

Characteristics of Trauma Patients with Multidrug-resistant Bacteria from an Epidemiological, Clinical, and Microbiological Perspective

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Abstract

Abstract

Trauma, healthcare-associated infections, and antimicrobial resistance are three major public health issues worldwide due to the high probability of patient morbidity and, ultimately, a tragic outcome. In the current study included all patients admitted to The NRI Medical College Hospital, (Mangalagiri, Andhra Pradesh, India) intensive care units between October 20, 2022 and April 20, 2023. Patients with first bacteremia were found to have MRSA, VRE, and carbapenem-resistant Gram-negative bacteria. In terms of demographic and clinical data, patients with MR bacteremia in the general and trauma cohorts were compared to patients without MR bacteremia. PCR was used to detect carbapenemases and the SCCmec gene in the strains. We included 1528 patients, 302 of whom had trauma and 66 (4.3%) of whom had MR-agent-induced bacteremia. Mechanical ventilation, renal replacement therapy, and surgery were all independent risk factors for MR agent bacteremia. In the trauma cohort, haemodialysis alone was associated with an increased risk of MR agent bacteremia. *S. aureus*, MRSA (n=27), and *K. pneumoniae* (n=26) were the two most common isolating agents. The blaKPC gene was found in 83% of the *K. pneumoniae* strains (while the NDM gene was found in only one). Injuries have no effect on the development of bacteremia caused by MR agents. Certain risk factors appear to be associated with the severity of MR bacteremia cases.

Keywords: Microbiological Characteristics, Trauma Patients, Hospital infection; Microbial drug resistance; Resistance mechanism; Polymerase chain reaction.



1. Introduction

Trauma is defined medically as acute overexposure to any form of energy (mechanical, thermal, electrical, chemical, or radiation) in excess of the threshold of physiologic tolerance, resulting in severe organic level injury (Nauth et al., 2021). Knowing that up to 25% of patients who suffer polytrauma from traffic accidents have a fatal outcome due to inadequate management, the health system and its members must be prepared to handle this type of situation, have knowledge, tools, process equipment for proper damage control when assisting a patient who has suffered a polytrauma and thus be able to offer them better chances of survival (Weihs et al., 2022). There are 13-15 accidental deaths in India per hour. The number of individuals killed in RTAs in India in 2011—roughly 142,485—was the most it had ever been anywhere in the globe. Based on current trends, it is estimated that the number of lives lost on the world's roads would rise by almost 66% in the next two decades. The rate is only about 28% in high-income and industrialised countries, but it's risen by over 92% in China and 147% in India due to deaths caused by road traffic accidents. In 2018, there were a reported 4,67,044 traffic accidents in the 50 states and 7 union territories (UTs). By 2024, the RTA fatality rate could reach 2/10,000 in low-income nations, while it is expected to drop in high-income countries. By 2020, it is expected that road traffic injuries in India would account for 150% more deaths and hospitalisations than they do today. Although trauma injuries are widely established in terms of their nature, their aetiology remains a mystery to many. The evidence on the prevalence of trauma in underdeveloped nations is limited, as there are few studies on the topic. (Kashid et al., 2020) Microorganisms that are resistant to multiple kinds of antibiotics are said to be multiresistant (MMR) from an epidemiological standpoint. The idea of multiresistant bacteria may have different nuances depending on whether one takes a clinical, microbiological, or epidemiological stance. To be more precise, Gram-negative bacteria (GNB) are considered multiresistant if they show resistance to three or more classes of antibiotics to which they typically respond favourably. These classes include beta-lactams (penicillin and cephalosporins), carbapenems, aminoglycosides, and quinolones (Huang et al., 2019).

In 2019, the results of the SENTRY (Shortridge et al., 2019) antimicrobial surveillance program, were published. Over 20 years, 264,901 strains were isolated from more than 200 medical centers located in 45 countries. The frequency of Enterobacteriaceae classified as MDR increased from 6.2% between 1997 and 2000 to 15.8% between 2013 and 2016, mainly among hospital isolates. The frequency of these agents also varies by region, with the highest rates observed in Latin America (28.1%). Recently, there has been an

increase in the number of publications of cohorts of patients transferred from wars in Syria, Lebanon, Afghanistan and Iraq to support hospitals located in European countries (notably, Germany). Colonization and infection rates by MDR agents, mainly carbapenem-resistant Enterobacteriaceae (ERC), were published, and their resistance mechanism was identified through molecular biology techniques and, in some cases, genetic sequencing. Through a prospective cohort of patients admitted to the ICU, trauma victims or not, with epidemiological and clinical data collection, it would be possible to identify risk factors for bacteremia by MDR agents. Unlike the other studies presented in the introduction, a cohort of trauma patients in an urban area would be formed. In addition, resistance mechanisms would be identified through molecular biology and genetic sequencing techniques in order to assess their clonality.

We believe that the study could be justified by the scarcity of data on factors associated with bacteremia by MDR agents in a population of critically ill patients and trauma victims in Indian urban area. The current study aims to Identify risk factors for bacteremia by MDR agents (bloodstream infection by carbapenem-resistant Enterobacteriaceae, methicillin-resistant *S. aureus*, vancomycin-resistant Enterococcus sp; carbapenem-resistant *P. aeruginosa*, and carbapenem-resistant *A. baumannii*) in the population of patients hospitalized in the Intensive Care Unit for trauma and in the general cohort and to identify the epidemiological and clinical characteristics of the population hospitalized in the ICU regarding bacteremia caused by MDR agents.

