Laboratory confirmed bloodstream infection aetiology in an intensive care unit: eight years study

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Key words: Bloodstream infection, aetiology, surveillance, ICU
Parole chiave: Setticemia, eziologia, sorveglianza, rianimazione

Riassunto

Eziologia delle setticemie in una unità di terapia intensiva: otto anni di studio

Gli A.A. hanno condotto uno studio prospettico sulla eziologia delle setticemie nell’unità di terapia intensive (UTI) del Policlinico Umberto I di Roma.
Lo studio, applicando le definizioni di caso secondo i CDC, ha incluso tutti i pazienti con degenza ≥ 48 ore ricoverati nel periodo 2000-2007. Sono stati valutati anche eventuali fattori di rischio (i.e. età, sesso, patologie di base...), procedure invasive (intubazione tracheale, cateterismo vascolare ed urinario), microrganismi isolati e la loro suscettibilità agli antibiotici.
In totale sono stati arruolati 1741 pazienti (64.8% maschi, 35.2% femmine), che presentavano un’età media di 58.1 ± 19.8 anni, un SAPS II score di 45.1 ± 17 ed una degenza di 14.0 ± 21.1 gg. In generale, 167 (9.6%) pazienti hanno sviluppato 203 (11.7%) episodi di setticemia la cui sorgente era CVC (39.8%), sconosciuta (39.3%), tratto respiratorio (12.4%), sito chirurgico (6.5%) e tratto urinario (2.0%). Dal 2000 al 2007 l’incidenza di setticemie/1000 gg paziente (14.8‰ vs. 7.8‰; p<0.05) e setticemie/1000 gg CVC (20.7‰ vs. 11.4‰; p<0.05) è diminuita. Lo sviluppo della setticemia dal ricovero in UTI è stato di 19.5 ± 17.7 (media) e 13 giorni (mediana). La mortalità grezza era 34.8%, e la mortalità associata a setticemia ha evidenziato un RR 1.61; 95%CI 1.37 – 1.89; p<0.01. I microrganismi più frequentemente isolati sono stati stafilococchi coagulasi negativi (SCN) (26.2%), Staphylococcus aureus meticillino-resistente (MRSA) (14.9%), Pseudomonas aeruginosa (13.5%), enterococchi (9.3%) e Acinetobacter baumannii (7.5%). Il tempo di sviluppo della setticemia dal ricovero in UTI è stato maggiore (p<0.01) nei Gram-negativi (16.6 ± 15.9), fungi (23.8 ± 25.3).Elevata mortalità precoce (≤7 gg dopo diagnosi di setticemia) è stata associata ad A. baumannii (37.5%), Candida spp. (30.0%) e S. aureus (29.7%). Gli stafilococchi hanno presentato una elevate meticillino-resistenza. P. aeruginosa e A. baumannii hanno evidenziato rispettivamente una elevata multi-antibiotico resistentia (25% e 68.7%). Oltre 1/3 delle Enterobacteriaceae presentavano extended spectrum beta-lactamase (ESBL), ma non risultavano resistenti ai carbapenemici.
La sorveglianza ha evidenziato un’elevata incidenza di setticemie associate a procedure invasive e la pre-senza di microrganismi multi-resistenti.
**Introduction**

Laboratory confirmed bloodstream infection (LC-BSI) is a major problem in intensive care units (ICU), where it affects >10% of patients, causing a high associated mortality >20% (26, 32, 34) and adding costs (3).

Crucial to improving outcomes for patients with LC-BSIs is the administration of appropriate antibiotics in a timely manner, as the prescription of not active antimicrobials represents an independent risk factor for mortality (20). Furthermore, treatment is usually prescribed before the isolated microorganism antimicrobial susceptibility is available, hence it is very useful for physicians to know the ICU microbiological epidemiology before starting the empiric therapy.

Unfortunately antimicrobial resistance among pathogens responsible for LC-BSI is increased, demonstrating a need for surveillance programs to define the species distribution, the resistance patterns of pathogens causing LC-BSIs and ultimately helping clinicians to choose the most appropriate antimicrobial therapy for hospitalized patients (18, 34).

We therefore organized a surveillance program in the ICU of a large teaching hospital in Rome, to determine the LC-BSI incidence, the related risk factors, the microorganisms responsible for infection and their antimicrobial susceptibility.

