# Antibiotic-Resistant Bloodstream Infections in Hospitalized Patients: Specific Risk Factors in a High-Risk Population?

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## Abstract

**Background:** The aim of this study was to explore characteristics that are associated with bloodstream infections due to specific multiresistant microorganisms (methicillin-resitant *Staphylococcus aureus*, MRSA; vancomycin-resistant enterococci, VRE; third-generation cephalosporin-resistant Enterobacteriaceae) or *Candida* spp. in hospitalized patients.

**Patients and Methods:** All patients who experienced a bloodstream infection with one of the aforementioned pathogens between September 1999 and October 2001 were included into a statistical analysis of independent risk factors. The possible impact of previous antibiotic and antifungal therapies was evaluated.

**Results:** Of the study population, 22% had two or more episodes with different pathogens. In the 314 patients with a single bloodstream infection MRSA was isolated in 189 patients, VRE in 31, Enterobacteriaceae in 13, and *Candida* spp. in 80 patients. Crude mortality was high in the study population (overall 40%) and varied between 33% (MRSA bacteremia only) and 58% (VRE bacteremia only). Patients who yielded more than one of the pathogens under surveillance had crude mortalities ranging from 41% to 83% (all four pathogens). In this group of high-risk patients, the following factors were independently associated with the individual pathogen: prior chemotherapy (OR 4.88 CI$_{95}$ 1.50–15.87) and bronchoscopy (OR 3.17 CI$_{95}$ 1.05–9.52) for VRE patients; burns (OR 4.50 CI$_{95}$ 0.90–22.73), presence of a tracheostomy (OR 4.22 CI$_{95}$ 1.15–15.38) and acute dialysis (OR 3.62 CI$_{95}$ 0.99–13.16) for patients with Enterobacteriaceae; and an underlying malignant disease (OR 1.98 CI$_{95}$ 0.99–3.97), performance of a bowel endoscopy (OR 2.80 CI$_{95}$ 1.27–6.13) and presence of a central venous catheter (CVC) (OR 12.34 CI$_{95}$ 1.63–90.91) for patients with candidemia.

**Conclusion:** Patients with bacteremia due to VRE, Enterobacteriaceae or *Candida* spp. had more severe risk factors associated with the respective pathogen than patients with MRSA bacteremia.

## Introduction

Many studies have been performed to identify risk factors for acquiring nosocomial bloodstream infection caused by multiresistant bacteria or yeasts. A statistically significant relationship can be demonstrated for host factors (underlying disease or conditions, such as immunosuppression) and environment exposures (intensive care unit [ICU] stay, prevalence of specific nosocomial pathogens) or prior procedures including surgery, invasive devices, mechanical ventilation, nutritional support and dialysis [1–7]. We sought to define factors that distinguish patients who had acquired bloodstream infections due to one of four target organisms during the study period of September 1999 to October 2001 in a single institution.

## Patients and Methods
### Setting

The Medical College of Virginia Hospitals (MCVH) is a 750-bed tertiary care facility in Richmond, Virginia. Approximately 30,000 patients are admitted annually. The hospital houses bone marrow and solid organ transplantation units as well as nine ICUs, including two pediatric ICUs and a burn unit.

### Study Design

The study population consisted of all adolescent and adult patients with a bloodstream infection due to *Candida* spp. or a multiresistant bacterium (defined below), who experienced their first

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infectious episode between September 27, 1999 and October 31, 2001. The patients were identified by searching the microbiology laboratory database. Patients who had polymicrobial bloodstream infections or consecutive episodes with more than one of the target microorganisms were excluded from the analysis.

Patients were considered to have had bacteremia with a multiresistant pathogen if at least one blood culture yielded positive growth for any one of the following:
- Methicillin-resistant *Staphylococcus aureus* (MRSA),
- Vancomycin-resistant enterococci (VRE),
- Enterobacteriaceae resistant to third-generation cephalosporins.

