



# MORBIDITY AND MORTALITY OF BLOODSTREAM INFECTIONS IN PATIENTS WITH SEVERE BURN INJURY

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**Background** Bloodstream infections are common in burn patients.

**Objective** To evaluate the effects of bloodstream infections in patients with severe burn injuries.

**Methods** A retrospective, pairwise-matched, risk-adjusted cohort study in a 6-bed burn unit was done. "Exposed" patients with microbiological evidence of bloodstream infections ( $n = 76$ ) were compared with nonexposed patients ( $n = 103$ ) matched for burn severity (identical Belgian Outcome in Burn Injury score) and length of hospitalization ( $\geq$ time-to-event in exposed patients). Main outcome measures were length of hospitalization and mortality.

**Results** Predominant pathogens were *Staphylococcus aureus*, enterococci, *Pseudomonas aeruginosa*, *Escherichia coli*, coagulase-negative staphylococci, and *Candida* species. Median patient age was 42 years (interquartile range [IQR], 31-52). Median total burned surface area was 40% (IQR, 25%-50%). Inhalation injury occurred in 54%. Median burn injury score was 4 (IQR, 2-5). Median length of stay before onset of bacteremia was 11 days (IQR, 5.3-19.8). Appropriate antimicrobial therapy was initiated within the first 48 hours in 76%. The exposed group had a higher need for vasopressive/inotropic support ( $P = .02$ ); need for ventilatory assistance and renal replacement therapy did not differ significantly between groups. Hospital mortality did not differ ( $P = .30$ ). However, bloodstream infection was associated with longer durations of hospitalization ( $P < .001$ ) and mechanical ventilation ( $P < .001$ ).

**Conclusions** In this cohort of burn patients, bloodstream infections did not adversely affect survival, but greater durations of ventilator dependency and hospital stay increased costs of care. (*American Journal of Critical Care*. 2010;19:e81-e87)

**A**dvances in burn care have substantially improved outcomes for patients with severe burn injuries.<sup>1</sup> After survival during the acute phase improved, infectious complications became more prominent; bloodstream infections (BSIs) are among the most prevalent.<sup>2-5</sup> Burn patients are at high risk for BSI because of large skin defects. The odds of BSI increase with burn size and depth.<sup>4</sup> Early debridement and wound closure are advocated to decrease infection risk, but even then colonization of burns is difficult to avoid, potentially leading to systemic invasion of microbes.<sup>6-8</sup> Furthermore, burn patients are at risk for BSI because of the use of invasive devices, multiple surgical procedures, and prolonged hospitalization.

On the basis of 9 years of data from a single center, Bang et al<sup>9</sup> reported a 23.5% mortality among 166 burn patients with BSI. In an earlier study,<sup>10</sup> BSI was a dominant cause of death. In burn patients with *Stenotrophomonas maltophilia* BSI, mortality was 31.7%.<sup>11</sup> In a study<sup>12</sup> of US military casualties who had burns, BSI was associated with a 2.6-fold increase in the risk of death.

Estimated fatality rates associated with BSI in burn victims are 20% to 30%. However, because BSIs generally occur in more severely burned patients, distinguishing mortality due to the infection from mortality due to general trauma severity can be difficult. Hence, matched cohort designs may be advocated to assess the clinical impact of BSI.<sup>13</sup> In one case-control investigation,<sup>14</sup> mortality was 31% in 29 burn patients with *Acinetobacter baumannii* BSI and 14% in matched nonexposed patients. In a matched cohort study by Vinsonneau et al,<sup>15</sup> mortality was significantly higher in burn patients with candidemia (30.0%) than in nonexposed patients (7.8%). As far as we know, no study has addressed the attributable

mortality of BSI in general (including all pathogens) in a burn population. Therefore, the objective of this study was to evaluate morbidity and mortality associated with BSI in severely burned patients. We used a matched cohort study to provide an adjustment for burn-related mortality that was as adequate as possible.

## Methods

### Setting

The study was conducted in the burn unit of Ghent University Hospital, Ghent, Belgium. The unit serves a geographic area of about 2.6 million inhabitants. Approximately 60 to 80 patients are admitted to the unit each year. Among the total population of burn patients, the median total burned surface area (TBSA) is 13%, median age is 30 years, approximately 12% have inhalation injury, the median length of stay is 12 days, and mortality is 7%.<sup>1</sup>

The unit has 6 separate isolation rooms; each room is equipped with a shower and bath. Intensivists from the surgical intensive care unit and plastic surgeons are responsible, respectively, for intensive care and wound care.

