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Community-Acquired Bloodstream Infection in Critically Ill Adult Patients*

Impact of Shock and Inappropriate Antibiotic Therapy on Survival

Jordi Vallés, MD, PhD; Jordi Rello, MD, PhD; Ana Ochagavía, MD; José Garnacho, MD, PhD; and Miguel Angel Alcalá, MD; for the Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias†

Design: **The objectives were to characterize the prognostic factors and evaluate the impact of inappropriate empiric antibiotic treatment and systemic response on the outcome of critically ill patients with community-acquired bloodstream infection (BSI).**
Patients: **A prospective, multicenter, observational study was carried out in 339 patients admitted in 30 ICUs for BSI.**
Results: **Crude mortality was 41.5%. Septic shock was present in 184 patients (55%). The pathogens most frequently associated with septic shock or death were *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, which accounted for approximately half of the deaths. Antibiotic treatment was found to be inappropriate in 14.5% of episodes. Patients in septic shock with inappropriate treatment had a survival rate below 20%. Multivariate analysis identified a significant association between septic shock and four variables: age ≥ 60 years (odds ratio [OR], 1.96), previous corticosteroid therapy (OR, 2.58), leukopenia (OR, 2.32), and BSI secondary to intra-abdominal (OR, 2.38) and genitourinary tract (OR, 2.29) infections. The variables that independently predicted death at ICU admission were APACHE (acute physiology and chronic health evaluation) II score ≥ 15 (OR, 2.42), development of septic shock (OR, 3.22), and inappropriate empiric antibiotic treatment (OR, 4.11). This last variable was independently associated with an unknown source of sepsis (OR, 2.49). Mortality attributable to inappropriate antibiotic treatment increased with the severity of illness at ICU admission (10.7% for APACHE II score < 15 and 41.8% for APACHE II score ≥ 25, $p < 0.01$).**
Conclusions: **Inappropriate antimicrobial treatment is the most important influence on outcome in patients admitted to the ICU for community-acquired BSI, particularly in presence of septic shock or high degrees of severity. Initial broad-spectrum therapy should be prescribed to septic patients in whom the source is unknown or in those requiring vasopressors.**
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Key words: appropriate antibiotic treatment; bacteremia; community-acquired infection; outcome; septic shock

Abbreviations: APACHE = acute physiology and chronic health evaluation; BSI = bloodstream infection; CI = confidence interval; OR = odds ratio

Bloodstream infection (BSI) continues to be a severe, often life-threatening condition. Despite the emergence of new antimicrobial agents and the development of adjunctive therapies and sophisticated life-support facilities, BSI remains associated with high mortality rates. In recent years, studies of epidemiology, microbiological etiology, and prognosis of hospitalized patients with BSI have been performed all over the world,[1–10] including specific studies of community-acquired episodes.[11–13] How-

*From the Intensive Care Department (Drs. Vallés and Ochagavía), Hospital de Sabadell, Sabadell; Critical Care Department (Dr. Rello), Hospital Joan XXIII, University Rovira i Virgili, Tarragona; Intensive Care Department (Dr. Garnacho), Hospital Universitario Virgen del Rocío, Seville; and Intensive Care Department (Dr. Alcalá), Fundación Jiménez Díaz, Madrid, Spain.
†The other members of the Spanish Collaborative Group for Infections in Intensive Care Units are listed in the Appendix.

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Correspondence to: Jordi Vallés, MD, PhD, Intensive Care Department, Hospital Sabadell, Parc Taulí s/n, 08208 Sabadell, Spain

ever, we do not know of any epidemiologic studies focusing solely on community-acquired BSI on admission to the ICU.

The immediate cause of death in patients with BSI is often the severity of systemic response, but at same time a delay in appropriate antibiotic administration may lead to progressive deterioration and the development of intractable complications. The correlation between survival time, degree of inflammatory response, and delay in appropriate antibiotic therapy is not fully understood.

In order to examine these issues, we undertook a large multicenter, prospective, observational study, enrolling all patients admitted with bloodstream infections to 30 ICUs in Spain, in two periods. The characteristics and prognostic factors of the nosocomial BSIs in patients who had been previously admitted to the ICU for other conditions have been reported elsewhere.[14] In the current study, we report characteristics of those patients who acquired a BSI in the community, before hospital admission, and who required monitoring or life-support treatments in the ICU secondary to the infection. This subset of patients may present features of their own because infection develops spontaneously without any association with medical interventions, and because it occurs in an environment with lower resistance pressure.

The objectives of this study were to describe the epidemiology, etiology, sources, prognostic factors, and the impact of systemic response and inappropriate empiric antimicrobial treatment on outcome of patients admitted to the ICU with community-acquired BSI. We hypothesized that a substantial proportion of the deaths of adults during ICU hospitalization for community-acquired BSI are due to septic shock, and that outcome may be independent of antibiotic prescription. However, the outcome of patients who acquire a less severe systemic response may be influenced more by the initial antibiotic prescription. Our specific aim was to identify subpopulations most at risk of receiving inappropriate antibiotic therapy. Better understanding of the correlations between these factors may improve the outcome of patients with BSI and contribute to the design of more effective interventions able to increase survival.

