ORIGINAL RESEARCH

Bloodstream infection complicating trauma

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Abstract

Background: Bloodstream infection (BSI) is recognized as an important infectious complication of major trauma. However, its occurrence, the risk factors contributing to its development, and its outcomes have not been well described.
Design: Cohort with linkage of regional trauma and microbiology databases.
Patients: Adult trauma patients with injury severity score (ISS) ≥ 12 admitted to a regional trauma centre during a 33-month period.
Results: Of 1797 victims of acute trauma identified (median ISS 20; interquartile range [IQR] 16–25), 71 (4%) had 77 episodes of BSI, for an overall rate of 2.9 per 1000 hospital days. BSI in the majority of patients (37 of 72, or 52%) had onsets within the first week of hospitalization; 7 (10%) patients had community-acquired BSI (onset within 2 d). Independently associated with the development of nosocomial BSI were higher ISSs (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.07); requirement for ICU admission (OR 7.06, CI 3.38–14.75); and burns (OR 5.75, CI 2.16–15.30). Although trauma-related BSI was a predictor of increased in-hospital case fatality (15/71 v. 208/1726; relative risk 1.75, CI 1.10–2.78), it was not an independent predictor of death.
Conclusion: In our series, 1 in 25 major trauma cases was complicated by BSI. The infection occurred within the first week after injury in over half of our cases. Knowledge of the epidemiology of these infections will be important for planning preventive or early therapeutic efforts.

Résumé

Contexte : L'infection de la circulation sanguine (ICS) est reconnue comme une complication infectieuse importante des traumatismes majeurs. Son occurrence, les facteurs de risque qui contribuent à son apparition et ses résultats ne sont toutefois pas bien décrits.
Conception : Cohorte reliée à des bases de données régionales sur la traumatologie et la microbiologie.
Patients : Patients traumatisés adultes présentant un indice de gravité de la blessure (IGB) ≥ 12 admis à un centre régional de traumatologie au cours d'une période de 33 mois.
Résultats : Sur 1797 victimes d'un traumatisme aigu identifié (IGB médian de 20; intervalle interquartile [IIQ] de 16–25), 71 (4 %) ont présenté 77 épisodes d'ICS, soit un taux global de 2,9 pour 1000 jours d'hospitalisation. Chez la majorité des patients (37 sur 72, ou 52 %), l'ICS est apparue dans la première semaine suivant l'hospitalisation; 7 (10 %) des patients avaient une ICS d'origine communautaire (apparition dans les 2 j). L'apparition d'ICS nosocomiales était indépendamment associée à des IGB plus élevés (coefficient de probabilité [CP] 1,04, intervalle de confiance [IC] à 95 %, 1,02–1,07), à la nécessité d'admission aux soins intensifs (CP 7,06; IC 3,38–14,75) et aux brûlures (CP 5,75, IC 2,16–15,30). Même si l'IGB relié au traumatisme était un prédicteur de mortalité accrue chez les sujets hospitalisés (15/71 c. 208/1726; risque relatif 1,75, IC 1,10–2,78), il ne constituait pas un prédicteur indépendant de décès.
Conclusion : Dans notre série, l'ICS a constitué une complication dans un cas de traumatisme sur 25. L'infection a fait son apparition dans la première semaine suivant le traumatisme chez plus de la moitié de nos cas. La connaissance de l'épidémiologie de ces infections sera importante pour la planification d'efforts de prévention ou de traitement rapide.

Bloodstream infection (BSI) is an important infectious complication seen among hospitalized patients, and victims of trauma are recognized to be at particularly high risk.[1,2] However, few studies have focused on the epidemiology of BSI occurring among trauma patients. A 1-year surveillance study conducted by Papia and associates[3] in Toronto found that bacteremia occurred in 6% of 563 patients. In a case–control study of 190 critically ill trauma patients in Baltimore, El-Masri and colleagues[4] found that the development of BSI is associated with increased severity of illness and length of stay. These and other studies[5–7] were limited either by their focus on selected populations or by small sample sizes. As a result, the occurrence and risk factors for development of BSI among trauma patients and its influence on outcome is not well defined.