In a first step the four groups of patients were compared to define factors that significantly differentiate the groups. In a second step, independent risk factors for bloodstream infections with each pathogen were identified via comparing each group of patients with a specific pathogen with all other patients (controls).

### Data Collection

Data were collected from the electronic hospital information system, as well as from concurrent medical record review by infection control nurses.

The following variables were analyzed:
- Demographic data and comorbid conditions,
- Clinical characteristics on admission,
- Clinical features including presence of neutropenia (< 500 PMN/dl) ≤ 72 h before bloodstream infection,
- Invasive procedures and medications, including presence of central venous catheters (CVCs) ≤ 48 h before bloodstream infection, initiation of total parenteral nutrition (TPN) ≤ 7 days before positive blood culture and receipt of steroids, antibacterial and antifungal drugs ≤ 7 days before positive blood culture. Carbapenems, clindamycin, and metronidazole were designated anti-anaerobic drugs. The sum of all antibacterial and/or antifungal drugs given per day is presented. For individual substances the therapy days with the specific drug ≤ 7 days before positive blood culture were added.
- Microbiological data.

### Statistics

Comparisons between groups were performed by means of the $\chi^2$ test for categorical variables or analysis of variances (ANOVA) for continuous variables. Length of hospital stay was analyzed after log transformation. All categorical variables that were significantly different between the patient groups were included in a multinomial logistic model with backward elimination of variables. Univariate and multivariate analyses were performed with SPSS software (SPSS 10.0, Chicago, IL). All tests of significance were two-tailed, and alpha was set at 0.05.

### Results

A total of 403 patients with bloodstream infections due to ≥ 1 multiresistant bacteria and/or *Candida* spp. was identified during the observation period. Bacteremia with only one of the pathogens under surveillance was detected in 314 patients (78%), but 66 patients (16%) had bloodstream infections with two different pathogens, and 17 and six patients yielded three or four pathogens, respectively (Table 1). The majority of patients studied, i.e. 263 individuals (65%) had MRSA bacteremia, 147 (36%) had candidemia, 71 patients (18%) had VRE bacteremia, and 39 (10%) pa-

tients had bacteremia with third-generation cephalosporin-resistant gram-negative rods.

In patients with candidemia, *Candida albicans* (52%), *Candida glabrata* (24%), and *Candida parapsilosis* (13%) were identified as the predominant species. *Enterobacter* spp. was the pathogen in 61% of all bloodstream infections due to third-generation cephalosporin-resistant Enterobacteriaceae.

161 patients (40%) expired. There was a dose-response relationship between the number of episodes of bloodstream infections and crude mortality (p = .002): one pathogen (38%), two pathogens (41%), three pathogens (65 %) and four pathogens (83%).

For the remainder of the analysis, patients who had more than one bacteremic episode were excluded to avoid misclassification bias. The four groups of patients were not significantly different regarding gender, age or urgency of admission. With regard to the underlying conditions of the patient population, only burns, malignancy, transplantation, and neutropenia were not equally distributed in the groups of patients (Table 2). Whereas there were no differences in the proportions of patients who underwent surgical procedures, esophagoscopy, and cardiac catheterization, there were significant differences in the proportions of patients undergoing bowel endoscopy, bronchoscopy, mechanical ventilation > 96 h, tracheostomy, and acute dialysis. Only CVCs were not used in comparable proportions of patients in each group. Medication and nutrition of the patients differed in the proportions of individuals receiving chemotherapy, immunosuppression, and TPN across the four groups (Table 2).

