

## TRENDS IN NOSOCOMIAL BLOODSTREAM INFECTIONS IN A BURN INTENSIVE CARE UNIT: AN EIGHT-YEAR SURVEY

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**SUMMARY.** This study was designed to evaluate the frequency and profile of bloodstream infection (BSI) in a burn intensive care unit (BICU) in Tripoli, Libya, from 1st January 2000 to 31st December 2007 and to determine the prevalence of different bacteria involved in such infections and their antimicrobial susceptibilities. During the eight-year study period, 995 patients were admitted to the BICU. Blood cultures were collected from each septicaemic case and reviewed for age, sex, total body surface area burned, isolated micro-organisms, and antibiotic sensitivity. There were 430 episodes of BSI among 830 cases; the annual true positive rate varied between 40.0 and 59.4%, the majority (87.9%) being caused by one species only. However, 22% had two or more episodes with different pathogens during hospitalization. The leading isolate was *Staphylococcus aureus* (40.4%) (methicillin-resistant, 55.7%). *Pseudomonas* spp ranked second (23.9%). *Klebsiella* spp were third, responsible for 7.4%; the rate of extended spectrum beta lactamase among *Klebsiella* isolates was 47%. *Candida* spp were the fourth most common pathogen (6.7%), the majority (55%) being *C. albicans*. *Staphylococci* were generally resistant to trimethoprim (91%) and fusidic acid (80%). *Pseudomonas* spp proved moderately resistant (38-43%) to tobramycin, ciprofloxacin, amikacin, and imipenem but remained relatively susceptible to ceftazidime (72%). *Klebsiella* isolates demonstrated moderate resistance (46-58%) to most agents tested, and relatively low resistance (19-27%) to meropenem, imipenem, and ceftazidime. We suggest that extra infection control measures should be implemented and antibiotic policy and guidelines introduced to reduce the high resistance rate among isolates such as *Pseudomonas*, *Acinetobacter*, and MRSA.

**Keywords:** Bloodstream infection, burn intensive care unit, MRSA, *Pseudomonas*

### Introduction

Hospital-acquired bloodstream infection (BSI) is a serious health care problem worldwide associated with significant morbidity and mortality.<sup>1,2</sup> It accounts for 10-15% of hospital-acquired infections and increases costs of hospitalization.<sup>3,4</sup> In the United States, 10-20% of nosocomial infections are estimated to involve the bloodstream.<sup>5</sup> Appropriate antimicrobial treatment of BSI is critical in decreasing morbidity and mortality due to BSI;<sup>6</sup> many surveillance studies indicate a trend of increasing antimicrobial resistance among common pathogens such as staphylococcal species, the most common bacteria reported for BSI among patients in intensive care units.<sup>7</sup> Some previous reports of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) found higher mortality rates, increased morbidity, and longer length of hospital stay.<sup>8,9</sup> Risk

factors for MRSA blood infections have been extensively described but vary among institutions and patient populations.<sup>10,11</sup> *Candida albicans* was reported to be associated with the highest mortality rate, ranging from 40-70%,<sup>12,13</sup> and BSI with Gram-negative bacteria (17%).<sup>14</sup> The frequency of Gram-negative sepsis has diminished over the last 20 years; however, *P. aeruginosa* is considered an important nosocomial BSI pathogen with a high associated mortality.<sup>15</sup>

Identification of BSI bacterial pathogens combined with determination of antimicrobial susceptibility of the bacteria can help clinicians to select appropriate agents for rigorous empirical treatment of BSI.<sup>16</sup> Although eradication of infection in burn patients is impossible, a well-conducted effective surveillance, infection control and a prevention measures programme can help to reduce the incidence. In recent years, studies of epidemiology, microbiological ae-

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tiology, and prognosis have been performed worldwide.<sup>17-21</sup> The aim of the current study is to evaluate the frequency and profile of bacteraemia and antimicrobial susceptibilities of BSI among patients at the Burn Plastic Surgery Centre, Tripoli, Libya.

