AKADÉMIAI KIADÓ

Bacteriological aspects of bacteremia in the intensive care unit of the Mohammed V Military Hospital: 10 months prospective study

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ORIGINAL RESEARCH PAPER

FATIMA ZAHRA ADIL[1,2*], ELMOSTAFA BENAISSA[1,3], YASSINE BENLAHLOU[1,3], HICHAM BAKKALI[4], NAWFAL DOGHMI[4], HICHAM BALKHI[4], ADIL MALEB[3,5] and MOSTAFA ELOUENNASS[1,3]

[1] Department of Bacteriology, Mohammed V Military Teaching Hospital, Rabat, Morocco

[2] Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco

[3] Research Team of Epidemiology and Bacterial Resistance, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco

[4] Department of Anesthesiology and Critical Care, Military Teaching Hospital Mohammed V, Rabat, Morocco

[5] Laboratory of Microbiology, Faculty of Medicine and Pharmacy of Oujda, Mohammed the First University, Oujda, Morocco

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ABSTRACT

Introduction: Bacteremia is responsible for high rates of morbidity and mortality. The increasing prevalence of multidrug-resistant (MDR) bacteria in intensive care units (ICU) is a growing concern. Hence, prior knowledge of bacterial epidemiology and resistance phenotypes is required to optimize these infections' management. The objective of this study was to determine the epidemiological profile of bacteremia in ICU settings, as well as the place occupied by MDR bacteria in these infections. *Methods:* It is a prospective study carried out over 10 months on episodes of bacteremia in the ICU of Mohammed V Military Teaching Hospital (Rabat, Morocco). Microorganism growth was detected using fluorescent technology, species identification was based on morphological and biochemical characteristics. Antimicrobial susceptibility testing was performed following the recommendations of the Antibiogram Committee of the French Society of Microbiology (CA-SFM) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). *Results:* Among 504 hospitalized patients, sixty-one (12.1%) presented at least one episode of bacteremia. Forty patients (65.6% of bacteremic patients) presented at least one episode of bacteremia due to MDR bacteria. Male gender, cardiovascular diseases, diabetes and previous hospitalization were significant risk factors for the acquisition of MDR bacteremia. Isolated bacteria were mainly Gram-negative bacilli (GNB) (n = 62; 68.9%) dominated by *Acinetobacter baumannii* (n = 19; 21.1%) and *Klebsiella pneumoniae* (n = 16; 17.8%). MDR bacteria were represented by multi-resistant *Acinetobacter baumannii* (n = 19; 44.2%), extended-spectrum beta-lactamases-producing Enterobacterales (n = 9; 20.9%) and carbapenem-resistant Enterobacterales (n = 7; 16.3%). Carbapenems (n = 40; 65.6%), Aminoglycosides (n = 32; 52.5%) and Polypeptides (n = 24; 39.3%) were the most used antimicrobials. Mortality rates were 66.6% (n = 40) and 85% (n = 43) in patients with non MDR bacteremia and MDR bacteremia respectively. *Conclusion:* Limiting the spread of MDR bacteria and improving the management of bacteremic patients require continuous monitoring of bacteremia as well as adapting the therapeutic and preventive strategy.

KEYWORDS

bacteremia, multidrug-resistant bacteria, intensive care unit

*Corresponding author.
E-mail: adilfatimazahra95@gmail.com

INTRODUCTION

Bacteremia is the presence of viable bacteria in the circulating blood [1]. It is responsible for organ dysfunctions such as sepsis and septic shock that are associated with high morbidity and mortality [2, 3]. This infection's incidence variates depending on demographic characteristics, risk factors, and the number of blood cultures performed [4]. The frequent use of invasive devices in the intensive care unit (ICU) makes it a high-risk area for bacteremia [5].

Multidrug-resistant (MDR) isolates are defined as microorganisms with acquired resistance to at least one agent in three or more antimicrobial classes. This acquisition can either be endogenous with selection of resistant strains from the patient's own body flora, or exogenous from skin contact mainly hand related [6, 7]. MDR Gram-negative bacilli (GNB) including Extended-Spectrum Beta-Lactamase (ESBL) producing or Carbapenem-Resistant Enterobacterales (CRE) and non-fermenters such as *Acinetobacter baumannii*, are widely reported as causing bloodstream infections (BSI) in critical care units [3, 7–9]. This is mainly related to the predominance of healthcare-associated bacteremia whose source is usually pulmonary or urinary in ventilated patients or those with urinary catheters. In addition, the massive use of broad-spectrum antimicrobials like third-generation cephalosporins and carbapenems leads to the selection of these microorganisms [9].

