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# Multidrug Resistant Bacteremia: Clinical And Bacteriological Epidemiology In Hematopoietic Stem Cell Transplant Recipients

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## Research Article

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**List of abbreviations:** AR: Antibiotic Resistance; MRSA: Methicillin Resistant Staphylococcus Aureus; WHO: World Health Organisation

**ABSTRACT**

**Background:** Bacteremia becomes increasingly fearsome in hematopoietic stem cell transplant (HSCT) recipients with the emergence of multidrug-resistant (MDR) strains.

The purpose of our study was to investigate the prevalence of MDR bacteremia in HSCT recipients at the Tunisian National Bone Marrow Transplant Center (NBMTC), the associated factors and the attributable mortality rate.

**Patients/methods:** This is a retrospective study which included all MDR bacteremia in the Hematology department, occurring between January 2010 and December 2017.

**Results:** The prevalence of MDR bacteremia among HSCT recipients was 5.9% (48/816) with a stable trend over time (rs=0.18; p=0.6). Neutropenia, prior hospitalization, prior antibiotherapy and prior colonization with MDR pathogens were observed in 59%, 58%, 48% and 31% of cases, respectively. Imipenem was the most prescribed first-line antibiotic (50%). The first-line antibiotherapy was adequate in 44% of bacteremia. The mortality rate due to MDR bacteremia was 13%. The MDR bacteria (n=48) belonged to ESBL-E (60%) followed by MDR P. aeruginosa (19%), MDR A. baumannii (13%), MRSA (4%) and VRE (4%). For ESBL-E and P. aeruginosa, the rates of antibiotic resistance were respectively, 17% and 44% to imipenem, 31% and 56% to amikacin and 15% and 0% to colistin. Strains of A. baumannii were susceptible only to colistin. The MRSA (n=2) were resistant to ciprofloxacin and gentamicin and susceptible to glycopeptides. The VRE (n=2) were susceptible to linezolid and tigecycline.

**Conclusion:** Low prevalence of MDR bacteremia in HSCT recipients but high attributable mortality rate, requiring continued screening and reinforcement of hygiene measures.

## INTRODUCTION

Antibiotics are Hematopoietic stem cell transplantation is a potentially curative treatment of many malignant and non-malignant hematologic diseases. It has prolonged the survival of transplant patients at the cost of increased risk of infectious complications. Bacteremia is among the most frequent complications in hematopoietic stem cell transplant (HSCT) recipients. In fact, these populations are exposed to myeloablative chemotherapy, which induces a worsening of the immune system and a mucosal damage favoring the occurrence of bacteremia by translocation.

Moreover, the high pressure of antibiotics selection to which HSCT recipients are subjected is causing an increase of MDR strains. Bacteremia caused by MDR strains are a well-known cause of mortality and morbidity in immune compromised patients [1].

The aim of our study was to investigate the prevalence of MDR bacteremia at the Tunisian National Bone Marrow Transplant Center (NBMTC), the associated factors and the attributable mortality rate.

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# METHODS

### Patients

The NBMTC is a university referral center specialized in all types of hematopoietic stem cell transplantation and the treatment of patients with immunodeficiency in Tunisia. Our study was carried out at the adult hospital ward which contains a transplant unit with 9 laminar flow cabins and a hematology unit with 10 conventional rooms. A total of 45 geno-identical HLA allografts and 60 autografts are performed annually at the NBMTC.

Our study was conducted between January 2010 and December 2017. It was carried out in patients hospitalized at the hematology ward of NBMTC for HSCT or post-HSCT complication and who later presented at least one MDR bacteremia. An interval of four weeks between bacteremia caused by the same pathogen in the same patient was required to consider bacteremia as different [2].

The screening for MDR bacteria was performed by rectal swabs at hospital admission and weekly until discharge. A digestive tract decontamination based on enteral colimycin, gentamicin and fungizone was administered to all patients on admission after the first rectal swab to eliminate Gram-negative rods (GNR) and fungi. No systemic antibioprophylaxis was used. The protocol for the management of febrile neutropenic episodes in the absence of clinical or microbiological evidence was based empirically on the combination of a β-lactam (piperacillin-tazobactam) and an aminoglycoside (amikacin) or ciprofloxacin. Imipenem was indicated in case of colonization with MDR strains or in case of severity of the clinical presentation (sepsis, septic shock).

