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Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: An Italian multicentre prospective survey / Treccarichi, E. M.; Pagano, L.; Candoni, A.; Pastore, D.; Cattaneo, C.; Fanci, R.; Nosari, A.; Caira, M.; Spadea, A.; Busca, A.; Vianelli, N.; Tumbarello, M.. - In: CLINICAL MICROBIOLOGY AND INFECTION. - ISSN 1198-743X. - 21:4(2015), pp. 337-343. [10.1016/j.cmi.2014.11.022]

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05/11/2024 03:19

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Accepted Manuscript

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

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PII: S1198-743X(14)00108-6

DOI: [10.1016/j.cmi.2014.11.022](https://doi.org/10.1016/j.cmi.2014.11.022)

Reference: CMI 107

To appear in: *Clinical Microbiology and Infection*

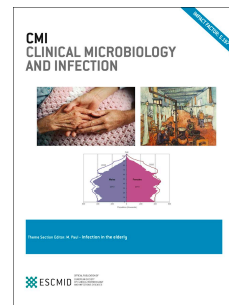
Received Date: 30 June 2014

Revised Date: 16 October 2014

Accepted Date: 20 November 2014

Please cite this article as: Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, Nosari A, Caira M, Spadea A, Busca A, Vianelli N, Tumbarello M, for the HEMABIS registry – SEIFEM group, Italy, Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with haematological malignancies: an Italian multicentre prospective survey, *Clinical Microbiology and Infection* (2015), doi: 10.1016/j.cmi.2014.11.022.

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

4
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18
19 Running title: Epidemiology and mortality of BBSIs in HMs patients.

20
21 Key words: Bacterial bloodstream infections; haematological cancer; antimicrobial resistance;
22 multidrug resistance; epidemiology; mortality.

23
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1

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ACCEPTED MANUSCRIPT

1 **Summary**

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

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

8 A total of 668 bacterial isolates were recovered in 575 BBSI episodes. Overall, the
9 susceptibility rates of Gram-negative bacteria were 59.1% to ceftazidime, 20.1% to ciprofloxacin,
10 79.1% to meropenem, 85.2% to amikacin, 69.2% to gentamicin, and 69.8% to
11 piperacillin/tazobactam. Resistance to third generation cephalosporins was found in 98/265 (36.9%)
12 of *Enterobacteriaceae* isolates. Among *Klebsiella pneumoniae* strains, 15/43 (34.9%) were resistant
13 to carbapenems. Out of 66 *Pseudomonas aeruginosa* isolates, 46 (69.7%) were multidrug-resistant.
14 Overall, the susceptibility rates of Gram-positive bacteria were 97.4% to vancomycin and 94.2% to
15 teicoplanin. Among the monomicrobial cases of BBSI, the 21-day mortality rate was significantly
16 higher for those caused by Gram-negative bacteria compared to those caused by Gram-positives
17 (47/278, 16.9% vs. 12/212, 5.6%; $P < 0.001$). Among Gram-negatives, the mortality rate was
18 significantly higher for BBSI caused by *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter*
19 *baumannii*.

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

23

1 **Introduction**

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

8 Gram-positive bacteria have been reported as the most frequent and significantly increasing
9 cause of BBSIs in cancer patients in the last three decades, with frequencies reaching 76% in 2000
10 [2]. However, in recent years, a trend reversal in the epidemiology of BBSIs among patients with
11 HMs has been demonstrated, and Gram-negative bacteria have been reported as the prevalent cause
12 of BBSIs in some studies [4,7]. In addition, the extensive emergence of antimicrobial resistance
13 among bacteria, especially Gram-negatives (e.g., cephalosporin- and/or carbapenem-resistant
14 *Enterobacteriaceae* and multidrug-resistant [MDR] *P. aeruginosa*), causing BBSIs in cancer
15 patients has been highlighted [3,7-9].

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

1 MATERIALS AND METHODS

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

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

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

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

17 Definitions

18 The following terms were defined prior to data analysis:

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

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

1 Neutropenia was defined as an absolute neutrophil count (ANC) <500 neutrophils/ μ L at the
2 onset of BBSI; neutropenia was considered prolonged if the duration was \geq 10 days.

3 Bacterial isolates were considered hospital-acquired if the index culture had been collected
4 >48 hours after admission and the signs and symptoms of infection had been absent at admission. If
5 the cultures had been collected \leq 48 hours after the admission date, the isolate was classified as
6 *healthcare*-associated or community-acquired [12].