Knowledge of the epidemiology of BSI in trauma patients is important to establish the burden of disease, to identify microbial etiologies for guiding appropriate empiric antibiotic therapy pending culture results, and for targeted implementation of early treatment or preventive efforts. To define the epidemiology of BSI complicating traumatic injury, we linked 2 regional databases. This permitted us to investigate the incidence, risk factors and outcomes of trauma-related BSI for all patients presenting with major trauma to a large Canadian regional trauma centre over a period of 33 months.

Methods

Patient population

The Calgary Health Region (CHR) is a fully integrated, publicly funded health system providing all medical and surgical care to the residents of the cities of Calgary and Airdrie and approximately 20 nearby small towns, villages and hamlets.[8] Adult trauma services in the CHR are regionalized to the Foothills Medical Centre (FMC), which is the only tertiary adult trauma centre servicing southern Alberta, Canada. All adult (≥ 18 yr) victims of traumatic injury with an Injury Severity Score (ISS) of ≥ 12 presenting from July 1999 through March 2002 were included.[9] This study was nested within a large population-based trauma study that was approved by the Conjoint Health Research Ethics Board at the University of Calgary and the Calgary Health Region.

Study protocol

The study database was created by linkage of 2 large regional databases. The CHR trauma registry was used to identify and obtain detailed information on all patients treated at FMC. It prospectively identifies and reviews clinical information on all trauma patients assessed in the CHR with an ISS ≥ 12. All episodes of BSI occurring in these patients were then identified through a linkage to culture data at Calgary Laboratory Services, which has performed all routine blood cultures in the region since 1996.[10] Data from the 2 sources were linked with Access 2000 software (Microsoft Corp., Redmond, WA) according to a unique hospital number, screened for duplicates and errors before analysis.

Definitions

Trauma-related BSI was defined by isolation of a pathogenic organism from at least 1 set of blood cultures within 30 days of major trauma (ISS ≥ 12) or at any time during a patient's initial hospitalization for acute trauma. The blood culture set consisted of an aerobic and anaerobic pair of BacT/Alert FAN bottles.[11] At least 2 positive sets of blood cultures within 2 days were required to diagnose BSI. Common skin contaminants included coagulase-negative staphylococci or *Bacillus*, *Corynebacterium* or *Propionibacterium* species. Community-acquired infections (cBSI) were classified as those with the first positive culture drawn within 2 days of admission. Antibiotic-resistant organisms (ARO) included methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus fæcalis* or *E. fæcium*, and any Gram-negative organism resistant to ciprofloxacin, tobramycin, gentamicin, ceftazidime, piperacillin or carbapenems.[12] A repeat BSI was diagnosed only if patients fulfilled criteria for a BSI with a different etiology more than 2 days after the first episode.

Statistical analysis

All analyses were performed with Stata version 7.0

software (Stata Corp., College Station, Tex.) and were restricted to a patient's first admission for trauma. Missing data were not replaced; a reduced number (n) of subjects was reported wherever that occurred. Before analysis, all variables were assessed for underlying distribution qualitatively with histograms. Means and standard deviations (SD) were used to describe normally or near-normally distributed variables, and medians with interquartile ranges (IQR) to describe non-normally distributed variables. Differences in proportions were compared with Fisher's exact test; means, with Student's t test; and medians with the Wilcoxon rank–sum test.

Multivariable logistic regression models were developed to assess baseline independent risk factors for developing nosocomial BSI (nBSI) and for death. Initial models included age, sex, ISS and those variables with $p \leq 0.1$ level in univariate analyses. Backward stepwise variable elimination and pairwise interaction testing was then performed to develop the final model. Model calibration was assessed with the Hosmer–Lemeshow goodness-of-fit test; discrimination, with the area under the receiver–operator curve (ROC). Correction for multiple testing was not performed. Unless otherwise stated, $p < 0.05$ was considered to represent statistical significance.