The increasing prevalence of MDR bacteria, is a challenge, as treating infected patients becomes difficult with a pejorative prognosis [7]. Therefore, an updated knowledge of bacterial epidemiology and resistance phenotypes is required [8].

In Morocco, studies concerning bacteremia and MDR bacteria are relatively rare despite the high mortality rates related to these infections, which is concerning, especially in the ICU settings. This study aims to determine the epidemiological profile of bacteremia in ICU as well as the role of MDR bacteria in these infections.

METHODS

This is a prospective study carried out for over ten months (May 2019 to February 2020), on blood samples and episodes of bacteremia in the medical and surgical intensive care units (10 beds each) of Mohammed V Military Teaching Hospital in Rabat (Morocco). Bacteremia was defined by at least one positive blood culture. Regarding commensal microorganisms such as coagulase-negative Staphylococci (CoNS), at least two different sets of positive blood culture were required, in addition to clinical features and at least one of the following parameters: White blood cells (WBC) > 10,000/mm3, C-reactive protein (CRP) > 5 mg L^{-1}, procalcitonin (PCT) > 0.5 ng mL^{-1}. Excluded were sterile, contaminated blood cultures, as well as duplicates (the same isolates with the same susceptibility profile isolated several times from the same patient for less than five days).

In patients with two or more episodes of bacteremia, an episode was considered new either after identifying a different microorganism or when isolating the same microorganism after more than seven days under appropriate antibiotic therapy.

In the case of multiple ICU stays, we only considered those in which the patients presented an episode of bacteremia. Bacteremia occurring within the first 48 h of admission to the ICU was considered community-acquired, otherwise, it was considered healthcare-associated.

Bacteremia was defined as secondary when the same microorganism was isolated in both blood culture and the first site of infection within a maximum of 17 days. For this purpose, the patient's bacteriological record was taken into consideration, including respiratory, urinary, catheter, skin, and other samples. The source of the infection was considered unknown if no other bacteriological samples were taken, or if the germ isolated in the blood culture was not found elsewhere.

Antibiotic therapy was considered adequate when the isolated bacteria were sensitive in vitro to at least one of the prescribed antibiotics. It was considered probabilistic in the absence of microbiological documentation and documented when an antibiogram was available. Favorable evolution was based on clinical improvement and normalization of the biological parameters.

In case of suspected bacteremia, blood samples were collected, usually in pairs of aerobic/anaerobic bottles (Becton Dickinson Bactec Plus Aerobic medium and Becton Dickinson Bactec Lytic Anaerobic medium, Becton Dickinson, Winnersh Triangle, Wokingham, Berkshire, United Kingdom), and incubated at 37°C in the Becton Dickinson BACTEC 9240 (Becton Dickinson, Winnersh Triangle, Wokingham, Berkshire, United Kingdom) Blood Culture System. We made subcultures in adequate growth medium from each positive bottle. We also performed smears for direct examination and Gram staining, and the results were immediately communicated to initiate or adjust antibiotic therapy. Species identification was based on morphological and biochemical characteristics (API gallery, bio-Mérieux SA, Marcy l'Étoile/France). Antimicrobial susceptibility testing was performed following the recommendations of the Antibiotic susceptibility Committee of the French Society of Microbiology (CA-SFM) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10].

Statistical analysis was performed using the software SPSS v23.0. Categorical variables were compared using the Chi-square test. Quantitative variables were compared using the Mann-Whitney *U* Test. For all statistical tests, results were considered significant when $P < 0.01$.

Ethics statement

The agreement of the data exploitation was obtained via consent forms that the patients or their parents signed.

RESULTS

During this study, five hundred and four patients were admitted to the medical and surgical ICU. Sixty-eight episodes of bacteremia were recorded in 61 patients, relating to an incidence of 12.1% of hospitalized patients. Forty-one episodes of bacteremia due to MDR bacteria were recorded in 40 patients, corresponding to 65.5% of bacteremic patients. Table 1 demonstrates a comparison of demographic and clinical data, risk factors, as well as nonspecific biological markers of patients with non MDR and MDR bacteremia.