Materials and Methods

Study Location and Patients

This prospective, multicenter study was carried out in 30 ICUs in Spain. All adults admitted to the 30 participating ICUs during two 9-month periods (April 1993 through December 1993, and April 1998 through December 1998) who presented at least one true-positive blood culture finding on ICU admission or within the first 48 h of ICU stay were considered eligible for the study. Further episodes were excluded from analysis. The participating institutions were either primary or tertiary care hospitals with a large number of specialized units, including bone marrow, kidney, heart, or liver transplantation units. Clinical, epidemiologic, and laboratory data of episodes considered true BSI were prospectively recorded using a standardized worksheet, and were stored in a computer database.

Definitions

An episode was considered to be community acquired when a BSI developed in a patient prior to hospital and ICU admission, or if this episode developed within the first 48 h of hospital and ICU admission. A further requirement was that the BSI should not be associated with any procedure performed after hospital or ICU admission. A period of at least 2 weeks was stipulated to define the bacteremic episode as community acquired in patients with previous hospitalizations. Cases in which more than one microorganism was isolated during a single bacteremic episode were defined as polymicrobial BSI.

Each positive blood culture finding was evaluated by at least one predetermined physician with specific expertise in ICU infections at each institution (see Appendix) to determine whether it represented true infection or contamination. This decision was based on multiple factors, including the patient's history, findings of the physical examination, body temperature, microbiological results of blood cultures, clinical course, results of cultures of specimens from other body sites, and percentage of positive blood culture findings. These criteria applied have also been used in a previous study.[4]

Also in line with previously published criteria,[1,8,14] the source of infection was classified as one of the following: lower respiratory tract, intra-abdominal, genitourinary tract, other, or unknown. Secondary BSI was defined as an episode developing subsequent to a documented infection with the same microorganism at another body site. Episodes in which there was no documented distal source were defined as primary BSI. Endocarditis was documented on the basis of clinical, echocardiographic, or pathologic evidence. The APACHE (acute physiology and chronic health evaluation) II scoring system devised by Knaus et al[15] was used to assess the severity of an acute illness. The definitions described previously by Knaus et al[15] were used to characterize the previous chronic underlying diseases. A hematologic malignancy was considered present when results of the peripheral blood examination or the bone marrow or lymph node biopsy were consistent with this diagnosis. Nonhematologic malignancies were considered to be present only when a histologic diagnosis was available.

Patients were considered to have received immunosuppressive treatment if they had been administered corticosteroid or cytotoxic therapies. Corticosteroid therapy was considered as prednisone, 20 mg/d (or an equivalent dosage) for at least 2 weeks or prednisone, 30 mg/d, for at least 1 week before the positive blood culture result. Cytotoxic therapy was defined as antineoplastic treatment for at least 4 weeks before the bacteremic episode. Organ transplant patients and patients with positive serology results for HIV were also considered immunocompromised. Patients were considered to have diabetes mellitus if they had previously required insulin therapy. Splenectomy before admission to the ICU was also considered as a risk factor for BSI development. Leukopenia was considered if the total leukocyte count was $< 4{,}000/\mu L$ and granulocytopenia if the absolute granulocyte count was $< 500/\mu L$.

The systemic response to BSI was classified as sepsis, severe sepsis, or septic shock as previously defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[16] Disseminate intravascular coagulation

was considered when a platelet count $< 100 \times 10^9$/L was associated with d-dimer > 500 ng/mL and fibrinogen < 100 mg/dL.[17] ARDS due to BSI was considered present when pulmonary failure was severe (PaO_2 < 75 mm Hg with fraction of inspired oxygen > 0.5), requiring ventilatory support with positive end-expiratory pressure of at least 5 cm H_2O, associated with the presence of diffuse bilateral infiltrates, poor pulmonary compliance, and pulmonary artery occlusion pressure < 18 mm Hg.[18] Acute renal dysfunction was defined by a serum creatinine level > 2 mg/dL or a 50% reduction in previous creatinine clearance. Acute hepatic dysfunction was defined by an increase in bilirubin level of > 3 mg/dL, prothrombin time of < 60%, and a twofold increase of transaminase level.[19] Multiorgan dysfunction was considered when a patient had two or more organ system dysfunctions for at least 24 h as a consequence of BSI.

Crude mortality included all ICU deaths in the cohort of patients with BSI on admission. Patients discharged alive from the ICU were followed up until hospital discharge.

Antibiotic Treatment

Following Gross et al,[20] we chose antimicrobial susceptibility as the basis for defining and determining the appropriateness of antibiotic use. For the purposes of this investigation, inappropriate antimicrobial treatment of a BSI was defined as the microbiological documentation of infection in the blood culture that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known. Therapy for the bacteremic episode was considered appropriate when at least one effective drug was included in the empirical antibiotic treatment within 24 h of the identification of bacteremia. In practice, this involves targeting the therapy to the desired pathogens, and using the appropriate drug, dose, and duration. This definition is in agreement with recent statements issued by the Centers for Disease Control and Prevention.[21]

On the basis of the assessment of inappropriate antibiotic therapy, as well as the presence of septic shock, each episode was classified into one of four categories: category A, patients in septic shock receiving inappropriate antibiotic therapy; category B, patients in septic shock receiving appropriate antibiotic therapy from the beginning; category C, patients without septic shock but receiving inappropriate antibiotic therapy; and category D, patients without septic shock receiving appropriate initial antibiotic therapy.

