spp.	0	5 (3)

In exposed, only pathogens treated inadequately are shown in this table. In addition, the following pathogens were also isolated in these patients and treated adequately with the empirical therapy: *Enterococcus* spp. (3), *E. coli* (3), *Streptococcus* spp. (3), *Proteus* sp. (1), *Pseudomonas* sp. (1) and *B. fragilis* (1). Bacteraemia was polymicrobial in two exposed subjects. All pathogens isolated in unexposed (adequate empirical therapy) are shown in this table. Bacteraemia was polymicrobial in five unexposed subjects.

statistically different between the two groups [17 (range from 3 to 60 days) versus 12 (range from 4 to 78 days); $P = 0.31$].

APACHE II score at admission was within an interval of 2 points in all matched patients. In 73 (83.9%) matched patients, age was within 10 years. Exposed and unexposed subjects did not significantly differ with regard to severity of illness, demographic characteristics and recorded co-morbidities (Table 1).

Pathogens isolated in blood and the sites of infection are shown in Table 2. Bacteraemia was detected in 51 exposed and 53 unexposed patients. Median delta-SOFA was significantly higher in exposed than in unexposed patients [2 (IQR 0–5) versus 0 (IQR 0–1); $P < 0.0001$]. Eleven patients with inadequate empirical antimicrobial therapy (exposed) and 8 patients with adequate empirical antimicrobial therapy (unexposed) died in the first 2 days after ICU admission. Excluding these patients, median delta-SOFA was also significantly higher in exposed than in unexposed subjects [2 (IQR 1–2.5) versus 0 (IQR 0–2); $P < 0.0001$].

Fifty-one of the 87 exposed patients died in the ICU, representing a crude mortality of 58.6%, whereas 24 of the 87 unexposed patients died, representing a crude mortality of 27.6% ($P < 0.0001$). In-hospital, 59 of the 87 exposed patients died, representing a crude hospital mortality of 67.8% (95% CI, 58.0–77.6%), whereas 25 of the 87 unexposed patients died, representing a crude mortality of 28.7% (95% CI, 19.2%–38.2%) ($P < 0.0001$). Excess in-hospital mortality was estimated to be 39.1%.

In 40 pairs, both exposed and unexposed subjects were bacteraemic. Bacteraemia was polymicrobial in two exposed subjects and in five unexposed. Thirty of these 40 exposed patients died, representing a crude hospital mortality of 75%, whereas 11 of the 40 unexposed died, representing a crude mortality of 27.5% ($P < 0.0001$). Septic shock at admission was present in 54 pairs. Forty-two exposed patients with septic shock and 20 unexposed patients died during hospitalization (crude hospital mortality 77.8% versus 37%; $P < 0.0001$).

The LOS in hospital was not significantly different in the entire group (Table 3). However, among the 27 pairs in which both exposed and unexposed survived the hospital stay, the median length of ICU stay was 11 (IQR 7–19) days for exposed and 7 (IQR 6–19) days for unexposed patients ($P < 0.001$). In-hospital duration of stay in surviving pairs was also significantly longer ($P < 0.001$) in exposed than in unexposed patients [32 (IQR 19–45) versus 17 (IQR 12–25); $P < 0.001$]. This represents an excess of hospitalization in the ICU of 4 days for each patient with inadequate empirical therapy. The excess of hospitalization in the general ward was 15 days.

Development of nosocomial infection in the ICU was significantly more frequent ($P = 0.013$) in patients with inadequate empirical therapy (14/87; 16.1%) than in those treated empirically with adequate antibiotics (3/87; 3.4%). Fourteen exposed patients developed nosocomial infections. Five of them presented two nosocomial infections in the ICU. These nosocomial

Table 3. Duration of hospitalization (days) in the entire group and in those pairs without nosocomial infections

	All pairs			Surviving pairs		
	exposed	unexposed	*P*	exposed	unexposed	*P*
Entire group ($n = 87$)						
ICU LOS	9 (5–17)	8 (6–11)	0.001	11 (7–19)	7 (6–19)	<0.001
in-hospital LOS	17 (6–33)	17 (11–30)	0.65	32 (19–45)	17 (12–25)	<0.001
Pairs without NI ($n = 70$)						
ICU LOS	9 (4–14.5)	7 (5.5–10.5)	0.02	10.5 (7.5–15.5)	7 (6–9)	<0.001
in-hospital LOS	15.5 (4.5–30)	17 (8.5–31)	0.55	32 (19.5–47)	17 (12–24.5)	<0.001

Data are presented as median (interquartile range).
LOS, length of stay; NI, nosocomial infections.

infections were VAP = 10 episodes, CRBSI = 7 episodes and primary bacteraemia = 2 episodes. In contrast, four episodes of nosocomial infections were diagnosed in three unexposed subjects: VAP=2 episodes and CRBSI=2 episodes.