Regarding the timing of bloodstream infections in patients with single bacteremias, MRSA bacteremia was in most cases the earliest to occur after a mean of 12.9 ± 17.8 days, followed by candidemia (19.1 ± 16.6 days), bacteremia with Enterobacteriaceae (19.8 ± 14.3 days) and VRE

Table 1

**Distribution and number of patients with two or three pathogens of interest: Methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Candida* spp. and Enterobacteriaceae resistant to third-generation cephalosporins.**

| Pathogens | No. of patients |
|---|---|
| MRSA + *Candida* spp. | 34 |
| MRSA + VRE | 13 |
| MRSA + Enterobacteriaceae | 6 |
| VRE + *Candida* spp. | 9 |
| VRE + Enterobacteriaceae | 0 |
| *Candida* spp. + Enterobacteriaceae | 4 |
| MRSA + VRE + *Candida* spp. | 7 |
| MRSA + VRE + Enterobacteriaceae | 3 |
| MRSA + *Candida* spp. + Enterobacteriaceae | 5 |
| VRE + *Candida* spp. + Enterobacteriaceae | 2 |

bacteremia (25.7 ± 22.4 days). The differences in time to bacteremia were statistically significant (p = 0.001).

Multivariate analysis revealed independent predictors for patients who developed only one bacteremic episode with VRE, Enterobacteriaceae or *Candida* spp., respec-

tively (Table 3). Patients with malignancies, patients who had a CVC in place and/or underwent bowel endoscopy had a significantly higher risk for developing candidemia. Treatment with chemotherapy or performance of a bronchoscopy placed the patient at increased risk for VRE bac-

Table 2

**Characteristics of the population of patients with bloodstream infections due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Candida* spp. and Enterobacteriaceae resistant to third-generation cephalosporins (GN).**

| Variable | MRSA<br>n = 189 | *Candida* spp.<br>n = 80 | VRE<br>n = 31 | GN<br>n = 13 | P-value |
|---|---|---|---|---|---|
| Male | 52.4% | 48.8% | 58.1% | 69.2% | > 0.05 |
| Age | 56.1 ± 17.3 | 52.6 ± 18.6 | 48.6 ± 18.1 | 52.9 ± 23.2 | > 0.05 |
| **Admission** | | | | | > 0.05 |
| Elective | 14.8% | 17.5% | 12.9% | 15.4% | |
| Urgent | 27.5% | 26.3% | 35.5% | 30.8% | |
| Emergency room | 57.7% | 56.3% | 51.6% | 53.8% | |
| **Transfer ext. hospital** | 16.9% | 12.5% | 9.7% | 0% | > 0.05 |
| **Time to bacteremia (days)** | 12.9 ± 17.8 | 19.1 ± 16.6 | 25.7 ± 22.4 | 19.8 ± 14.3 | 0.001 |
| **Service** | | | | | 0.001 |
| Medicine | 52.9% | 66.3% | 74.2% | 15.4% | |
| Surgery | 40.2% | 31.3% | 25.8% | 61.5% | |
| Burn unit | 6.9% | 2.5% | 0% | 23.1% | |
| Crude mortality | 33.3% | 40.0% | 58.1% | 38.5% | 0.066 |
| **Diagnosis/condition** | | | | | |
| Trauma | 9.0% | 6.3% | 0% | 7.7% | > 0.05 |
| Burn | 4.2% | 2.5% | 0% | 23.1% | 0.004 |
| Malignancy | 14.3% | 26.3% | 32.3% | 15.4% | 0.029 |
| Transplantation | 6.9% | 10.0% | 25.8% | 7.7% | 0.011 |
| Neutropenia | 4.2% | 7.5% | 19.4% | 7.7% | 0.020 |
| HIV positive | 4.8% | 3.8% | 12.9% | 0% | > 0.05 |
| Gastrointestinal disorder | 14.8% | 18.8% | 16.1% | 30.8% | > 0.05 |
| Cardiovascular disease | 25.9% | 27.5% | 22.6% | 30.8% | > 0.05 |
| Chronic respiratory disease | 17.5% | 17.5% | 12.9% | 0% | > 0.05 |
| Liver cirrhosis | 10.6% | 10.0% | 12.9% | 0% | > 0.05 |
| Neurological disorder | 18.0% | 20.0% | 9.7% | 7.7% | > 0.05 |
| Diabetes | 30.2% | 18.8% | 29.0% | 38.5% | > 0.05 |
| Morbid obesity | 4.2% | 2.5% | 0% | 15.4% | > 0.05 |
| Pressure ulcer | 5.8% | 3.8% | 3.2% | 7.7% | > 0.05 |
| **Procedures** | | | | | |
| Surgery | 50.3% | 58.8% | 48.4% | 84.6% | > 0.05 |
| Esophagoscopy | 15.3% | 20.3% | 16.1% | 7.7% | > 0.05 |
| Bowel endoscopy | 6.9% | 21.3% | 9.7% | 7.7% | 0.007 |
| Bronchoscopy | 11.1% | 18.8% | 32.3% | 15.4% | 0.022 |
| Cardiac catheterization | 2.6% | 2.5% | 6.5% | 0% | > 0.05 |
| Acute dialysis | 7.4% | 11.2% | 19.4% | 30.8% | 0.011 |
| Chronic dialysis | 10.6% | 6.3% | 16.1% | 7.7% | > 0.05 |
| **Mechanical ventilation** | | | | | |
| > 96 h | 37.0% | 52.5% | 32.3% | 76.9% | 0.004 |
| Tracheostomy | 21.7% | 22.5% | 9.7% | 61.5% | 0.002 |
| **Devices** | | | | | |
| Central venous catheter (CVC) | 75.1% | 96.3% | 77.4% | 92.3% | < 0.001 |
| Chest tube | 9.5% | 11.3% | 3.2% | 7.7% | > 0.05 |
| Enterostomy | 15.4% | 18.8% | 9.7% | 7.7% | > 0.05 |
| **Medication/nutrition** | | | | | |
| Steroids | 26.5% | 36.3% | 48.4% | 23.1% | > 0.05 |
| Chemotherapy | 3.2% | 5.0% | 22.6% | 0% | < 0.001 |
| Immunosuppression | 27.0% | 38.8% | 54.8% | 23.1% | 0.046 |
| Total parenteral nutrition | 20.1% | 41.3% | 35.5% | 15.4% | 0.002 |