Statistical Analysis

Descriptive analysis was performed. Continuous variables were expressed as means ± SD. Associations of categorical variables with mortality were assessed with the χ^2 test or the Fisher test. The Student *t* test was used for continuous variables.[22]

To control for potential confounding factors, a multivariate logistic regression analysis was performed evaluating the possible covariates of source of infection, microorganisms involved, delay in antibiotic therapy, and previous comorbidities on prediction of septic shock. In the multivariate analysis of patients' prognosis, variables that were not available within the 24 h of ICU admission (*eg*, blood culture findings and noninfectious complications) and that did not require early intervention were not included in the model. In the multivariate analysis, variables were entered in the logistic regression model if at least 10 of the patients exhibited the characteristic and if the variables were significantly associated with mortality at a p value < 0.1 in the univariate analysis. Logistic regression was used for the estimation of coefficients and their SEs. The odds ratios [ORs] and 95% confidence intervals [CIs] were calculated according to standard methods after adjusting for confounding factors and are expressed as an approximation of relative risk.[23] Kaplan-Meier survival curves were estimated and compared by means of the log-rank test. Statistical significance was defined as $p < 0.05$.

Results

During the two study periods, a total of 33,211 patients were admitted to the 30 participating ICUs. Three hundred thirty-nine patients with a mean ± SD APACHE II score of 19 ± 7 and a mean age of 58 ± 18 years presented true BSI on ICU admission, accounting for a BSI rate of 10.2 episodes per 1,000 ICU admissions (9.2 episodes in 1993 and 11.1 episodes in 1998 per 1,000 ICU admissions). One hundred forty-one of these 339 patients died in the ICU, representing an ICU crude mortality of 41.6% (45.6% in 1993 and 38.6% in 1998, $p > 0.20$). Five other patients died after ICU discharge, increasing the hospital mortality to 43.1%.

A summary of demographics, severity, and comorbidities is shown in Table 1. Cardiovascular diseases, diabetes, COPD, and chronic hepatic failure were present in > 10% of patients. In addition, 15% of patients had previously received with corticosteroids or cytotoxic therapies. No significant differences were demonstrated between 1993 and 1998, excepting the presence of more patients with HIV infection patients in 1993 than in 1998 (12 patients vs 5 patients, $p < 0.05$).

The most common sources of BSI were lower respiratory tract infections (20.6%), intra-abdominal infections (20.1%), and genitourinary tract infections (19.8%) [Table 2]. The rate of primary BSI was 29.2%. Gram-negative bacilli were isolated in 42.1% of blood cultures. The pathogen most commonly found was *Escherichia coli,* which accounted for 60.1% of Gram-negative episodes. In 43.6% of the episodes, Gram-positive microorganisms were responsible for BSI, and two thirds of these cases were due to *Streptococcus pneumoniae* or *Staphylococcus aureus*. A detailed distribution of isolates is shown in Table 3. Polymicrobial episodes were found in 9.4% of cases. *S aureus* was isolated more frequently in 1993 than in 1998 (27 cases vs 19 cases), as was *Acinetobacter baumannii* (4 cases vs 0 cases) [$p < 0.05$].

The systemic response to BSI was classified as sepsis in 86 episodes (25%), severe sepsis in 69 cases (20%), and septic shock in the remaining 184 cases (55%). BSI episodes complicated by septic shock showed a significantly higher mortality (55.4%) in the ICU than episodes presenting as severe sepsis (27.3%) or sepsis (23.2%) [$p < 0.001$]. Acute renal failure (49.5%) and disseminate intravascular coagulation (37.7%) were the complications most fre-

Table 1—*Prognosis and Incidence of Septic Shock According to Characteristics and Comorbidities of Patients With Community-Acquired BSI*

Variables	Patients, No. (%)	Septic Shock, %	Death, %
Age, yr			
< 60	152 (44.8)	43.4*	41.7
≥ 60	187 (55.2)	63.1	41.7
Sex			
Male	194 (57.2)	52.1	42
Female	145 (42.8)	57.2	41.4
APACHE II score			
< 15	93 (27.4)	23.7*	20.4*
15–24	160 (47.2)	58.8	42.5
≥ 25	86 (25.4)	79.1	63.5
Comorbidities			
Cardiovascular	59 (17.4)	54.2	44.1
Diabetes mellitus	52 (15.3)	57.7	45.1
COPD	42 (12.4)	57.1	35.7
Chronic hepatic failure	43 (12.7)	48.8	42.9
Hematologic malignancies	13 (3.8)	69.2	61.5
Nonhematologic malignancies	20 (5.9)		
Corticosteroid therapy	30 (8.8)	70.0	56.7
Cytotoxic therapy	22 (6.5)	68.2	59.1
HIV infection	17 (5.0)	23.5†	52.9
Solid-organ transplantation	6 (1.8)	16.7	33.3
Splenectomy	5 (1.5)	60.0	40.0
Laboratory data			
Leukopenia, < 4,000/μL	66 (19.4)	66.7†	53.0†
Comorbidities, No.			
0	131 (38.6)	53.4	35.9
1	119 (35.1)	56.3	41.2
≥ 2	89 (26.3)	52.8	51.1
Inappropriate empiric treatment			
Yes	49 (14.5)	59.2	69.4*
No	290 (85.5)	53.4	37.0

*$p < 0.05$ comparing mortality or septic shock between different groups.
†$p < 0.05$ comparing mortality or septic shock with and without the variable analyzed.

quently associated with BSI, and 33.9% of cases presented multiorgan dysfunction.

