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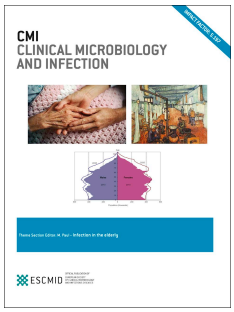


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# Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with haematological malignancies: an Italian multicentre prospective survey

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Running title: Epidemiology and mortality of BBSIs in HMs patients.

Key words: Bacterial bloodstream infections; haematological cancer; antimicrobial resistance; multidrug resistance; epidemiology; mortality.

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**Summary**

Bacterial bloodstream infections (BBSIs) represent the most common severe infectious complications in patients with haematological malignancies (HMs). The extensive emergence of antimicrobial resistance among bacteria causing BBSI has been recently reported in HM patients.

A prospective cohort study was conducted in 9 haematology wards at tertiary care centres or at university hospitals located throughout Italy from January 2009 to December 2012. All of the cases of BBSI occurring in adult patients suffering from HMs were included.

A total of 668 bacterial isolates were recovered in 575 BBSI episodes. Overall, the susceptibility rates of Gram-negative bacteria were 59.1% to ceftazidime, 20.1% to ciprofloxacin, 79.1% to meropenem, 85.2% to amikacin, 69.2% to gentamicin, and 69.8% to piperacillin/tazobactam. Resistance to third generation cephalosporins was found in 98/265 (36.9%) of *Enterobacteriaceae* isolates. Among *Klebsiella pneumoniae* strains, 15/43 (34.9%) were resistant to carbapenems. Out of 66 *Pseudomonas aeruginosa* isolates, 46 (69.7%) were multidrug-resistant. Overall, the susceptibility rates of Gram-positive bacteria were 97.4% to vancomycin and 94.2% to teicoplanin. Among the monomicrobial cases of BBSI, the 21-day mortality rate was significantly higher for those caused by Gram-negative bacteria compared to those caused by Gram-positives (47/278, 16.9% vs. 12/212, 5.6%; P<0.001). Among Gram-negatives, the mortality rate was significantly higher for BBSI caused by *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter baumannii*.

Our results confirm the recently reported shift of prevalence from Gram-positive to Gram-negative bacteria as causative agents of BBSIs among patients suffering from HMs, and highlight a worrisome increasing frequency in antimicrobial resistance among Gram-negatives.

## Introduction

Patients suffering from haematological malignancies (HMs) are at a high risk of infectious complications, and bacterial bloodstream infections (BBSIs) represent the most severe among these. The reported prevalence of BBSIs among HM patients ranges from 11% to 38%, and the crude mortality rate reaches up to 40% [1-5]. In a recent Italian survey, the incidence of microbiologically documented bacterial infections among patients with newly diagnosed HMs was 9.4%, and BBSIs represented 85.1% of these cases [6].

Gram-positive bacteria have been reported as the most frequent and significantly increasing cause of BBSIs in cancer patients in the last three decades, with frequencies reaching 76% in 2000 [2]. However, in recent years, a trend reversal in the epidemiology of BBSIs among patients with HMs has been demonstrated, and Gram-negative bacteria have been reported as the prevalent cause of BBSIs in some studies [4,7]. In addition, the extensive emergence of antimicrobial resistance among bacteria, especially Gram-negatives (e.g., cephalosporin- and/or carbapenem-resistant *Enterobacteriaceae* and multidrug-resistant [MDR] *P. aeruginosa*), causing BBSIs in cancer patients has been highlighted [3,7-9].

The aim of this study was to evaluate the clinical and epidemiological characteristics and mortality rates of BBSIs that occurred in a large cohort of patients suffering from HMs, with particular emphasis on the antimicrobial resistance profiles of bacterial isolates.

## MATERIALS AND METHODS

The present prospective study was conducted in 9 haematology wards at tertiary care centres or university hospitals located throughout Italy from January 2009 to December 2012.

Antibacterial prophylaxis was administered to patients among all participating centres according to Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) criteria [10].

