Epidemiology and Prognostic Determinants of Bloodstream Infections in Surgical Intensive Care

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Hypothesis: A set of clinical variables available at the bedside can be used to predict outcome in critically ill patients with bloodstream infection (BSI).

Design: A 3-year retrospective cohort study.

Setting: A surgical intensive care unit in Switzerland.

Patients: All patients with BSI were potentially eligible.

Main Outcome Measures: Clinical variables, organ dysfunctions, and outcome.

Results: Among 4530 admissions to the surgical intensive care unit, 224 clinically significant episodes of BSI were recorded (incidence, 4.9%), with a 28-day fatality of 36%. A total of 110 patients had primary bacteremia, of which 39 (35%) were catheter related. Although gram-positive organisms were the most frequently isolated pathogens (58% [159/275]), they were associated with lower case-fatality (30%) than BSI due to gram-negative bacteria (44%). Organ dysfunctions associated with the highest risk of death were neurologic dysfunction (hazard ratio [HR], 6.9; 95% confidence interval [CI], 3.3-14.5), hepatic dysfunction (HR, 3.9; 95% CI, 2.1-7.4), and disseminated intravascular coagulation (HR, 3.0; 95% CI, 1.5-6.1). By multivariate analysis, 2 independent predictors of mortality were the APACHE II (Acute Physiology and Chronic Health Evaluation II) score at onset of BSI (HR per 1-point increase, 1.08; 95% CI, 1.04-1.12) and the number of evolving organ dysfunctions (HR, 1.4; 95% CI, 1.2-1.7). Appropriate antimicrobial therapy was associated with improved outcome (HR, 0.4; 95% CI, 0.2-0.6).

Conclusions: Bloodstream infection in critically ill patients is a common and frequently fatal condition. Its outcome can be predicted by the severity of illness at onset of BSI and the number of organ dysfunctions evolving thereafter. Appropriate antimicrobial therapy is an important determinant for survival.

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Bloodstream infections (BSIs) associated with severe sepsis or septic shock are frequently encountered conditions and represent a major cause of death in patients admitted to intensive care units (ICUs).1,2 Despite promising advances in the early diagnosis and care of critically ill patients with severe sepsis,3,4 case-fatality from bacteremic sepsis causing organ dysfunction is still high, ranging from 25% to 50%.5,6

Most data about either the incidence of BSI in critical care or prognostic factors associated with this life-threatening complication have been derived from international clinical trials designed to test adjuvant therapies for severe sepsis2 or from multicenter cohort studies performed in the United States, France, and Spain.5,6,10 For patient populations in other health care systems and for patients not enrolled in clinical trials, estimates of the incidence and clinical implications of BSI in critically ill patients remain limited. Differences in patient characteristics, hospital types, and treatment approaches further confound comparisons across studies and countries.

See Invited Critique at end of article

In the present observational 3-year cohort study, we undertook an analysis of critically ill patients with BSI hospitalized in a large surgical ICU (SICU) in Switzerland. We sought to determine the incidence, microbiologic spectrum, and case-fatality rate of BSI and risk factors associated with death. In particular, we assessed the effect of antimicrobial therapy on outcome.

METHODS

The University of Geneva Hospitals is a 2300-bed primary and tertiary care medical center that admits approximately 44,000 patients annually. The SICU is a 22-bed referral unit that admits more than 1500 patients per year for

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close observation and treatment after multiple trauma and major surgery for a mean of 4.5 days. The microbiology laboratory at the University of Geneva Hospitals analyzes, on average, 2000 blood cultures per year, of which approximately 2000 yield bacteria or fungi.11

The source population consisted of all patients admitted to the SICU between June 1, 1994, and May 31, 1997. Patients were included if they had microbiologically confirmed BSI (bacteremia or fungemia). We reviewed the medical records of all patients with positive blood culture results and established the diagnosis of BSI according to predefined criteria.12

Only episodes thought to represent clinically significant BSI were included in the final analysis. Coagulase-negative staphylococci and other common skin flora (eg, Bacillus and Corynebacterium species) were considered contaminants and were removed from the analysis if all of the following criteria were met: (1) the organism was isolated from only a single blood culture, (2) the type of underlying infection was not likely to be caused by the microorganism, and (3) the positive blood culture result was followed by the absence of clinical signs of untreated sepsis in the subsequent 48 hours.13 Evaluation of physicians’ notes, microbiologic and clinical data, and, when available, postmortem examination reports assisted in making the diagnosis in cases of difficult ascertainment.