Results

Of a total of 1797 patients admitted with severe injury during the study period, 1347 (75%) were male. The median age was 41 years (IQR 27–58 yr); median ISS score, 20 (IQR 16–25) points. Nearly all cases (1671) were of blunt trauma (93%), with 74 penetrating injuries (4%) and 33 burns (2%). In 19 cases (1%), the type of injury was not classified.

A total of 71 patients (4%) had 77 episodes of BSI; 5 patients had 2 episodes; and 1 had 3 discrete episodes. The overall rate of BSI was 2.9 per 1000 hospital days. First episodes of BSI occurred a median of 6 days (IQR 3–13 d) after hospital admission. Six patients had cBSI: 1 had BSI with a viridans-group streptococcus on the day of admission, and 5 patients developed BSI the next day (1 with *Escherichia coli*, 1 with *Hæmophilus influenzae* and 3 with polymicrobial Gram-positive coccus infections). The remaining patients developed BSI 2 or more days after presentation.

A total of 91 organisms were isolated during the 77 episodes of BSI (Table 1). Of these 77 infections, 12 (16%) were polymicrobial; 37 (48%), monomicrobial Gram-positive cocci; 25 (32%), monomicrobial Gram-negative; and 3 (4%), *Candida albicans*. BSI associated with an antimicrobial-resistant pathogen occurred in 14 episodes (18%), 13 of which were at first presentation. Among patients with BSI, the median time to development of infections associated with ARO (9 d, IQR 4–15 d) did not differ significantly from that of those without ARO (6 d, IQR 3–11 d; $p = 0.2$).

Nosocomial BSIs occurred in 65 of 1638 patients (4%). Univariate analyses identified several factors as being associated with the development of nBSI, as listed in Table 2. There was an overall proportional difference among injury type and development of nBSI ($p < 0.001$), attributable to the high rate of BSI in patients with burns, whose risk (7/27 or 26%) was 7 times that of other patients (58/1611, 4%; relative risk [RR] 7.2; 95% confidence interval [CI] 3.63–14.30; $p = 0.0001$). Number of surgical procedures

Table 1: Etiology of trauma-associated bloodstream infections in 91 patients, Foothills Medical Centre, Calgary, Alberta

Organism	Mono-microbial	Poly-microbial	Total	% of orgs*
Streptococcus aureus	18	5	23	25
Streptococcus species	6	7	13	14
Coagulase-negative staphylococci	7	3	10	11
Enterococcus species	6	4	10	11
Escherichia coli	7	—	7	8
Enterobacter species	3	1	4	4
Klebsiella pneumoniae	1	1	2	2
Morganella morganii	2	—	2	2
Other Gram-neg bacilli	4[a]	1[b]	5	5
Acinetobacter species	3	1	4	4
Pseudomonas aeruginosa	3	1	4	4
Candida albicans	3	—	3	3
Other	2[c]	2[d]	4	4

neg = negative; orgs = organisms
* Of 77 episodes of infection among 71 patients, 12 infections were polymicrobial (>1 etiology identified, as specified below), for a total of 91 organisms found.
[a] One each of group B *Salmonella* species, *Serratia marcescens*, *Citrobacter freundii*, and a Gram-negative bacillus not speciated
[b] *Stenotrophomonas maltophilia*
[c] One each of *Neisserria* species (not *meningitidis*) and *Haemophilus influenzae*
[d] One each of *Clostridium sporogenes* and *Stomatococcus mucilaginosus*

required was associated with development of nBSI (median number of operations 2 [IQR 1–3] v. 1 [IQR 0–1], $p < 0.0001$). However, the median time to first operation was not predictive of nBSI development ($p > 0.1$). When logistic regression modeling was used, only 3 variables were identified at baseline to be independent predictors of the development of nBSI (Table 3).