### Patients and methods

Between January 2000 and December 2007, information regarding all patients with microbiological evidence of septicaemia admitted to the burn intensive care unit (BICU) at the Burn Plastic Surgery Centre in Tripoli, Libya, was collected and reviewed for age, sex, and TBSA, isolation of micro-organisms and antibiotic sensitivity. Blood was obtained under aseptic conditions. At least two sets of blood cultures were collected for each case. Ten ml of blood were aseptically collected from adults and 2-5 ml from paediatric cases. The samples were added to bottles of blood culture medium (OXOID, England), incubated at 37 °C, and monitored for 7 days. All bottles designated positive were examined by Gram stain and subcultured on blood agar and MacConkey and Sabouraud agar (OXOID, England), and also screened on selective and differential chromogenic medium, MRSA ID medium (bioMérieux, France). Green colonies on MRSA ID plates at 24 and 48 h were identified as MRSA; all isolates were identified using standard diagnostic microbiological methods of micro-organism isolation.<sup>22</sup> Specimens that grew more than one organism were also subcultured, the organisms being separated and identified by standard diagnostic methods. *Candida* species that were isolated from blood cultures were identified using API-20 C AUX system (bioMérieux, Lyons, France). A single positive blood culture was necessary for a diagnosis of BSI. The detection of the same organism in one or more blood cultures from the same patient within one week was defined as a single episode.<sup>23</sup> The antibiotic susceptibility of each isolate was tested manually according to the Clinical Laboratory Standards Institute (CLSI) guidelines,<sup>24</sup> and all isolates were inoculated onto Mueller Hinton medium (OXOID, England). Detection of methicillin resistance was carried out according to CLSI guidelines for detection of MRSA by using disk diffusion technique (cefoxitin 30 µg and oxacillin 1 µg). All *S. aureus* isolates were further evaluated and confirmed by detection of PBP2a latex agglutination (bioMérieux, France); *S. aureus* ATCC 33591 was included as a reference strain for quality control. All *Klebsiella* isolates were subjected to extended spectrum beta lactamas (ESBL) detection by using chromogenic medium, ESBL ID medium (bioMérieux, France).

### Results

During the study period, 995 patients were admitted

**Table I** - Episodes of bloodstream infection in the burns intensive care unit (2000-07)

Year	Admissions	Blood culture	Positive (%)
2000	154	111	54 (48.6)
2001	117	116	69 (59.4)
2002	123	93	48 (51.6)
2003	89	98	54 (55.1)
2004	86	122	63 (51.6)
2005	122	100	54 (54)
2006	183	131	64 (48.8)
2007	121	60	24 (40)
Total	995	830	430 (51.8)

**Table II** - Polymicrobial episodes (52 episodes) of bloodstream infection (2000-07)

Year	Two isolates	Three isolates
2000	10	1
2001	8	4
2002	5	1
2003	6	2
2004	6	0
2005	3	0
2006	6	0
2007	0	0
Total	44 (84.6%)	8 (15.4%)

to BICU for periods ranging from 14-45 days. The majority had indwelling vascular catheters and respiratory intubation and were on broad-spectrum antimicrobial therapy including gentamicin, amikacin, ciprofloxacin, ceftriaxone, impenem, meropenem, or cefepime. In addition, vancomycin was used to treat all MRSA cases. There were 585 males (58.5%) and 410 females, with a male:female ratio of 1.4:1. The median age was 35 (range 2 months-85 years). The mean TBSA was 55% (range 10-90%). There were 430 (51.8%) episodes of BSI identified among 830 patients; the annual proportion of BSI varied between 40-59.4% (*Table I*). However, 22% of these cases had two or more episodes of BSI detected at different intervals and caused by different pathogens during hospitalization at BICU. Among the 430 episodes of BSI, the majority (87.9%) were caused by a single species while only 52/430 (12.1%) were caused by a combination of more than one species of micro-organism. Overall, 44/52 cases (84.6%) had simultaneous infection caused by two isolates, while a combination of three different micro-organisms was observed in 8/52 (15.4%). No infections due to two or more species were observed during the last year of the study (*Table II*).