Data relating to our patients were gathered from medical records. Collected data were gender, age, underlying disease, prior hospital stay, prior antibiotherapy, transplant procedures, prior colonization or infection with the same MDR strain, neutrophil counts at the time of MDR bacteremia, presence of central venous catheter, graft versus host disease (GVHD), MDR bacteremia (clinical presentation, treatment and outcome).

Day of infusion of HSCT was considered day 0.

### Bacteriological Study

Blood cultures were indicated in case of fever or systematically in patients on corticosteroids. These samples were analyzed in the laboratory according to the "Référentiel En Microbiologie Médicale" [3]. Bacterial identification was based on morphologic, cultural and biochemical characteristics (Api systems, BioMérieux®).

Antimicrobial susceptibility testing was performed by the diffusion method on agar medium according to the CA-SFM standards [4]. The minimal inhibitory concentrations (MIC) for colistine for extended spectrum β-lactamase producing *Enterobacteriacae* (ESBL-E), MDR *P. aeruginosa* and MDR *A. baumannii* were performed by using microdilution method (Biocentric®). The MIC for glycopeptides for methicillin-resistant *S. aureus* (MRSA) and vancomycin resistant *E. faecium* (VRE) were determined by microdilution method (Biocentric®) and E-test (BioMérieux®), respectively. ESBL identification was determined by the double disk synergy test.

### Definitions

MDR bacteremia was defined as the isolation in the blood of a MDR bacteria [ESBL-E, P. aeruginosa and A. baumannii resistant to at least three families of antibiotics (β-lactam, aminoglycoside, fluoroquinolone, colistin), MRSA and VRE]. Catheter related-bacteremia was defined according to the Infectious Diseases Society of America [5]. Mortality was due to MDR bacteremia if no other cause of death was found [6].

### Statistical Analysis

Absolute and relative frequencies were calculated for the qualitative variables. Averages, medians and extreme values were determined for the quantitative variables. Clinical features (age, gender, and medical history and post-HSCT complications) were estimated according to the number of patients. Variables relative to bacteremia were studied according to the number of bacteremia. The evolution of MDR bacteremia over time was studied by Spearman rank correlation coefficient (rs). For all statistical tests, the significance level (p) was set at 0.05.

# RESULTS

### Patients' Characteristics

During the study period, out of a total of 816 HSCT recipients, 48 MDR bacteremia were recorded in 45 patients. The median age of patients was 36 years (7-65 years) and the sex ratio Man/Woman was 1.04. The prevalence of MDR bacteremia in hematopoietic stem cells allografted and autografted patients was 10% and 2.5%, respectively. Aplastic anemia was the most frequent underlying hematological disease (18.6%) followed by acute leukemia (16%), lymphoma (3.6%) and myeloma (2%) (**Table 1**).

**Table 1.** Patients and transplant characteristics (GVHD: Graft versus host disease).

| Clinical Features | Number of patients (percentage) |
|---|---|
| Total of patients | 45(100%) |
| **Hematological disease** | |
| Acute myeloblastic leukemia | 10(22%) |
| Acute lymphoblastic leukemia | 7(16%) |
| Aplastic anemia | 13(29%) |
| Lymphoma | 7(16%) |
| Myeloma | 6(13%) |
| Myelodysplastic syndrome | 1(2%) |
| Gaucher disease | 1(2%) |
| **Treatment** | |
| Allograft | 33(73%) |
| Autograft | 12(27%) |
| **Factors associated with Bacteremia** | |
| Neutropenia | 28(59%) |
| Mucositis | 7(16%) |
| Acute GVHD grade ≥ 3 | 22(49%) |
| Presence of central venous catheter | 42(93%) |

**Prevalence and Timing of Multidrug-Resistant Bacteremia**

Forty-five patients among 816 HSCT recipients (5.51%) developed one (n=42) or two (n=3) episodes of MDR bacteremia with a prevalence of 5.88% (48/816). This prevalence was stable over time. The prevalence of EBLS-E bacteremia was the highest one (**Table 2**). Post-graft median time of MDR bacteremia was +98 days (range: -5 to 890 days). Thirty-three MDR bacteremia (63%) occurred within 100 days.

