Epidemiology and etiology of blood stream infections in a Belgian burn wound center

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Epidemiology and etiology of blood stream infections in a Belgian burn wound center

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ABSTRACT

Background: Infections are a major cause of morbidity in burn patients. We aimed to investigate the epidemiology and antibiotic susceptibility of blood stream infections in order to gain a better understanding of their role and burden in our Burn Wound Center.

Methods: This retrospective epidemiological investigation analyzed data derived from medical files of patients admitted to our Burn Wound Center having had at least one positive blood culture between 1 January and 31 December 2018. We focused on the prevalence of causative agents in blood stream infections in function of the time after injury and on their drug sensitivity.

Results: Among the 363 patients admitted to our Burn Wound Center during the study period, 29 had at least one episode of blood stream infection. Gram-negative organisms accounted for 56.36% of the pathogens in blood stream infections, Gram-positives for 38.17%, and yeasts for 5.45%. *Pseudomonas aeruginosa* was the most common bacterium (20%), followed by *Staphylococcus epidermidis* (16.36%), *Escherichia coli* and *Klebsiella pneumoniae* (9.09% each). A third of the Gram-negative isolates were multidrug resistant. Gram-positive cocci were isolated from blood cultures at a median of 9 days after the injury, earlier than Gram-negative rods (median 15 days). The main sources of blood stream infections were the burn wounds, followed by infected catheters.

Conclusions: Multidrug resistant bacteria must be considered when selecting empirical antibiotic therapy in septic burn patients. In our center, we need to update our antibiotic guidelines, to review the hospital infection control measures and to introduce routine typing technology.

1 Introduction

Burns are one of the most common forms of trauma. Because of the important role of the skin as a barrier to microbial invasion, the risk of burn wound infection and systemic infection correlates with the size of the burn injury [1,2]. Besides the loss of the protective skin barrier, there are also several other factors that predispose severely burned patients to septic complications: burn trauma causes a generalized immune deficit due to impaired function of both the cellular and humoral immune systems and the massive systemic inflammatory response syndrome causes a general systemic disarray. Burn patients are more at risk of gastrointestinal translocation and are more likely to be ventilated and to require the use of invasive catheter and monitoring devices [1,3]. During the past decades, the mortality following burn injury has gradually declined as a result of improved burn wound management and reanimation techniques, but also as a result of the decrease over time of the average extent of burn injury [4–7]. Several factors have been shown to influence the outcome of burn victims, some patient-related, such as the presence of major risk factors for death (age 60 years or over, total burn surface area (TBSA) above 40%, the presence of inhalation injury) and some management-related: practices such as fluid resuscitation, early excision and grafting of the burn wound, continuous feeding of high-carbohydrate, high-protein diets, aseptic techniques employed in managing these patients, as well as the emergence of highly equipped and specialized burn wound centers (BWC) [1,7–13]. Blood stream infections (BSI) in patients with severe burn injuries are associated with longer durations of hospitalization and mechanical ventilation [14].

The aims of this study were to investigate the incidence, etiology and antibiotic susceptibility of BSI in...
our BWC in order to gain a better understanding of their impact, to issue actualized local antibiotic guidelines and to better monitor our preventive strategies.

2 Materials & methods

2.1 Study design

We conducted a monocentric retrospective observational study of all adult patients admitted to our BWC, which consists of a Burn Intensive Care Unit (BICU) with 7 separate isolation rooms and a Burn Medium Care Unit (BMCU) with 16 separate isolation rooms, having had at least one positive blood culture between 1 January and 31 December 2018. Documentation of all bacterial and fungal blood isolates from the BWC was obtained from medical records retrieved retrospectively from a computerized, hospital-wide database. We collected the following data from the electronic medical records: demographic characteristics (age, sex, length of hospital stay, type of hospitalization unit), underlying diseases, mechanism of burn, percentage of TBSA burnt, inhalation injury, delay between accident and admission to the BWC, length of mechanical ventilation, types of catheters and length of catheter usage, delay between the burn injury and the positive blood culture (BC), the clinicians’ diagnosis, type and length of antibiotic treatment and outcome at discharge. Furthermore, we gathered the antibiotic susceptibility analysis of all available blood, urine, sputum, wound and catheter cultures. To determine the relationship between BSI and infections in other clinical sites, a comparison was done between the isolates found in the BC and the results of the urine, sputum, wound and catheter cultures collected on the same day as the positive blood cultures or on the previous or the following day. When deciding on the origin of the Septic episodes, the following elements were also taken into account: the patients’ clinical and radiological findings and the clinicians’ diagnosis at the moment of the positive BC result.

