ARTICLE ORIGINAL

Multidrug resistant bacteremia in hematopoietic stem cell transplant recipients

Bactériémies à bactéries multirésistantes chez les greffés de cellules souches-hématopoïétiques

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RÉSUMÉ

Introduction : Les bactériémies sont redoutables chez les greffés de de cellules souches-hématopoïétiques (CSH) avec l'émergence des bactéries multirésistantes (BMR).

But : Étudier la prévalence des bactériémies à BMR chez les greffés de CSH dans le service d'Hématologie au Centre National de Greffe de Moelle Osseuse, les facteurs associés et la mortalité attribuable.

Méthodes : Étude rétrospective incluant les bactériémies à BMR (Janvier 2010-Décembre 2017) [entérobactéries productrices de β-lactamase à spectre étendu (E-BLSE), P. aeruginosa et A. baumannii multirésistants, S. aureus résistant à la méticilline (SARM) et E. faecium résistant à la vancomycine (ERV)].

Résultats : La prévalence des bactériémies à BMR était de 5,9% avec une tendance stable au cours du temps (rs = 0,18). Une neutropénie, des antécédents d'hospitalisation, d'antibiothérapie et de colonisation par des BMR étaient notés dans 59%, 58%, 48% et 31% des cas, respectivement. L'imipénème était l'antibiotique le plus prescrit (50%). Le taux de mortalité attribuable était de 13%. Les BMR (n=48) étaient des E-BLSE (60%), P. aeruginosa (14%), A. baumannii (13%), SARM (4%) et ERV (4%). L'antibiorésistance des E-BLSE et de P. aeruginosa étaient, respectivement, de 17% et 44% à l'imipéneme, 31% et 56% à l'amikacine et 15% et 0% à la colistine. A. baumannii n'étaient sensibles qu'à la colistine. Les SARM (n=2) étaient résistants à la ciprofloxacine et à la gentamicine et sensibles aux glycopeptides. Les ERV (n=2) étaient sensibles au linézolide et à la tigécycline.

Conclusion : Prévalence faible des bactériémies à BMR mais mortalité associée élevée imposant le renforcement d'hygiène.

Mots clés : Multirésistance, Greffe, Cellules souches hématopoïétiques, Bactériémie, Facteurs associés, épidémiologie.

SUMMARY

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

Aim: Our purpose was to investigate the prevalence of MDR bacteremia in HSCT recipients at the Tunisian National Bone Marrow Transplant Center, associated factors and attributable mortality rate.

Methods: Our retrospective study (January 2010-December 2017) included all MDR bacteremia in the Hematology department. MDR rods were: extended spectrum beta-lactamase producing Enterobacterales (ESBL-E), P. aeruginosa and A. baumannii resistant to at least three families of antibiotics, methicillin-resistant S. aureus (MRSA) and vancomycin resistant E. faecium (VRE).

Results: The prevalence of MDR bacteremia among HSCT recipients was 5.9% (48/816) with a stable trend over time (rs=0.18). 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 attributable mortality rate was 13%. MDR bacteria (n=48) belonged to ESBL-E (60%), P. aeruginosa (19%), 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 reinforcement of hygiene measures.

Key words: Multidrug-resistance; hematopoietic stem cell transplantation; bloodstream infection; associated factors; epidemiology.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative treatment of many hematologic diseases, at the cost of increased risk of infectious complications. Bacteremia are among the most frequent complications in HSCT recipients. In fact, this population is exposed to chemotherapy, which induces a worsening of the immune system and a mucosal damage favoring the occurrence of bacteremia by translocation.

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

Our aim 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.

METHODS

Patients

The NBMTC is a university referral center specialized in all types of HSCT and the treatment of patients with immunodeficiency in Tunisia. A total of 45 geno-identical HLA allografts and 60 autografts are performed annually.