2 Materials and Methods:

2.1 Location and Sampling

The NRI Medical College, Hospital has 1170 beds, 87 of which are adult intensive care units. There are two ICUs in the service, which are geographically separated and have different medical and nursing teams. Admission to the ICU is determined by availability (no distinction is made between clinical and surgical patients). The study will include all patients who are newly admitted to either of the two intensive care units at NRI Medical College, General Hospital in Guntur between October 20, 2022 and April 20, 2023. The exclusion criteria will be this patient's readmission to any ICU during this hospitalization; the patient being considered unknown (no date of birth recorded) until the moment of its outcome; and the patient having an ICU stay of less than 24 hours.

2.2 Collection of Microbiological Data

Clinical samples: The bacterial identification of the strains and their respective sensitivity tests were performed using an automated method (bioMérieux Vitek 2, Hazelwood, MO,

USA) and the cutoff points of the Clinical and Laboratory Standards Institute (2015) were used.

Any Enterobacteriaceae that showed resistance to at least one of the tested carbapenems would be considered: ertapenem, meropenem or imipenem. The isolates were considered resistant to meropenem or/and imipenem with MIC ≥ 4 $\mu\text{g}/\text{dl}$ and/or to ertapenem with MIC ≥ 2 $\mu\text{g}/\text{dl}$. As for non-fermenting gram negative bacteria, isolates whose MIC for these drugs was > 4 $\mu\text{g}/\text{dl}$ were considered resistant to meropenem or/and imipenem. As for the *S. aureus* isolates, they were considered resistant if the MIC for oxacillin was ≥ 4 $\mu\text{g}/\text{dl}$. Vancomycin resistance in enterococci was defined when the MIC for vancomycin was equal to or greater than 32 $\mu\text{g}/\text{ml}$. All isolates that met the above criteria were sent to the Laboratory of Medical Investigation of Bacteriology, NRI General Hospital of NRI medical College, where tests were performed to detect the genes described below. The isolates were stored in BHI (brain heart infusion) – glycerol at -70° .

Variables collected from all patients included in the study: Using a standardized instrument, the following data were collected: age, gender, reason for admission to the ICU, previous diagnoses of hypertension (SAH), diabetes (DM), neoplasia, other comorbidity (smoking or alcohol consumption were not considered), severity score Simplified Acute Physiology Score (SAPS III) calculated at admission to the ICU by a nurse hired for this purpose, presence of invasive devices (indwelling urinary catheter, mechanical ventilation, central venous access, catheter for haemodialysis), time of use of the devices, surgical intervention, length of stay in the ICU ((Falcone, 2016), antimicrobials prescribed and time of use, total length of stay in the institution and outcome.

Regarding trauma patients, the following data were collected: type of trauma (classified as ATT, physical aggression, unintentional event, occupational accident, attempted self-extinction, fall to the ground and fall from another height); trauma severity (measured by the Revised Trauma Score– RTS) (Dkhar et al., 2019); involvement of the segments (cranioencephalic/face injury; abdominal injury; thoracic injury; injury to the extremities and pelvis) and open fracture of the skull or long bones. As for ATT, victims were classified as occupants of cars, motorcycles, buses or trucks and cyclists or victims of being run over. As for physical aggression, whether there was beating, use of a firearm or bladed weapon. Unintentional events included accidents during leisure time.

Variables collected from patients diagnosed with MDR agent bacteraemia: MDR agents were defined as those resistant to at least one agent from three or more antimicrobial classes. Despite the definition, we chose to consider enterobacteria resistant to at least one of the carbapenems, *P. aeruginosa* and carbapenem-resistant *A. baumannii*, methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* sp.

Bacteremia was defined as growth in blood culture collected from a patient admitted to the ICU of one of the aforementioned organisms (only the first positive blood culture of the patient at that hospitalization was considered). MDR etiologic agents were defined as carbapenem-resistant enterobacteria, carbapenem-resistant *P. aeruginosa*, *Acinetobacter baumannii* resistant to more than three classes of antimicrobials, MRSA, and vancomycin-resistant *Enterococcus* spp., and only the initial episode of bacteremia was considered. The presence of one of these organisms in a blood culture was considered bacteremia, and the first time a blood culture was taken was considered the commencement of bacteremia. The sites of infection were defined according to the criteria used for epidemiological surveillance of HAI recommended by the National Healthcare Safety Network (NHSN).

Detection of genes encoding KPC, OXA-48 and NDM through polymerase chain reaction (PCR):

In-house PCR was performed to identify KPC, OXA-48 and NDM genes in all enterobacterial isolates. First, the bacterial lysate was made by thermal lysis, 15 minutes at 95°C and immediate centrifugation at 13,000 rpm for 15 minutes at 4°C . The supernatant was separated and kept at -20°C until use. Multiplex PCR for *blaKPC*, *blaNDM* and *blaOXA-48* was performed according to the technique already described by Poirel et al., (2011).

The primers used to detect the genes encoding KPC, OXA-48 and NDM are described below in Table 1:

Table 1. Primers used to detect genes encoding KPC, NDM and OXA-48

Enzyme	Oligonucleotide sequence (5'-3')	Molecular Weight (bp)
<i>blaKPC</i>	AGTCAACGCTTTGTTCTCCG	893
	TTCAGTTTTACCGCACTGCC	
<i>blaNDM-1</i>	GGACGGGATCTGCAGTCACA	287
	CGCACTCACAAAGATCCTGCT	
<i>blaOXA-48-F</i> <i>blaOXA-48-R</i>	TTATCTTGCGTGTGGGAT	177
	GAMTGGTTRTTCGCAATGC	

Detection of carbapenemase production through phenotypic methodology:

Enterobacteriaceae isolates were also submitted to a colorimetric assay to detect carbapenemases. In this case, Carbapenembac® (Probac, India) was used.