In patients with septic shock, the most frequently identified pathogens were *E coli* (29.8%), *S aureus* (14.1%), *S pneumoniae* (10.8%), anaerobic flora (4.9%), and *Klebsiella pneumoniae* (4.3%). Gram-negative bacilli and anaerobic pathogens were associated with a significantly higher incidence of septic shock than Gram-positive microorganisms in the univariate analysis ($p = 0.001$). Polymicrobial BSIs also presented a significantly higher incidence of septic shock ($p = 0.01$).

The overall incidence of inappropriate antibiotic treatment was 14.5%, and its effect on survival increased in parallel to the increase in the severity at ICU admission (Table 4), but it did not vary according to the severity of systemic response. Patients with septic shock showed an incidence of inappropriate antibiotic therapy of 15.8%, whereas the incidence in the remaining patients was 12.9% ($p > 0.20$). In both groups of patients, the survival rate was significantly lower when the treatment was inappropriate. The correlations between survival time, systemic response to BSI, and inappropriate antibiotic treatment are shown as Kaplan-Meier curves in Figures 1, 2 ($p < 0.001$ log-rank test).

In the 70 patients with a stay in the ICU ≤ 48 h, septic shock was present in 53 patients (75.7%), and the remaining 17 patients presented severe sepsis or sepsis. The incidence of inappropriate antibiotic treatment did not differ notably ($p > 0.20$) in the two groups (28.3% in septic shock subjects vs 29.4% in the remaining patients). However, the mortality rate was significantly higher in the patients with septic shock (86.8%) than in the group without septic shock (23.5%) [$p < 0.001$].

The incidence of different systemic response and mortality according to source of BSI is shown in Table 2. Variables significantly associated with a higher incidence of septic shock at ICU admission in the univariate analysis are shown in Tables 1, 2. The lowest incidence of septic shock was found in patients with HIV infection, and the highest in urinary and intra-abdominal infections. The mortality of patients with septic shock did not differ statistically according to the sources of BSI. A logistic regression model identified five variables independently associated with the development of septic shock: age ≥ 60 years (OR, 1.9; 95% CI, 1.23 to 3.15), leukopenia (OR, 2.32; 95% CI, 1.28 to 4.21), BSI secondary to urinary tract infection (OR, 2.29; 95% CI, 1.25 to 4.18), BSI secondary to intra-abdominal infection (OR, 2.38; 95% CI, 1.28 to 4.42), and previous corticosteroid therapy (OR, 2.5; 95% CI, 1.09 to 6.07). The results did not vary significantly when the appropriateness of empiric antibiotic treatment was introduced in the model as a dichotomous variable.

Variables significantly associated with death in the univariate analysis are shown in Tables 1, 2. In the multivariate model, we include all significant variables in the univariate analysis identified at ICU admission plus infection-related variables such as the type of microorganisms (Gram-negative, Gram-positive, anaerobes, or fungi), source of BSI (unknown origin, respiratory tract, genitourinary tract, intra-abdominal, or others), and systemic response. The variables that independently predicted a poor prognosis were a delayed appropriate antibiotic treatment (OR, 4.11; 95% CI, 2.03 to 8.32), presence of septic shock (OR, 3.22; 95% CI, 1.69 to 6.13), and APACHE II score ≥ 15 at ICU admission (OR, 2.42; 95% CI, 1.30 to 4.51). As antibiotic therapy would be expected to have little influence on early deaths, we reanalyzed mortality after excluding all deaths that

Table 2—*Distribution of Systemic Response, Antibiotic Choice, and Outcome by Sources in 339 Episodes of Community-Acquired BSI in Adult Critically Ill Patients**

Source	Overall	Systemic Response			Death	Inappropriate Treatment
		Sepsis	Severe Sepsis	Septic Shock		
Secondary BSI						
Lower respiratory tract	70 (20.6)	19 (27.1)	17 (24.3)	34 (48.6)	31 (44.3)	6 (8.6)
Intra-abdominal	68 (20.1)	12 (17.6)†	9 (13.2)	47 (69.1)‡	30 (44.1)	9 (13.2)
Genitourinary tract	67 (19.8)	6 (9.0)†	17 (25.4)	44 (65.7)‡	23 (34.3)	5 (7.5)
Other§	35 (10.3)	13 (37.1)	4 (11.4)	18 (51.4)	13 (37.1)	8 (22.9)
Primary BSI‖	99 (29.2)	36 (36.4)	22 (22.2)	41 (41.4)	44 (44.9)	21 (21.2)
Overall	339 (100)	86 (25)	69 (20)	184 (55)	141 (41.5)	49 (14.5)

*Data are presented as No. (%).
†Genitourinary and intra-abdominal infections showed a lower incidence of sepsis than other sources ($p < 0.01$).
‡Genitourinary and intra-abdominal infections showed a higher incidence of septic shock than other sources ($p < 0.01$).
§Including sources such as soft tissues (n = 114), meningitis (n = 5), bone and joint (n = 5), skin (n = 4), upper respiratory tract (n = 4), and indwelling catheters (n = 3).
‖Including 85 episodes of unknown origin and 14 episodes of endocarditis.

occurred within 48 h of presentation (n = 50). Multivariate analysis again confirmed that inappropriate initial antibiotic choice was an independent predictor of worse outcome (OR, 3.23; 95% CI, 1.52 to 6.83). The results did not vary significantly when the period (1993 vs 1998) was introduced in the model.