2.2 Ethics

This study was approved by the Institutional Medical Ethics Committee (reference CE 2018/81). Data collection required no contact with the patients and no clinical samples other than those relevant for their treatment were collected. Patient records/information were anonymized and de-identified prior to analysis.

2.3 Microbiological methods and definitions

All cultures were examined in the hospital’s microbiology laboratory. Wound swabs were routinely obtained twice a week. BC was obtained from a peripheral vein when possible, using aseptic techniques to prevent contamination. When venipuncture was not possible because of extensive burn wounds, the BC was obtained via the external hub of the existing catheters. At least 10 ml of blood was collected, with aerobic bottles collected first. BC was examined using the BACT/ALERT System (BioMérieux, France). Microbe identification was done using MALDI-TOF MS (Biotype IV 4.2.80, Bruker Daltonics, Germany). Antimicrobial susceptibility testing was performed with the Vitek 2 system (BioMérieux, France). When necessary, additional testing was done using disk diffusion or Epsilometer test (Etest), both manufactured by BioMérieux, France. The antimicrobial susceptibility was reported using the clinical breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), version 8.0, 1 January 2018 [15].

BSI was defined as the isolation of bacteria and fungi that are not normally known to colonize the skin from at least one BC. Catheter-related blood stream infection (CRBSI) was considered positive in patients having an intravascular device and at least one positive BC result and a positive catheter tip culture with the same isolate. Central line-associated blood stream infection (CLABSI) was defined as BSI with clinical manifestations of infection and no apparent source with the exception of the catheter [16–18]. For coagulase negative staphylococci (CNS), which are normal skin colonizing bacteria, positive BC was considered to be true BSI when at least two separate positive blood cultures with the same isolate were present or when a CLABSI or CRBSI was suspected because of clinical local catheter signs and/or a simultaneous positive catheter culture with the same isolate as in the BC was detected.

If a patient presented more than one positive BC during hospitalization, BC with positive results yielding the same organism that had been recovered from blood samples obtained in the previous 6 days was excluded when counting the number of BSI.

The percentage of TBSA burnt was calculated using the Wallace rule of nines. Bronchoscopy was performed in patients with suspected inhalation injury to confirm the diagnosis.

Resistant bacteria were classified using the definitions proposed by Magiorakos et al. [19]: multidrug-resistant (MDR) as non-susceptible to ≥1 agent in >3 antimicrobial categories, extensively drug-resistant (XDR) as non-susceptible to ≥1 agent in all but ≤2 categories and pandrug-resistant (PDR) as non-susceptible to all antimicrobial agents.

2.4 Statistical analysis

Continuous data were presented as mean ± standard deviation or percentage (%) if normally distributed.
Abnormally distributed variables (such as duration of hospital stay) were represented by median values (range). Abnormally distributed values were compared using the Mann–Whitney test. A p value of <0.05 was considered significant. All analyses were conducted in SPSS 21 (IBM, 2012).

3 Results
3.1 Descriptive epidemiology

A total of 363 patients were admitted to our BWC between 1 January and 31 December 2018. Seventy-nine were admitted to the BICU and 284 to the BMCU. Among the 363 patients, 315 were admitted for burn wounds, 10 for electrical burns, 7 for inhalation and/or CO intoxication without burn wounds, 6 for gas gangrene, 3 for necrotic fasciitis, 3 for degloving injuries, 2 for frostbite injuries, one for a Stevens–Johnson syndrome and one for a Lyell syndrome. The remaining 15 patients were former burn wound patients, readmitted for reconstructive surgery. During this period, a total of 1810 BC were performed for the BWC patients, of which 95 were positive for one or more microorganisms. We identified 42 episodes of BSI in 29 patients: 19 (66%) patients had one episode, 8 (28%) had two episodes, one (3%) had three episodes and one patient (3%) had four episodes of BSI during hospitalization. Among the 10 patients with two or more BSI episodes, 7 had BC yielding different bacteria and/or Candida species. For the three patients having positive BC growing the same bacterium, we relied on the clinical and biological evolution and on the clinicians’ diagnostic to differentiate between episodes. BC with positive results yielding the same organism that had been recovered from blood samples obtained in the previous 6 days was excluded when counting the number of BSI. The most common type of burn lesion in BSI patients was caused by fire (15 patients), followed by scald (3 patients), explosion (2 patients), unknown mechanism of injury (1 patient), and electrical injury (1 patient). The other BSI patients had been admitted for gas gangrene (2 patients), smoke inhalation, necrotic fasciitis, pyelonephritis, Stevens–Johnson syndrome, and Lyell syndrome (1 patient each, respectively). The demographic characteristics of our study group are presented in Table 1.