All episodes of BBSIs that occurred in hospitalised patients aged >18 years suffering from haematological malignancies were included. The data that were collected from the hospital charts and the laboratory database included patient demographics, disease and disease stage at time of BBSI, the type of HSCT (autologous or allogeneic), and the outcome of infection; for each bacterial isolate, the antimicrobial susceptibility was determined and analysed. All of the information was entered into the case report forms and then recorded in a specific database. Recurrent infections were excluded, and only the first episode per patient was included in our registry.

The ethics committee at each participating site approved the use of the Haematological Malignancies Associated Bloodstream Infections Surveillance (He.M.A.B.I.S.) registry, and informed consent was obtained from each patient.

### Definitions

The following terms were defined prior to data analysis:

BBSI was defined as an infection that was manifested by (1) the presence in at least 1 blood culture that sustained bacterial growth other than skin contaminants (i.e., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative *Staphylococci* [CoNS], and *Micrococci*) or (2) the presence in at least 2 consecutive blood cultures that sustained growth of skin contaminants.

BBSI was defined as central venous catheter (CVC)-related according to the Centers for Disease Control and Prevention criteria [11].

Neutropenia was defined as an absolute neutrophil count (ANC) <500 neutrophils/μL at the onset of BBSI; neutropenia was considered prolonged if the duration was ≥10 days.

Bacterial isolates were considered hospital-acquired if the index culture had been collected >48 hours after admission and the signs and symptoms of infection had been absent at admission. If the cultures had been collected ≤48 hours after the admission date, the isolate was classified as *healthcare*-associated or community-acquired [12].

If the infecting pathogen demonstrated resistance (as determined by in vitro susceptibility testing) to the administered antimicrobial(s), the initial treatment was classified as *inadequate*.

**Statistical analysis.** Continuous variables were compared by Student's *t*-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were evaluated using the $\chi^2$ or two-tailed Fisher's exact test. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association that emerged. Values are expressed as the means ± standard deviation (SD) (continuous variables), or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; a P value of $< 0.05$ was considered significant. All statistical analyses were performed using the Intercooled Stata program, version 11, for Windows (Stata Corporation, College Station, Texas, USA).

## RESULTS

A total of 575 episodes of bacterial BBSI were included in our registry during the study period.

### Patient characteristics

The majority (529/575, 92%) of patients were neutropenic. The epidemiological and clinical characteristics of the patients with BBSIs, divided according to neutropenic status, are presented in Table 1.

### Aetiologic agents of BBSIs

Because 83/575 (14.4%) episodes of BBSI were polymicrobial, a total of 668 bacteria were isolated. Table 2 shows the results of causative bacteria according to the neutropenic status of the patients. Overall, Gram-negative organisms were recovered in 52.8% (353/668) of the BBSI cases and Gram-positives were recovered in 46.6% (311/668) of cases. Among the Gram-negatives, *Escherichia coli* represented the most frequent species (187/353, 52.9%), followed by *P. aeruginosa* (66/353, 18.7%), *Klebsiella pneumoniae* (43/353, 12.2%), and *Enterobacter cloacae* (26/353, 7.7%). Among the Gram-positives, CoNS were the most common species (166/311, 53.4%), followed by *Enterococcus* spp. (67/311, 21.5%), *Viridans Group Streptococci* (VGS) (36/311, 11.5%), and *S. aureus* (18/311, 5.8%). BBSI caused by Gram-negative bacteria was significantly more frequent in patients with neutropenia, compared to non-neutropenic patients (P=0.006); conversely, the latter patients were more likely suffering from BBSI caused by Gram-positives (P=0.004).

### Antimicrobial resistance profiles of Gram-negative organisms

The antimicrobial susceptibility profiles of all Gram-negatives and of the most frequently isolated bacterial species (i.e., *E. coli, K. pneumoniae, P. aeruginosa,* and *E. cloacae*) are reported

in Table 3. Overall, the susceptibility rates of Gram-negative bacteria were 59.1% to ceftazidime, 20.1% to ciprofloxacin, 79.1% to meropenem, 85.2% to amikacin, 69.2% to gentamicin, and 69.8% to piperacillin/tazobactam. Resistance to third generation cephalosporins was found in 98/265 (36.9%) of *Enterobacteriaceae* isolates. Among the *K. pneumoniae* strains, 15/43 (34.9%) were resistant to carbapenems. Out of 66 *P. aeruginosa* isolates, 46 (69.7%) were MDR, as previously defined [13].