Among variables independently associated with a poor prognosis, inadequate antimicrobial treatment

Table 3—*Systemic Response, Outcome, and Appropriateness of Empiric Antibiotic Treatment According to Microorganisms Causing Community-Acquired BSI**

Microorganism	Overall	Immunocompromised Patients**	Septic Shock	Inappropriate Treatment	Death
Monomicrobial episodes (n = 307)					
S pneumoniae	55	18 (32.7)	20 (36.4)‡	4 (7.3)	18 (33.3)
S aureus	46††	15 (32.6)	26 (56.5)	15 (32.6)	27 (58.7)‖
CNS	8	3 (37.5)	1 (12.5)‡	2 (25)	3 (37.5)
Streptococcus pyogenes	6	2 (33.3)	3 (50)	1 (16.7)	1 (16.7)
Streptococcus agalactiae	5	1 (20)	2 (40)	—	2 (40)
Enterococcus sp	10	2 (20)	7 (70)	1 (10)	5 (50)
Listeria monocytogenes	5	3 (60)	1 (20)	1 (20)	2 (40)
Other Gram positive¶	13	1 (7.7)	2 (15.4)‡	1 (7.7)	3 (23.1)
Global Gram positive	148 (43.6)	45 (30.4)†	62 (41.9)†	25 (16.9)	61 (41.5)
E coli	86	12 (14)†	55 (64)‡	8 (9.3)	34 (39.5)
K pneumoniae	11	2 (18.2)	8 (72.7)	1 (9.1)	6 (54.5)
Neisseria meningitidis	13	1 (7.7)	7 (53.8)		2 (15.4)
Pseudomonas aeruginosa	8	5 (62.5)†	5 (62.5)	1 (12.5)	3 (37.5)
A baumannii	4	1 (25)	2 (50)	1 (25)	3 (75)
Haemophilus influenzae	4	2 (50)	2 (50)		2 (50)
Other Gram negative#	17	2 (11.7)	9 (52.9)	3 (17.6)	5 (29.4)
Global Gram negative	143 (42.1)	25 (17.5)†	88 (61.5)‡	14 (9.8)§	55 (38.5)
Anaerobic	14 (4.1)	2 (14.3)	9 (64.3)	3 (21.4)	6 (42.9)
Fungi	2 (0.6)	1 (50)	1 (50)	2 (100)§	2 (100)
Polymicrobial episodes (n = 32)	32 (9.4)	6 (18.8)	24 (75)‡	5 (15.6)	17 (53.1)

*Data are presented as No. (%).
†$p < 0.05$ comparing immunosuppression vs nonimmunosuppression.
‡$p < 0.05$ comparing septic shock vs absence of septic shock.
§$p < 0.05$ comparing inappropriate treatment vs initial appropriate therapy.
‖$p < 0.05$ comparing survival vs death.
¶*Streptococcus viridans* group (n = 6), Streptococcus spp (n = 3), Corynebacterium spp (n = 4).
#Proteus spp (n = 3), Citrobacter spp (n = 3), *Enterobacter aerogenes* (n = 3), *Salmonella enteritidis* (n = 3), *Aeromonas hydrophila* (n = 3), *Brucella melitensis* (n = 1), *Moraxella catarrhalis* (n = 1).
**Patients with malignancies, corticosteroid and cytotoxic therapy, transplantation, or splenectomy.
††Ten cases were methicillin-resistant *S aureus*.

Table 4—*Correlation Between Survival Time and Empiric Appropriate Treatment According to Severity of Illness at ICU Admission (APACHE II Score)

APACHE II Score	Appropriate Treatment		Inappropriate Treatment		Attributable Mortality, %	p Value
	Patients, No.	Survival Rate, %	Patients, No.	Survival Rate, %		
0–14 (n = 93)	84	80.7	9	70.0	10.7	NS
15–24 (n = 162)	136	63.6	26	28.6	35	0.001
≥ 25 (n = 84)	70	41.8	14	0	41.8	0.004
Overall (n = 339)	290	63	49	30.6	32.4	0.001

*NS = not significant.

was the most important of those that were modifiable. A new multiple logistic regression analysis using inappropriate antibiotic choice as dependent variable was performed with variables available at ICU admission. Unknown origin of BSI was the only variable independently associated with the administration of inadequate antimicrobial treatment (OR, 2.49; 95% CI, 1.27 to 4.80). The most frequently isolated pathogens in episodes of unknown origin were as follows: *S aureus* (25.2%), *S pneumoniae* (17.1%), *Neisseria meningitidis* (13.1%), *E coli* (6%), and miscellaneous (33.3%).