**Methods**

**Setting**

The study was carried out in the 13 bed general ICU of the 1.300 bed University hospital “Policlinico Umberto I” of Rome. All patients admitted to the ward ≥48h between January 2000 and December 2007 were prospectively surveyed for LC-BSI. During the year 2002 the ICU underwent general reconstruction and therefore the data are not shown.

**Definitions**

We followed the definition for LC-BSI used by the Centers for Disease Control (13). Only LC-BSI’s occurring ≥48h after admission to the ICU were considered ICU-acquired.

**Data Collection**

During the eight years survey an infection control team (ICT), composed by one physician specialised in intensive care, two in infectious diseases and one epidemiologist, actively participated to the surveillance.

Data were collected prospectively by two physicians specially trained, using a specific data-base oriented software (Epiinfo version 2005, CDC). The following information was recorded: demographic characteristics (i.e. sex, age...), date of admission and discharge, patient origin (i.e. emergency, operating rooms, wards, other ICU), admission diagnosis, severity score (SAPS II), underlying diseases presence (diabetes mellitus, chronic renal failure, cirrhosis, chronic obstructive pulmonary disease) and final ICU outcome. Invasive procedures are associated to BSI’s in ICU patients, therefore surveillance also included central venous catheter (CVC), mechanical ventilation and urinary tract catheter exposure and duration (16, 19, 24, 32).

All LC-BSI isolated microorganisms and their antibiotic susceptibility were screened and recorded.

All patient samples were taken for culture according to the general principles of specimen collection and transport (33). The species identification and the antimicrobial susceptibility testing were performed on the isolated strains by using the VITEK system. Among Gram negative microorganisms the multi-drug
Laboratory confirmed bloodstream aetiology in an intensive care unit

Resistance (MDR) was defined according to European Antimicrobial Resistance Surveillance System (EARSS) (Enterobacteriaceae and Pseudomonas aeruginosa) (8) and National Healthcare Safety Network (NHSN) (Acinetobacter baumannii) (14).

ICU-acquired LC-BSI was expressed either as the number of patients with LC-BSI’s per 100 patients or the number of LC-BSI’s episodes per 100 patients, but following the CDC we also evaluated the rates per 1000 central vascular catheter days exposure (7). Also crude and BSI associated mortality was determined. We defined early mortality as death occurring ≤7 days after BSI diagnosis and very early mortality as death occurring ≤3 days after BSI diagnosis (2, 31).

Data Analysis
Statistical analyses were performed using Epi-Info (version 2005, CDC, Atlanta, GA). The chi-square was used to examine differences between groups. Statistical significance was defined as a P value of less then 0.05. The univariate relationship between infection and death was tested using relative risk and its 95% confidence interval (CI 95). Logistic regression analysis was used to adjust for potential confounders.

Results
Sample characteristics
Between January 2000 and December 2007 a total of 1741 patients (64.8% males and 35.2% females) were included in the study. The mean age was 58.1 ± 19.8 (min. 54.8 ± 20.3, max 63.4 ± 17.4), the SAPS II score 45.1 ± 17.5 (min. 41.5 ± 17.1, max 49.4 ± 18.2) and the ICU stay 14.0 ± 21.1 days (min. 12.9 ± 12.1, max 16.2 ± 24.4). Most patients came from outside the hospital (>50%). Along the eight years the principal primary diagnosis of admission were respectively medical (44% - 57%), surgical (24% - 40%) and traumatic (17% - 23%). The most common underlying diseases were represented by heart disease (30.3%), chronic obstructive pulmonary disease (21.5%), hypertension (20.1%) and diabetes (10.2%). Patients exposure to CVC was 70.3% (min. 56.3% - max 71.3%) and the duration time 12.0 ± 13.6 days (min. 10.6 ± 10.3, max 14.3 ± 18.1).

Bloodstream episodes
Overall, 167 (9.6%) patients developed 203 (11.7%) ICU-acquired LC-BSI during the study period and the major sources of infection were CVC (39.8%), unknown (39.3%), respiratory tract (12.4%), surgical wound (6.5%) and urinary tract (2.0%).