*Table III* summarizes the distribution of micro-organisms isolated over the eight years. Gram-positive species represented 231 of the 430 cases (53.7%), Gram-negative

**Table III** - Isolates from 430 episodes of bloodstream infection (2000-2007)

1. Gram positive : 231 (53.7%)	
<i>S. aureus</i>	174 (40.4)
CNS*	24 (5.5)
<i>Streptococcus pyogenes</i>	18 (4.1)
Enterococci	15 (3.4)
2. Gram negative : 170 (39.5%)	
<i>Pseudomonas</i> spp	103 (23.9)
<i>Klebsiella</i> spp	32 (7.4)
<i>Acinetobacter</i> spp	10 (2.3)
<i>Enterobacter</i> spp	9 (2.0)
<i>Escherichia coli</i>	7 (1.6)
<i>Proteus</i> spp	6 (1.3)
<i>Serratia</i> spp	2 (0.4)
<i>Erwinia</i> spp	1 (0.2)
3. Fungal	
<i>Candida</i> spp	29 (6.7%)

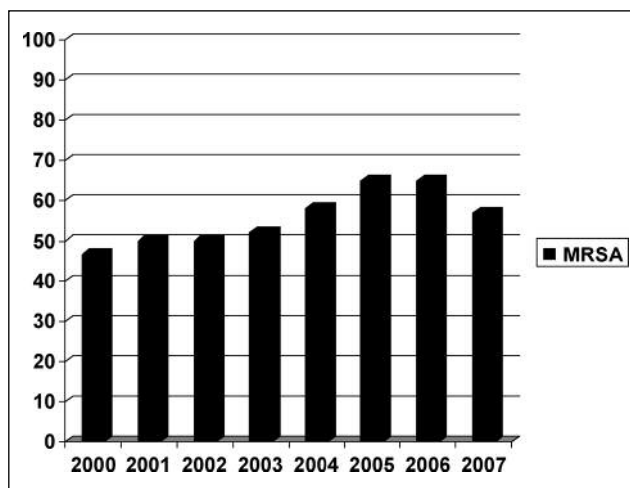
\* Coagulase-negative *Staphylococci*

**Table IV** - Resistance of *Pseudomonas* and *Klebsiella* isolates to antimicrobial agents

Antibiotic	<i>Pseudomonas</i>	<i>Klebsiella</i>
Trimethoprim	74	81
Gentamicin	62	77
Tobramycin	38	54
Amikacin	40	47
Augmentin	67	73
Ceftriaxone	65	58
Cefoxitime	62	83
Ceftizidim	57	78
Cefepime	28	19
Ciprofloxacin	40	46
Meropenem	64	25
Impenem	43	27

accounted for 170/430 (39.5%), and 29/430 (6.7%) were caused by *Candida* species. Among Gram-positive organisms, the leading isolate was *S. aureus* (174/430, 40.4%) and 97 (55.7%) were MRSA. The percentage of MRSA varied during the successive eight years of the study, as follows: 46.6%, 50%, 50%, 52%, 58%, 65%, 65%, 57% respectively; the average was 55.5% (Fig. 1). Methicillin resistance was detected among coagulase-negative staphylococcal isolates (7/24, 29.1%).

*Pseudomonas* spp (103/430, 23.9%) were the most common Gram-negative isolate, the majority (85/103, 82.5%) being *P. aeruginosa*. *Klebsiella* spp were the second most common (32/430, 7.4%). The proportion of ES-BL among *Klebsiella* isolates was 47%. *Candida* species



**Fig. 1** - Distribution of MRSA between 2000-2008.

were the fourth most common isolate (29/430, 6.7%) (Table III). *Candida albicans* was the most common (55%). Many of the candidaemia episodes (21/52, 40.3%) were associated with other isolates such as *Staphylococci*, *Pseudomonas*, and *Klebsiella*. Candidaemia was not detected during the last two years of the study.