Discussion

This study is the first to correlate timing of ICU death with presence of septic shock and inappropriate antibiotic therapy in a cohort of adults hospitalized in the ICU for community-acquired BSI. We found that inadequate antibiotic therapy is the most important determinant of survival. Initial appropriate empiric antibiotic therapy is critical, particularly in patients with vasopressors or unknown source of sepsis, who may die immediately if adequate antibiotic treatment is not administered. So improving survival is highly dependent on correct initial antibiotic prescription. Our results suggest that initial broad-spectrum therapy followed by de-escalating is the optimal approach in bacteremic patients. These findings have a direct bearing on the design and evaluation of new trials for treatment of bacteremic patients in ICU, and also stress the need to improve antibiotic prescription in patients with BSI.

We found the main sources of community-acquired BSI to be respiratory tract, intra-abdominal, and genitourinary tract infections. These three

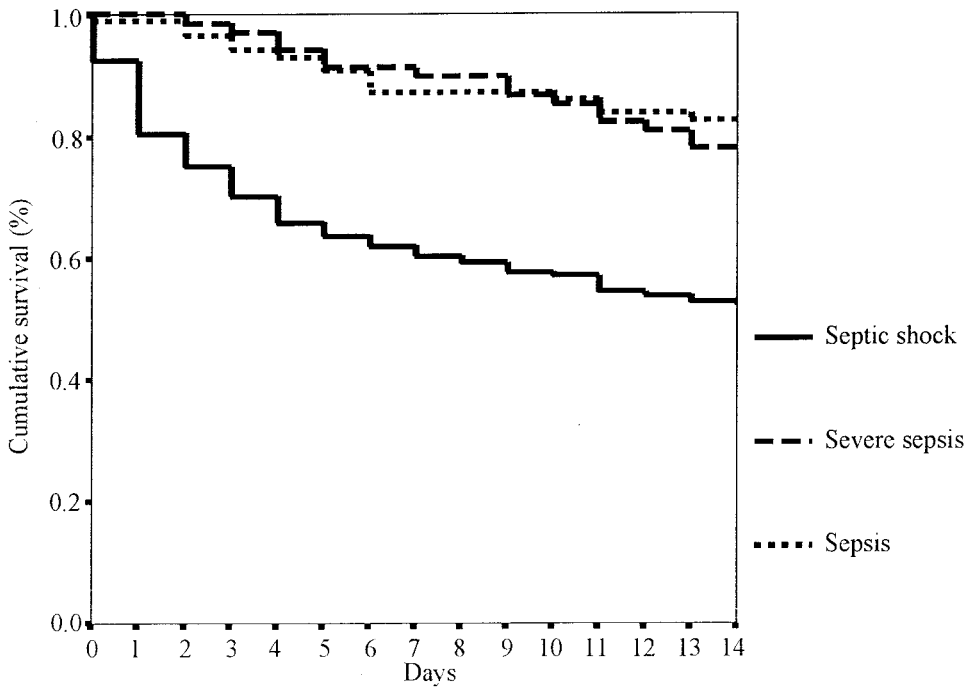

Figure 1. Proportion of survivors according to systemic response (log-rank test, p = 0.01).

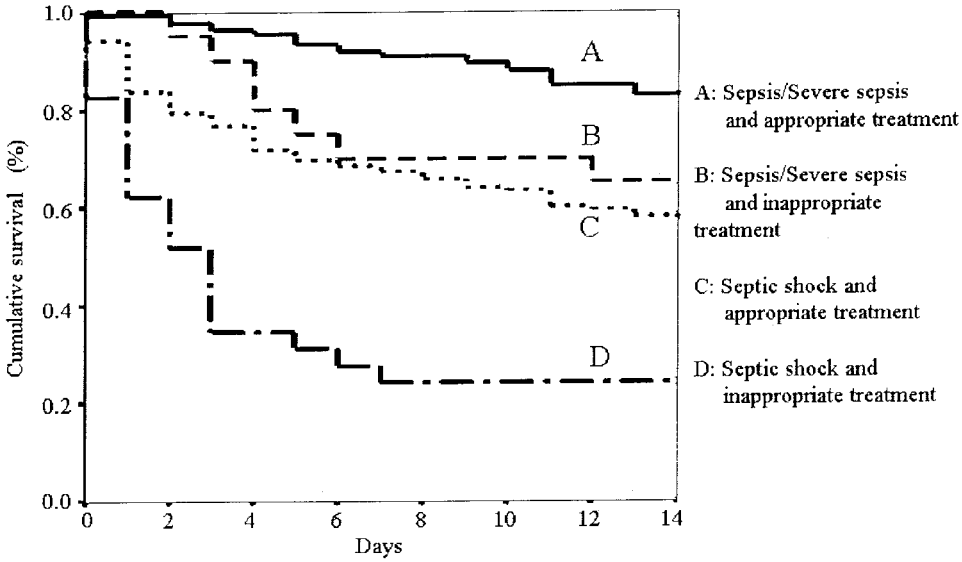

FIGURE 2. Survival rate according to the presence of shock and empiric antibiotic treatment (log-rank test, $p < 0.001$).

sources represented almost 60% of the episodes reported. In agreement with other studies,[4,24,25] these findings show that bacteremic patients coming from the community and admitted to the ICU present largely the same sources as patients admitted to general wards,[11,24] and that nonspecific origins of BSI are more likely to require ICU admission.