**Factors Associated with Multidrug-Resistant Bacteremia**

A total of 28 MDR bacteremia (59%) occurred during the neutropenia period with a median pre-bacteremia duration of 45 days (7 -190 days). Mucositis and acute GVHD were detected in seven (16%) and twenty-two (67%) patients, respectively. Forty-two (93%) patients had central venous catheter (CVC) with a median pre-bacteremia duration of catheterization of 31.4 days (3-131 days). Fecal colonization with the same MDR strains, anterior or concomitant to bacteremia, was noticed in 31% of cases. The median time between colonization and bacteremia was 10 days (-22 days, +1 day). Infections with the same MDR pathogen within three months prior to the MDR bacteremia was observed in 23% of cases (**Table 1**).

A history of hospital stay within three months prior to the MDR bacteremia was observed in 58% of bacteremia. The median length of hospitalization was 44.8 days (6-147 days). Prior broad-spectrum antibiotic prescription within a month prior to bacteremia was observed in 48% of bacteremia, with a median duration of 15 days (6-35 days). This antibiotherapy was based on monotherapy (n=3, 13%) or a combination of two or more antibiotics (n=20, 87%). Imipenem (n=12), teicoplanin (n=11) and ciprofloxacin (n=7) were the most prescribed antibiotics.

**Clinical Presentation, Treatment and Outcome**

Isolated fever was present in 48% of cases at the time of bacteremia. Bacteremia was related to CVC in 21% of cases. One or more secondary infectious localizations were associated with bacteremia in 21% of cases. The most common were cutaneous (11%), pulmonary (4%) and ear nose and throat infectious foci (4%). In our study, first-line antibiotherapy was based on a monotherapy in 19% of cases and a dual therapy in 81% of cases. The median time to start it was two days (1-3 days). The most commonly prescribed antibiotic was imipenem (50%), mainly in combination with amikacin (27%). This first-line antibiotherapy was adequate in 44% of bacteremia. A second-line antibiotherapy was indicated in 63% of cases (n=30) either because of antimicrobial resistance (n=27) or persistence of fever or worsening of symptomatology (n=3).

In ESBL-E bacteremia (n=29), a second-line antibiotherapy was prescribed in 20 cases (69% of ESBL-E bacteremia). It was based on colistin (n=12), imipenem (n=10), fosfomycin (n=5) or ciprofloxacin (n=1).

Regarding MDR *P. aeruginosa* bacteremia (n=9), the use of a second-line antibiotherapy was noted in 6 cases. Colistin (5/6), imipenem (5/6) and amikacin (4/6) were prescribed in these bacteremia.

For MDR *A. baumannii* bacteremia (n=6), a second-line antibiotherapy was necessary in 3/6 cases. It was based on colistin in three cases and on fosfomycin in two cases.

For VRE bacteremia (n=2), pristinamycin was prescribed as a second-line therapy in combination with linezolid in one case. First line antibiotic therapy, based on teicoplanin, was appropriate in MRSA bacteremia (n=2).

In our study, mortality was attributable to MDR bacteremia in 13% (6/45) of cases: 4/29 ESBL-E and 2/9 MDR *P. aeruginosa*. Clinical features of patients with attributable mortality to multidrug-resistant bacteremia are detailed in **Table 2.**

**Bacteriological study**

The rate of MDR responsible for bacteremia in HSCT recipients was 37.5% (48/128 strains isolated from blood cultures). This rate was stable during the study period (rs=0.18; p =0.6).

MDR bacteria were dominated by ESBL-E (60%) followed by MDR *P. aeruginosa* (19%), MDR *A. baumannii* (13%), MRSA (4%) and VRE (4%). Among the ESBL-E (n=29), *K. pneumoniae* (n=17) and *E. coli* (n=5) were the most isolated strains (59% and 17%, respectively) (**Table 3**).

**Table 3.** Prevalence of bacteremia according to the type of multidrug-resistant bacteria.

| Type of multidrug-resistant bacteria | Prevalence of bacteremia n (%) |
|---|---|
| Extended spectrum beta-lactamase producing *Enterobacteriaceae* | 29(3,6) |
| Multidrug-resistant *P. aeruginosa* | 9(1,1) |
| Multidrug-resistant *A. baumannii* | 6(0,7) |
| Vancomycin resistant *E. faecium* | 2(0,24) |
| Methicillin resistant *S. aureus* | 2(0,24) |

For ESBL-E, antibiotic resistance rates were as follows: Ertapenem 31% (MIC ranged from 0.75 to 32 mg/L), imipenem 17% (MIC ranged from 3 to 32 mg/L), ciprofloxacin 83%, amikacin 31%, fosfomycin 10% and colistin 15%. *For P. aeruginosa*, the rates of antibiotic resistance were 78% to piperacillin-tazobactam, 67% to ceftazidim, 44% to imipenem (MIC ranged from 8 to 64 mg/L), 56% to amikacin and 100% to ciprofloxacin. No strain was resistant to colistin.