Among the seven deceased patients, three died during the septicemic episode (one BSI involving an Enterobacter cloacae, one involving an Escherichia coli and one involving a Candida albicans). However, none of these deaths were directly attributed to the BSI, as the first patient died as a direct result of smoke inhalation, and the other two patients, aged 75 and 76, respectively, had extensive wounds (TBSA burnt of 25%, and 65%, respectively) and several comorbidities. A fourth and a fifth patient died of extensive wound infections (both with XDR Pseudomonas aeruginosa isolates) after the septicemic episode had resolved. Two deaths had non-infectious causes: one patient died as a direct result of the extensive burn wounds and smoke inhalation and another of pulmonary embolism. The origin of the BSI was considered to be the burn wound in 15 cases (35,7%), CRBSI in 9 cases (21,4%), pneumonia in 2 cases (4,8%), pyelonephritis in 2 cases (4,8%), CLABSI in one case (2,4%), abdominal in one case (2,4%) and endocarditis in one case (2,4%). In six cases (14,2%), the origin was attributed to both an infected catheter and the burn wound, as the isolates detected in the blood were also cultivated from the wounds and from the tip of the catheters, inserted in the proximity of the wounds. In five cases (11,9%) the origin of the BSI was uncertain (digestive translocation was suspected).

Thirty-two episodes of BSI (76%) were monomicrobial, 7 episodes (17%) involved 2 isolates and 3 episodes (7%) involved 3 isolates. A total of 55 pathogens were cultivated from the BC.

3.2 Microbiology

From the 55 culture isolates, Gram-negative bacteria accounted for 56,36% of the organisms, Gram-positive bacteria accounted for 38,18% and yeasts accounted for 5,45%. Table 2 details the microorganisms isolated from the BC and their suspected starting points.

P. aeruginosa was the most common pathogen with 11 cases (20%), followed by Staphylococcus epidermidis with 9 cases (16,36%), E. coli and Klebsiella pneumoniae spp pneumoniae with 5 cases (9,09%) each. The yeasts consisted entirely of Candida species: 2 cases (3,63%) of C. albicans and 1 case (1,81%) of C. glabrata. All Staphylococcus aureus isolates were susceptible to mexitilin, while 90,90% of the CNS were resistant to mexitilin. The only Streptococcus pneumoniae was susceptible to penicillin. All Enterococcus faecalis and the only Enterococcus faecium isolate were susceptible to ampicillin. All Gram-positive cocci (GPC) were susceptible to vancomycin. Among the Gram-negative rods (GNR), 7 isolates (22,58%) were MDR and 3 isolates (9,67%) were XDR organisms. The overall resistance rates of GNR to ciprofloxacin, piperacillin-tazobactam, ceftazidime, meropenem and gentamicin were 40%, 23,33%, 26,66%, 23,33% and 10%, respectively. One

<table>
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<th>Table 1. Demographic characteristics of the patients. SD: standard deviation.</th>
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<td>Characteristics</td>
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<td>Age (years), mean ± SD (range)</td>
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<td>% Affected TBSA ± SD (range)</td>
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TBSA: total body surface area.
of the _K. pneumoniae_ spp _pneumoniae_ strains exhibited resistance to colistin, confirmed by broth microdilution method. Two GNR (one _K. pneumoniae_ and one _Serratia marcescens_) were ESBL-producing bacteria. Two _K. pneumoniae_ spp _pneumoniae_ were carbapenemase-producing (one produced OXA-48). The mechanism of resistance was not available for all isolates, as our laboratory did not have the necessary resources. The rates of resistance of the _P. aeruginosa_ strains to ciprofloxacin, piperacillin-tazobactam, ceftazidime, meropenem, tobramycin and gentamicin were 36.36%, 9.09%, 9.09%, 27.27%, 18.18% and 9.09%, respectively. One _P. aeruginosa_ isolate was MDR and one XDR. All _Acinetobacter baumannii_ isolates were MDR and were resistant to fluoroquinolones, piperacillin-tazobactam, third and fourth generation cephalosporins and trimethoprim-sulfamethoxazole. Two-thirds (66.6%) of the _A. baumannii_ isolates were resistant to carbapenems, but none were resistant to colistin, tobramycin or tigecycline.