The onset of infection in patients followed ICU admission by 19.5 ± 17.7 (mean) and 13 days (median). The duration of ICU stay was significantly (p<0.01) higher among infected (36.2 ± 32.6 days) compared to uninfected (11.6 ± 18.0 days). LC-BSI were more frequent among males than females (RR 1.61; 95%CI 1.15-2.25; p<0.01), to a lower age (mean 52.3 ± 19.5 years vs. mean 58.8 ± 19.7 years; p<0.01) and coming from outside the hospital (RR 1.64; 95%CI 1.21-2.23; p<0.01). No association was found with preceding infection at admission.

In logistic regression analysis with CVC, mechanical ventilation, gender, age, coming from outside the hospital associated with infection, the results underlined the importance of CVC (OR=9.34; 95%CI 4.50 – 19.37; p<0.01) and mechanical ventilation (OR=4.98; 95%CI 1.55 – 16.00; p<0.01).

During the study period LC-BSI/1000 patient days was 7.8‰ (mean), and LC-BSI/1000 CVC days 13.1‰ (mean). However between 2000 and 2007 the
incidence of LC-BSI/1000 patient days (14.8‰ vs. 7.8‰; p<0.05) and LC-BSI/1000 CVC days (20.7‰ vs. 11.4‰; p<0.05) decreased.

The study population crude mortality was 34.8%, and mortality associated with LC-BSI showed a RR 1.61; 95%CI 1.37 – 1.89; p<0.01. Logistic regression analysis with CVC, mechanical ventilation, BSI, gender, age, coming from outside the hospital was also carried out. Mortality was significantly associated mostly with mechanical ventilation (OR=4.37; 95%CI 2.47– 7.73; p<0.01), CVC (OR=2.89; 95%CI 2.13 – 3.93; p<0.01) and BSI (OR=2.00; 95%CI 1.39 – 2.88; p<0.01).

**Microrganisms**

Gram-positive bacteria were predominant (55.1%), followed by Gram-negative bacteria (40.2%) and yeasts (4.7%) (Table 1). Overall the most commonly isolated microrganism species were coagulase negative staphylococci (CNS) (26.2%), methicillin-resistant *Staphylococcus aureus* (MRSA) (14.9%), *P. aeruginosa* (13.5%), enterococci (9.3%) and *A. baumannii* (7.5%).

Results showed that onset time (days) between ICU admission and BSI was higher (p<0.01) among Gram-negative (22.9 ± 18.4) compared to Gram-positive (16.6 ± 15.9), whereas for fungi were (23.8 ± 25.3) (Table 2).

Mortality rate due to Gram-positive organisms was higher (56.8%) than for Gram-negative (41.9%), although infrequent, candida associated mortality was 70.0% (Table 3). Among Gram-positive MRSA showed the highest associated

<table>
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<th>Microrganisms</th>
<th>2000</th>
<th>2001</th>
<th>2003</th>
<th>2004</th>
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<th>2007</th>
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<td>5</td>
<td>3</td>
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<td>32</td>
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<td>0</td>
<td>0</td>
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<td>5</td>
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<td>7</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>56</td>
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<td>1</td>
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<td>1</td>
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<td>1</td>
<td>2</td>
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<td>7</td>
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<td>10</td>
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<tr>
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<td>3</td>
<td>1</td>
<td>2</td>
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<td>0</td>
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<td>24</td>
<td>22</td>
<td>27</td>
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</table>
mortality (71.9%), whereas the leading Gram-negative were *A. baumannii* (75.0%). Results showed a high very early death (≤3 days after BSI diagnosis) associated to *A. baumannii* (31.3%), and a high early death (≤7 days after BSI diagnosis) associated to *A. baumannii* (37.5%), *Candida* spp. (30.0%) and *S. aureus* (29.7%). All together *Enterobacteriaceae* presented the lowest associated mortality rate (Table 3).

Staphylococci presented a very high methicillin resistance (>85%), but were largely sensitive to glycopeptides as enterococci (Table 4). Data on susceptibility testing showed a remarkable antimicrobial resistance among Gram-negative organisms. *P. aeruginosa* was relatively resistant to carbapenems (57.1%), 3rd generation cephalosporins (50.0%) and fluoroquinolones (33.3%). The proportion of multidrug-resistance among *P. aeruginosa*...
strains was 25%. Significant antimicrobial resistance was found in *A. baumannii* to fluoroquinolones (68.7%), 3rd generation cephalosporins (68.7%) and carbapenems (43.7%), multidrug-resistance among *A. baumannii* strains was 68.7%. Over 1/3 of Enterobacteriaceae isolates were extended spectrum beta-lactamase (ESBL) producers (Table 4). Also resistance to fluoroquinolones and aminoglycosides was detected (>25%).