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

9
10 **Statistical analysis.** Continuous variables were compared by Student's *t*-test for normally
11 distributed variables and the Mann-Whitney U test for non-normally distributed variables.
12 Categorical variables were evaluated using the χ^2 or two-tailed Fisher's exact test. The odds ratios
13 (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any
14 association that emerged. Values are expressed as the means \pm standard deviation (SD) (continuous
15 variables), or as percentages of the group from which they were derived (categorical variables).
16 Two-tailed tests were used to determine statistical significance; a P value of < 0.05 was considered
17 significant. All statistical analyses were performed using the Intercooled Stata program, version 11,
18 for Windows (Stata Corporation, College Station, Texas, USA).

19

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

1 in Table 3. Overall, the susceptibility rates of Gram-negative bacteria were 59.1% to ceftazidime,
2 20.1% to ciprofloxacin, 79.1% to meropenem, 85.2% to amikacin, 69.2% to gentamicin, and 69.8%
3 to piperacillin/tazobactam. Resistance to third generation cephalosporins was found in 98/265
4 (36.9%) of *Enterobacteriaceae* isolates. Among the *K. pneumoniae* strains, 15/43 (34.9%) were
5 resistant to carbapenems. Out of 66 *P. aeruginosa* isolates, 46 (69.7%) were MDR, as previously
6 defined [13].

7 The susceptibility to colistin was tested in 110/353 Gram-negative isolates, and only two
8 (1.8%; 2 *Pseudomonas putida* isolates) of these were resistant. The susceptibility to tigecycline was
9 tested in 160/285 Gram-negative isolates other than *Pseudomonas* spp., and nine (3.6%; 4 *K.*
10 *pneumoniae*, 4 *E. cloacae*, and 1 *A. baumannii* isolates) of these were resistant.

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

12 The antimicrobial susceptibility profiles of all Gram-positives and of the most frequently
13 isolated bacterial species (i.e., CoNS, *S. aureus*, *Enterococcus* spp., and VGS) are reported in Table
14 4. The susceptibility rates to oxacillin were 15.7% and 63.6% for CoNS and *S. aureus*, respectively.
15 Overall, 40.3% of the *Enterococcus* spp. isolates were susceptible to ampicillin; the susceptibility
16 rates to ampicillin were 88.9% for *E. faecalis* and 5.4% for *E. faecium* isolates; 89.2% and 97.3% of
17 *E. faecium* (and 100% of *E. faecalis*) isolates were susceptible to vancomycin and teicoplanin,
18 respectively. Among the VGS isolates, 63.9% were susceptible to penicillin, whereas all of these
19 were susceptible to glycopeptides. Overall, the susceptibility rates of Gram-positive bacteria were
20 97.4% to vancomycin and 94.2% to teicoplanin.

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

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

1 with neutropenia with a duration of <10 days (20/214, 9.3%; P=0.03), and for those patients who
2 had received an inappropriate initial antimicrobial therapy (32/142, 22.5%) versus those who had
3 received an appropriate empirical antibiotic treatment (44/433, 10.1%; P<0.001). In Table 5, the
4 mortality rates for patients with monomicrobial BBSIs are reported according to the most frequent
5 bacterial species. Overall, the 21-day mortality rate was significantly higher for patients with BBSI
6 caused by Gram-negative bacteria compared to those with BBSI caused by Gram-positives (47/278,
7 16.9% vs. 12/212, 5.6%; P<0.001). Among Gram-negatives, the mortality rate was significantly
8 higher for BBSI that was caused by *K. pneumoniae* (P=0.006), *P. aeruginosa* (P<0.001), and
9 *Acinetobacter baumannii* (P=0.004). There were no differences in the mortality rate among BBSIs
10 caused by Gram-positive bacterial species, except for BBSI that was caused by *Viridans Group*
11 *Streptococci* (VGS) and CoNS, which were associated with survival (P=0.05 and <0.001,
12 respectively). Among the more frequent antibiotic resistant Gram-negative bacterial species causing
13 monomicrobial BBSI, the mortality rate was significantly higher for patients with BBSI that was
14 caused by third generation cephalosporin-resistant *Enterobacteriaceae* compared to third generation
15 cephalosporin-susceptible *Enterobacteriaceae* (22/84, 26.2% vs. 6/124, 4.6%; P<0.001), for those
16 with BBSI that was caused by carbapenem-resistant *K. pneumoniae* compared to carbapenem-
17 susceptible *K. pneumoniae* (6/13, 46.1% vs. 3/20, 15%; P=0.04), and for those with BBSI that was
18 caused by MDR *P. aeruginosa* compared to non-MDR *P. aeruginosa* (14/19, 42.4% vs. 2/16, 12.5%;
19 P=0.03).