Assays were performed according to the manufacturer's instructions. The isolates were placed in a Petri dish with the Carbapenembac tape together with 150 μl of a suspension with turbidity equal to 10 on the McFarland scale of the selective solution. The plate was incubated between 35° and 37° for 60 minutes. Subsequently, 200 μl of the special iodine solution was placed on the tape. Reading was performed after 30 minutes.

Detection of genes encoding SCCmec from strains of MRSA: the multiplex polymerase chain reaction (m-PCR) method was used, as described by Zhang et al., (2005). The primers used in SCCmec type characterization was performed on all samples identified as MRSA. For molecular characterization of SCCmec, these reactions are described in Table 2 below.

Table 2. Sequence of primers used in m-PCR to determine the types of SCCmec

Primer		Oligonucleotide sequence (5'-3')	amplicon size (bp)	Specificity (SCCmec type)
Type I	F	GCGTTACAGTAGGCTTTAAAGGT	612	SCCmec I
	R	GTTTCTCATATGATAGCGTCCC		
Type II	F	CGCGTGTGAAGAGATGATA	399	SCCmec II
	R	CGAAATCAATGGTTAATGGACC		
Type III	F	CTACATGTTGTATACGGCG	281	SCCmec III
	R	CCGTTTATGTAGTCACCAGATG		
Type IVa	F	GCATTCTTCGAAAGCAACG	775	SCCmec IVa
	R	CTACCTCTTCTAAAAGGGTCG		
Type IVb	F	TCTTCTAGCTGCGAATGTAC	490	SCCmec IVb
	R	AAACAATACTCGCTCTTCC		
Type IVc	F	ACAGTAATAGATTGGAGCTTTATC	202	SCCmec IVc
	R	TTGTATGGAGATTGTGCTGG		
Type IVd	F5	CAAGGACTCCAAATACTACAATA	880	SCCmec IVd
	R6	TAGCATTGGTACTAAAGCTC		
Type V	F	GTTAATGAGCGACTAAACATTGT	320	SCCmec V
	R	TGCCTGAAAGTTGCCTACACTA		
MecA147	F	GGATACAATTCTGAAGATAGT	150	mecA
	R	ATGCAATATATAAGGATGCTGG		

Analysis of the clonality of MRSA strains: For clonality analysis, the MRSA isolates were subjected to pulsed field gel electrophoresis (PFGE) as described above.

2.3 Statistical analysis

Bivariate analyses were performed to assess factors associated with MDR bacteremia, bacteremia in trauma patients, carbapenem-resistant K. pneumoniae bacteremia, and MRSA bacteremia. For dichotomous variables, relative risk was determined with a confidence interval of 95%. For continuous variables, t test was used. P values less than 0.05 were considered significant.

3. Results and Discussion

3.1 Clinical and epidemiological characteristics of the cohort:

From October 20, 2022 and April 20, 2023, 1621 patients were admitted to NRI General Hospital's two Intensive Care Units. 86 were omitted because they were admitted for the second time; 6 because they were unknown (no identification and no date of birth); and 3 because they stayed in this sector for less than 24 hours. As a result, 1528 patients were included in the research. Table 3 describes the clinical and epidemiological features of the patients who took part in the study.

Table 3. Clinical and epidemiological characteristics of the 1,528 patients admitted to the ICU from October, 2022 and April, 2023.

	n	% /(\pm SD)
Age (years), mean	55.6	\pm 18.2
Age > 60 years	733	47.97
Male gender	891	58.31
Mean length of stay prior to the ICU (days)	2.4	\pm 4.6
SAPS III value, mean	53.9	\pm 16.4
median	53	
Main reason for ICU admission		
Trauma	302	19.76
neurological diseases	295	19.31
infectious diseases	206	13.48
cardiovascular diseases	185	12.11
ICU admissions for immediate PO	637	41.69
Arterial hypertension	753	49.28
Diabetes	367	24.02
Neoplasms	203	13.29
CNS	78	5.10
TGI	56	3.66
urinary tract	27	1.77
Hematology	13	0.85
Breast cancer	12	0.79
Pulmonary	6	0.39
Use of mechanical ventilation	905	59.23
Mechanical ventilation time (days), mean	6.5	\pm 9.8
Use of central venous access	979	64.07
Time of use of central venous access (days), mean	6.4	\pm 8.7
Use of indwelling urinary catheter	1259	82.40
Indwelling urinary catheter use time (days), mean	7	\pm 8.4
Patients on renal replacement therapy	139	9.10
TRS time (days), mean	12.1	\pm 10.5
Patients undergoing surgical procedures	717	46.92
Length of ICU stay (days), mean	10.2	\pm 10.2
Use of antifungals	42	2.75
Antimicrobial use	1086	71.07
Fluroquinolone as 1st choice	39	2.55
Carbapenem as 1st choice	26	1.70
Patients diagnosed with bacteremia by MDR agents	66	4.32

Bloodstream Infection Surgical Site Infection Pneumonia		
Current Infection	47	3.08
Bloodline Surgical Site Infection	10	0.65
Pneumonia	7	0.46
Urinary tract infection	2	0.13
Etiological agent	69	
<i>S. aureus</i>	28	46.67
<i>K. pneumoniae</i>	26	43.33
<i>A. baumannii</i>	5	8.33
<i>P. aeruginosa</i>	3	5.00
<i>Enterobacter spp</i>	2	3.33
<i>E. faecium</i>	2	3.33
<i>E. faecalis</i>	1	1.67
<i>M. morgannii</i>	1	1.67
<i>S. marcescens</i>	1	1.67
In-hospital mortality	627	41.03
Length of hospital stay (from), mean	18.3	±17.7

SD standard deviation; ICU Intensive Care Unit; SAPSIII Simplified Acute Physiology Score III; postoperative PO; CNS Central Nervous System; TGI Gastrointestinal Tract; RRT Renal Replacement Therapy; MDR Multiresistant

The diagnosis of MDR agent bacteremia was made in 63 patients and 69 strains were isolated. Two patients were diagnosed with co-infection: the first with bloodstream infection by *S. aureus* and *A. baumannii* and the second by *M. morgannii*, *S. aureus* and *K. pneumoniae*.