To rule out the possibility that the higher mortality and the longer LOS in patients with inadequate empirical therapy than in unexposed patients (adequate therapy) could be influenced by the greater rate of nosocomial infections, we analysed those 70 pairs that did not acquire a new infection in the ICU. APACHE II score [19.6 (6.5) versus 19.7 (6.5)] and SOFA score [8.6 (4.2) versus 8.5 (4.2)] at admission, demographic characteristics and underlying diseases were similar in both matched groups. Bacteraemia was detected in 41 exposed patients and in 42 controls. In this subgroup of patients without nosocomial infection, 41 of the 70 exposed patients died, representing a crude ICU mortality of 58.6% (95% CI, 47.1–70.1%), whereas 23 of the 70 unexposed patients died, representing a crude mortality of 32.9% (95% CI, 21.9–43.9%) ($P < 0.001$). In-hospital, 46 of the 70 exposed patients died, (a crude hospital mortality of 65.7%), whereas 24 of the 70 unexposed patients died (a crude mortality of 34.3%) ($P < 0.001$). Therefore, excess in-hospital mortality was estimated to be 31.4%.

LOS in the ICU was less in six exposed patients than in their corresponding unexposed controls. LOS in the hospital was less in four exposed patients than in the corresponding unexposed patients. Median length of ICU stay in the pairs that survived the ICU stay ($n = 28$) was significantly longer in exposed than in unexposed subjects (Table 3). In-hospital duration of stay was also significantly longer in exposed than in unexposed [32 (IQR 19.5–47) versus 17 (IQR 12–24.5); $P < 0.001$], evaluating those 25 surviving pairs without nosocomial infections.

Discussion

The results of the present study confirm that in critically ill septic patients, inadequate empirical antimicrobial therapy at admission to the ICU is associated with a significant attributable mortality. Importantly, among those survivors who did not receive adequate initial therapy, there is a significant increase in ICU and hospital LOS with the aftermath that this implies.

Although antibiotic therapy is the cornerstone in the treatment of infections, several studies have questioned that inadequate initial antibiotic treatment of sepsis and bacteraemia is associated with increased mortality.[8–10] In our matched cohort study, excess in-hospital mortality associated with inadequate initial treatment at admission to the ICU was estimated to be 39%.

Despite the fact that both groups were well matched at admission to the ICU, the incidence of nosocomial infections was significantly higher in patients with inadequate empirical antimicrobial therapy than in those with initial adequate antibiotics. As diverse studies have determined the attributable mortality rates of different infections in critically ill patients such as catheter-related or primary bacteraemias[19] and VAP,[20] we also analysed those pairs that did not develop a new infection in the ICU. Again, a significant increased mortality (31%) was found in this subgroup of patients without nosocomial infections.

The high rate of bacteraemic sepsis in our sample is worth mentioning.[21,22] This may be explained in part by the fact that only patients with microbiologically documented sepsis were included in our study as the adequacy of empirical therapy cannot be determined in those episodes with negative cultures. In patients with bacteraemic sepsis and in those with septic shock at admission, the excess mortality is more than 40%.

Matched cohort studies generate valid information when the matching procedure is adequately performed to avoid the effect of confounding variables and sampling bias.[23] Crucial in the interpretation of matched cohort studies is the level of agreement between exposed and unexposed patients. As mortality of sepsis varies depending on the source of infection and the clinical presentation, these criteria were identical in all pairs. In addition, severity of illness on admission is an important variable influencing outcome in critically ill patients.