Fifty-four (88.5%) of bacteremic patients presented a single episode of bacteremia. Sixty-five (95.6%) of bacteremia episodes were healthcare-associated, and fifty-four (79.4%) were monomicrobial. Sources of non MDR bacteremia and MDR bacteremia, when identified, were principally respiratory and urinary tract infections (Table 2). In the 68 episodes of bacteremia included in this study, ninety microorganisms were isolated, among which forty-three (47.7%) were MDR. GNB was predominant (n = 62; 68.9%), Enterobacterales and non-fermenting GNB represented 38.9% (n = 35) and 30% (n = 27) respectively. The most encountered species were *Acinetobacter baumannii* followed by *Klebsiella pneumoniae* (Table 2). Antimicrobial resistance rates are shown in Table 3.

In 41 episodes of MDR bacteremia, forty-three MDR bacteria were isolated. MDR *Acinetobacter baumannii*, Extended-Spectrum Beta-Lactamase producing Enterobacterales (ESBL-E), and Carbapenem-Resistant Enterobacterales (CRE) were the most frequently isolated MDR bacteria. In MDR Enterobacterales, *Klebsiella pneumoniae* was predominant (Fig. 1). Regarding MDR rates per species, all *Acinetobacter baumannii* isolates (n = 19; 100%) were MDR, nine (25.7%) of Enterobacterales isolates were ESBL-E while seven (20%) were CRE, three (37.5%) of *Pseudomonas aeruginosa* isolates were MDR. In Gram-positive cocci, glycopeptide resistance was observed in four (26.6%) of *Enterococcus* isolates, while one (16.6%) *Staphylococcus aureus* was Methicillin-resistant.

Table 1. Comparison of demographic and clinical data, risk factors, and non-specific biological markers of non MDR bacteremic patients and MDR bacteremic patients (MDR: Multi-Drug Resistant, CRP: C-Reactive Protein, PCT: Procalcitonin, WBC: White Blood Cells, NS: Non-Significant)

		Non MDR bacteremia		MDR bacteremia		P value
		n = 21	%	n = 40	%	
Age	<20	1	4.8	4	10	–
	20–39	4	19	5	12.5	
	40–59	5	23.9	14	35	
	60–79	8	38	14	35	
	≥80	3	14.3	3	7.5	
Median age [minimum – maximum]		56 [18–85]		57 [14–95]		NS
Gender	Male	17	80.9	31	77.5	P < 0.01
	Female	4	19.1	9	22.5	–
Gender ratio		4.25		3.44		–
Comorbidities	Cardiovascular disease	15	71.4	7	17.5	P < 0.01
	Diabetes mellitus	13	62	7	17.5	P < 0.01
	Cancer	8	38	9	22.5	NS
	Chronic renal failure	7	33.3	6	15	NS
	Respiratory disease	1	4.7	2	5	NS
	Liver disease	5	23.8	5	12.5	NS
	Other	3	14.3	2	5	–
Mean length of stay ± Standard Deviation		28.1 ± 23.7		16.6 ± 19.5		NS
Risk factors	Mechanical ventilation	19	90.4	33	82.5	NS
	Urinary catheterization	18	85.7	30	75	NS
	Central venous catheterization	15	71.4	31	77.5	NS
	Hemodialysis	5	23.8	12	30	NS
	Inadequate probabilistic antibiotic therapy	10	47.6	27	67.5	NS
	Previous hospitalization (3 months)	2	9.5	21	52.5	P < 0.01
	Previous antibiotic therapy (3 months)	2	9.5	17	42.5	NS
Clinical features	Fever (≥38 °C)	17	80.9	21	52.5	–
	Sepsis	12	57.1	19	47.5	
	Septic shock	5	23.8	20	50	
Non-specific biological markers	CRP > 5 mg L^{-1}	21	100	40	100	–
	PCT > 0.5 ng mL^{-1}	21	100	40	100	
	WBC > 10,000 mm^{-3}	14	66.6	23	57.5	

Table 2. Microorganisms responsible of bacteremia and different sources of infection ($n = 90$) (MDR: Multi-Drug Resistant, UN: Unknown, R: Respiratory tract, U: Urinary tract, CVC: Central venous catheterization)