teremia. VRE patients, however, were less likely to have been ventilated for more than 96 h. Patients with severe burns, undergoing acute dialysis and those with tracheostomies had an increased risk for developing bloodstream infections with third-generation cephalosporin-resistant Enterobacteriaceae. Patients who had MRSA bacteremia seemed to be the least morbid patient group. They were less likely to have malignancies, receive bowel endoscopy, or have a CVC in place than the patients in the other groups.

The antibiotic and antifungal therapies that the patients received ≤ 7 days before their first positive blood culture for one of the pathogens under surveillance are shown

**Table 3**
**Results of a multinomial logistic model with backward elimination of variables to identify factors associated with bloodstream infection due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Candida* spp. and Enterobacteriaceae resistant to third-generation cephalosporins. For each pathogen, a comparison is made between all patients with a specific pathogen versus all other patients who did not have this pathogen. Only patients with a single episode were included.**

| Variable | MRSA n = 189 | *Candida* n = 80 | VRE n = 31 | Enterobacteriaceae n = 13 |
|---|---|---|---|---|
| Burn | | | | 4.50 CI$_{95}$ 0.90–22.73 |
| Malignancy | 0.44 CI$_{95}$ 0.86–0.23 | 1.98 CI$_{95}$ 0.99–3.97 | | |
| Chemotherapy | | | 4.88 CI$_{95}$ 1.50–15.87 | |
| Bowel endoscopy | 0.45 CI$_{95}$ 0.21–0.99 | 2.80 CI$_{95}$ 1.27–6.13 | | |
| Bronchoscopy | | | 3.17 CI$_{95}$ 1.05–9.52 | |
| Mechanical ventilation > 96 h | | | 0.38 CI$_{95}$ 0.14–1.08 | |
| Tracheostomy | | | | 4.22 CI$_{95}$ 1.15–15.38 |
| Acute dialysis | | | | 3.62 CI$_{95}$ 0.99–13.16 |
| Presence of CVC | 0.30 CI$_{95}$ 0.11–0.78 | 12.34 CI$_{95}$ 1.63–90.91 | | |