A mixed crystalloid-colloid scheme is used for fluid replacement. In the 1980s, human albumin was used as the colloid; since the 1990s, semisynthetic colloids such as starches and gelatin solution have been used. Replacement is started with an hourly dose of 2 mL/kg per 1% burned surface area. On the first day, one-half of the calculated fluid requirement is administered within the first 8 hours after the burn; the other one-half is administered during the next 16 hours. In the first 24 hours after the burn, one-third of the total fluid volume consists of colloids; the other two-thirds, hypertonic saline (1 L

Burn patients are at high risk for blood stream infections due to large skin defects

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of 0.9% sodium chloride + 50 mEq sodium bicarbonate). During the second 24 hours, colloids account for two-thirds of the total fluid volume. Volume replacement is guided by a patient's urine output and hemodynamic status.

Early enteral nutrition has been the practice in the unit since 1998. During the period 1985 to 2001, patients were showered daily with chlorhexidine solution. During the last 2 years of the study, a povidone-iodine solution was used. From 1985 to 1998, partial-thickness burns were covered with silver sulfadiazine; thereafter hydrocolloid dressings have been used. Full-thickness burns are covered with cerium nitrate-silver sulfadiazine.

Early excision of burn wounds has never been the practice in the burn unit. Use of polarized light to stimulate wound healing in partial-thickness burns was introduced in the unit for scientific purposes in 1996. Since 1998, all partial-thickness burns are treated with polarized light, limiting the need for surgery for full-thickness burns and difficulty in healing deep dermal burn wounds. Twice weekly microbiological monitoring indicates each patient's colonization status. No antibiotic prophylaxis is used.

### Design

A retrospective, pairwise-matched (matching ratio 1:2 or, if not feasible, 1:1), risk-adjusted cohort study was performed with "exposed" patients admitted to the burn unit between 1992 and 2006 in whom microbiological evidence indicated BSI.

Nonexposed patients were selected from a database that included all burn patients admitted to the unit. The study was approved by the appropriate ethics committee.

### Case Finding

A prospective, case- and laboratory-based surveillance program of BSIs by the infection control team was used for the retrospective search for all burn patients with BSI. Patients were presumed to have a BSI if microorganisms were detected in blood cultures. Subsequent ad hoc determination of clinical significance, and presumed or definite initial focus of infection were established by mutual agreement among the attending intensivist, infectiologist, and microbiologist. In patients who had multiple episodes, only the first BSI episode was considered.

### Matching Procedure

The purpose of matched cohort studies is to achieve reliable estimates of attributable mortality through accurate adjustment for confounding covariates. Hence, strict matching on prognostic factors is crucial.<sup>13,16-21</sup> Therefore, exposed patients were matched with nonexposed patients according to identical Belgian Outcome in Burn Injury (BOBI) scores.<sup>22</sup> For the BOBI 10-point classification, 3 major risk factors—mortality, age, and TBSA—and inhalation injury are considered.<sup>22,23</sup> Age is divided into 4 risk categories (0-3 points); TBSA, into 5 (0-4 points). The presence of inhalation injury is scored as 3 additional points. This matching procedure resulted in an equal a priori expected mortality and allows assessment of the impact of a subsequent complication. Nonexposed patients were selected within a 5-year time frame before or after the admission year of the index BSI patient. Nonexposed patients were required to have a time to discharge at least equal to the time to event in the corresponding exposed patient.<sup>17</sup> Selection of nonexposed patients was made without knowledge of outcome. If data on more than 2 potential nonexposed patients were available, matching was based on the admission date nearest to that of the index exposed patient.

### Definitions and Outcome Measures

Definitions of BSI, determination of BSI sources, methods for antimicrobial susceptibility testing, and appropriate antimicrobial therapy have been reported elsewhere.<sup>24-26</sup> Antimicrobial resistance was defined<sup>24,27,28</sup> as resistance to fluconazole for *Candida* species, as resistance to methicillin for staphylococci, as resistance to vancomycin for enterococci, as resistance to ampicillin for streptococci, as production of extended-spectrum  $\beta$ -lactamases for *Enterobacter* species, and as resistance to 1 of the following agents for gram-negative nonfermenting bacteria: ceftazidime, piperacillin, ciprofloxacin, imipenem, or meropenem.