Microbiologic tests were performed and antimicrobial therapy was prescribed by physicians according to the usual practice in the SICU, which includes at least 2 sets of blood cultures in cases of suspected BSI.

DATA COLLECTION AND DEFINITIONS

On a standardized form, we recorded patient demographics, principal diagnosis, vital signs, respiratory variables, routine blood test results, and microbiologic culture results after onset of BSI. The primary diagnosis was defined according to the International Classification of Diseases, 10th Revision, system. Patients were classified into 3 categories depending on the severity of underlying illness according to the classification proposed by McCabe and Jackson.14 Comorbidities were recorded according to the score proposed by Charlson et al.15 The severity of the patient’s condition was measured according to the Simplified Acute Physiology Score II system16 and the APACHE II (Acute Physiology and Chronic Health Evaluation II) score.17 Survival or death was assessed during follow-up of up to 28 days.

Organ dysfunctions were recorded according to the type and number of days of organ dysfunction, based on preestablished definitions.2,18,19 In brief, organ failures assessed at baseline and during the 28 days after BSI were characterized as follows: (1) renal—serum creatinine level greater than 3.0 mg/dL (≥265 µmol/L) or, in the case of preexisting renal dysfunction, a doubling of previous serum creatinine values; (2) hepatic—acute elevation of total bilirubin concentration to greater than 3.0 mg/dL (≥51 µmol/L) and elevation of the alanine aminotransferase or aspartate aminotransferase level to 3 times the upper limit of normal in the absence of primary liver disease; (3) hematologic—disseminated intravascular coagulation defined as prothrombin time and partial thromboplastin time more than 2 times the normal range, platelet count of less than 100 × 10^9/L or less than half of a previous count, and fibrin degradation products greater than 10 µg/mL; (4) central nervous system—Glasgow Coma Scale score of less than 10 or a decrease in the score of at least 3 if primary central nervous system injury is present; (5) acute lung injury—acute-onset respiratory failure with bilateral diffuse chest infiltrates, a PaO2/fraction of inspired oxygen ratio of 200 mm Hg or less, a left filling pressure of 18 mm Hg or less, and presence of a known risk factor for acute lung injury; (6) acute respiratory distress syndrome—acute-onset respiratory failure with bilateral dif-
lyzed. After thorough review of all microbiologic and clinical data, 118 patient episodes (34%) were excluded as probable contaminants: 105 were positive for coagulase-negative staphylococci in only a single bottle and 8 blood cultures were positive for *Propionibacterium* species, 2 for *Micrococcus* species, 2 for *Corynebacterium* species, and 1 for *Bacillus* species. Thus, 224 patients had at least 1 episode of clinically relevant BSI (incidence, 4.9 per 100 admissions) and entered the analysis.

Characteristics of the 224 bacteremic patients are given in Table 1. We recorded 236 surgical interventions among 177 bacteremic patients. Gastrointestinal surgery (89 interventions in 58 patients), cardiovascular surgery (72 interventions in 59 patients), and neurosurgery (27 interventions in 24 patients) were the most frequent procedures.

### MICROBIOLOGIC FINDINGS AND INFECTION SITES

One hundred eighty-four patients had monomicrobial and 40 had polymicrobial BSIs; 46 patients had 2 or more episodes of BSI. Gram-positive bacteria represented 58% (159/275) of all microorganisms identified: gram-negative bacteria, 34% (94/275); anaerobes, 4% (10/275); and fungi, 4% (n=12/275). The leading pathogens were coagulase-negative staphylococci (24%, n=66), *Staphylococcus aureus* (15%, n=42), *Escherichia coli* (10%, n=27), and *Pseudomonas aeruginosa* (6%, n=17). Five cases of bacteremia from methicillin-resistant *S aureus* occurred during the study.