In this first prospective long-term study of community-acquired BSI in the critically ill patient, crude overall mortality was 41.5%. In previous studies, mortality rates from BSI have varied from 20 to 42%,[5,24,26,27] but those studies cannot be compared with our findings because they analyzed patients with community and hospital-acquired BSIs and admitted to general wards and the ICU. This high mortality found in our study is related to the high frequency of severe systemic response present in the studied population. In fact, when we compared our results with studies[24,25] that analyzed the bacteremic episodes in the ICU separately—that is, community and hospital acquired—the mortality rates were > 50%.

In the present study, three variables were independently associated with an increased risk of death: severity score at admission in the ICU (APACHE II score ≥ 15), development of septic shock, and adequacy of empiric antibiotic treatment. Although the source of bloodstream infection did not show significant differences in the univariate analysis of mortality, we included this variable as well as etiologic agents in the multivariate analysis, because we hypothesized that variables directly related to infection, such as sources and microorganisms, might influence the outcome. The multivariate model did not select either origin of BSI or microorganism as variables associated with a poor prognosis.

Following the recommendations of the American College of Chest Physicians and the Society of Critical Care Medicine,[16] the systemic response to infection was also evaluated. Seventy-five percent of our patients presented severe sepsis or septic shock at admission in the ICU. So this study, focusing exclusively on ICU patients, shows a higher frequency of severe sepsis and septic shock during BSI than studies including both ward and ICU patients. To the best of our knowledge, only one prior report in ICU patients has used the same definitions to classify the systemic response secondary to BSI.[24] In that study, the frequency of severe sepsis during BSI differed markedly between wards and ICUs (17% vs 65%, $p < 0.001$).

The present study also focused on the influence of host factors and infection-related variables over the incidence of septic shock. Among the infection-related variables, only the source of infection was predictive of septic shock in this selected population of bacteremic patients. Intra-abdominal infection was associated with the highest incidence of septic shock and with the highest mortality rate. Most studies have found[1,5,8] that the BSI secondary to intra-abdominal infection are associated with a higher morbidity and mortality due to the difficulty of treating peritoneal infections and due to the higher incidence of polymicrobial BSI. Indeed, in our study the incidence of septic shock was also higher in the episodes of polymicrobial BSI, most of which originated in the abdomen (75% vs 52.1%,

$p = 0.03$). Another interesting finding in our study is that the genitourinary tract is the second source of septic shock in this selected population of bacteremic patients, but it was associated with the lowest mortality rate. This is probably because the diagnosis of urinary tract infection presents no difficulty and treatment of urinary tract obstruction is also straightforward. The result coincides with prior observations in series evaluating BSI and septic shock.[5,20,24] Additionally, Wong et al[28] reported that in the group with the most severe condition (APACHE II score > 15 at admission), the crude mortality of patients with urinary sepsis and shock was 11.5% compared with 36.2% when the septic shock derived from other sources.

Inadequate antimicrobial treatment was administered in 14.5% of episodes, a rate similar to a recent study reported by Ibrahim et al.[29] In the univariate analysis, *S aureus* was associated with a higher incidence of inappropriate treatment and mortality. These findings were associated with a higher incidence of unknown origin of bacteremia and with the presence of methicillin resistance in a 22% of cases.

In the patients with septic shock, the appropriateness of empiric antimicrobial treatment was no different from the remaining patients, but the prognosis was extremely poor if the empiric treatment was inappropriate. In a prior study, Leibovici et al[30] also found that the appropriateness of antibiotic treatment was not considered as a risk factor for the development of septic shock in bacteremic patients, but they found that the fatality rate in patients with vasopressors receiving appropriate empiric treatment was lower than in patients with inappropriate treatment (74.9% vs 84.7%, $p = 0.01$). Our findings confirm these results in this specific group of ICU patients, and suggests that although the severity of systemic response may be responsible for most early deaths, appropriate empiric antibiotic treatment also increases survival rates after septic shock has occurred. Indeed, in our group of patients with septic shock, the survival rate in the first 48 h with adequate empiric antimicrobial treatment was 79.4% vs 51.7% when the therapy was inappropriate. The appropriateness of antibiotic therapy in the remaining patients with a less severe systemic response and excluding early deaths that could be caused by shock also had a significant influence on the prognosis of patients with BSI. Our findings show that the influence of appropriate antibiotic therapy on the survival of patients with BSI is greater the more severe the patient's condition (Table 4). Additionally, Reyes et al[31] also observed that patients with septic shock with obvious clinical source of infection and positive culture findings showed a lower crude mortality than patients with septic shock and without obvious source of infection or negative culture findings (66% vs 85%, $p < 0.05$), attributing this in part to the impossibility of adjusting the antibiotic therapy when microbiological data become available. These results are in agreement with our findings that show that unknown origin of BSI is associated with a higher incidence of inappropriate antibiotic therapy.