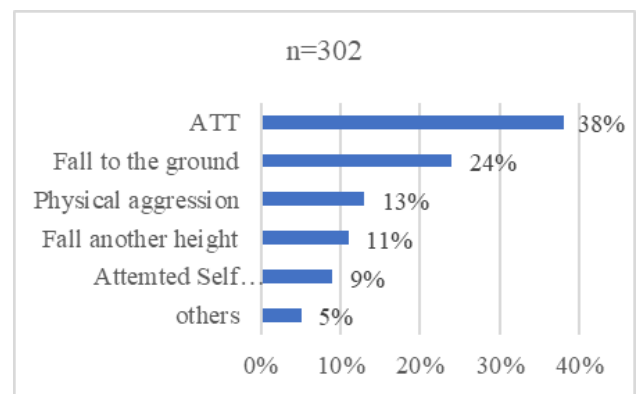
The main site of bacteremia in this cohort of 1528 patients was primary bloodstream infection (n=47) of which 93% (n=44) were bloodstream infections related to central venous access. The etiologic agents identified were MRSA (n = 28), *K. pneumoniae* (n = 14), *A. baumannii* (n = 4), *P. aeruginosa* (n = 1), *E. cloacae* (n = 1), *S. marcescens* (n = 1) and *M. morgannii* (n = 1). The second site was surgical site infection (n = 10) whose main etiologic agent was *K. pneumoniae* (n = 7). Of these, 6 patients were postoperative of abdominal surgeries and two were postoperative of trauma patients (one arthrodesis and one decompressive craniectomy).

The third site of bacteremia was attributed to nosocomial pneumonia (n = 7), whose main agents were *K. pneumoniae* (n = 3) and *P. aeruginosa* (n = 2). Urinary tract infection was responsible for two cases of bacteremia and the etiologic agent responsible was *K. pneumoniae*.

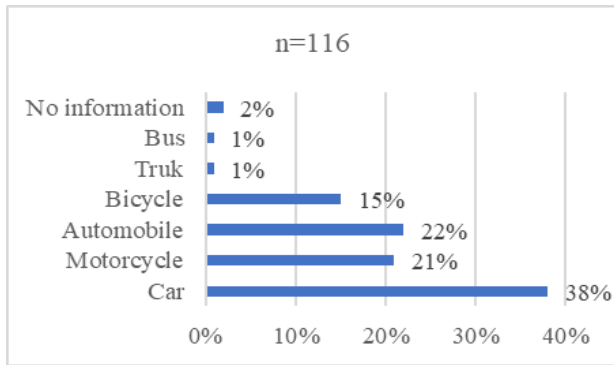
3.2 Clinical and epidemiological characteristics of the trauma cohort

Among the patients diagnosed with trauma (n=302), there was a predominance of males (77.15%) and 88 patients were

aged over 60 years (29.14%). The main causes of trauma are shown in Graph 1 and the classification of RTA in Graph 2. The outcomes of each type of injury are shown in table. Next, Table 4 shows the clinical characteristics of the trauma cohort.



Graph 1. Main causes of Trauma (n = 302)



Graph 2. Classification of ATT (n=116)

Table 4. Main reasons for trauma, gender, mean age and their respective outcomes (302 patients)

	n (%)	male gender n (%)	Age years (mean ± SD)	Death n (%)
ATT	116 (38%)	87 (75%)	37.6±17	23 (2%)
fall to the ground	73 (24%)	49 (66%)	67.5±16.7	31 (42%)
Age > 60 years	53 (71%)			
Physical aggression	38 (12%)	34 (89%)	33.7±13	14 (36%)
FAF	17 (44%)			
FAB	5 (13%)			
caustic soda ingestion	1 (2%)			
No information	15 (39%)			
fall from another height	33 (11%)	31 (93%)	48.3±12	13 (39%)
self-extermination attempt	26 (8.6%)	21 (81%)	36.9±10	7 (27%)

Table 5. describes epidemiological and clinical data from the 302 trauma patients and 1226 non-trauma patients.

	Total Patients	trauma patients	Patients without trauma	p.Value
number of patients	1528	302	1226	
Age (years). mean ± SD	55.6 ± 18.2	46.1 ± 20.7	57.9 ± 16.8	< 0.00001
Age > 60 years n	733	88	645	< 0.00001
(%)	48%	29%	52%	
male gender n (%)	891 (58%)	233 (77%)	658 (53%)	< 0.00001
Value of SAPS III. mean ± SD and	53.9 ± 16.4	48.7 ± 14.7	55.1 ± 16.5	< 0.00001
median	53	48		