Blood samples for cultures were obtained routinely if a patient's temperature increased to more than 38.4°C or if bacteremia was suspected because of unstable hemodynamic status, chills, or new organ failure. Samples were processed according to the BacT/Alert (Organon Teknika Corp, Durham, North Carolina) procedure. Susceptibility testing was done in accordance with the latest guidelines recommended by the National Committee on Clinical Laboratory Standards or the Clinical and Laboratory Standards Institute at any time during the study period.

Early patients showered daily with chlorhexidine and with betadine in the last 2 years.

Use of polarized light limits the need for surgery to full thickness burns.

**Table 1**  
Microorganisms involved in 76 episodes of bloodstream infection in patients with severe burn injuries<sup>a</sup>

Microorganism	No. of episodes (%)	No. of episodes with single isolated pathogen (%)	No. of antimicrobial resistant pathogens (%) <sup>b</sup>
<b>Gram-positive bacteria (46 isolated pathogens)</b>	<b>41 (54)</b>	<b>21 (46)</b>	<b>14 (30)</b>
Coagulase-negative staphylococci	12 (16)	8 (67)	9 (75)
<i>Staphylococcus aureus</i>	14 (18)	10 (71)	4 (29)
Enterococci	14 (18)	2 (14)	0 (0)
Streptococci	6 (8)	1 (17)	1 (17)
<b>Gram-negative bacteria (45 isolated pathogens)</b>	<b>42 (55)</b>	<b>26 (58)</b>	<b>9 (20)</b>
<i>Enterobacter</i> species	9 (12)	6 (67)	3 (33)
<i>Pseudomonas aeruginosa</i>	12 (16)	6 (50)	1 (8)
<i>Sphingobacterium meningosepticum</i>	1 (1)	1 (100)	1 (100)
<i>Klebsiella</i> species	7 (9)	2 (29)	1 (14)
<i>Acinetobacter baumannii</i>	3 (4)	3 (100)	3 (100)
<i>Escherichia coli</i>	12 (16)	8 (67)	0 (0)
<i>Serratia marcescens</i>	1 (1)	0 (0)	0 (0)
<b>Candida</b> species (10 isolated pathogens)	<b>10 (13)</b>	<b>8 (80)</b>	<b>0 (0)</b>
<b>Total (101 isolated pathogens)</b>	<b>76 (100)</b>	<b>55 (54)</b>	<b>23 (23)</b>
Polymicrobial bloodstream infections	21 (28)	0	3 (6.5)

<sup>a</sup> Only the first episode is included.

<sup>b</sup> Antimicrobial resistance was defined as resistance to fluconazole for *Candida* species, resistance to methicillin for staphylococci, resistance to vancomycin for enterococci, resistance to ampicillin for streptococci, production of extended-spectrum  $\beta$ -lactamases for *Enterobacter* species, and resistance to one of the following agents for gram-negative nonfermenting bacteria: ceftazidime, piperacillin, ciprofloxacin, imipenem, or meropenem.

Evaluation of clinical outcome was based on the need for organ support (eg, mechanical ventilation, renal replacement therapy, vasopressor or inotropic support) and in-hospital mortality. Excess length of hospitalization and ventilator dependency were used as major indicators of added morbidity. Excess length of hospitalization was calculated by subtracting the median length of hospitalization of the nonexposed group from the median length of hospitalization of the exposed group. Because exposed patients were matched on the basis of exposure time (time to event in exposed patients vs time to discharge in nonexposed patients), the difference in length of stay indicates the added proportion of hospitalization due to the infectious complication.<sup>17</sup>

### Statistical Analysis

Mann-Whitney U and  $\chi^2$  tests were used as appropriate. Relationships with mortality were assessed by using logistic regression analysis. The following variables were entered in the regression model and were stepwise removed if  $P > .10$ : age, sex, TBSA, inhalation injury, duration of hospitalization, BSI, acute kidney injury, and need for vasopressor support. Odds ratios and 95% confidence intervals are reported. Covariates with a plausible relationship with mortality or  $P < .10$  in univariate analysis were included in the model. Because BSI was the variable of interest, it was kept in the model regardless of the associated  $P$  value. All tests were 2 tailed.