A total of 110 patients had primary bacteremia; 39 (35%) were catheter related. The most common source of secondary bacteremia was the respiratory (26%) or the abdominal (16%) tract.

### TREATMENT

Of 217 patients who stayed in the ICU for more than 24 hours, 161 (74%) received appropriate antimicrobial therapy and 56 (26%) received no appropriate antimicrobial therapy within 24 hours of onset of BSI. Among these patients, 34 (16%) received no antibiotic treat-

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Table 1. Demographic Features and Characteristics of 224 Critically Ill Patients With BSI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 148)</th>
<th>Nonsurvivors (n = 76)</th>
<th>Total (n = 224)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>110 (74)</td>
<td>58 (76)</td>
<td>168 (75)</td>
<td>.74</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>56 (14-88)</td>
<td>65 (19-89)</td>
<td>61 (14-89)</td>
<td>.908</td>
</tr>
<tr>
<td>Type of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>55 (37)</td>
<td>32 (42)</td>
<td>87 (39)</td>
<td>.47</td>
</tr>
<tr>
<td>Surgical</td>
<td>118 (80)</td>
<td>59 (78)</td>
<td>177 (79)</td>
<td>.72</td>
</tr>
<tr>
<td>Length of SICU stay, median (range), d</td>
<td>12 (1-143)</td>
<td>9 (1-54)</td>
<td>10 (1-143)</td>
<td>.07</td>
</tr>
<tr>
<td>Comorbid illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Charlson index score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>101 (68)</td>
<td>41 (54)</td>
<td>142 (63)</td>
<td></td>
</tr>
<tr>
<td>2-5</td>
<td>45 (30)</td>
<td>31 (41)</td>
<td>76 (34)</td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>2 (1)</td>
<td>4 (5)</td>
<td>6 (3)</td>
<td>.02</td>
</tr>
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<td>McCabe classification</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Nonfatal</td>
<td>119 (80)</td>
<td>51 (67)</td>
<td>170 (76)</td>
<td></td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>19 (13)</td>
<td>15 (20)</td>
<td>34 (15)</td>
<td></td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>10 (7)</td>
<td>10 (13)</td>
<td>20 (9)</td>
<td>.08</td>
</tr>
<tr>
<td>Primary diagnosis on SICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac disease</td>
<td>40 (27)</td>
<td>21 (28)</td>
<td>61 (27)</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>24 (16)</td>
<td>21 (28)</td>
<td>45 (20)</td>
<td>.07</td>
</tr>
<tr>
<td>Trauma</td>
<td>33 (22)</td>
<td>8 (11)</td>
<td>41 (18)</td>
<td>.05</td>
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<tr>
<td>Neurologic disease</td>
<td>19 (13)</td>
<td>9 (12)</td>
<td>28 (13)</td>
<td>&gt;.80</td>
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<td>Infectious condition</td>
<td>13 (9)</td>
<td>6 (8)</td>
<td>19 (8)</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Respiratory tract disease</td>
<td>7 (9)</td>
<td>5 (7)</td>
<td>12 (5)</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7 (5)</td>
<td>4 (5)</td>
<td>11 (5)</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>3 (2)</td>
<td>2 (3)</td>
<td>5 (2)</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Nontumourary disease</td>
<td>2 (1)</td>
<td>0</td>
<td>2 (1)</td>
<td>&gt;.80</td>
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<tr>
<td>APACHE II score, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>18 (3-40)</td>
<td>26 (6-48)</td>
<td>19 (3-48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At onset of BSI</td>
<td>17 (2-39)</td>
<td>27 (7-47)</td>
<td>20 (2-47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SAPS score, median (range)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>38 (11-88)</td>
<td>59 (25-104)</td>
<td>42 (11-104)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At onset of BSI</td>
<td>36 (7-88)</td>
<td>60 (20-104)</td>
<td>41 (7-104)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SIRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>115 (78)</td>
<td>67 (88)</td>
<td>182 (81)</td>
<td>.06</td>
</tr>
<tr>
<td>At onset of BSI</td>
<td>127 (86)</td>
<td>69 (91)</td>
<td>196 (87)</td>
<td>.37</td>
</tr>
</tbody>
</table>
ment at all for at least 24 hours. A total of 26 patients (12%) had breakthrough bacteremia.