Our study was carried out between January 2010 and December 2017, 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. After that, a digestive tract decontamination based on enteral colimycin, gentamicin and fungizone was administered to all patients on admission to eliminate Gram-negative rods (GNR) and fungi. The management of febrile neutropenic episodes in the absence of clinical or microbiological evidence was based empirically on the combination of piperacillin-tazobactam and amikacin or ciprofloxacin. Imipenem was indicated in case of colonization with MDR strains or severe 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, HSCT, prior colonization or infection with the same MDR strain, neutrophil counts at the time of MDR bacteremia, presence of central venous catheter (CVC), 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 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 *Enterobacteriales* (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

Clinical features (age, gender, 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 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 was 1.04. The prevalence of MDR bacteremia in 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

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%)

GVHD: Graft versus host disease

Prevalence and timing of MDR bacteremia

Forty-five patients among 816 HSCT recipients (5.51%) developed one (n=42) or two (n=3) 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.

Table 2. 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 *Enterobacteriales*	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)

Factors associated with MDR bacteremia

Twenty-eight 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 CVC with a median pre-bacteremia duration of catheterization of 31.4 days (3-131 days). Fecal colonization with the same MDR strains 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 were 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 six cases. Colistin (5/6), imipenem (5/6) and amikacin (4/6) were prescribed.

For MDR *A. baumannii* bacteremia (n=6), a second-line antibiotherapy was necessary in 3/6 cases, based on colistin in three cases and 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 antibiotherapy, based on teicoplanin, was appropriate in MRSA bacteremia (n=2).

In our study, MDR bacteremia attributable mortality was 13% (6/45): 4/29 ESBL-E and 2/9 MDR *P. aeruginosa* (Table 3).

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 over time (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 2).

For ESBL-E, antibiotic resistance rates were as follows: ertapenem 31% (MIC: 0.75- 32 mg/L), imipenem 17% (MIC: 3-32 mg/L), ciprofloxacin 83%, amikacin 31%, fosfomycin 10% and colistin 15%. *P. aeruginosa* were resistant in 78% to piperacillin-tazobactam, 67% to ceftazidim, 44% to imipenem (MIC: 8-64 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 population.

We noticed a low prevalence of MDR bacteremia in our center (5.9%). This prevalence was higher in GNR (4.7%) than in Gram Positive Cocci (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 determine the prognosis factors for bacteremia.

MDR bacteremia were more common in patients with aplastic anemia (18.6%) and acute leukemia (16%). 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%). In the

Table 3. Clinical features of patients with attributable mortality to multidrug-resistant bacteremia

N/Age/ sex	Hematologic diseases Type of HSCT	Date of bacteremia/ HSCT	Neutrophil counts/ mm^3	Duration of neutropenia	Concomitant Colonization with the same MDR strain	GVHD	MDR species	Antibiotherapy Molecule, appropriate (time from bacteremia)		Concomitant infection	Date of death/ bacteremia	outcome	Date of death/ HSCT
								1st line	2nd line				
1/7/M	AA Allogenic PBSC transplant	Day+83	10	190 days	Yes	Yes	*K. p* (ESBL)	IMP+AKN, no (day0)	CS+FOS, yes (day1)	-	Day+2	septic shock	Day +85
2/16/F	AA Allogenic BM transplant	Day+2	0	179 days	Yes	Yes	*P. aer R* (B-lac, CIP, Gen)	IMP+CIP, no (day1)	CS+FOS, yes (day4)	-	Day+15	septic shock	Day +17
3/33/M	AA Allogenic BM transplant	Day-1	0	62 days	Yes	No	*K. p* (ESBL)	TYG+PTZ, no (day1)	FOS, yes (day4)	-	Day+15	ARDS	Day +14
4/38/M	AML Allogenic BM transplant	Day+154	380	10 days	Yes	No	*K.p* (ESBL)	CS+FOS, yes (day0)	IMP+AKN, yes (day3)	-	Day+8	septic shock	Day +162
5/30/M	Myeloma autologous HSCT	Day+11	0	19 days	No	No	*P. aer R* (B-lac, FOS, CIP, Gen)	IMP+AKN, no (day0)	CS, yes (day3)	-	Day+13	septic shock	Day +24
6/56/F	NHL autologous HSCT	Day 0	700	7 days	No	No	*S. mar* (ESBL)	PTZ+AKN, no (day0)	IMP+CS, yes (day4)	*K.p* and *E. cloacae bacteremia*	Day+8	septic shock	Day +8