Arterial hypertension n (%)	733 (49%)	51 (17%)	702 (93%)	< 0.00001
Diabetes n (%)	367 (24%)	18 (5.96)	349 (28%)	< 0.00001
Neoplasms n (%)	203 (13%)	2 (0.60%)	201 (16%)	< 0.00001
Use of mechanical ventilation n (%)	905 (59%)	215 (71%)	690 (56%)	< 0.00001
VM usage time (days). mean ± SD	6.5 ± 9.8	7.9 ± 9.6	6.2 ± 9.8	0.97
Use of central venous access n (%)	979 (64%)	190 (63%)	789 (64%)	0.3
Time of use of CVC (days). mean ± SD	6.39 ± 8.73	6.38 ± 8.54	6.40 ± 8.78	0.79
Use of indwelling urinary catheter n (%)	1259 (82%)	275 (91%)	984 (80%)	< 0.00001
Time of use of SVD (days). mean ± SD	7.02 ± 8.44	7.81 ± 8.82	6.83 ± 8.33	0.9
Patients on renal replacement therapy n (%)	139 (9%)	6 (4%)	133 (11%)	< 0.000001
Time of renal replacement therapy (days). mean ± SD	12.12 ± 10.46	12.66 ± 5.53	12.1 ± 10.64	0.89
Patients undergoing surgical procedures n (%)	717 (47%)	215 (71%)	502 (41%)	< 0.000001
Length of stay in the ICU (days). mean ± SD	10.18 ± 10.2	10.68 ± 10.1	10.07 ± 10.22	0.34
Use of antifungal n (%)	42 (2%)	3(1%)	39(3%)	0.013
Use of antimicrobial n (%)	1086 (71%)	226 (75%)	860 (70%)	0.05
First choice fluoroquinolone n (%)	39 (3%)	1 (%)	38(4%)	0.0005
First choice carbapenem n (%)	26 (2%)	2(1%)	24(3%)	0.042
Patients diagnosed with bacteremia by MDR agents n (%)	66 (4%)	13(4%)	53(23%)	0.49
Bacteria isolated n (%)	69	14	55	
<i>S. aureus</i>	28 (40%)	5 (35%)	23 (41%)	0.41
<i>K. pneumoniae</i>	26 (38%)	6 (43%)	20 (37%)	0.32
<i>A. baumannii</i>	5 (7%)	2 (14%)	3 (5%)	
<i>P. aeruginosa</i>	3 (4%)	1 (7%)	2 (3%)	
<i>Enterobacter spp</i>	2 (3%)		2 (3%)	
<i>E. faecium</i>	2 (3%)		2 (3%)	

<i>E. faecalis</i>	1 (1.5%)		1 (2%)	
<i>S. marcescens</i>	1 (1.5%)		1 (2%)	
<i>M. morganni</i>	1 (1.4%)		1 (2%)	
Bacteremia interval (days). mean ± SD	17.13 ± 8.18	19 ± 11.32		0.57
Overall in-hospital mortality n (%)	627 (41%)	92 (30%)	535 (43%)	0.00001
Length of hospital stay (days). mean ± SD	18.34 ±17.69	19.1 ± 20.06	18.15 ±17.06	0.39

In-hospital mortality of patients diagnosed with trauma is lower than that of patients without trauma (30% vs. 43%; RR 0.81; 95% CI 0.74 – 0.88; p < 0.0001).

The overall features of the group of patients admitted to the ICU with MDR etiologic agent infection and those without MDR infection are shown below (Table 6).

3.3 Results of bivariate analysis between patients with and without MDR agent bacteremia

Table 6. Bivariate analysis of risk factors associated with MDR bacteremia (66 patients with MDR bacteremia x 1562 patients without MDR bacteremia).

	Total Patients	Patients with MDR bacteremia	Patients without MDR bacteremia	RR (IC 95%)	p value
Number of patients (n)	1528	66	1462		
Age (years). mean ± SD	55.59 ± 18.28	60.50 ±15.71	55.37 ±18.35		0.02
Age greater than 60 years	733	38	695	1.01	0.07
n (%)	47%	57%	47%	(0.99-1.03)	
Gênero masculino n (%)	891	40	851	0.99	0.41
	58%	60%	58%	(0.97-1.01)	
Value of SAPS III. mean ± SD	53.92 ±16.41	63.19 ±14.3	53.48 ±16.39		<0.001
Arterial hypertension n	753	33	720	1.03	0.5
(%)	49%	50%	49%	(0.98-1.02)	
Diabetes n	367	19	348	1.01	0.21
(%)	24%	29%	23%	(0.98-1.03)	
Neoplasms n	203	8	195	0.99	0.47
(%)	13%	12%	13%	(0.96-1.02)	
Trauma n	302	13	289	0.99	0.55
(%)	20%	19%	19%	(0.97-1.02)	

Use of mechanical ventilation n	905	60	845	1.06	<0.0001
(%)	59%	91%	58%	(1.04-1.08)	
Use of central venous access n	979	62	917	1.06	<0.0001
(%)	64%	94%	62%	(1.04-1.07)	
Use of indwelling urinary catheter n	1259	65	1194	1.05	<0.0001
(%)	82%	98%	81%	(1.03-1.06)	
Patients on renal replacement therapy n	139	18	121	1.1	<0.0001
(%)	9%	27%	8%	(1.03-1.18)	
Patients undergoing surgical procedures	717	38 (677	1.01	0.04
(%)	47%	57%)	46%	(0.99-1.04)	
Length of stay in the ICU (days). mean ± SD	10.19±10.20	21.45 ±12.86	9.67 ± 9.76		
Use of antifungals n	42	6	36	1.11	0.007
(%)	20%	9%	2%	(0.98-1.26)	
Use of antimicrobials n	1086	66	1020	1.06	<0.0001
(%)	71%	100%	70%	(1.04-1.08)	
Fluoroquinolone as 1st choice n	39	4	35	1.04	0.2
(%)	3%	6%	3%	(0.94-1.16)	
Carbapenems as 1st choice n	26	3	23	1.06	0.2
(%)	2%	4%	2%	(0.92-1.22)	
In-hospital mortality n	627	51	576	1.07	<0.0001
(%)	41%	77%	39%	(1.04- 1.09)	
Length of hospital stay (days). mean ± SD	18.34 ± 17.69	28.24 ± 15.36	17.88 ± 17.66		

multidrug resistant MDR; RR relative risk; CI confidence interval; SD standard deviation; SAPSIII Simplified Acute Physiology Score III; postoperative PO; ICU Intensive Care Unit