The susceptibility to colistin was tested in 110/353 Gram-negative isolates, and only two (1.8%; 2 *Pseudomonas putida* isolates) of these were resistant. The susceptibility to tigecycline was tested in 160/285 Gram-negative isolates other than *Pseudomonas* spp., and nine (3.6%; 4 *K. pneumoniae*, 4 *E. cloacae*, and 1 *A. baumannii* isolates) of these were resistant.

**Antimicrobial resistance profiles of Gram-positive organisms**

The antimicrobial susceptibility profiles of all Gram-positives and of the most frequently isolated bacterial species (i.e., CoNS, *S. aureus*, *Enterococcus* spp., and VGS) are reported in Table 4. The susceptibility rates to oxacillin were 15.7% and 63.6% for CoNS and *S. aureus*, respectively. Overall, 40.3% of the *Enterococcus* spp. isolates were susceptible to ampicillin; the susceptibility rates to ampicillin were 88.9% for *E. faecalis* and 5.4% for *E. faecium* isolates; 89.2% and 97.3% of *E. faecium* (and 100% of *E. faecalis*) isolates were susceptible to vancomycin and teicoplanin, respectively. Among the VGS isolates, 63.9% were susceptible to penicillin, whereas all of these were susceptible to glycopeptides. Overall, the susceptibility rates of Gram-positive bacteria were 97.4% to vancomycin and 94.2% to teicoplanin.

**21-day mortality rates of causative bacterial isolates from BBSI episodes**

Overall, the 21-day mortality rate in patients with BBSIs was 13.2% (76/575); it was higher for patients with polymicrobial BBSIs (16/83, 19.3%) compared to those with monomicrobial BBSIs (60/492, 12.2%; P=0.07), with prolonged neutropenia (56/361, 15.5%) compared to those

with neutropenia with a duration of <10 days (20/214, 9.3%; P=0.03), and for those patients who had received an inappropriate initial antimicrobial therapy (32/142, 22.5%) versus those who had received an appropriate empirical antibiotic treatment (44/433, 10.1%; P<0.001). In Table 5, the mortality rates for patients with monomicrobial BBSIs are reported according to the most frequent bacterial species. Overall, the 21-day mortality rate was significantly higher for patients with BBSI caused by Gram-negative bacteria compared to those with BBSI caused by Gram-positives (47/278, 16.9% vs. 12/212, 5.6%; P<0.001). Among Gram-negatives, the mortality rate was significantly higher for BBSI that was caused by *K. pneumoniae* (P=0.006), *P. aeruginosa* (P<0.001), and *Acinetobacter baumannii* (P=0.004). There were no differences in the mortality rate among BBSIs caused by Gram-positive bacterial species, except for BBSI that was caused by *Viridans Group Streptococci* (VGS) and CoNS, which were associated with survival (P=0.05 and <0.001, respectively). Among the more frequent antibiotic resistant Gram-negative bacterial species causing monomicrobial BBSI, the mortality rate was significantly higher for patients with BBSI that was caused by third generation cephalosporin-resistant *Enterobacteriaceae* compared to third generation cephalosporin-susceptible *Enterobacteriaceae* (22/84, 26.2% vs. 6/124, 4.6%; P<0.001), for those with BBSI that was caused by carbapenem-resistant *K. pneumoniae* compared to carbapenem-susceptible *K. pneumoniae* (6/13, 46.1% vs. 3/20, 15%; P=0.04), and for those with BBSI that was caused by MDR P. aeruginosa compared to non-MDR P. aeruginosa (14/19, 42.4% vs. 2/16, 12.5%; P=0.03).

## DISCUSSION

In this large multicenter Italian cohort study, we examined the clinical characteristics and the outcome of BBSI episodes in patients suffering from HMs, as well as the spectrum of susceptibility patterns of bacterial isolates.