Of the entire cohort of 1797 trauma patients, 223 (12%) died during their initial hospitalization. A diagnosis of BSI was associated with a higher case-fatality rate than in patients without (15/71 v. 208/1726, RR 1.75, CI 1.10–2.78; $p = 0.04$). However, when included in a multivariable logistic regression model with variables ISS, hypotension (systolic blood pressure < 90 mm Hg at first assessment at FMC), requirement for operation, age, requirement for intensive care unit (ICU) admission and traumatic brain injury, BSI was not an independent predictor for death (OR 1.2, CI 0.57–2.61; $p = 0.6$).

Discussion

This is one of the largest cohort studies investigating the epidemiology of BSI complicating major trauma. We identified an occurrence of BSI of 4%, comparable with a previous Canadian study[3] but much lower than the dramatic 26% seen in a small study of critically ill trauma patients in Italy.[6]

Observation of early-onset BSI was not uncommon, with 10% of cases fulfilling a standard definition for community-acquired infection: onset within 2 d. This is contrary to the widely accepted notion that infectious complications are uncommon in trauma patients during the first few days after injury.[13] More than one-half (37/71; 52%) of our patients had BSI diagnosed within the first week of presentation. This finding of a high rate of early-onset BSI complicating trauma is consistent with the findings of Antonelli and coworkers,[6] who found that 30% of BSI in their trauma patients occurred within 96 hours of admission. Previous lack of recognition of early-onset BSI may be related to small sample sizes that may not have detected a low but significant rate. Although the numbers of patients in this category were too small to draw meaningful conclusions, it is inter-

Table 3: Logistic-regression modelling of baseline risk factors for nosocomial, trauma-associated bloodstream infection*

Factor	Odds ratio	95% CI	*p* value
ISS (per point)	1.04	1.02–1.07	0.001
Burn	5.75	2.16–15.30	<0.001
Admission to ICU	7.06	3.38–14.75	<0.001

*Area under the receiver–operator curve ROC = 0.83; goodness of fit $p = 0.9$; no pairwise interactions present in the final model (n = 1638).
CI = confidence interval; ICU = intensive care unit; ISS = Injury Severity Score

Table 2: Univariate analysis of significant predictive factors ($p \leq 0.1$) for nosocomial trauma-associated bloodstream infection (BSI)

Factor	Nosocomial BSI	*n*	No BSI	*n*	Total	*n*	*p* value
Male gender, no. (and %)	55 (85)	65	1181 (75)	1573	1236 (75)	1638	0.1
ISS, median (and IQR)	29 (24–38)	65	19 (16–25)	1573	20 (16–25)	1638	<0.0001
Temperature, mean (and SD), °C	36.0 (1.3)	52	36.6 (1.2)	1194	36.6 (1.2)	1246	<0.001
Hypothermia <35°C, no. (and %)	8 (15)	52	85 (7.1)	1194	93 (7.5)	1246	0.05
Hyperthermia >37.8°C, no. (and %)	2 (4)	52	142 (12)	1194	144 (12)	1246	0.08
Systolic BP, mean (and SD), mm Hg	124.3 (32.4)	62	132.5 (26.4)	1554	132.2 (26.7)	1616	0.02
Hypotension: systolic BP <90 mm Hg, no. (and %)	7 (11)	62	67 (4.3)	1554	74 (4.6)	1616	0.02
Pulse rate/min, mean (and SD)	100 (27)	64	91 (22)	1554	91 (22)	1618	<0.001
Tachycardia ≥100/min, no. (and %)	31 (48)	64	474 (31)	1554	507 (31)	1618	<0.001
Respiratory rate/min, mean (and SD)	22 (6)	31	20 (5)	1214	20 (5)	1245	0.05
Severe brain trauma, no. (and %)	14 (22)	65	146 (9.3)	1573	160 (9.8)	1638	<0.01
Burn, no. of cases (and %)	7 (11)	65	20 (1.3)	1573	27 (1.6)	1638	<0.001
ICU admission, no. (and %)	55 (85)	65	512 (33)	1573	567 (35)	1638	<0.001
Operation required, no. (and %)	50 (77)	65	858 (55)	1571	908 (56)	1636	<0.001

Patients admitted for < 2 days were excluded. In column *n*, reduced numbers of patients show where data were missing; maximum sample numbers are as indicated in the first row. BP = blood pressure; ICU = intensive care unit; IQR = interquartile range; ISS = injury severity score; SD = standard deviation

esting that 5 of the 6 patients with cBSI had head injuries.