ORGAN DYSFUNCTIONS

Follow-up for the 224 patients represented 2301 patient-days. During that time, 80% of the patients had at least 1 organ dysfunction. Hypotension was present in more than half of the patients (54%), followed by neurologic (49%), gastrointestinal tract (33%), or cardiac (32%) dysfunction (Table 2). The most frequent organ dysfunctions in terms of organ failure-days were neurologic dysfunction (511 days), hypotension (434 days), acute lung injury (373 days), and acute respiratory distress syndrome (349 days).

MORTALITY

There were 148 survivors and 76 patients who died after onset of BSI (SICU mortality, 34%). The 28-day fatality was 36%. Of the 76 patients who died in the SICU, 63 (83%) died within 2 weeks after BSI. Patients with sepsis had an almost 6-fold increased risk of death compared with the overall ICU population (relative risk, 5.8; 95% CI, 4.7-7.2; P < .001).

Autopsy was performed in 30 patients. The direct cause of death was of infectious origin in 40% of the patients who underwent autopsy (n = 12). Other causes were of respiratory (n = 5, 18%), neurologic (n = 4, 14%), and cardiac (n = 4, 14%) origin.

Although gram-positive organisms were the most frequently isolated BSI pathogens (58% [159/275]), they were associated with lower case-fatality than gram-negative bacteria (30% vs 44%). The microorganisms associated with the highest crude case-fatality rates were *Candida* species (67%), *Enterobacter* species (53%), *P aeruginosa* (47%), and *E coli* (41%). *Staphylococcus aureus* and *Staphylococcus epidermidis* were associated with lower case-fatality (24% and 19%, respectively).

Baseline patient characteristics and organ dysfunctions significantly associated with SICU mortality by univariable comparison are given in Tables 1 and 2. Comparison between survivors and nonsurvivors showed significant differences for age, severity of illness scores, and most organ dysfunctions.

OUTCOME PREDICTION

The figure displays the Kaplan-Meier survival curves for the entire cohort and according to the adequacy of antibiotic treatment after onset of BSI. By univariate Cox regression analysis, 15 variables were associated with death (P < .10 for all) (Table 3). Admission diagnosis and pulmonary dysfunction after BSI were not associated with an increased risk of death. Organ dysfunctions associated with the highest risk of death were neurologic dysfunction (HR, 6.9; 95% CI, 3.3-14.5), hepatic dysfunction (HR, 3.9; 95% CI, 2.1-7.4) and disseminated intravascular coagulation (HR, 3.0; 95% CI, 1.5-6.1). Systemic inflammatory response syndrome at ICU admission (HR, 1.1; 95% CI, 0.6-2.3) and onset of BSI (HR, 1.1; 95% CI, 0.5-2.6) did not predict mortality. After adjusting for confounding variables (Table 3), the APACHE II score on the day of BSI (HR, 1.08; 95% CI, 1.04-1.12) and the number of evolving organ dysfunctions (HR, 1.4; 95% CI, 1.2-1.7) were independent predictors of mortality. Appropriate antimicrobial therapy was independently associated with decreased mortality (HR, 0.35; 95% CI, 0.2-0.6).

This study provides important information about the epidemiologic features of BSI in a large cohort of critically ill surgical patients admitted to a tertiary care center in Europe. We showed that after adjustment for confounding variables, the APACHE II score at onset of BSI and the number of organ dysfunctions evolving after onset of BSI are independent predictors of mortality. The analysis showed that installation of effective and timely antimicrobial treatment had a favorable effect on patient outcome, independent of the confounding effect of evolving organ dysfunctions and severity of acute illness at time of sepsis.