Family	Bacteria	Total (%)	Non MDR bacteremia (%)	Source of infection (%)					MDR bacteremia (%)	Source of infection (%)				
				UN	R	U	CVC	Other		UN	R	U	CVC	Other
Enterobacterales ($n = 35$; 38.9%)	*Escherichia coli*	5 (5.6%)	3 (60%)	1 (33.3%)	0	2 (66.7%)	0	0	2 (40%)	0	0	1 (50%)	0	1 (50%)
	Klebsiella pneumoniae	16 (17.8%)	6 (37.5%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	0	10 (62.5%)	4 (40%)	3 (30%)	2 (20%)	0	1 (10%)
	Enterobacter cloacae	5 (5.6%)	3 (60%)	1 (33.3%)	0	1 (33.3%)	1 (33.3%)	0	2 (40%)	2 (100%)	0	0	0	0
	Enterobacter aerogenes	2 (2.2%)	0	–	–	–	–	–	2 (100%)	1 (50%)	1 (50%)	0	0	0
	Proteus mirabilis	3 (3.3%)	3 (100%)	2 (66.7%)	0	1 (33.3%)	0	0	0	–	–	–	–	–
	Serratia liquefaciens	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
	Morganella morganii	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
	Providencia stuartii	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
	Citrobacter freundii	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
non-fermenting Gram-negative bacilli ($n = 27$; 30%)	*Acinetobacter baumannii*	19 (21.1%)	0	–	–	–	–	–	19 (100%)	11 (57.9%)	7 (36.8%)	0	1 (5.3%)	0
	Pseudomonas aeruginosa	8 (8.9%)	5 (62.5%)	1 (20%)	3 (60%)	1 (20%)	0	0	3 (37.5%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	0
Staphylococci ($n = 9$; 10%)	*Staphylococcus aureus*	6 (6.7%)	5 (83.3%)	2 (40%)	2 (40%)	0	1 (20%)	0	1 (16.7%)	1 (100%)	0	0	0	0
	Coagulase-negative staphylococci	3 (3.3%)	3 (100%)	3 (100%)	0	0	0	0	0	–	–	–	–	–
Streptococci ($n = 2$; 2.2%)	*Streptococcus pneumonia*	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
	Streptococcus pyogenes	1 (1.1%)	1 (100%)	1 (100%)	0	0	0	0	0	–	–	–	–	–
Enterococci ($n = 15$; 16.7%)	*Enterococcus faecalis*	7 (7.8%)	6 (85.7%)	3 (50%)	0	3 (50%)	0	0	1 (14.3%)	0	0	0	0	1 (100%)
	Enerococcus faecium	8 (8.9%)	5 (62.5%)	4 (80%)	0	0	1 (20%)	0	3 (37.5%)	2	0	0	1	0

Yeasts			Source of infection				
			UN	P	U	CVC	Other
Candida ($n = 2$; 2.2%)	*Candida glabrata*	1 (1.1%)	0	0	1 (100%)	0	0
	Candida sphaerica	1 (1.1%)	1 (100%)	0	0	0	0

Table 3. Resistance rates (3GC: Third-generation cephalosporins, FQ: Fluoroquinolones, AMK: Amikacin, IMP: Imipenem, COL: Colistin, TZP: Tazobactam-Piperacillin, FOX: Cefoxitin, LZD: Linezolid, VAN: Vancomycin, TEI: Teicoplanin)

Enterobacterales	**3GC**	**FQ**	**AMK**	**IMP**	**COL**	**TZP**
Klebsiella pneumoniae (n = 16)	62%	62%	12%	37%		
Escherichia coli (n = 5)	40%	40%	0%	0%		
Enterobacter sp. (n = 7)	57%	28%	28%	14%		
Non fermenters GNB	**3GC**	**FQ**	**AMK**	**IMP**	**COL**	**TZP**
Acinetobacter baumannii (n = 19)	100%	100%	79%	100%	0%	–
Pseudomonas aeruginosa (n = 8)	25%	12%	12%	25%	–	25%
Staphylococci		**FOX**			**LZD**	
Staphylococcus aureus (n = 6)		17%			0%	
CoNS (n = 3)		100%			0%	
Enterococci	**LZD**		**VAN**		**TEI**	
Enterococcus faecalis (n = 7)	0%		14%		14%	
Enterococcus faecium (n = 8)	0%		37%		25%	

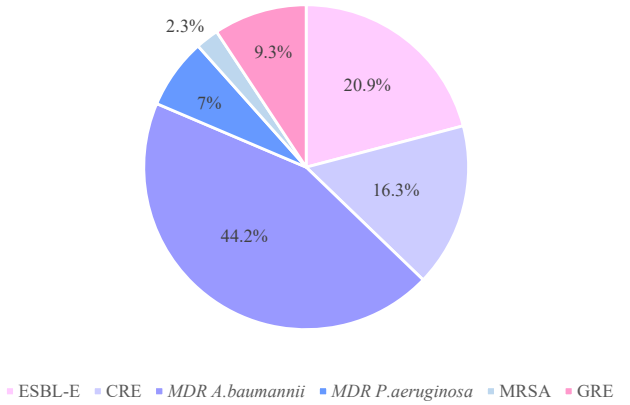

Fig. 1. MDR bacteria responsible of bacteremia (n = 43) (ESBL-E: Extended-Spectrum Beta-Lactamase producing Enterobacterales, CRE: Carbapenem-Resistant Enterobacterales, MDR: Multi-Drug Resistant, MRSA: Methicillin-resistant *Staphylococcus aureus*, GRE: Glycopeptide-resistant Enterococci)