In a bivariate study, bacteremia was significantly correlated with age, SAPS III score value, use of mechanical ventilation, use of central venous catheter, use of urine catheter, surgical technique, renal replacement therapy, and

use of antifungal. The diagnosis of MDR bacteremia was unrelated to trauma. Comparing patients with and without MDR bacteremia, patients with MDR bacteremia had a higher mortality rate (77.27%), which was statistically

significant (77.31% x 39.39%; RR 1.09 1.03 - 1.08; 95%CI p< 0.0001). Next, in table 7, the result of the multivariate analysis of these risk factors.

Table 7: Bivariate analysis between patients with bacteremia (n = 13) and without bacteremia (n = 289) in a cohort of trauma patients (n = 302)

	Trauma patients	Patients with trauma and bacteremia	Patients with trauma and without bacteremia	RR (IC 95%)	p value
number of patients	302	13	289		
Age years). Mean ± SD	46.11 ±20.72	42.84 ±14.94	46.26 ±20.95		0.62
Age > 60 years n	88	3	85	0.93	0.44
(%)	29%	23%	29%	(0.93-1.03)	
male gender n	233	11	222	0.9	0.39
(%)	77%	84%	77%	(0.71-1.15)	
Value of SAPS III. mean ± SD	48.71 ±14.69	53.58 ±11.77	48.50 ±14.79		0.24
ATT n (%)	116	6	110	1.01	0.37
	38%	46%	38%	(0.96-	
Falls to the ground n	73	1	72	0.96	0.13
(%)	24%	7%	25%	(0.92-1.0)	
physical aggression n	38	4	34	1.07	0.06
(%)	12%	30%	11%	(0.96-1.2)	
Postoperative immediate n (%)	200	11	189	1.03	0.12
	66%	84%	65%	(0.99-1.0)	
TCE n (%)	160	8	152	1.01	0.36
	53%	61%	52%	(0.96-	
exposed fracture n	32	4	28	1.1	0.037
(%)	10%	30%	9%	(0.96-1.2)	
RST. mean ± SD (for an n = 160)	6.45 ±1.88	6.18 ± 1.59	6.47 ± 1.9		0.6
Glasgow on admission. mean ± SD (for n = 228)	10.61 ±4.39	8.63 ± 4.67	10.71 ±4.36		0.13
Arterial hypertension n (%)	51	0	51	0.94	0.085
	17%		17%	(0.92-0.97)	
Diabetes n (%)	18	1	17	1.01	0.55
	6%	7%	6%	(0.9-1.13)	

use of ventilation	215	13	202	1.16	0.01
mechanics n (%)	71%	100%	70%	(1.0-9.2)	
MV time	7.91 ±	16.07 ±	7.54 ±		0.01
(days). average. ± SD	9.66	9.12	9.53		
access usage	190	11	179	1.04	0.08
central venous n (%)	63%	84%	62%	(0.9-1.08)	
CVC time	6.38 ±8.54	12 ± 9.47	6.12 ± 8.42		0.01
(days). average. ± SD					
Use of SVD n (%)	275	13	262	1.04	0.28
	91%	100%	90%	(1.02-1.07)	
SVD time	7.81 ±8.82	14.46 ±8.43	7.51 ±8.74		0.005
(days). mean ± SD					
patients in	6	2	4	1.4	0.02
renal replacement therapy n (%)	2%	15%	1%	(0.81-	
Use of antifungals	3	1	2	1.4	0.12
n (%)	1%	8%	0.70%	(0.64-	
Use of	226	13	213	1.04	0.021
antimicrobial n (%)	75%	100%	73%	(1.02-1.09)	
Time to	10.68 ±10.1	19.15 ±7.09	10.30 ±10.06		0.001
ICU admission					
(days). mean ± SD					
Surgical procedure	215	13	202	1.06	0.01
n (%)	71%	100%	70%	(1.02-1.1)	
Length of hospital stay (days). mean ± SD	19.10 ±20.06	24.76 ±13.77	18.85 ±20.28		0.05
Mortality	92	6	86	1.05	0.06
intrahospital n (%)	30%	46%	29%	(0.98-1.11)	

*

not possible to calculate; RR relative risk; RST Revised Trauma Score; MV mechanical ventilation; CVC central venous catheter; SVD indwelling bladder probe; ICU Intensive Care Unit

In-hospital mortality in the trauma cohort (n = 302) in patients diagnosed with bacteremia by MDR was higher than

in patients without bacteremia, but in the bivariate analysis there was no statistical difference (46.15% x 29.41%; RR 1, 5; 95%CI:0.84 - 2.7; p=0.06).

In the bivariate analysis, open fracture, use of mechanical ventilation, use of renal replacement therapy, use of

antimicrobials and surgical procedure are associated with MDR bacteremia in trauma patients.

We chose to analyse the risk factors associated with MRSA bacteremia in the cohort of critically ill patients, since it was the most prevalent etiologic agent of bacteremia. The results were as follows (Table 8).