**Table 4**
**Antibiotic and antifungal treatment as well as application of specific drugs ≤ 7 days before the onset of bloodstream infection caused by methicillin-resistant *S. aureus* (MRS), vancomycin-resistant enterococci [VRE], *Candida* spp. and Enterobacteriaceae resistant to third-generation cephalosporins (GN). Only patients with a single episode were included.**

| Pathogen | Anti-bacterials/day | Antifungals/day | Vancomycin | Anti-anearobic drugs | Ceftazidime | Quinolones |
|---|---|---|---|---|---|---|
| | (mean days ± SD) | | | | | |
| MRSA No. = 131 | 1.1 ± 0.9 | 0.2 ± 0.4 | 0.7 ± 1.4 | 1.5 ± 2.4 | 0.8 ± 1.7 | 1.4 ± 2.4 |
| VRE No. = 27 | 1.8 ± 0.9 | 0.3 ± 0.4 | 2.5 ± 3.0 | 2.9 ± 3.3 | 1.4 ± 2.3 | 1.9 ± 2.7 |
| GN No. = 12 | 1.2 ± 0.9 | 0.2 ± 0.3 | 0.6 ± 1.2 | 2.2 ± 3.0 | 1.2 ± 2.5 | 0.6 ± 2.0 |
| *Candida* No. = 74 | 1.7 ± 1.0 | 0.2 ± 0.4 | 2.6 ± 2.8 | 3.1 ± 3.2 | 1.1 ± 2.3 | 1.3 ± 2.3 |
| P-value (ANOVA) | < 0.001 | > 0.05 | < 0.001 | 0.001 | > 0.05 | > 0.05 |

in Table 4. Patients with MRSA bacteremia had the least antibiotic burden ($1.1 \pm 0.9$ antibiotics per day) as well as the shortest duration of vancomycin ($0.7 \pm 1.4$ days) and ceftazidime ($0.8 \pm 1.7$ days) therapy. Patients with candidemia had received the most treatment with anti-anaerobic antibiotics ($3.1 \pm 3.2$ days) before the onset of bloodstream infection. Patients with VRE bacteremia had received the most antifungal drugs ($0.3 \pm 0.4$ per day) and most treatment days with ceftazidime ($1.4 \pm 2.3$ days) and quinolones ($1.9 \pm 2.7$ days) before the onset of bacteremia. The differences in the amount of antibacterial substances per day as well as length of therapy with vancomycin and anti-anaerobic drugs, respectively, were statistically significant.

### Discussion
To our knowledge this is the first study to investigate a high-risk population simultaneously for factors associated with bloodstream infections (BSI) due to one of three leading antibiotic-resistant pathogens or *Candida* spp. We compared characteristics in one patient group with a specific pathogen to conditions present in all other of these high-risk patients. By using this approach we were not able to identify risk factors for the development of BSI.

It has not been previously reported that approximately 20% of hospitalized patients with BSI caused by highly resistant pathogens and/or yeasts had at least two episodes with these organisms of interest. Our patients with these BSIs had an extremely high crude mortality (ranging from 33 to 58% and reaching 83% for patients with bacteremias due to all four pathogens under surveillance) compared to a mortality of about 27% and 40% reported for all patients with nosocomial BSI (SCOPE) or patients with BSI-associated sepsis, respectively [8, 9].

Regarding the individual pathogens and their corresponding risk factors the predominant characteristics could be described as follows.