Sepsis remains associated with high morbidity and attributable mortality in the critical care setting. Early risk assessment of patients with sepsis may guide decisions regarding new therapeutic interventions and application of clinical pathways that direct patient care and use of clinical resources. Tools that enhance the clinician’s ability to rapidly and accurately assess patient risk profiles are thus of substantial interest. In previous studies, *Staphylococcus aureus* and *Staphylococcus epidermidis* were associated with lower case-fatality (24% and 19%, respectively).

Baseline patient characteristics and organ dysfunctions significantly associated with SICU mortality by univariable comparison are given in Tables 1 and 2. Comparison between survivors and nonsurvivors showed significant differences for age, severity of illness scores, and most organ dysfunctions.
Several studies conducted in the 1960s and 1970s showed that appropriate antimicrobial therapy leads to lower mortality in patients with gram-negative bacteremia compared with similar patients receiving inappropriate therapy. In contrast, Bryan et al showed that early antibiotic selection for the first 24 hours did not affect survival, regardless of the appropriateness of the antibiotics selected. However, this latter study showed improved survival in patients receiving appropriate antibiotics after the first day of therapy. More recently, Ibrahim et al showed the favorable impact of early adequate antibiotic treatment on outcome of patients with ICU-acquired BSI. Similarly, other studies demonstrated that inadequate antimicrobial treatment was an independent risk factor of mortality for patients with BSI.

In our study population, although BSI was a major cause of morbidity and mortality, as much as 26% of patients received inappropriate antibiotic therapy. The main reason was the time delay between the presence of signs of bacteremic sepsis, laboratory identification, and notification of the responsible clinicians. Moreover, antibiotic-resistant organisms and candidal or polymicrobial infections made it impossible to ensure prompt, complete empiric coverage in all cases. Nonetheless, this finding emphasizes the urgent need for quick diagnostic kits at the bedside. In the case of bacteremia, this would ideally identify the microorganism on the same day as the blood sample is taken and would allow immediate appropriate antibiotic coverage. Molecular diagnosis using polymerase chain reaction is not yet a standard technique for detection of viable bacteria in the blood. Despite the use of automated processing, the polymerase chain reaction method is time-consuming, labor intensive, and expensive compared with standard culturing methods.

The serious consequences of untreated BSI require a high degree of suspicion of infection in clinically unstable patients. However, clinical signs (eg, high fever) lack the desirable diagnostic power to discriminate between infected and uninfected patients. Therefore, numerous attempts have been made throughout the past 20 years to improve the early diagnosis of sepsis in critically ill patients. Procalcitonin in particular seems to be a promising indicator of sepsis in critically ill patients, capable of complementing clinical signs and routine laboratory variables suggestive of severe infection. Thus, adding procalcitonin to the standard workup of critically ill patients with suspected sepsis could increase diagnostic certainty and improve antibiotic management.

Although unequivocal choices are not available, empiric treatment of BSI is often based on the local suscep-
tibility patterns of the most suspected pathogens. For example, in our SICU, empiric therapy of gram-negative bacteremia should include imipenem-cilastatin, cefepime, ciprofloxacin, or amikacin. Those recommendations are in accordance with results of several surveillance studies from the United States and Europe in which imipenem-cilastatin, cefepime, and amikacin were the most active agents in vitro for empiric treatment of severe gram-negative infections. Of note is that only 5 cases of bacteremia due to methicillin-resistant Staphylococcus aureus occurred during the study. Owing to this low incidence, we do not routinely include vancomycin in the empiric treatment of suspected BSI. Finally, we strongly discourage the continued use of surgical prophylaxis beyond 24 hours after surgery, since this practice does not decrease postoperative infections and may select for antibiotic-resistant pathogens.

Few population-based cohort studies exist that accurately delineate risk factors for sepsis, its course, and its outcome. A recent review by Brun-Buisson summarized important studies reporting the epidemiologic determinants of bacteremic sepsis in ICUs. According to this article, the hospitalwide incidence of bacteremic sepsis is 0.82 cases (95% CI, 0.75-0.88) per 100 admissions. This rate is more than 8-fold higher in the critical care setting (6.9 cases [95% CI, 5.9-8.0] per 100 admissions). Another recently published study using census data from 7 US states determined that 192,980 cases of severe sepsis occur annually in the United States, yielding national estimates of 751,000 cases (2.26 cases per 100 hospital discharges), of whom 383,000 (51%) received intensive care. Mortality was 28.6%, corresponding to 215,000 deaths nationally.