3.4 Results of the bivariate analysis of factors associated with MRSA bacteremia in the cohort of 1,528 patients

Table 8. Bivariate analysis of risk factors associated with MRSA bacteremia (n = 28) in the cohort of 1,528 patients

	Total Patients	Patients with MRSA bacteremia	Patients without MRSA bacteremia	RR (95%CI)	p-Value
Number of patients (n)	1528	28	1500		
Age (years). mean ± SD	55.59 ± 18.28	57.64 ± 17.25	55.56 ± 18.29		0.55
Age greater than 60 years n (%)	733 48%	17 60%	716 47%	1 (0.99-1.02)	0.12
male gender n (%)	891 58%	15 53%	876 58%	1 (0.98-1.01)	0.37
Value of SAPS III. mean ± SD	53.92 ± 16.41	60.92 ± 12	53.56 ± 18.29		0.02
HAS n (%)	753 49%	11 39%	742 49%	0.99 (0.97-1.00)	0.19
Diabetes n (%)	367 24%	9 32%	358 -24%	1 (0.99-1.02)	0.2
Neoplasms n (%)	203 13%	4 14%	199 -13%	1 (0.98-1.02)	0.52
Trauma n (%)	302 20%	5 -18%	297 -20%	0.99 (0.98-1.01)	0.51
VM usage n (%)	905	23	882	1.01	0.008

	59%	82%	59%	(1.00-1.03)	
Use of CVC n (%)	979	27	952	1.02	<0.001
	64%	-96%	-63%	(1.01-1.03)	
Use of SVD n (%)	1259	28	1231	1.02	0.004
	82%	100%	82%	(1.01-1.03)	
Patients on renal replacement therapy n (%)	139	8	131	1.04	0.002
	9%	28%	8%	(1.00-1.09)	
Surgical procedures n (%)	717	13	704	0.99	0.55
	47%	46%	47%	(0.98-1.01)	
Mean length of stay in the ICU (days) ± SD	10.19 ±10.2	18.32 ± 8.61	10.03 ±10.16		*

28 patients were diagnosed with MRSA bacteremia in our cohort. The mortality of these cases was 40.01% (RR 1.49 with 95%CI 0.94– 2.89; p < 0.019). SAPSIII value, use of mechanical ventilation, use of central venous catheter, submission to renal replacement therapy, and use of antimicrobials were associated with MRSA bacteremia.

3.5 Results of the bivariate analysis of factors associated with *K. pneumoniae* bacteremia in the cohort of 1,528 patients

As it is the second most prevalent agent in our cohort, we chose to assess factors associated with carbapenem-resistant *K. pneumoniae* bacteremia. The results were as follows (Table 9):

Table 9. Bivariate analysis of factors associated with carbapenem-resistant *K. pneumoniae* bacteremia in the cohort of 1,528 patients

	Total patients	Patients with KPC bacteremia	Patients without KPC bacteremia	RR (IC 95%)	p. value
Number of patients (n)	1528	26	1502		
Age (years)	55.59 ±18.28	60.19 ±15.07	55.52 ±18.32		0.19

mean ± SD					
Age greater than 60 years (n)	733	11	722	0.9	0.35
(%)	48%	42%	48%	(0.98-1.00)	
male gender (n)	891	21	870	0.98	0.01
(%)	58%	81%	58%	(0.97-0.99)	
Value of SAPS III.	53.92 ±16.41	62.50 ±17.72	53.75 ±16.36		0.008
mean ± SD					
SAH (n)	753	15	738	1	0.25
(%)	48%	57%	49%	(0.99-1.01)	
diabetes (n)	367	8	359	1	0.27
(%)	24%	3%	24%	(0.98-1.02)	
neoplasms(n)	203	3	200	0.99	0.53
(%)	13%	11%	13%	(0.97-1.01)	
trauma(n)	302	6	296	1	0.41
(%)	2%	23%	19%	(0.98-	
Use of VM(n)	905	26	879	1.02	<0.001
(%)	59%	100%	58%	(1.01-1.04)	
Use of CVC(n)	979	24	955	1.02	<0.001
(%)	64%	92%	63%	(1.01-1.03)	
Use of SVD (n)	1259	25	1234	1.01	0.04
(%)	82%	96%	82%	(1.00-1.02)	
Patients on renal replacement therapy (n)	139	6	133	1.03	0.02
(%)	9%	23%	9%	(0.99-1.06)	
Surgical procedures(n)	717	18	699	1.01	0.017
(%)	47%	69%	46%	(1.00- 1.02)	
Mean length of stay in the ICU (days)	10.19 ±10.2	25.92 ±13.85	9.91 ± 9.91		*
± SD					
Use of antifungals(n)	42	4	38	1.08	0.004
(%)	2%	15%	2%	(0.98-1.20)	
Use of antimicrobials(n)	1086	26	1060	1.02	<0.001
(%)	71%	100%	70%	(1.01-1.03)	

Fluroquinolone as 1st choice (n)	39	1	38	1	0.61
(%)	3%	4%	3%	(0.95-1.05)	
Carbapenems as 1st choice (n)	26	1	25	1.01	0.47
(%)	2%	4%	2%	(0.93-1.09)	
Average length of stay	18.34 ±17.69	32.26 ± 15.5	18.09 ±17.63		*

* It was not possible to calculate;

Twenty-six patients were diagnosed with KPC bacteremia in our cohort. The mortality of these cases was 88.46% (RR= 5.18 with 95%CI =1.78-15.03; p < 0.001). Male gender, SAPSIII value, use of mechanical ventilation, use of central venous catheter, submission to renal replacement therapy, surgical procedure, use of antifungals and use of antimicrobials were associated with carbapenem-resistant *K. pneumoniae* bacteremia.