AA : aplastic anemia ; AKN : amikacin ; AML : acute myeloblastic leukemia ; ARDS : acute respiratory distress syndrome ; B-lac : beta-lactams ; BM : bone marrow ; CIP : ciprofloxacin ; CS: colistin; FOS: fosfomycin ; Gen : gentamicin ; GVHD: graft versus host disease; HSCT: hematopoietic stem cell transplant ; IMP: imipenem ; *K. p* : *Klebsiella pneumoniae ;* MDR: multi-drug resistant; NHL : non hodgkin lymphoma ; *P.aer* : *Pseudomonas aeruginosa ;* PBSC: peripheral blood stem cells; PTZ: piperacillin-tazobactam ; R : resistant *; S. mar* : *Serratia marsescens ;* TYG : tigecycline

literature, it has been reported that bacteremia was two to three times more frequent after allogeneic HSCT [9].

In the literature, the most common identified factors associated with MDR bacteremia 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 [7, 8, 10, 11] and colonization or previous infection with the same MDR pathogen [12]. We found these factors in 58%, 48%, 31% and 23% of MDR bacteremia, respectively.

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

MDR colonization was a prerequisite for infection in neutropenic patients [10]. The association between colonization and bacteremia was reported for MDR strains [14].

In our study, bacteremia was associated to CVC in 21% of bacteremia. In onco-hematology, 17% to 20% of bacteremia were due to CVC [15]. The risk of bacteremia depends on 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. Because of neutropenia, patients have a low capacity to produce an inflammatory infiltrate which makes the clinical presentation poor [2]. In addition, corticosteroids may mask the inflammatory signs associated with bacteremia [16].

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

In our study, first-line antibiotherapy was appropriate in 44.8% of ESBL-E bacteremia (13/29). Second-line antibiotherapy was based on colistin, imipenem, fosfomycin and ciprofloxacin. A study was conducted to compare the efficacy of the association of β-lactam (2^{nd} and 3^{rd} generation cephalosporins, aztreonam)/β-lactamase inhibitors with carbapenems to treat patients with ESBL-E bacteremia. No significant differences were found in the 30-day mortality rates between the two groups [17]. This association might be a good strategy to stop the emergence of carbapenem resistant *Enterobacteriales.* Studies have shown the superiority of carbapenems over colistin and tigecycline in the treatment of ESBL-E bacteremia. However, colistin remains the most effective in bacteremia with carbapenem-resistant strains [18-20]. For MDR *P. aeruginosa* bacteremia, first-line antibiotherapy was appropriate in only three cases (3/9). The most used antibiotics in the second-line were colistin, imipenem and amikacin. In MDR *P. aeruginosa* infections, colistin and fosfomycin have been shown to be effective [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 antibiotherapy was appropriate in three cases (3/6). Second-line antibiotherapy was based on colistin and fosfomycin. With the emergence of carbapenem-resistant strains, several combinations of antibiotics were tested such as carbapenem / ampicillin-sulbactam, carbapenem / colistin, rifampicin / colistin and tigecycline / colistin and glycopeptide/ polymyxins [24, 25].

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 VRE infections.

For MRSA bacteremia, first-line treatment was appropriate, based on teicoplanin. Glycopeptides are the antibiotics of choice in these cases.

Mortality rate was 13% (6/45) in our study. Five patients were neutropenic at the time of bacteremia and five 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 hematologic malignancies: aplastic anemia, acute myeloblastic leukemia, myeloma and non-hodgkin lymphoma. Hematological malignancies are considered as a factor of poor prognosis in the

outcome of bacteremia [27].

The overall rate of MDR responsible for bacteremia was 37.5% (48/128) in our study. This rate is similar to that found in a Turkish study (40%) [26].

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

The high levels of antibiotic resistance in ESBL-E is explained by the common localization on the same plasmid of the genes coding for ESBLs and 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. It remains an effective molecule with very low resistance rates in MDR *P. aeruginosa* [35, 36].

All MDR *A. baumannii* were resistant to the antibiotics tested except colistin, which was active in all cases. *A. baumannii* is able to acquire 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 isolated VRE had a high level of resistance to vancomycin and teicoplanin. 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 order to optimize first-line antibiotherapy for any febrile neutropenia.

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