Antimicrobial sensitivity data for the most frequently isolated organisms are shown in Table IV. The results showed variability in susceptibility among pathogens and among antimicrobial agents.

*Staphylococci* were generally resistant to trimethoprim (91%) and fusidic acid (80%) but relatively less resistant to ciprofloxacin (52%). *Pseudomonas* spp proved moderately resistant (38-43%) to tobramycin, ciprofloxacin, amikacin and imipenem but remained relatively susceptible to cefepime (72%). *Klebsiella* isolates demonstrated moderate resistance (46-58%) to most agents tested such as tobramycin, amikacin, cefoxitime, ceftriaxone, and ciprofloxacin, but there was relatively little resistance (19-27%) to meropenem, imipenem, and cefepime.

Generally, most pathogens studied were resistant to trimethoprim (74-91%). The activity of cephalosporins against Gram-negative organisms was mixed - cefepime was often more active than the other cephalosporins. Among the aminoglycosides, amikacin was relatively active against the most commonly isolated organisms compared with gentamicin, while ciprofloxacin proved to be a moderate active agent against these organisms. No antifungal susceptibility was carried out in the study. However, all patients received fluconazole as treatment for candidaemia.

### Discussion

During the eight-year study period, out of 830 blood

cultures from suspected cases with clinical evidence of septicemia referred to our laboratory, 51.8% were found to be blood-culture positive by the conventional diagnostic techniques used in the study. Data from the National Nosocomial Infections Surveillance System (NNIS) from 1995 to 2000, involving nearly 800 intensive care units (ICUs) demonstrated that BSI rates were higher in burns ICUs compared with other types of ICU.<sup>25</sup> Similarly to our results, specialized Brazilian BICUs showed that primary BSI was the most common infection (49%).<sup>26</sup> However, two separate studies conducted in burns care units in Iran and Turkey recently demonstrated that the BSI rate (18.6% and 19.9% respectively) was lower than in our study.<sup>27,28</sup> In a different setting, it was demonstrated that among haemodialysis patients the incidence of BSI among the patients who used a double-lumen central venous catheter was very high (61%), and it was concluded that the risk factors for developing BSI were the use of a catheter in the internal jugular vein, the duration of catheter use, and length of hospitalization.<sup>29</sup> In another study, up to 49% of cancer patients admitted to an ICU developed nosocomial BSI.<sup>30</sup>

The causative organisms of BSI have changed over time. In the 1960s and 1970s, Gram-negative bacteria were more predominant causative agents but over the last few decades there has been a shift toward predominance by Gram-positive bacteria.<sup>31</sup> There have been reports suggesting 70-81% of the bacteria isolated from BSI are Gram-positive.<sup>32,33</sup> Similar trends were also observed in BICUs.<sup>26,28</sup> The distribution of micro-organisms isolated over the eight years was as follows: Gram-positive species (53.7%) figured as the leading cause of BSI, followed by Gram-negatives (39.5%), and *Candida* spp (6.7%). Santucci and colleagues found that the pattern of the main micro-organisms associated with BSI in BICUs was *S. aureus* (24%), *P. aeruginosa* (18%), and *Acinetobacter* (14%), followed by *Candida* (8%).<sup>26</sup>

In this study, the majority (87.9%) of BSI episodes were caused by a single species and only 12.1% of the cases were polymicrobial. In addition, among the population studied, 22% had two or more episodes of BSI detected at different intervals caused by different pathogens during hospitalization in the BICU. No polymicrobial episodes were detected during the last year of the study. A previous study<sup>34</sup> showed that patients with polymicrobial infection involving *P. aeruginosa* had worse clinical courses and developed shock more frequently. A major difficulty is the choice of an appropriate antimicrobial treatment for polymicrobial infection involving *P. aeruginosa*.<sup>35</sup> This problem is even greater if *Candida* is the co-pathogen.<sup>36</sup> Similarly, in this study the majority of polymicrobial BSI episodes involved *Candida* spp as a co-pathogen associated with *Staphylococci*, *Pseudomonas*, and *Klebsiella* spp. Many studies have associated polymicrobial infection with