Strains of *A. baumannii* were resistant to all antibiotics tested (piperacillin-tazobactam, ticarcillin-clavulanic acid, ceftazidim, cefepime, imipenem, gentamicin, amikacin and ciprofloxacin) except for colistin which was active in all cases.

Both strains of MRSA were resistant to gentamicin and ciprofloxacin and susceptible to pristinamycin, rifampicin, tigecycline, linezolid and glycopeptides.

VRE strains were both resistant to ampicillin and susceptible to linezolid, tigecyclin and quinupristin-dalfopristin. High level resistance to gentamicin was observed in one strain.

## DISCUSSION

Bacteremia is frequent in HSCT recipients especially in the first month post-HSCT. With the spread of MDR strains, bacteremia are becoming fearsome in such immune compromised population.

We noticed a low prevalence of MDR bacteremia in our center (5.9%). This prevalence was higher in GNR (4.7%) than in GPC (0.4%). The prevalence of MDR GNR bacteremia was similar to that reported by a prospective multicenter study (5%) in Brazil in onco-hematology [7]. Factors associated with MDR bacteremia are numerous. However, a case-control study including more patients is needed to better determine the factors associated with MDR bacteremia and to identify prognosis factors for this bacteremia.

MDR bacteremia were more common in patients with aplastic anemia (18.6%) and acute leukemia (16%). Indeed, these two diseases are associated with a deep and prolonged immunodeficiency [8].

In our study, MDR bacteremia prevalence was higher in patients who received allogenic HSCT (10%) than in whom treated with autologous HSCT (2.5%). In the literature, it has been reported that bacteremia was two to three times more frequent after allogeneic HSCT [9].

Many studies were interested in the factors associated with MDR bacteremia in patients with hematological malignancies. The most common identified associated factors were prior hospital stay within three months of MDR bacteremia, long hospital stay >21 days, prior exposure to broad-spectrum antibiotics within a month of bacteremia and colonization or previous infection with the same MDR pathogen [7,8,10,11,12]. In our study, these factors were found in 58%, 48%, 31% and 23% of MDR bacteremia, respectively.

Several studies in onco-hematology have shown that exposure to third generation cephalosporins, carbapenems, fluoroquinolones and glycopeptides promotes the acquisition of MDR pathogens and that the resistance rates increase with the number and the duration of prescribed antibiotics [7,8,13].

MDR colonization was a prerequisite for infection in neutropenic patients [10]. The association between colonization and bacteremia was reported for several MDR strains such as ESBL-E, MDR *P. aeruginosa* and VRE [14].

In our study, bacteremia was associated to CVC in 21% of bacteremia. In literature, 17% to 20% of bacteremia in patients with hematological malignancies was due to CVC [15]. The risk of bacteremia depends on several factors including the type of CVC, its physio-chemical composition, its insertion site, the frequency of its manipulation and the duration of catheterization [1].

In our work, isolated fever was the most common clinical manifestation (48% of cases). Because of neutropenia, these patients have a low capacity to produce an inflammatory infiltrate which makes the clinical presentation poor and often limited to isolated fever [2]. In addition, corticosteroids may mask the inflammatory signs associated with bacteremia in HSCT recipients [16].

For all MDR bacteremia, first-line antibiotherapy was appropriate in 44% of cases. This antibiotic prescription was guided by the results of the systematic rectal swabs performed in our center to identify the colonization with MDR pathogens. The most prescribed first-line antibiotic was imipenem (50%), mainly in combination with amikacin (27%). Imipenem is highly prescribed to oncohematology patients to treat MDR infections. Some authors proposed to preserve imipenem to patients with severe symptoms because of the alarming emergence of carbapenem resistance.