**Discussion**

Although many studies have been carried out on LC-BSI (1, 4, 17, 23, 25, 26, 27, 28, 32, 34), knowledge on local patterns can aid clinicians in their decision making processes, resulting in improved quality of care. Therefore we decided to perform an epidemiological study in order to assess more detailed data on the incidence of LC-BSI aetiology, antimicrobial resistance and associated risk factors in patients admitted to the ICU of a large teaching hospital in Rome.

Calfee et al. (5) showed how healthcare management changes may cause a false modification of nosocomial infection rates. In our study, although some of physicians working in the ICU changed, the ICT staff carrying out the infection diagnosis remained the same during all the study period. Furthermore important clinical parameters as gender, age, SAPS II score, diagnosis on admission, ICU stay and percentage of patients coming from outside the hospital remained constant along the eight study years. Therefore we feel confident that the result was entirely genuine.

The study included almost 2000 patients admitted to the ICU for >48h (high-risk population, excluding all patients only in post surgery observation) and as reported by others males outnumbered females by 2:1 (1, 17, 32). Demographically
the population appeared homogeneous with SAPS II score (>40), case-mix and most patients admitted from out the hospital confirming it was a general ICU of a large teaching hospital.

Central venous catheters are very useful to monitor and administer therapy in critically ill patients. However, considering the associated infection risk their use and length of time should be limited to the required conditions (24). In this study CVC utilization rate (0.60) was similar to NHSN data from medical/surgical major teaching ICUs (0.58) (6), Hospital in Europe link for infection control through surveillance HELICS (0.65) (9) and the multicentre Italian survey SPIN-UTI (0.58) (1).

During the first two years preliminary results showed high LC-BSI rates associated to invasive procedures which emphasized the need to reconsider the ward invasive procedures policy and encouraged major selectivity and reducing patients exposed to CVC (11, 22). Overall the incidence of BSI was 8.3/1000 patient days, decreasing from 14.8/1000 to about 7/1000 patient days in the last three years. During the same period the Italian multicenter study SPIN-UTI (1) reported a lower BSI rate of 4.0/1000 patient days, but in the latter it must be considered that >80% of ICU’s were not located in university teaching hospitals.

When considering the origin of LC-BSI we noticed that catheter related infections (40%) were more frequent than reported for Italy (<30%) by the European Centre for Disease Prevention and Control (ECDC) healthcare-associated infection surveillance (9), probably as a consequence of the high BSI rates associated to CVC in our ICU.

Although the study investigated only ICU-acquired LC-BSI, the number of patients infected before the admission to the ward remained constant.

Overall, the length of stay in the ICU for patients with LC-BSI was three-fold higher than for patients without BSI, approximately similar to that reported by ECDC surveillance (9).

Median time from ICU admission to first positive blood culture in those acquiring LC-BSI in our study was 13 days, within the data reported by others (9, 25, 26, 34).

As reported by ECDC surveillance patients with LC-BSI had significantly increased associated mortality rates (9).

As already widely reported in literature (6, 16, 24), multiple regression analysis confirmed CVC (OR = 9.3) and mechanical ventilation (OR = 5.0) as principal BSI associated risk factors. Multiple regression analysis confirmed also for mortality the importance of invasive devices and LC-BSI.

Infections were predominantly caused by Gram-positive microrganisms, particularly staphylococci (>40%).

The distribution of microrganisms by LC-BSI day of onset showed that the percentage of all Gram-negatives was much higher among the late onset than early onset BSI. Also infections by Candida spp. presented a late onset (9, 25, 26, 34).

Although Gram-positive organism mortality, specially staphylococci (60%), was higher than Gram-negative, it was impressive the very early death (≤ 3 days) among specific gram negatives as A. baumannii (>30%). Whereas mortality in MRSA is generally expected as a consequence of its well known pathogenic features, A. baumannii high very early death (≤ 3 days) rate may was consequence of an inappropriate empirical therapy. The latter was susceptible to colistin and tigecycline which at the time were not included in the first line empirical therapy by clinicians (15). In our institution resistance to carbapenems in Enterobacteriaceae emerged only later (12, 21).
On the contrary Enterobacteriaceae (over 1/3 represented by Klebsiella spp.) exhibited the lowest death rate. May be in relation to susceptibility at carbapenems and piperacillin/tazobactam which were usually included in empirical treatment for suspected Gram-negative infections (30).