1 DISCUSSION

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

5 We found that Gram-negative bacteria were the most frequent microorganisms that were
6 isolated (52.8%) and these data are consistent with the recently reported shift of prevalence from
7 Gram-positive to Gram-negative bacteria among severe bacterial infections in patients with cancer
8 [4,7]. In addition, Mikulska et al., who recently compared a questionnaire survey that was
9 conducted in 2011 on the aetiology and resistance in BBSI episodes that occurred in adult cancer
10 patients in 39 centres (in 18 countries) to data that was collected from a literature review of BBSI
11 episodes in adult cancer patients from papers that were published between 2005 and 2011,
12 demonstrated that the survey showed a recent reduction in the Gram-positive to Gram-negative ratio
13 (55%:45% vs. 60%:40%) [14]. Notably, the median rate of bacterial species causing BBSI that was
14 reported in this ECIL-4 questionnaire survey was very similar to the bacterial species distribution in
15 our cohort, in that *E. coli* was the most frequent species (27.9% in our cohort vs. 30% in the ECIL-4
16 questionnaire survey), followed by CONS (24.8% vs. 24%), and *Enterococci* (10.1% vs. 8%), and
17 excepting the prevalence of *P. aeruginosa* BBSI which was twice as high in our cohort (9.9% vs.
18 5%) [14].

19 Regarding antimicrobial susceptibility among Gram-positive bacteria, we found that the rates
20 were similar or higher compared to what was reported by Mikulska et al. among adults in the
21 literature review; in particular, the susceptibility to methicillin was similar for CoNS (15.7% vs.
22 20%) but somewhat higher for *S. aureus* (63.6% vs. 44%), whereas >92% of *Staphylococci* and
23 *Enterococci* were susceptible to glycopeptides in our cohort. In addition, we observed a lower
24 prevalence of vancomycin resistance among *E. faecium* isolates compared to previous reports
25 (10.8% vs. 23%) [14]. Similarly, the resistance to teicoplanin among the CoNS isolates was
26 significantly lower compared to what was previously reported [15].

1 In contrast, we have found a worrisome trend toward a decrease in the susceptibility rates to
2 the main antibiotic drugs among Gram-negative bacteria compared to what has been reported in
3 more recent epidemiologic studies, which have been recently reviewed [7]. In particular, only
4 20.1% of the Gram-negative bacteria isolates from our patients were susceptible to
5 fluoroquinolones; the susceptibility rates to fluoroquinolones were significantly lower compared to
6 those that were previously reported for *E. coli* (9.6% vs. 47.2%), *K. pneumoniae* (30.2% vs. 61.1%),
7 *E. cloacae* (50% vs. 95.7%), and *P. aeruginosa* (19.7% vs. 51.6%). In addition, we observed rates
8 of susceptibility of 61.5% and 44.2% to meropenem and piperacillin/tazobactam, respectively,
9 among *K. pneumoniae* isolates, which are considerably lower than what was reported in previous
10 studies (mean of 98.5% and 71.8%, respectively) [7]. We also found a significant decrease in the
11 susceptibility rate to almost all of the most common antibiotics among *P. aeruginosa* isolates
12 compared with previous reports: 28.8% vs. 50.1% to meropenem, 57.6% vs. 78.3% to
13 piperacillin/tazobactam, 45.4% vs. 62.3% to ceftazidime, and 22.7% vs. 78.3% to gentamicin; the
14 susceptibility of *P. aeruginosa* isolates in our cohort to amikacin (65.8%) was similar to what was
15 previously reported (61.8%) [7]. Approximately 70% of the bloodstream *P. aeruginosa* isolates
16 were designated MDR in our cohort, and this rate was similar to what was reported by Cattaneo et
17 al. (71.1%) [16], though more than twice as high as what was reported in a preliminary analysis that
18 was conducted by this group on a smaller population size (33%) [17]. However, it has to be taken
19 into account that our data are representative of a single country, and the Italian situation might not
20 be representative for all of Europe.