### MRSA
In our study population, patients who had only MRSA bacteremia were significantly less likely to have a malignant disorder, to have received a bowel endoscopy, or have a CVC in place. They had the lowest crude mortality (33.3%) compared to patients with other multiresistant bacteremias and candidemias. Thus, patients with MRSA bacteremia represent a broad, lower risk pool in an institution with a high prevalence of MRSA (approximately 52% of *Staphylococcus aureus* strains are resistant to methicillin). Colonization and subsequent bacteremia with MRSA might have occurred earlier than bloodstream infections with one of the other pathogens under observation due to this high colonization pressure.

### VRE
Most patients with VRE bacteremia are severely ill and/or immunocompromised [10–12]. In our study, neutropenia was most common in this patient group, and chemotherapy and bronchoscopy were independent risk factors. Cross-transmission has been identified as one of the factors propagating nosocomial VRE spread. In our hospital, patients receiving chemotherapy are treated in designated oncology units. Results of molecular typing of the VRE isolates is not available; thus, nosocomial transmission from colonized patients or the environment cannot be excluded. We consider, however, bronchoscopy as a marker for a more severe clinical course in VRE patients.

It seems of interest that VRE patients were significantly less likely to have been ventilated for more than 96 h. One possible explanation might be the hypothesis that after initiation of mechanical ventilation in these severely ill patients with the highest mortality of the population under observation, the chances of survival for a prolonged period of time were low.

### Third-Generation Cephalosporin-Resistant Enterobacteriaceae
A high proportion of ventilator-associated pneumonias is caused by Enterobacteriaceae [13]. This might explain why patients with bloodstream infections due to Enterobacteriaceae were more likely to have been ventilated for more than 96 h and have a tracheostomy. In previous studies, most of the highly resistant Enterobacteriaceae were shown to have been acquired during a prolonged hospitalization with prolonged antibiotic exposure to third-generation cephalosporins [14, 15]. In our patients, bacteremia with these pathogens appeared late in the course of hospitalization. Nearly 31% of the patients received acute dialysis and the majority underwent surgical procedures (85%). Independent risk factors identified in our study were the presence of a tracheostomy as an indicator of prolonged mechanical ventilation, performance of acute dialysis and a diagnosis of burn injury.

### *Candida* spp.
The characteristics of our patients with candidemia were comparable to the patients described in many other studies: patients had an average age of 53 years, the gender distribution was about 1:1, the crude mortality rate was 40% and *C. albicans* was identified as the predominant species. As has been observed before, our patients with candidemia were significantly more likely to suffer from a malignancy. Furthermore the presence of intravascular devices and performance of bowel endoscopy were independent predictors in the multivariate analysis. The association between bowel endoscopy and candidemia should be regarded as a surrogate marker for a more serious bowel disease. It cannot be overemphasized that the presence of a central venous device puts the patient at a 12-fold (OR 12.34, $CI_{95}$ 1.63–90.91) increased risk for candidemia in this study. Other authors have observed from 1- to 26-fold increased risks [7, 16–20].

Many authors have discussed the impact of antibiotic therapy on the emergence of multiresistant organisms. We

restricted our analysis to the 7 days preceding the bacteremia. There were significant differences between the pathogens: As a rule, before MRSA bacteremia, patients received less antibacterial and antifungal therapy. The literature discussing a causal relationship between preceding antimicrobial therapies and subsequent systemic MRSA infection remains controversial [21–24]. In contrast, patients with VRE bacteremia not only received the most antibiotics and antifungals per day, but had the most treatment days with vancomycin, ceftazidime and anti-anaerobic agents if compared to patients with MRSA or Enterobacteriaceae bacteremia. Many studies have linked the application of vancomycin, anti-anaerobic agents and/or third-generation cephalosporins to the emergence of VRE [4, 10, 25, 26]. Patients with candidemia had the highest number of treatment days with anti-anaerobic drugs of all patients before their bloodstream infection. In previous studies, antifungal therapy has been shown to be protective, and anti-anaerobic drugs have been identified as a risk factor for developing candidemia [7, 27]. These observations should be considered in planning the anti-infective therapy of hospitalized patients, because inappropriate initial empirical antibiotic therapy is associated with a higher mortality [28].

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