Antibiotic therapy was documented in 31 (45.6%) episodes of bacteremia, and empiric in 30 (48.5%). Carbapenems (n = 40; 65.6%), Aminoglycosides (n = 32; 52.5%) and Polypeptides (n = 24; 39.3%) were the most used antibiotics. In terms of antibiotic combination, dual therapy was widely used (n = 35; 57.4%) especially the association of Imipenem with Amikacin or Colistin.

Fourteen (66.6%) patients with non MDR bacteremia and 34 (85%) with MDR bacteremia died. Table 4 shows MDR species responsible for mortality.

Table 4. Mortality rate of MDR bacteremic patients by species (MDR: Multi-Drug Resistant, GNB: Gram Negative Bacilli, GPC: Gram-positive cocci, ESBL-E: Extended-Spectrum Beta-Lactamase producing Enterobacterales, CRE: Carbapenem-Resistant Enterobacterales, MRSA: Methicillin-resistant *Staphylococcus aureus,* GRE: Glycopeptide-resistant Enterococci)

MDR bacteria		*n*		%	
GNB	MDR *Acinetobacter baumannii*	14	29	41.2	85.3
	ESBL-E	6		17.7	
	CRE	6		17.7	
	MDR *Pseudomonas aeruginosa*	3		8.8	
GPC	MRSA	3	4	8.8	11.8
	GRE	1		3	

DISCUSSION

ICU stay is associated with a high risk of infection owing to the patients' critical condition and the use of invasive devices. However, bacteremia rates are widely variable because of inconsistent diagnosis criteria and therapeutic intervention measures, as well as adherence to hand hygiene protocols [11–14].

The incidence of bacteremia in our study was 12.1%, it remains the highest when compared to those of El Kettani et al. (5.1%), Merzougui et al. (11.3%) and Kallel et al. (9.5%) [11, 12, 14]. Our demographic data demonstrates that patients over the age of 55 years are prone to develop bacteremia, in agreement with Lachhab et al. and Tabah et al. [3, 8], this could be explained by the weakening of the immune system in the elderly. Male patients were predominant in our study, the same result was found by Kallel et al. (67,3%) and Lachhab et al. (62%) [8, 14]. It is related to differences in lifestyle, access to health care, sex hormones, and genetic variability between males and females [15]. In addition, according to the analysis of our statistical data, male gender was a significant risk factor for MDR bacteremia.

The comorbidities found in our patients with non MDR bacteremia and MDR bacteremia were mainly diabetes, cardiovascular diseases and cancer, in agreement with other studies [8, 14]. The statistical analysis data showed that cardiovascular disease and diabetes are significant risk factors for MDR bacteremia. In fact, diabetic patients are immunocompromised. On the other hand, cardiovascular diseases may not be directly related to these infections but they are common worldwide, and the age of their occurrence corresponds to the patients' median age in our study.

Furthermore, we showed that patients with MDR bacteremia have a shorter ICU stay compared to patients with non MDR bacteremia, which is in contrast to a study by Kallel et al., who demonstrated longer stay in patients with ESBL-E

Table 5. Comparison of antibiotic resistance rates (MDR: Multi-Drug Resistant, ESBL: Extended-Spectrum Beta-Lactamase, 3GC: Third-generation cephalosporins, FQ: Fluoroquinolones, AMK: Amikacin, IMP: Imipene, TZP: Tazobactam-Piperacillin)

MDR bacteria	Antibiotic	Elouennass et al. [9]	Lachhab et al. [8]	Our study
MDR *Acinetobacter baumannii*	3GC	68.7%	100%	100%
	FQ	77.8%	100%	100%
	AMK	27%	50%	79%
	IMP	31.4%	100%	100%
ESBL producing *Klebsiella pneumoniae*	3GC	40%	60%	62%
	FQ	40%	70%	62%
	AMK	0%	0%	12%
Carbapenem-resistant *Klebsiella pneumoniae*	IMP	0%	0%	37%
MDR *Pseudomonas aeruginosa*	TZP	22.2%	20%	25%
	3GC	16.6%	20%	25%
	FQ	26%	20%	12%
	AMK	0%	20%	12%
	IMP	10.5%	20%	25%
Glycopeptide-resistant Enterococci	Glycopeptides	_	0%	27%
Methicillin-resistant *Staphylococcus aureus*	Methicillin	52.94%	20%	17%

bacteremia [14]. This may be explained by the early mortality of patients with MDR bacteremia in our case, which is closely related to late initiation of appropriate therapeutic intervention.