For ESBL-E bacteremia, first-line antibiotherapy was appropriate in 44.8% of cases (13/29) in our study. Second-line antibiotherapy was based on colistin, imipenem, fosfomycin and ciprofloxacin. A retrospective study was conducted to compare the efficacy of the association of β-lactam (2nd generation cephalosporins, 3rd generation cephalosporins, aztreonam)/β-lactamase inhibitors with carbapenems to treat oncohematology patients with ESBL-E bacteremia. No significant differences were found in the 30 day mortality rates between the two groups of patients [17]. However, this association might be a good strategy to stop the emergence of carbapenem resistant Enterobacteriaceae. Several studies have shown the superiority of carbapenems over colistin and tigecycline in the treatment of ESBL-E bacteremia. However, colistin remains the most effective molecule in bacteremia with carbapenem-resistant strains [18-20]. For the treatment of MDR P. aeruginosa bacteremia, first-line antibiotic therapy was appropriate in only three cases (3/9). The most used antibiotics in the 2nd line were colistin, imipenem and amikacin. In MDR *P. aeruginosa* infections, colistin and fosfomycin have been shown to be effective in several studies [21,22]. A new antibiotic, ceftolozane-tazobactam, is currently considered to be the most active β-lactam on MDR P. aeruginosa [23].

For MDR *A. baumannii* bacteremia, first-line antibiotic therapy was appropriate in three cases (3/6). Second-line antibiotic therapy was mainly based on colistin and fosfomycin. With the emergence of carbapenem-resistant strains, several combinations of antibiotics have been tested such as carbapenem / ampicillin-sulbactam, carbapenem / colistin, rifampicin / colistin and tigecycline / colistin and glycopeptide/ polymyxins [24,25].

Both VRE bacteremia were treated with linezolid in the first line. Linezolid, approved by the Food and Drug Administration, is an effective molecule in the treatment of infections caused by VRE.

For both MRSA bacteremia, first-line treatment was appropriate and based on teicoplanin. Glycopeptides are the antibiotics of choice for the treatment of these infections.

Non negligible mortality rate was found in our study (13%, 6/45). Five out of six patients were neutropenic at the time of bacteremia and five of them experienced a delay of three days (1-4 days) to start an adequate antibiotherapy. Death occurred after bacteremia complicated with septic shock (n=5) or acute respiratory distress syndrome (n=1). Reported significant risk factors of mortality were inadequate initial antibiotic treatment, profound and prolonged neutropenia and type of pathogen [26]. Dead patients had as underlying hematologic malignancies: aplastic anemia, acute myeloblastic leukemia, myeloma and non-hodgkin lymphoma. Indeed, hematological malignancies are considered as a factor of poor prognosis in the outcome of bacteremia when they are compared to solid tumors [27].

During the study period, the overall rate of MDR responsible for bacteremia was 37.5% (48/128). This rate is similar to that found by Bastug in a study conducted in Turkey in onco-hematology (40%) [26].

In our center, the rate of MDR strains responsible for bacteremia was stable over time (rs=0,18, p=0,6). However, in the literature, the rate of MDR bacteremia has increased in recent years in both immunocompromised and immunocompetent patients [28-30].

Isolated ESBL-E strains had high levels resistance to antibiotics. This is explained by the common localization on the same plasmid of the genes coding for ESBLs and those coding for resistance to different families of antibiotics [31]. Antimicrobial resistance rates were varying between 43% and 81.1% for ciprofloxacin, and between 3.2% and 37% for amikacin in the literature [32-34].

Regarding MDR *P. aeruginosa*, no strain was resistant to colistin. Indeed, in cases of MDR P. aeruginosa, colistin remains an effective molecule with very low or even no resistance rates according to several studies [35,36].

MDR *A. baumannii* were all resistant to the different antibiotics tested except colistin, which was active in all cases. *A. baumannii* is able to acquire various resistance mechanisms through different genetic supports [37]. Both strains of MRSA were resistant to all aminoglycosides and ciprofloxacin but susceptible to glycopeptides, linezolid, streptogramins and tigecycline. Around of 100% of susceptibility to glycopeptides, linezolid, streptogramins and tigecycline have been reported in Eastern Europe and France in patients in onco-hematology [38,39].

The two isolated VRE had a high level of resistance to vancomycin (MIC>256mg/L) and teicoplanin (MIC between 12 and 64 mg/L). These strains were susceptible to linezolid, streptogramins and tigecycline which is in concordance with the literature [39].

## CONCLUSION

Despite their low prevalence, MDR bacteremia were associated with a significant mortality rate in our center, requiring a rapid adjustment of treatment with colistin in HSCT recipients, in order to optimize first-line antibiotic therapy for any febrile neutropenia.

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