## Results

### Patients With BSI (Exposed Cohort)

During the 15-year period, 1125 patients were admitted to the burn unit. In total, 178 episodes of BSI occurred (prevalence, 15.8 episodes per 100 admissions) in 76 patients. Among the 76 patients with BSI, 43 had multiple episodes (mean, 3.4 episodes). Table 1 summarizes the causative pathogens involved. In 28% of the BSI episodes, multiple bacteria were detected. Median time between admission and onset of BSI was 11 days (IQR, 5-20). A total of 39 episodes were primary BSIs (39/76, 51%); of these, 23 were due to contaminated catheters (23/76, 30%). The burn wound was the main source of secondary BSIs (36/76, 47%). In 58 patients, appropriate antibiotic therapy was initiated within 48 hours. In-hospital mortality was 12% ( $n = 9$ ) among the 76 patients who had BSI and 9% ( $n = 5$ ) among the 55 patients whose first episode was due to a single pathogen. Of the 21 patients with a polymicrobial first episode, 19% died ( $n = 4$ ).

### Matched Cohort

Matching was successful for all patients, but for 42 exposed patients, only 1 suitable nonexposed patient was found. Thus, the matching procedure resulted in a matched cohort study with 76 exposed

Hospital mortality did not differ between those with and without BSI.

**Table 2**  
**Characteristics of patients with severe burn injuries and a blood-stream infection (exposed) and matched nonexposed patients<sup>a</sup>**

Characteristics	Exposed group (n = 76)	Nonexposed group (n = 103)	P
Age, median (interquartile range), y	42 (31-52)	41 (23-68)	.91
Male sex, %	66	67	.87
Total burned surface area, median (interquartile range), %	40.0 (25.3-50.0)	30.0 (13.0-47.0)	.005
Inhalation injury	41 (54)	54 (52)	.84
BOBI score, <sup>22</sup> median (interquartile range)	4 (2-5)	4 (2-5)	.91
BOBI score-related expected mortality, median (interquartile range), %	20.0 (5.0-30.0)	20.0 (5.0-30.0)	.91
Time to event/time to discharge, median (interquartile range), d <sup>b</sup>	11 (5-20)	31 (14-55)	<.001
Vasopressive/inotropic support	44 (58)	41 (40)	.02
Mechanical ventilation	46 (61)	57 (55)	.49
Renal replacement therapy	5 (6.6)	2 (1.9)	.11
Duration of hospitalization, median (interquartile range), d	61 (42-119)	36 (20-57)	<.001
Duration of mechanical ventilation, median (interquartile range), d	21 (16-33)	10 (6-21)	<.001
In-hospital mortality	9 (12)	18 (17)	.30

<sup>a</sup> Data are reported as No. of patients (%) unless indicated otherwise.

<sup>b</sup> The time to discharge in the nonexposed group should be at least as long as the time to event in the exposed group. Consequently, the a priori risk for bloodstream infection is at least as high in the nonexposed group.

Abbreviation: BOBI, Belgian Outcome in Burn Injury.

**Table 3**  
**Logistic regression analysis to assess the relationship between in-hospital mortality and covariates<sup>a</sup>**

Variable	Odds ratio (95% confidence interval)	P
Age (per 10-year increase)	2.01 (1.37-2.95)	<.001
Total burned surface area (per 10% increase)	2.30 (1.61-3.29)	<.001
Acute kidney injury	24.20 (1.70-344.83)	.02
Need for vasopressive/inotropic support	3.70 (1.06-12.95)	.04
Bloodstream infection	0.83 (0.22-3.16)	.78
Total hospital stay (per day increase)	0.96 (0.94-0.98)	<.001

<sup>a</sup> Sex and inhalation injury were stepwise removed from the model because these variables did not have a significant effect on mortality.

and 103 nonexposed subjects. Table 2 summarizes the characteristics of the exposed and nonexposed groups. Compared with nonexposed patients, patients with BSI had a higher need for vasopressor or inotropic support. Need for ventilatory assistance and renal replacement therapy did not differ significantly between the 2 groups. Hospital mortality also did not differ significantly between the groups. However, duration of hospital stay was 25 days longer for patients with BSI (61 days) than for nonexposed

patients (36 days) and duration of mechanical ventilation was 11 days longer (21 vs 10 days). Logistic regression analysis confirmed that BSI did not affect survival (Table 3).