Only a limited number of patients with severe sepsis have microbiologically documented infection. In the present study, we confirm recently reported trends demonstrating an increase in gram-positive microorganisms in the respiratory tract as becoming the leading source of BSI in the ICU. These trends were also reported in the review by Friedman and colleagues. According to this review, gram-negative infections were causative in 90% of infections between 1958 and 1979 but in only 69% of infections between 1980 and 1997. The site of secondary infection changed noticeably over the years. Between 1984 and 1988, the predominant site of infection was the abdomen (31%), and between 1994 and 1997, the chest became the primary site (26%).

Several limitations of this study merit consideration. First, the study population was surgical, so the results may not be representative of medical or pediatric ICUs. Second, because the data were collected retrospectively, and because the established diagnoses and sources of infection depend on the quality of documented data, case ascertainment may have been incorrect in some patients. Third, we may have missed patients with occult bacteremia, since blood cultures were only drawn on the basis of clinical signs suggestive of BSI. Finally, the observational nature of this investigation does not allow us to draw an absolute causal relationship between exposure to inadequate antimicrobial therapy and death.

Despite these limitations, this study provides important epidemiologic information about the occurrence of BSI in critically ill patients, which remains a common and frequently fatal condition. Moreover, we identified several factors affecting survival that must be taken into account for use in future therapeutic trials. Prevention of organ dysfunctions evolving after onset of BSI should be a primary target for further research. For example, previous findings suggest an association between the decreased incidence of organ failure and the subsequent shorter length of stay in patients with severe sepsis receiving immunomodulating therapy. Finally, new diagnostic approaches aimed at the reduction of inadequate antimicrobial treatment are urgently needed.

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REFERENCES

This study by a group of renowned experts in the field is, indeed, welcomed. Bloodstream infection in critically ill patients portends excessive morbidity and mortality throughout the world.

The epidemiologic characteristics of bloodstream infection is remarkably similar in Switzerland compared with the rest of the world. The authors confirm the same determinants of outcome identified in several other excellent studies, including older age, comorbidity as defined by APACHE II (Acute Physiology and Chronic Health Evaluation II) and Simplified Acute Physiology scores, and sequential organ failure. The presence of gram-negative vs gram-positive, or polymicrobial vs monomicrobial, infection is also linked to increased mortality. The improved survival trend in the injured patient is likely owing to youthfulness, while the enhanced mortality trend in those with underlying gastrointestinal disease is presumably owing to a higher incidence of fungemia with significantly increased mortality. In contrast, the presence of systemic inflammatory response syndrome adds little and confirms the lack of usefulness of this nonspecific inflammation as a discriminator of outcome. In contrast to all other organs, the onset of acute lung injury or acute respiratory distress syndrome seems overly sensitive and has no predictive value.

Importantly, inappropriate or delayed implementation of antimicrobial therapy was associated with increased mortality. The authors correctly focus on needed prevention of multiple organ failure, the best approach being efficacious treatment of bloodstream infections on patient outcomes. In contrast to all other organs, the onset of acute lung injury or acute respiratory distress syndrome seems overly sensitive and has no predictive value.

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Importantly, inappropriate or delayed implementation of antimicrobial therapy was associated with increased mortality. The authors correctly focus on needed prevention of multiple organ failure, the best approach being efficacious treatment of severe infectious complications using appropriate early empiric therapy. The organisms identified had an exceptionally low incidence of resistant organisms, such as methicillin-resistant Staphylococcus aureus, and one would expect that empiric coverage should have been easily achieved. However, what is unclear and unaddressed in this retrospective survey is why 1 in 4 patients was still inappropriately treated with antibiotics, a persistent international problem.

While a superb epidemiologic study, the Holy Grail for improved predictors of clinical relevance to enhance or focus our therapeutic interventions was not achieved and remains elusive.

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