In this study, BSI was diagnosed within 1 to 126 days after hospitalization (median 11 days, IQR = 5–27). When analyzing the cohort of patients hospitalized for burn wounds, the median number of days from the burn injury to the occurrence of BSI was 15 days (IQR = 5–28). From the day of the accident, GPC were isolated in the blood culture the earliest after a median of 9 days (IQR = 5–31), followed by GNR with a median of 15 days (IQR = 6–27), _C. albicans_ (26 days) and _Bacillus cereus_ (126 days). Figure 1 details the time duration between injury and positive blood culture by classes of microorganisms and by source of infection and Figure 2 details the time between the injuries and the detection of the positive blood culture for each microorganism.

In this study, the most common pathogen encountered in the first week after the injury was _S. epidermidis_, followed by _E. coli_, _P. aeruginosa_ and _Enterobacter cloacae_. While the GPC and the GNR are equally detected during the first 2 weeks after the injury, a marked shift to GNR is observed beginning with the third week, with _P. aeruginosa_ becoming the dominant pathogen.
4 Discussion

The overall mortality of patients exhibiting a BSI was 24.1% in this study, comparable or lower to the mortality reported in other similar studies [20–22]. Understanding the local epidemiology of our BWC and the extent of bacterial resistance is essential for developing actualized local antibiotic guidelines and for adapting the strategies designed to reduce hospital-acquired infections.

In this study, Gram-negative organisms accounted for 56.36%, Gram-positives for 38.17%, and yeasts for 5.45% of the causative pathogens for BSI. Other BWC also reported a predominance of GNR in blood cultures [14,22–24]. Among the GNR, a third of the strains were at least MDR organisms (22.58% strains were MDR and 9.67% strains were XDR organisms). The overall resistance rates of the GNR to large spectrum antibiotics such as third-generation cephalosporins and meropenem were 26.66% and 23.33%, respectively. One of the possible explanations for this particular epidemiology could be a patient selection bias. Our BWC is one of the largest in the region and frequently receives patients with large TBSA burnt referred by other centers. The mean affected TBSA in this study was 38 ± 20%. Also, our BWC has agreements with some Eastern European and North African countries to accept transfers of severely burnt patients. These regions are known for reporting higher prevalences of MDR GNR [25,26]. Multidrug resistance is a known emerging problem in burn patients. In a study conducted by van Langeveld et al. [27], MDR infections resulted in longer hospitalization, longer need for mechanical ventilation, and longer duration of antibiotic treatment. Also, in their study, burn patients with MDR infections were more likely to progress into a state of sepsis or organ failure. All these factors contribute to making the treatment of MDR infections in burn patients a challenge.

P. aeruginosa was the most common pathogen encountered in BSI in this cohort. Other BWC also reported P. aeruginosa as the most prevalent pathogen in BSI [22–24,28]. The use of hydrotherapy in the treatment of the burn wounds, long hospital stays, previous administration of broad-spectrum antibiotics and delayed wound excision are all factors that provide a favorable niche for the development of P. aeruginosa. In this study, we found low rates of piperacillin-tazobactam, ceftazidime and gentamicin resistance in P. aeruginosa. However, almost a third of the isolates showed resistance to meropenem. One of the P. aeruginosa isolates was MDR and one was XDR. These findings were unsettling, as our center experienced MDR P. aeruginosa outbreaks in the nineties due to insufficient compliance with infection control measures and to selective pressure from systemic antibiotics and locally applied silver sulfadiazine-based antibacterial creams [29]. Unfortunately, neither genotyping nor serotyping was available for this study, making further differentiation of the isolates into distinct strains or clones impossible. Consequently, we could not further investigate the presence of known epidemic strains or differentiate between locally circulating or imported strains. MDR P. aeruginosa strains can lead to therapeutic ‘dead ends’, requiring alternative strategies for treatment. In our center, bacteriophage therapy is increasingly considered as part of the salvage therapy for patients in whom no alternative solution is available [30,31].