Apart from cases where the source of infection remained unknown, respiratory and urinary tracts were predominant in our study for both non MDR bacteremia and MDR bacteremia cases which was also reported by Lachhab et al. [8]. This can be related to the important use of mechanical ventilation and urinary catheters in ICU. However, the major causes of bacteremia reported in a French study were ventilator-associated pneumonia and catheters [14]. The low rate of catheter-related bacteremia would be linked to Coagulase-negative staphylococci (CoNS), often considered as commensal agents, hence, an underestimation of these infections would be possible.

Several studies showed that prior hospitalization and previous or inadequate antibiotic therapy could be considered as risk factors for MDR bacteremia [16–19]. This was also observed in our study. In addition, our statistical data analysis showed that hospitalization in the previous three months is a predisposing factor for MDR bacteremia.

The most frequently isolated bacteria were Gram-negative bacilli (68.9%), as reported in other studies [8, 9, 14]. *Acinetobacter baumannii* and *Klebsiella pneumoniae* were predominant, which reflect the important rates of healthcare-associated bacteremia in our study. The isolated microorganisms were MDR in 47.7% of cases, which agrees with a multicenter study (47.8%) carried out by Tabah et al. [3]. Antibiotic resistance rates were compared with those of two other studies conducted at the same facility as ours (Table 5); Increased rates were observed in GNB especially in third-generation Cephalosporins (3GC), Fluoroquinolones (FQ), Amikacin (AMK) and Imipenem (IMP), which would be the consequence of the bacteria capacity to rapidly accumulate resistance factors, the selection pressure of antibiotics, as well as the difficulty of controlling hygiene conditions.

The frequency of use of Imipenem, Amikacin, and Colistin in our study reflects the burden of MDR GNB in invasive infections in the ICU setting. Although prognosis and mortality are largely influenced by the choice of antibiotic therapy, the use of a therapeutic regimen against MDR bacteria is necessary, with all the consequences that it may have, including selection pressure of antibiotics and increased management costs.

Mortality rates in our study exceed those observed in other series, whether in non MDR or in MDR bacteremia [14, 20, 21]. This is probably related to the heterogeneity of age groups and comorbidities. On the other hand, the variability of diagnosis methods and therapeutic management of bacteremia would influence the mortality rate. Moreover, the increasing emergence of MDR bacteria, leading sometimes to therapeutic impasses, closely affects the patients' prognosis.

Like all studies, ours has many limitations. It is a monocentric study carried out on a limited number of cases. Moreover, the patients' outcome outside the ICU was not taken into consideration, this could therefore affect the data's exhaustivity. Concerning the techniques used in the laboratory of bacteriology, the molecular identification of resistance genes was not carried out, the resistant character was retained based only on the antibiograms.

CONCLUSION

This study highlights the important place occupied by GNB in bacteremia in ICUs. *Acinetobacter baumanni* and *Klebsiella pneumoniae* were most commonly isolated pathogens, reflecting the healthcare-associated nature of these infections and, consequently, the difficulties of hygiene control in ICU settings. The use of broad spectrum antimicrobials cannot be avoided given the increase in the rates of MDR GNB and the resulting infections. This makes it

essential to establish an epidemiological surveillance system, in addition to actions on selection pressure, hand hygiene, and optimization of cleaning practices in the ICU.

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Elmostafa Benaissa: data analysis and interpretation.

Yassine Benlahlou: data analysis and interpretation.

Hicham Bakkali: acquisition of clinical and therapeutic data.

Nawfal Doghmi: acquisition of clinical and therapeutic data.

Hicham Balkhi: acquisition of clinical and therapeutic data.

Adil Maleb: manuscript correction and linguistic review.

Mostafa Elouennass: study concept and design, data analysis and interpretation, manuscript correction and linguistic review.

All authors read and approved the final version of the manuscript.

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