We found that Gram-negative bacteria were the most frequent microorganisms that were isolated (52.8%) and these data are consistent with the recently reported shift of prevalence from Gram-positive to Gram-negative bacteria among severe bacterial infections in patients with cancer [4,7]. In addition, Mikulska et al., who recently compared a questionnaire survey that was conducted in 2011 on the aetiology and resistance in BBSI episodes that occurred in adult cancer patients in 39 centres (in 18 countries) to data that was collected from a literature review of BBSI episodes in adult cancer patients from papers that were published between 2005 and 2011, demonstrated that the survey showed a recent reduction in the Gram-positive to Gram-negative ratio (55%:45% vs. 60%:40%) [14]. Notably, the median rate of bacterial species causing BBSI that was reported in this ECIL-4 questionnaire survey was very similar to the bacterial species distribution in our cohort, in that *E. coli* was the most frequent species (27.9% in our cohort vs. 30% in the ECIL-4 questionnaire survey), followed by CONS (24.8% vs. 24%), and *Enterococci* (10.1% vs. 8%), and excepting the prevalence of *P. aeruginosa* BBSI which was twice as high in our cohort (9.9% vs. 5%) [14].

Regarding antimicrobial susceptibility among Gram-positive bacteria, we found that the rates were similar or higher compared to what was reported by Mikulska et al. among adults in the literature review; in particular, the susceptibility to methicillin was similar for CoNS (15.7% vs. 20%) but somewhat higher for *S. aureus* (63.6% vs. 44%), whereas >92% of *Staphylococci* and *Enterococci* were susceptible to glycopeptides in our cohort. In addition, we observed a lower prevalence of vancomycin resistance among *E. faecium* isolates compared to previous reports (10.8% vs. 23%) [14]. Similarly, the resistance to teicoplanin among the CoNS isolates was significantly lower compared to what was previously reported [15].

In contrast, we have found a worrisome trend toward a decrease in the susceptibility rates to the main antibiotic drugs among Gram-negative bacteria compared to what has been reported in more recent epidemiologic studies, which have been recently reviewed [7]. In particular, only 20.1% of the Gram-negative bacteria isolates from our patients were susceptible to fluoroquinolones; the susceptibility rates to fluoroquinolones were significantly lower compared to those that were previously reported for *E. coli* (9.6% vs. 47.2%), *K. pneumoniae* (30.2% vs. 61.1%), *E. cloacae* (50% vs. 95.7%), and *P. aeruginosa* (19.7% vs. 51.6%). In addition, we observed rates of susceptibility of 61.5% and 44.2% to meropenem and piperacillin/tazobactam, respectively, among *K. pneumoniae* isolates, which are considerably lower than what was reported in previous studies (mean of 98.5% and 71.8%, respectively) [7]. We also found a significant decrease in the susceptibility rate to almost all of the most common antibiotics among *P. aeruginosa* isolates compared with previous reports: 28.8% vs. 50.1% to meropenem, 57.6% vs. 78.3% to piperacillin/tazobactam, 45.4% vs. 62.3% to ceftazidime, and 22.7% vs. 78.3% to gentamicin; the susceptibility of *P. aeruginosa* isolates in our cohort to amikacin (65.8%) was similar to what was previously reported (61.8%) [7]. Approximately 70% of the bloodstream *P. aeruginosa* isolates were designated MDR in our cohort, and this rate was similar to what was reported by Cattaneo et al. (71.1%) [16], though more than twice as high as what was reported in a preliminary analysis that was conducted by this group on a smaller population size (33%) [17]. However, it has to be taken into account that our data are representative of a single country, and the Italian situation might not be representative for all of Europe.

Finally, we observed within our cohort a cumulative mortality rate of 13.2%, which is in line with previous reports on BBSI episodes in adult patients with HMs [8,9,18]. However, among patients with monomicrobial BBSI, the mortality rate was significantly higher for those with BBSIs that were caused by Gram-negative bacteria compared to those that were caused by Gram-positives. Although this result was expected and in line with previous large studies [19], some of the more recent reports evaluating the outcome in bacteremic patients with HMs according to the Gram stain

of causative agents had not found significant differences [8,20-22]; this could be related to the larger size of our cohort compared to previous studies, or to the prevalence of Gram-negative bacteria causing BBSI and the high rate of antimicrobial resistance among these bacteria which has been associated with mortality in previous studies of patients with BBSIs and HMs [20,23]. Confirming this latter hypothesis, among the Gram-negative bacterial species, the mortality rates were significantly higher for *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*, which are more frequently characterised by their patterns of multidrug resistance.