In our overall cohort, duration of hospitalization was in accordance with data from previous studies,[24] without difference between exposed and unexposed patients. However, analysing only those pairs that were discharged alive from the hospital, LOS was significantly longer in patients with inadequate empirical therapy than in those treated correctly. Information about the impact of empirical antimicrobial therapy on the duration of hospitalization in sepsis is scarce. Importantly, length of previous hospitalization in patients with nosocomial sepsis was not statistically different in exposed and unexposed subjects, as prolonged ward stay before ICU admission increases the probability of long ICU and hospital stays.[25]

In our previous study, hospital LOS was on average 15 days longer in surviving patients with inadequate empirical antibiotic

therapy [55.9 (68.6) days] than in those with adequate therapy [40.8 (33.8) days], although this difference was not statistically different.[2] A significant increment in the LOS has been documented in patients with bloodstream infections and sepsis receiving inadequate initial antimicrobial treatment when compared with those receiving adequate treatment,[26,27] although in other studies the LOS was unaffected by the adequacy of initial therapy.[9,10] More recently, in non-critically infected patients, administration of antimicrobial therapy inactive against the isolated bacteria was associated with prolonged duration of hospital stay.[13]

Total costs of sepsis are highly dependent on the severity of illness or the sites of infection and are clearly augmented in septic patients who developed a new episode of sepsis during the ICU Stay.[28,29] In 1995, the average costs in the USA were calculated to be more than $22 000 per case.[30] More recently, the cost of patients admitted to the ICU from January 2000 to December 2002 with the diagnosis of sepsis has been estimated to be more than €38 000 in Europe.[31]

Very little information is available about the impact of inadequate empirical antimicrobial therapy on the cost of hospitalization. In the 1990s, this expenditure was calculated to be more than €6000 in non-critically ill patients with intra-abdominal infections.[32] To the best of our knowledge, no data exist concerning the economical repercussion of prescribing an incorrect antibiotic treatment in septic patients.

In the present study, the median of the difference of stay in the ICU in surviving pairs was 4 days longer in exposed than in unexposed patients. Overall, the median of the difference of the stay in the general ward was 15 days longer in exposed subjects than their controls. Although total expenditures clearly depend on the patient case-mix and the type of institution, it is established that the most important factor determining the dimension of cost in septic patients is the LOS.[29] Therefore, the administration of adequate initial therapy can also be considered as a strategy that may minimize the high cost of hospitalizations involving sepsis. These findings are of paramount importance taking into account the economic burden and resource consumption that sepsis causes.

Management of septic patients involves infection control, organ support and manipulation of the inflammatory cascade. Control of infection is achieved through prompt administration of adequate antibiotics and surgical drainage when necessary. Organ support is more complex and expensive.[24] Importantly, patients receiving inadequate antimicrobial treatment presented a higher degree of organ dysfunction than those who received adequate antimicrobial therapy.[26]

Our study has several limitations. First, the sample was relatively small, and so our study may have missed other important risk factors or produced spurious findings. This drawback can be solved by matched studies that generate precise information from relatively few subjects.[23] Secondly, age was within 10 years in only 83.9% of matched patients. However, age is also included in the APACHE II score that was successfully matched in all pairs. Thirdly, in patients with septic shock, a delay of 24 h in starting adequate treatment is unacceptable because the prognosis of these patients is clearly influenced by prompt therapy.[14,33] Fourth, we did not match exposed and unexposed patients according to the type of microorganism. However, the severity of illness, source of infection and previous co-morbidities are more determinant of outcome than the pathogen involved.[2,29,34]

In summary, the strengths of our conclusions are based on our strict matching criteria that ensure that the unexposed subjects represent the same population as the exposed patients. This well-performed matching allows the estimation that inadequate antimicrobial therapy at admission to the ICU with sepsis is associated with excess mortality and LOS. From a practical point of view, clinicians should strive to know the prevailing pathogens that account for the community-acquired and nosocomial infections identified in their hospitals. With regard to the choice of antibiotic agents, initial therapy should cover a broader spectrum of possibilities in the critically ill patient. Once microbiological data are available, therapy should be tailored; a strategy that avoids the use of unnecessary antibiotic(s) and reduces costs.[35] Renewed efforts should be implemented to minimize the prescription of incorrect antimicrobials in septic patients. This may be considered not only as a life saving but also as a cost-effective strategy.

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