Some limitations of our investigation should be noted. First, this was an observational study, and the admission criteria in each ICU participating in the study, as well as the criteria to perform blood cultures, were not standardized. This point may have influenced the final incidence of BSI. In addition, the incidence may be different in other countries where more ICU beds per capita, and where patients with lower degrees of severity of illness may be admitted to the ICU. Second, interpretation of the mortality may be biased by the treatment applied in each hospital. Indeed, a recent epidemiologic study of the sepsis syndrome has demonstrated institutional differences related with the patient population.[32] Third, no information was available on some important data prior to ICU admission, such as previous antimicrobials administered in the community, time between onset of symptoms and clinical presentation, and the use of specific antibiotics in each ICU. This meant that we could not ascertain the effect of specific antibiotics on outcome. Some definitions, such as ARDS,[33] have been updated since the study was started. We are unable to evaluate the impact of these new definitions on our findings. Finally, the seasonal variation of community pathogens was not considered in the design.

The strengths of our study include the use of a national database that contained information over two periods separated by a 5-year interval to examine demographics, comorbidities, trends in bacterial pathogens, and emerging new therapies. Our sample size is large enough to ensure that important but infrequent variables were not missed. We identified cases of BSI based on diagnoses and approaches applied at participating institutions, reflecting a spectrum of diagnostic and therapeutic approaches that were not biased by the specific characteristics of a single institution. In addition, microbiological data were available prospectively and appeared consistent with those reported in the literature. Finally, this is the first study to investigate the outcome of community-acquired BSI in critically ill adults, focusing on correlating the time of death with the major determinants of outcome.

In summary, the identification of groups of patients at high risk for septic shock may be useful to help select patients for clinical trials or adjunctive treatments. Our results confirm that the severity of physiologic dysfunction at ICU admission, systemic response, and the appropriateness of antibiotic treat-

ment markedly influence the prognosis of patients admitted for community-acquired BSI. The link between short time to treatment and improved survival is critical. Our findings suggest that optimizing antibiotic treatment is the key step in the initial approach to critically ill adults admitted to the ICU with BSI from the community. Because of the improved outcome in patients treated early, broad-spectrum therapy is now recommended, followed by de-escalation.

Appendix

The other members of the Spanish Collaborative Group for Infections in the Intensive Care Units are as follows: C. Ortiz Leyba and J. Jiménez (Hospital Universitario Virgen del Rocío, Sevilla); E. Quintana, E. Ormaechea, C. Fernández, and J. Bellapart (Hospital Santa Creu y Sant Pau, Barcelona); A. Mateu, H. Torrado, L. Corral, and D. Rodríguez (Hospital de Bellvitge, Hospitalet de Llobregat); E. Arnau, A. Planes, M. Palomar, and J. Serra (Hospital del Valle Hebrón, Barcelona); J.M. Flores Cordero, R. Martínez, I. Herrera, and A. Vázquez (Unidad de Traumatología, Hospital Universitario Virgen del Rocío, Sevilla); J. Gudín, J. Cuñat, and A. Navarro (Hospital La Fé, Valencia); C. León, J.M. Castillo, M. Márquez, and A. Hierro (Hospital Universitario de Valme, Sevilla); E. Díaz (Hospital Parc Taulí, Sabadell); V. González and G. Marti (Hospital Miguel Servet, Zaragoza); L.A. Rocha, P. Rascado, E. Alemparte, and M.J. Castro (Hospital Juan Canalejo, La Coruña); A. Gamo (Fundación Jiménez Díaz, Madrid); E. Mesalles and P. Ricart (Hospital Germans Trías i Pujol, Badalona); M. Sánchez (Hospital Insular, Las Palmas); J. Insausti, J.P. Tirapu, and J. Barado (Hospital de Navarra, Pamplona); A. Mas and J. Gilabert (Centre Hospitalari de Manresa, Barcelona); J.A. Melgarejo, J. Martínez, and F. Martínez-Lozano (Hospital Sta. María del Rosell, Cartagena); F. Alvárez and I. Catalán (Hospital del Mar, Barcelona); A. Torres and M.J. Rodríguez (Hospital Clinic i Provincial, Barcelona); F. Felices, C. Palazón, and J.L. Espinosa (Hospital General Universitario, Murcia); R. Jordá, M. Rivera, C. Forteza, and G. Soriano (Hospital Son Dureta, Palma de Mallorca); A. Viñuales, L. García, M. Rodríguez, and V. Borillo (Hospital Lluis Alcanys, Xativa); E. Maraví, B. Salvador, and A. Lander (Hospital Virgen del Camino, Pamplona); A. Chánovas and I. Luna (Hospital Virgen de la Cinta, Tortosa); A. Varela and F. Mosquera (Policlínico Vigo, Vigo); M.A. Suarez, J.I. Corchero, and B. Zalba (Hospital Clínico Universitario, Zaragoza); P. Olaechea, R. de Celis, and A. de la Serna (Hospital de Galdakao, Vizcaya); M.J. López, S. Macías, and J.J. Cortina (Hospital General de Segovia, Segovia); R. Solans and R. García-Penche (Quinta Salud La Alianza, Barcelona); F. Castillo, R. Marco, A.M. Puppo, J.A. González, and J.M. López (Hospital Duque del Infantado, Sevilla); A. Sanz, M. Martínez, M. Arias, and A. Aranda (Hospital de Motril, Motril, Granada).

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Community-Acquired Bloodstream Infection in Critically Ill Adult Patients*: Impact of Shock and Inappropriate Antibiotic Therapy on Survival

Jordi Vallés, Jordi Rello, Ana Ochagavía, José Garnacho and Miguel Angel Alcalá

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