In conclusion, our data confirm the recently reported shift in the prevalence from Gram-positive to Gram-negative bacteria as causative agents of BBSIs among patients suffering from HMs and highlight a worrisome increasing frequency in the rate of antimicrobial resistance among Gram-negatives to all antibiotic classes that are recommended for empirical treatments in this setting. Furthering our understanding of the local distribution of pathogens and their susceptibility patterns and of patients' risk factors for resistant bacteria and for a complicated clinical course, as well as the judicious use of antibiotics and control measures to prevent the development and spread of antibiotic-resistant Gram-negative bacteria, are necessary steps that could improve the efficacy of therapeutic treatment protocols (according to recent recommendations in the European Conference on Infections in Leukaemia guidelines [24] for oncohaematologic patients).

## Transparency Declaration

The authors declare no conflicts of interest.

## Authorship/Contribution

Anna Candoni, Domenico Pastore, Chiara Cattaneo, Rosa Fanci, Annamaria Nosari, Morena Caira, Antonio Spadea, Alessandro Busca, and Nicola Vianelli were involved in data collection. Enrico Maria Trecarichi, Livio Pagano, and Mario Tumbarello designed and implemented the surveillance study and its evaluation. Enrico Maria Trecarichi and Mario Tumbarello performed the statistical analysis. Preparation of the first draft: Enrico Maria Trecarichi and Livio Pagano. All of the authors have read and approved the manuscript.

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**Table 1.** Clinical and epidemiological characteristics of cohort patients according to neutropenic status.

| Variables | Neutropenic (n = 529) | Non neutropenic (n = 46) | P values |
|---|---|---|---|
| Demographic information | | | |
| Male sex | 305 (57.7) | 32 (69.6) | 0.11 |
| Age (year [mean ± SD]) | 52 ± 14.88 | 51 ± 15.66 | 0.85 |
| Characteristics of BBSI | | | |
| Polymicrobial | 77 (14.6) | 6 (13.1) | 0.77 |
| Monomicrobial due to Gram-negatives | 263 (49.7) | 15 (32.6) | 0.02 |
| Monomicrobial due to Gram-positives | 187 (35.3) | 25 (54.3) | 0.01 |
| Hospital acquired | 448 (84.7) | 29 (63.0) | <0.001 |
| Healthcare-associated | 29 (5.5) | 9 (19.6) | <0.001 |
| Community-acquired | 52 (9.8) | 8 (17.4) | 0.10 |
| Hematological malignancy | | | |
| Acute myeloid leukemia | 336 (63.5) | 16 (34.8) | <0.001 |
| Chronic myeloid leukemia | 1 (0.2) | 0 | 0.77 |
| Acute lymphatic leukemia | 54 (10.2) | 9 (19.6) | 0.05 |
| Chronic lymphoid leukemia | 3 (0.6) | 0 | 0.61 |
| Non Hodgkin’s lymphoma | 88 (16.6) | 10 (21.7) | 0.38 |
| Hodgkin’s lymphoma | 11 (2.1) | 2 (4.3) | 0.32 |
| Multiple Myeloma | 30 (5.7) | 7 (15.2) | 0.01 |
| Other | 7 (1.3) | 2 (4.3) | 0.11 |
| Hematopoietic stem cell transplantation | 180 (34.0) | 12 (26.1) | 0.27 |
| Autologous | 83 (15.7) | 2 (4.3) | 0.04 |
| Allogeneic-Matched | 68 (12.8) | 4 (8.7) | 0.41 |

| | | | |
|---|---|---|---|
| Allogeneic-Mismatched | 33 (6.2) | 7 (15.2) | 0.02 |
| Antibiotic prophylaxis | 439 (83.0) | 27 (58.7) | <0.001 |
| Co-trimoxazole | 78 (14.7) | 8 (17.4) | 0.63 |
| Fluoroquinolones | 408 (77.1) | 19 (41.3) | <0.001 |
| Antifungal prophylaxis | 377 (71.3) | 21 (45.6) | <0.001 |
| 21-day mortality | 72 (13.6) | 4 (8.7) | 0.34 |

Values are n (%) unless otherwise noted.