## Discussion

In this cohort of burn patients with BSI, the infections did not contribute to mortality but did cause additional morbidity; compared with the nonexposed patients, patients with BSI had a greater need for vasopressors or inotropic agents and longer durations of ventilator dependency and hospitalization. The absence of mortality attributable to BSI in the exposed group was confirmed by multivariate regression analysis. Instead, older age, greater TBSA, renal replacement therapy, and need for vasopressors or inotropic agents were risk factors for mortality. Strangely enough, inhalation injury, a factor that strongly compromised prognosis in other studies,<sup>1,29-31</sup> was not associated with death. Probably, inhalation injury contributes more to early deaths, whereas our BSI cohort generally included survivors of the acute phase of injury who were prone to late-onset infectious complications.

In contrast to previous reports,<sup>9,10,14,15</sup> our findings indicate that once adjusted for prognostic covariates, BSI does not necessarily impede survival in burn victims. No excess mortality<sup>24,25,32-35</sup> and dramatic mortality

rates attributable to infection have been reported before in bacteremic critically ill patients.<sup>15,19,36,37</sup> The likelihood of survival depends on unchangeable characteristics such as severity of disease, causative pathogen, antimicrobial resistance, and the patient's age.<sup>12,13,38-40</sup> Optimizing the odds of survival requires prompt initiation of appropriate therapy<sup>3,41-43</sup>; in our study, 58 of the 76 patients (76%) received appropriate antibiotic therapy. However, mortality in patients who did not receive appropriate therapy within the critical time frame of 48 hours (12%) was not worse than mortality in patients who did receive appropriate therapy (11%). Possibly, most BSIs treated inappropriately were caused by coagulase-negative staphylococci (methicillin-resistant), known as low-virulence pathogens. Anyhow, insufficient power in the study hampered this particular analysis.

Because matched cohort studies are prone to selection and survival bias,<sup>13,17,44</sup> reliability of the nonexposed group is crucial. To avoid survival bias, we required that nonexposed patients have a time to discharge at least as long as the time to event (ie, onset of BSI) of the exposed patients. Additionally, we matched patients on the basis of the BOBI score because this classification summarizes the most powerful prognostic indicators.<sup>22,23</sup> An advantage of this matching procedure is that the validity of the nonexposed group can be judged by comparing the observed and expected mortality rates. In our study, the observed mortality of the nonexposed group (17.5%) was within the 95% confidence interval of the expected mortality (14.7%-30.9%), indicating a reliable nonexposed group with an outcome in line with the expectations. The percentages of TBSA differed statistically between the 2 groups, but the clinical relevance of the observed difference (30% vs 40%) was minor because mortality associated with the percentage of TBSA only starts to increase substantially from more than 40%, as indicated by Ryan et al.<sup>45</sup> Also in the BOBI score, TBSAs from 21% to 40% correspond to 1 point. Therefore, exposed and nonexposed patients might have different percentages of TBSA but still have identical BOBI scores and hence have similar outcome predictions. Consequently, our finding that TBSA was significantly lower among the nonexposed patients is overruled by the equal BOBI scores.

A disadvantage of this study is the single-center design. Nevertheless, the homogenous standard of care for both exposed and nonexposed patients is an advantage of this approach. Another potential weakness is that exposed patients were recruited during a long period in which favorable evolutions in survival occurred. We tried to counter this problem

by selecting nonexposed patients on the basis of the year of admission, but a 5-year frame was necessary to match all exposed patients. Selecting controls from a 5-year period may be borderline acceptable, because survival improved during the 5-year period (odds ratio, 0.73; 95% confidence interval, 0.56-0.94).<sup>1</sup>

In conclusion, in this cohort of burn patients, BSI did not adversely affect survival. BSI was, however, associated with a significant increase in the durations of mechanical ventilation and hospitalization, thereby representing a substantial economic burden. These data underscore the need for vigorous application of evidence-based, cost-effective preventive measures.

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#### FINANCIAL DISCLOSURES

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