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

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

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

18

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 \pm SD])	52 \pm 14.88	51 \pm 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			
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
<i>Escherichia coli</i>	187 (27.9)	181 (29.4)	6 (11.5)	0.006
<i>Klebsiella Pneumoniae</i>	43 (6.4)	39 (6.3)	4 (7.7)	0.70
<i>Enterobacter cloacae</i>	26 (3.4)	24 (3.9)	2 (3.8)	0.98
<i>Pseudomonas aeruginosa</i>	66 (9.9)	63 (10.2)	3 (5.8)	0.30
<i>Acinetobacter baumannii</i>	3 (0.4)	3 (0.5)	0	0.61
<i>Stenotrophomonas maltophilia</i>	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 <i>Staphylococci</i>	166 (24.8)	148 (24.0)	18 (34.6)	0.09
<i>Staphylococcus aureus</i>	11 (1.6)	7 (1.1)	4 (7.7)	<0.001
<i>Viridans group Streptococci</i>	36 (5.4)	35 (5.7)	1 (1.9)	0.25
<i>Streptococcus pneumoniae</i>	2 (0.3)	0	2 (3.8)	<0.001
<i>Enterococcus spp.</i>	67 (10.1)	63 (10.2)	4 (7.7)	0.56
<i>Enterococcus faecalis</i>	27 (4.1)	24 (3.9)	3 (5.8)	0.51
<i>Enterococcus faecium</i>	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)
<i>Escherichia coli</i>	187	131 (70.0)	18 (9.6)	184 (98.4)	183 (97.9)	155 (82.9)	156 (83.4)
<i>Klebsiella pneumoniae</i>	43	18 (41.9)	13 (30.2)	28 (65.1)	25 (58.1)	29 (67.4)	19 (44.2)
<i>Enterobacter cloacae</i>	26	12 (46.1)	13 (50.0)	24 (92.3)	23 (88.5)	23 (88.5)	12 (46.1)
<i>Pseudomonas aeruginosa</i>	66	30 (45.4)	13 (19.7)	19 (28.8)	43 (65.1)	15 (22.7)	38 (57.6)

^aThe 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 <i>Staphylococci</i>	166	26 (15.7)	-	-	164 (98.8)	150 (90.4)	155/156 (99.3) ^b	97/98 (98.9) ^c
<i>Staphylococcus aureus</i>	11	7 (63.6)	-	-	11 (100)	11 (100)	11 (100)	11 (100)
<i>Viridans group Streptococci</i> ^a	36	-	-	23 (63.9)	36 (100)	36 (100)	36 (100)	36 (100)
<i>Enterococcus</i> spp.	67	-	27 (40.3)	-	62 (92.5)	66 (98.5)	67 (100)	NA
<i>Enterococcus faecalis</i>	27	-	24 (88.9)	-	27 (100)	27 (100)	27 (100)	NA
<i>Enterococcus faecium</i>	37	-	2 (5.4)	-	33 (89.2)	36 (97.3)	37 (100)	NA

NA, not available.

^aThe susceptibility rate of *Viridans group Streptococci* isolates to ceftriaxone was 94.4% (34/36).

^bLinezolid was tested on a total of 156 coagulase-negative *Staphylococci* isolates and 155 (99.3%) were susceptible.

^cDaptomycin 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
<i>Escherichia coli</i>	16 (26.7)	142 (32.9)	0.74 (0.38-1.40)	0.33
<i>Klebsiella Pneumoniae</i>	9 (15.0)	24 (5.6)	3 (1.16-7.12)	0.006
<i>Enterobacter cloacae</i>	3 (5.0)	16 (3.7)	1.37 (0.25-4.99)	0.62
<i>Pseudomonas aeruginosa</i>	16 (26.7)	33 (7.6)	4.40 (2.08-8.97)	<0.001
<i>Acinetobacter baumannii</i>	2 (3.3)	1 (0.2)	14.86 (0.75-878.63)	0.004
<i>Stenotrophomonas maltophilia</i>	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 <i>Staphylococci</i>	4 (6.7)	117 (27.1)	0.19 (0.05-0.54)	<0.001
<i>Staphylococcus aureus</i>	0	8 (1.8)	-	0.29
<i>Viridans group Streptococci</i>	0	27 (6.2)	-	0.05
<i>Streptococcus pneumoniae</i>	1 (1.7)	1 (0.2)	7.30 (0.09-574.67)	0.10
<i>Enterococcus spp.</i>	4 (6.7)	27 (6.2)	1.07 (0.26-3.24)	0.90
<i>Enterococcus faecalis</i>	0	11 (2.5)	-	0.21
<i>Enterococcus faecium</i>	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