**Table 2.** Causal pathogens responsible for bacterial bloodstream infections in patients with hematological malignancies according to neutropenic status.

| Microorganisms | Total (n = 668) | Neutropenic (n = 616) | Non neutropenic (n = 52) | P values |
|---|---|---|---|---|
| Gram-negative, total | 353 (52.8) | 335 (54.4) | 18 (34.6) | 0.006 |
| *Escherichia coli* | 187 (27.9) | 181 (29.4) | 6 (11.5) | 0.006 |
| *Klebsiella Pneumoniae* | 43 (6.4) | 39 (6.3) | 4 (7.7) | 0.70 |
| *Enterobacter cloacae* | 26 (3.4) | 24 (3.9) | 2 (3.8) | 0.98 |
| *Pseudomonas aeruginosa* | 66 (9.9) | 63 (10.2) | 3 (5.8) | 0.30 |
| *Acinetobacter baumannii* | 3 (0.4) | 3 (0.5) | 0 | 0.61 |
| *Stenotrophomonas maltophilia* | 9 (1.3) | 8 (1.3) | 1 (1.9) | 0.71 |
| Gram-positive, total | 311 (46.6) | 277 (44.9) | 34 (65.4) | 0.004 |
| Coagulase-negative *Staphylococci* | 166 (24.8) | 148 (24.0) | 18 (34.6) | 0.09 |
| *Staphylococcus aureus* | 11 (1.6) | 7 (1.1) | 4 (7.7) | <0.001 |
| *Viridans group Streptococci* | 36 (5.4) | 35 (5.7) | 1 (1.9) | 0.25 |
| *Streptococcus pneumoniae* | 2 (0.3) | 0 | 2 (3.8) | <0.001 |
| *Enterococcus* spp. | 67 (10.1) | 63 (10.2) | 4 (7.7) | 0.56 |
| *Enterococcus faecalis* | 27 (4.1) | 24 (3.9) | 3 (5.8) | 0.51 |
| *Enterococcus faecium* | 37 (5.5) | 36 (5.8) | 1 (1.9) | 0.23 |
| Anaerobes | 4 (0.6) | 4 (0.6) | 0 | 0.56 |

**Table 3.** Antimicrobial susceptibility profiles of all Gram-negatives and of the most frequently isolated bacterial species.

| Microorganisms | Total | No. Susceptible (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Ceftazidime | Ciprofloxacin | Meropenem | Amikacin | Gentamicin | Piperacillin/ tazobactam |
| Gram-negative, total[a] | 344 | 203 (59.1) | 69 (20.1) | 272 (79.1) | 293 (85.2) | 238 (69.2) | 240 (69.8) |
| *Escherichia coli* | 187 | 131 (70.0) | 18 (9.6) | 184 (98.4) | 183 (97.9) | 155 (82.9) | 156 (83.4) |
| *Klebsiella pneumoniae* | 43 | 18 (41.9) | 13 (30.2) | 28 (65.1) | 25 (58.1) | 29 (67.4) | 19 (44.2) |
| *Enterobacter cloacae* | 26 | 12 (46.1) | 13 (50.0) | 24 (92.3) | 23 (88.5) | 23 (88.5) | 12 (46.1) |
| *Pseudomonas aeruginosa* | 66 | 30 (45.4) | 13 (19.7) | 19 (28.8) | 43 (65.1) | 15 (22.7) | 38 (57.6) |

[a] The total of Gram-negative bacteria was 344; *Stenotrophomonas maltophilia* isolates (9) were excluded.