Methicillin resistance, a common resistant phenotype among nosocomial Staphylococcus isolates, was seen in >85% of S. aureus and >90% of coagulase negative staphylococci. Among the latter about 1/5 showed also resistance to glycopeptides, in particular teicoplanin (20). Differently, as reported glycopeptide resistance in Italy is limited only one vancomycin resistant enterococci isolate was found in patients with BSI in this study (8).

A relevant antimicrobial resistance among Gram-negative bacteria was found in our hospital during the study period. One of the major concerns was the emergence of ESBL-producing strains in Enterobacteriaceae, about 1/3 of isolates, restricting therapy to carbapenems.

Among gram-negative nonfermenters the two most frequently isolated pathogens responsible for LC-BSI were A. baumannii and P. aeruginosa. Both showed a high MDR level as they are intrinsically resistant to a variety of commonly used antimicrobial agents, but also may acquire resistance by several mechanisms (20). In particular one-quarter of P. aeruginosa expressed MDR.

Although resistance rates vary widely according to the individual hospital, city or country involved, during the last two decades MDR A. baumannii have been reported increasingly (29), as in our institution. The ability of this microorganism to survive in the environment and resist to many antimicrobial agents makes it an important cause of infection specially in ICU (10).

The Authors succeeded in organizing a multidisciplinary ICT that created a partnership feeling with the ICU personnel. Surveillance is an important cornerstone of any infection control program and implementing a set of relatively simple infection control measures can significantly reduce infection rates and improve appropriate antimicrobial therapy.

Abstract

To evaluate laboratory confirmed bloodstream infection (LC-BSI) aetiology we carried out a prospective study in the general 13 bed ICU of the teaching hospital Policlinico Umberto I in Rome.

According to CDC case definitions for LC-BSI, all patients admitted ≥48h between 2000-2007 to ICU were included. Risk factors (i.e. age, sex, SAPS II), invasive procedures (i.e. endotracheal intubation, vascular and urinary catheterisation), microbiological isolates and their antibiotic susceptibility were screened.

Overall 1741 patients (64.8% males, 35.2% females) were included, mean age was 58.1 ± 19.8, SAPS II score 45.1 ± 17 and ICU stay 14.0 ± 21.1 days. Finally, 167 (9.6%) patients developed 203 (11.7%) ICU-acquired LC-BSI and sources of infection were CVC (39.8%), unknown (39.3%), respiratory tract (12.4%), surgical wound (6.5%) and urinary tract (2.0%). Between 2000 and 2007 the incidence of LC-BSI/1000 patient days (14.8‰ vs. 7.8‰; p<0.05) and LC-BSI/1000 CVC days (20.7‰ vs. 11.4‰; p<0.05) decreased. The onset of infection followed ICU admission by 19.5 ± 17.7 (mean) and 13 days (median). Crude mortality was 34.8%, and mortality associated with LC-BSI showed a RR 1.61; 95%CI 1.37 – 1.89; p<0.01. The most common pathogens were coagulase negative staphylococci (CNS) (26.2%), methicillin-resistant Staphylococcus aureus (MRSA) (14.9%), Pseudomonas aeruginosa (13.5%), enterococci (9.3%) and Acinetobacter baumannii (7.5%). Onset time (days) between ICU admission and LC-BSI was higher (p<0.01) among Gram-negative (22.9 ± 18.4) compared to Gram-positive (16.6 ± 15.9), fungi (23.8 ± 25.3). High early death (<7 days after BSI diagnosis) was associated to A. baumannii (37.5%), Candida spp. (30.0%) and S. aureus (29.7%). Staphylococci presented a very high methicillin resistance (>85%). P. aeruginosa and A. baumannii showed respectively 25% and 68.7% multidrug-resistance. Over 1/3 of Enterobacteriaceae isolates were extended spectrum beta-lactamase (ESBL), but non resulted resistant to carbapenems.
Surveillance showed a high incidence of LC-BSI associated to invasive procedures and the presence of multiresistant bacteria.

References

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