higher mortality.<sup>37,38</sup> During this study period, candidaemia was the fourth most frequent isolate, exceeded only by *Staphylococci*, *Pseudomonas*, and *Klebsiella*. No candidaemia was detected during the last two years of the study. *C. albicans* was the most common pathogen (55%). It has been shown that it continues to account for approximately half of all episodes of candidaemia reported worldwide; nevertheless, frequencies vary widely from institution to another.<sup>39,42</sup> However, our findings were similar to those in the United States of America (52-54%), reported from surveillance studies, and indicated that many candidaemia episodes (40.3%) were associated with other isolates such as *Staphylococci*, *Pseudomonas*, and *Klebsiella*.<sup>43-45</sup>

Antibiotic resistance was common, including MRSA, ESBL-producing isolates, and multiple drug-resistant (MDR) organisms, such as *Acinetobacter*. The three most common isolates were evaluated for susceptibility to antimicrobial agents. The results showed great variability in susceptibility among pathogens and among antimicrobial agents. With regard to pathogens, the leading isolate associated with BSI was *S. aureus* (40.4%); the incidence rate of *S. aureus* has increased over the years.<sup>6</sup> MRSA was responsible for 55.7% of the cases. The percentage of MRSA rate increased steadily during the first seven year of the study (46.6-65%) but declined to 57% during the last year of the study. Another study in Turkey demonstrated that MRSA among BICU patients was high (40%),<sup>28</sup> while BSI evaluated among Brazilian patients on haemodialysis identified the most frequently isolated organism as Gram-positive (49%), of which *S. aureus* was the most prevalent, while the MRSA rate was 43.4%.<sup>25</sup> Our results are comparable to many studies, as multi-resistant MRSA has been reported to be relatively high in African countries including Morocco, Kenya, Nigeria, and Cameroon.<sup>47</sup> Comparable results were also found in South Africa,<sup>48</sup> where 84.7% of MRSA isolates were resistant to at least four classes of antibiotics. The risk factors for methicillin resistance in *S. aureus* have been extensively described but vary among institutions and patient populations.<sup>49,50</sup> Recently, linezolid has been introduced into the therapeutic arsenal for combating MRSA infection in our BICU, on the basis of a study carried out on MRSA isolates obtained from burn patients,<sup>51</sup> but their clinical value is not yet clearly established for BSI. Most *Staphylococci* isolates were resistant to trimethoprim (91%) and fusidic acid (80%) but susceptible to ciprofloxacin. *Pseudomonas* species were resistant (38-43%) to tobramycin, ciprofloxacin, amikacin, and imipenem but remained relatively susceptible to ceftazidime. *Klebsiella* demonstrated resistance (46-58%) to tobramycin, amikacin, ceftazidime, cephtriaxone, and ciprofloxacin but relatively less resistance (19-27%) to meropenem, imipenem, and ceftazidime. The activity of cephalosporins against Gram-negative organisms was mixed - ceftazidime was often more active than

the other cephalosporins. However, clinical experience with cefepime in infections caused by ESBL-producing bacteria is limited, and evidence thus far favours the use of carbapenems.<sup>52</sup> Among the aminoglycosides, amikacin was relatively active against the most common isolated organisms compared with gentamicin, while ciprofloxacin proved to be a moderately active agent against these organisms. It has been demonstrated that *S. aureus* and *Pseudomonas* are the most common resistant organisms identified among burn populations.<sup>53</sup> ESBL-producing strains have become a difficult challenge for clinicians.<sup>52,54</sup> Overall, patients with BSI caused by ESBL-producing pathogens have a higher risk of death than those with BSI caused by non-ESBL-producing pathogens. A prospective study conducted in six countries analysed *K. pneumonia* bacteraemia, and showed that 19% of these organisms were ESBL-positive.<sup>55</sup> The rate of infections caused by ESBL-producing organisms was higher in patients who acquired their infection in hospital (31%), particularly ICU patients (44%). Comparable results were obtained in this study, with 47% of *K. pneumonia* isolates being ESBL-positive. The rate of infections caused by ESBL-producing organisms varied from 59% in Argentina to 25% in the USA and 12% in Belgium. *A. baumannii* is becoming an increasingly significant