**Table 4.** Antimicrobial susceptibility profiles of all Gram-positives and of the most frequently isolated bacterial species.

| Microorganisms | Total | No. Susceptible (%) Microorganisms | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Oxacillin | Ampicillin | Penicillin | Vancomycin | Teicoplanin | Linezolid | Daptomycin |
| Gram-positive, total[a] | 311 | - | - | - | 303 (97.4) | 293 (94.2) | - | - |
| Coagulase-negative *Staphylococci* | 166 | 26 (15.7) | - | - | 164 (98.8) | 150 (90.4) | 155/156 (99.3)[b] | 97/98 (98.9)[c] |
| *Staphylococcus aureus* | 11 | 7 (63.6) | - | - | 11 (100) | 11 (100) | 11 (100) | 11 (100) |
| *Viridans group Streptococci* [a] | 36 | - | - | 23 (63.9) | 36 (100) | 36 (100) | 36 (100) | 36 (100) |
| *Enterococcus* spp. | 67 | - | 27 (40.3) | - | 62 (92.5) | 66 (98.5) | 67 (100) | NA |
| *Enterococcus faecalis* | 27 | - | 24 (88.9) | - | 27 (100) | 27 (100) | 27 (100) | NA |
| *Enterococcus faecium* | 37 | - | 2 (5.4) | - | 33 (89.2) | 36 (97.3) | 37 (100) | NA |

NA, not available.

[a] The susceptibility rate of *Viridans group Streptococci* isolates to ceftriaxone was 94.4% (34/36).

[b] Linezolid was tested on a total of 156 coagulase-negative *Staphylococci* isolates and 155 (99.3%) were susceptible.

[c] Daptomycin was tested on a total of 98 coagulase-negative *Staphylococci* isolates and 97 (98.9%) were susceptible.

**Table 5.** Stratification of 492 patients with monomicrobial bacterial bloodstream infections by most frequent bacterial species recovered, according to 21-day mortality.

| Microorganisms | Non survivors (n = 60) | Survivors (n = 432) | ODDS (CI) | P values |
|---|---|---|---|---|
| Gram-negative, total | 47 (78.3) | 231 (53.5) | 3.14 (1.61-6.51) | <0.001 |
| *Escherichia coli* | 16 (26.7) | 142 (32.9) | 0.74 (0.38-1.40) | 0.33 |
| *Klebsiella Pneumoniae* | 9 (15.0) | 24 (5.6) | 3 (1.16-7.12) | 0.006 |
| *Enterobacter cloacae* | 3 (5.0) | 16 (3.7) | 1.37 (0.25-4.99) | 0.62 |
| *Pseudomonas aeruginosa* | 16 (26.7) | 33 (7.6) | 4.40 (2.08-8.97) | <0.001 |
| *Acinetobacter baumannii* | 2 (3.3) | 1 (0.2) | 14.86 (0.75-878.63) | 0.004 |
| *Stenotrophomonas maltophilia* | 1 (1.7) | 5 (1.2) | 1.45 (0.03-13.25) | 0.74 |
| Gram-positive, total | 12 (20.0) | 200 (46.3) | 0.29 (0.14-0.57) | <0.001 |
| Coagulase-negative *Staphylococci* | 4 (6.7) | 117 (27.1) | 0.19 (0.05-0.54) | <0.001 |
| *Staphylococcus aureus* | 0 | 8 (1.8) | - | 0.29 |
| *Viridans group Streptococci* | 0 | 27 (6.2) | - | 0.05 |
| *Streptococcus pneumoniae* | 1 (1.7) | 1 (0.2) | 7.30 (0.09-574.67) | 0.10 |
| *Enterococcus* spp. | 4 (6.7) | 27 (6.2) | 1.07 (0.26-3.24) | 0.90 |
| *Enterococcus faecalis* | 0 | 11 (2.5) | - | 0.21 |
| *Enterococcus faecium* | 4 (6.7) | 15 (3.5) | 1.98 (0.46-6.52) | 0.23 |
| Anaerobes | 1 (1.7) | 1 (0.2) | 7.30 (0.09-574.67) | 0.10 |

**Table 6.** Stratification of 83 patients with polymicrobial bacterial bloodstream infections, according to 21-day mortality.

| | Non survivors (n = 16) | Survivors (n = 67) | ODDS (CI) | P values |
|---|---|---|---|---|
| Only Gram-negative organisms | 3 (18.7) | 13 (19.4) | 0.95 (0.15-4.27) | 0.95 |
| Only Gram-positive organisms | 2 (12.5) | 23 (34.3) | 0.27 (0.02-1.37) | 0.08 |
| Both Gram positive and Gram negative organisms | 11 (68.7) | 31 (46.3) | 2.55 (0.71-10.33) | 0.10 |