Three independent predictors were identified for the development of nBSI (Table 3): ISS, need for ICU admission, and burns. Burns are well recognized as a risk for infection as a result of loss of the integrity of the skin barrier, injury-associated immunosuppression, and the mass of burned necrotic tissue that serves as a source of infection.[14] Higher ISS score and the need for ICU admission as independent risk factors are also unsurprising:[4] patients with greater severity of disease would be expected to require invasive interventions such as thoracostomy tubes, endotracheal intubation and mechanical ventilation, and intravascular access lines — all known to be sources of risk for development of nosocomial infections. We did not specifically collect data on the use of various invasive devices; but in our collective trauma and ICU experience and based on a previous multidisciplinary ICU review of practices in our regional ICUs,[1] we estimate that over 90% of trauma patients in FMC's ICU will have had at least 1 invasive vascular catheter early in their admission.

Identification of risk factors for the development of BSI is important, as it may allow targeting of enhanced preventive or early therapeutic measures to populations known to be most at risk for the development of infectious complications. For example, intranasal muciprocin, which has shown promise as a means for prevention of *Staphylococcus aureus* infections (80% of which arise endogenously from nasal colonization), may be particularly important to trauma patients, who have been shown to be at particularly high risk for the development of this infection.[15–18] A randomized trial assessing the effectiveness of intranasal mupirocin in reducing the incidence of nosocomial infections in critically ill or burned trauma patients is warranted.

Limitations

This study, which is based on the linkage of 2 regional databases, may be limited by the resolution of each database and by the shortcomings of database research in general. The Alberta Trauma Registry collects information on severe injuries only (ISS ≥ 12) and therefore does not reflect the experiences of patients with less severe injuries, including most cases of penetrating trauma. Furthermore, although it provided us with a unique perspective on complications of trauma, the Calgary Laboratory Services database provided information on BSIs only, not on the focus of sepsis. This limitation results in an underestimate of the burden of septic complications in our patients and underscores the need for more detailed studies so that avenues for prevention of specific types of infection can be more thoroughly explored.

This study, which provides data from a single trauma hospital on all severely injured patients without reference to their place of residence, is not population-based, as we did not confine its analysis to all cases of a health condition identified in residents of a defined geographic region, with nonresidents strictly excluded.[19,20] In this design, sampling is not performed, selection bias is minimized, and true incidence and mortality rates may be reported when the demographics of the underlying population are known. We excluded 130 trauma patents admitted to other sites in the region, because we did not have detailed clinical information on these patients. Since none of these patients had BSI, our rate may be falsely elevated. On the other hand, we did not exclude patients who lived outside of the region from our analysis, so the occurrence of trauma and trauma-related BSI may therefore be overestimated. It is reasonable to generalize the findings of this study to other similar regional tertiary-care centres. But because our study (like all previous studies investigating BSI in trauma patients) was not population-based, results should not be generalized to other populations at large.

This largest study investigating the epidemiology of BSI complicating traumatic injury identifies that these infections occur in 1 in 25 patients. It also provides evidence against the common notion that BSI is a late complication of traumatic injury. Furthermore, *Staphylococcus aureus* is confirmed as the most important cause of trauma-associated BSI, and risk factors for the development of nBSI were identified. These data provide important epidemiologic information for establishing the burden of disease caused by bloodstream infection in trauma patients and for identifying target groups for future studies of preventive and/or early treatment strategies.

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