pathogen, causing a number of infections including BSI and commonly associated with high mortality.<sup>56</sup> Infection caused by MDR *A. baumannii* led to a return of colistin to clinical practice.<sup>57,58</sup> Nevertheless, resistance to colistin has been reported not only for *A. baumannii*<sup>59</sup> but also for *K. pneumonia*<sup>60</sup> and *Pseudomonas* spp.<sup>61</sup> The emergence of these broadly resistant organisms may reflect selective pressure of the frequently used cephalosporins and fluoroquinolones among the patients.<sup>62,63</sup> Effective surveillance, proper antibiotic policy tailored to local findings, and good adherence to infection control measures may therefore reduce infection, mortality rates, the duration of hospitalization, and associated costs.

### Conclusion

In view of the high incidence of MRSA and the fact that the majority of *Pseudomonas*, *Klebsiella*, and *Acinetobacter* isolates are resistant to most commonly used antibiotics, a comprehensive education campaign is required, together with the institution of more efficient and effective quality control measures in hospital environments. Further study is needed to fingerprint the interrelations of all MRSA isolates.

**RÉSUMÉ.** Les auteurs de cette étude se sont proposés d'évaluer la fréquence et le profil des infections septicémiques dans une unité de soins intensifs pour les patients brûlés (USIB) à Tripoli, Libye, du premier janvier 2000 au 31 décembre 2007 et de déterminer la prévalence des différentes bactéries impliquées dans ces infections et leur sensibilité aux antimicrobiens. Au cours de la période d'étude de huit ans, 995 patients ont été admis à l'USIB. Des cultures sanguines ont été prélevées chez tous les patients atteints de septicémie et analysées du point de vue de l'âge, du sexe, de la surface totale du corps brûlée, des micro-organismes isolés et de la sensibilité aux antibiotiques. Dans 430 épisodes d'infection septicémique sur 830 cas le taux annuel de vrais positifs variait entre 40,0 et 59,4%, la majorité (87,9%) causée par une seule espèce. Toutefois, 22% des patients ont subi deux ou plusieurs épisodes, avec divers agents pathogènes, pendant l'hospitalisation. L'isolat le plus commun était *Staphylococcus aureus* (40,4%) (résistant à la méticilline, 55,7%), avec *Pseudomonas* spp au deuxième rang (23,9%), suivi par *Klebsiella* spp (7,4%); le taux de bêta-lactamase à spectre étendu parmi les isolats de *Klebsiella* était de 47%. Le quatrième agent pathogène était *Candida* spp (6,7%), la majorité (55%) *C. albicans*. Les *Staphylococci* étaient généralement résistants au triméthoprim (91%) et à l'acide fusidique (80%). Les *Pseudomonas* spp ont démontré une résistance modérée (38-43%) à la tobramicine, à la ciprofloxacine, à l'amikacine, et à l'impénème mais sont restés relativement sensibles à la céfépime (72%). Les isolats de *Klebsiella* présentaient une résistance modérée (46-58%) à la plupart des agents testés, et une résistance relativement faible (19-27%) au mérépénem, à l'impénem, et à la céfépime. Selon les auteurs, on devrait appliquer des mesures supplémentaires de contrôle des infections, introduire des politiques antibiotiques et suivre les lignes directrices mises en place pour réduire le taux de résistance élevé enregistré parmi les isolats tels que *Pseudomonas*, *Acinetobacter*, et *Staphylococcus aureus* résistant à la méticilline (40,4%).

**Mots-clés :** infection de la circulation sanguine, unité des soins intensifs des grand brûlés, MRSA, *Pseudomonas*

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