In this study, the median number of days to the occurrence of BSI was 15 days after burn injury. Our data reflect those of other BWC [21,22]. In our cohort, GPC were isolated in the blood culture after a median of 9 days from the day of the accident, followed by GNR with a median of 15 days. The most common pathogen encountered in the first week after the injury and the second most isolated organism overall was S. epidermidis. Our findings confirm that infections by Gram-positive organisms are characteristic of the early period of burn injuries [1,32]. Subsequently, Gram-negative organisms gradually replace Gram-positives, as wounds are colonized with microbes derived either from the patient’s own gastrointestinal and upper respiratory flora or with organisms transferred via health-care workers’ hands or from the hospital environment. Then, with delayed wound closure and an increase in the need for broad-spectrum antibiotics, further replacement with fungi and antibiotic-resistant bacteria takes place [1,32].

In this study, the majority of BSI originated in the burn wound. The burn wound was incriminated as the starting point in 35.7% of the episodes and in another 14.2% of the episodes, we could not establish with certainty if the exact origin of the BSI was the wound or the nearby inserted catheter, as the same organism was detected in the blood, wound and
catheter tip cultures and the incriminated catheter had been inserted either just at or in proximity to the burn wound site. The second cause of BSI in this cohort were infected catheters. These findings are consistent with those published by Lee and al [22]. CRBSI is one of the most frequent hospital-acquired infections [33–36] and are even more frequent in burn patients, in whom venous catheters are frequently inserted either just at or in proximity to the wound site because of the limited availability of intact skin. Given their proximity to the wound, the catheters can easily be contaminated, as demonstrated by Franceschi et al. [37]. Also, unlike other intensive care unit (ICU) patients, those with major burns cannot always be treated with common practices for preventing catheter infections [38]. Therefore, the incidence of CRBSI in patients in the BICU can be two to three times higher than that in patients in other ICU [39].

This study has several limitations. First, it is a small retrospective monocentric study, with a limited number of subjects and observed events. Due to the retrospective nature of the study, clinical data were sometimes incomplete so we relied upon the final diagnostic encoded by the clinician. Therefore, it is highly probable that some of the CNS detected in the BC were actually contaminants and that CNS BSI were overdiagnosed and overtreated. Another limitation is that no distinction was made between patients admitted to the BICU and the BMCU, mainly because some patients alternated between these locations, making it difficult to establish where they were infected. One limitation derives from the fact that our BWC uses hydrotherapy in the treatment of burn wounds, which is not the case in all centers. Therefore, our results cannot be extrapolated to BWC using other treatment protocols. Our study also has several limitations regarding the microbiology methods. Due to the extensive wounds presented by some of the patients, blood cultures drawn by the venipuncture of a peripheral vein were not always possible and we sometimes had to rely on blood cultures collected through the external hub of the catheters, which increases the risk of blood culture contamination. Another important limitation is the lack of strain typing data. Currently, neither serotyping nor genotyping nor other fingerprinting technology is available in routine in our hospital. Also, the mechanism of resistance was only available for some MDR isolates, as our laboratory did not have the possibility to do specific testing, such as carbapenemase detection, in 2018. Finally, the timespan of 1 year was too short to detect any significant trends in the evolution of pathogen diversity or antibiotic resistance patterns.

Nevertheless, the current study allowed us to have a better understanding of our local epidemiology. In the future, we aim to implement a strain fingerprinting technique and a prospective surveillance system of CRBSI.

5 Conclusions

In this study, Gram-negative organisms accounted for the majority of the causative agents of BSI in burned patients. The most commonly encountered pathogen in BSI was \textit{P. aeruginosa}. In our center, MDR bacteria must be taken into consideration when choosing empirical antibiotics in severe burn patients prior to receiving the results of the microbiological culture tests. In this cohort, the first two causes of bacteremia were burn wounds, followed by infected catheters. In addition to updating the local antibiotic guidelines, we need to review the bundles of hospital infection control measures and to introduce routine typing technology.

Authors’ contributions

DICS: Conceptualization, Methodology, Ethics Committee, Data Curation, Writing Original draft, Editing. JLG Microbiological diagnosis, Writing-Reviewing and Editing. PMF, MSP clinical supervision, Writing-Reviewing and Editing. DB: Data Curation. JPP, DDV, SD, PV: Writing-Reviewing and Editing. MS: Statistical analysis, Graphics, Writing-Reviewing and Editing. PS Methodology, Project Administration, Writing-Reviewing and Editing, Supervision, Validation.

Disclosure statement

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