3.6 Microbiological results

69 multidrug-resistant bacteria were identified (2 patients were co-infected): 5 *A. baumannii*; 1 *E. aerogenes*; 1 *E. cloacae*; 1 *E. faecalis*; 2 *E. faecium*; 26 *K. pneumoniae*; 1 *M. morgannii*; 3 *P. aeruginosa*; 28 *S. aureus* and 1 *S. marcescens*.

3.6.1 Sensitivity profile of MRSA strains

Sensitivity profiles were performed on 28 strains of methicillin-resistant *S. aureus*. The antimicrobials tested were cefoxitin, clindamycin, daptomycin, erythromycin, gentamicin, linezolid, oxacillin and bactrim. The results were as follows (Table 10):

Table 10. Sensitivity profile of 28 methicillin-resistant *S. aureus* isolates from the cohort of 1,528 patients

Antimicrobial tested (n)	Sensitive to antimicrobial (%)
Clindamycin (28)	10.71%
Daptomycin (27)	100%
Erythromycin (28)	5.55%
Gentamicin (28)	82.14%
Linezolid (27)	100%
Sulfamethoxazole/trimethoprim (28)	100%

Vancomycin (28)	100%
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3.6.2 Sensitivity profile of the other isolated strains

Two strains of *E. aerogenes* were included and their sensitivity profile is as follows: 50% resistant to amikacin; 100% resistant to amoxicillin/clavulanate, aztreonam, ceftriaxone, cefepime, ciprofloxacin, levofloxacin and ertapenem and 100% sensitive to imipenem and meropenem.

A strain of *M. morgannii* was included whose susceptibility profile is as follows: 100% sensitive to amikacin, ciprofloxacin, gentamicin and sulfamethoxazole/trimethoprim and 100% resistant to amoxicillin/clavulanate, ampicillin, ceftriaxone, cefepime, piperacillin/tazobactam, ertapenem, imipenem and meropenem.

Only one *S. marcescens* strain was included in the analysis and the sensitivity profile follows: 100% sensitive to amikacin, levofloxacin, sulfamethoxazole/trimethoprim and ertapenem and 100% resistant to amoxicillin/clavulanate, ampicillin, aztreonam, ceftriaxone, cefepime, ciprofloxacin, piperacillin/tazobactam, tigecycline, imipenem and meropenem. As for enterococci, three strains were inserted (two strains of *E. faecium* and one of *E. faecalis*) that present the same sensitivity profile: 100% sensitive to gentamicin; 100% resistant to penicillin, ampicillin and vancomycin.

4. Discussion

Trauma is the leading cause of death for those under the age of 40 worldwide and is a significant contributor to morbidity, particularly in developing nations. In our country, 4–25% of emergency department admissions are made up of trauma

patients. Health care-related infections (HAIs) are a public health concern because they have a significant negative impact on morbidity and mortality, lengthen hospital stays, and increase the price of diagnostic and therapeutic operations. Knowledge about the clinical and epidemiological characteristics of a population of critically ill patients and the identification of risk factors for bacteremia by MDR agents are essential to adapt infection prevention and control strategies.

4.1 General Cohort: In the two ICU sectors of this service whose main reasons for admission are trauma and neurological diseases (mainly neurovascular and postoperative CNS tumor resection), 4.32% (n = 66) of patients admitted over 18 months had MDR agent bacteremia. Bivariate analysis of risk factors associated with bacteremia by MDR agents showed that age (p < 0.02), SAPS III score (p < 0.001), use of mechanical ventilation (p < 0.001), use of venous catheter central (p < 0.001), use of a urinary catheter (p < 0.001), surgical procedure (p < 0.04), renal replacement therapy (p < 0.001) and antifungal use (p < 0.001) were significantly associated with bacteremia.

In the multivariate analysis, it was observed that mechanical ventilation (OR 3.89; CI 1.12 – 7.98; p < 0.019), RRT (OR 3.20; 95% CI 1.70 - 5.91; p < 0.0003) and surgical procedure (OR 1.69, 95% CI 1 – 2.8; p < 0.03) were independent risk factors for MDR bacteremia. All factors are possibly related to the severity of the patient.

Trauma was not considered a risk factor for MDR bacteremia. As an example, we cite the incidence density of CVC-related bloodstream infection reported by in 2016, was 2.01 / 1000 catheters-day in trauma patients and in the general population, 1.1 / 1000 catheters-day (Major et al., 2015). In an Argentine cohort, a higher BSI-CVC rate was also observed in trauma patients compared to non-trauma patients (6.79/1000 catheters-day x 1.1/1000 catheters-day).

4.2 Trauma Cohort: As expected, trauma patients were younger than the average age of the overall cohort (46.1 ± 20.7 years x 55.6 ± 18.27) and predominantly male (77.15%). However, it is worth noting that 29.14% were over

60 years of age. In a retrospective cohort of 144 trauma patients performed at a university hospital in Cascavel (PR), Machado et al., (2017) showed a younger population (mean age of 33.3 years), with a predominance of males (83%) in which 60% were victims of RTA and 31% were victims of physical aggression. The overall mortality rate was 22.9%. Trauma patients with MDR bacteremia had a higher mortality rate than those without MDR infection (46% x 29%), but without statistical significance (RR 1.05; 95% CI 0.98 – 1.11; p < 0.06). As mentioned above, trauma referral centers tend to report a higher incidence of HAI, but not necessarily a higher mortality rate.

In our bivariate analysis, open fracture, mechanical ventilation, RRT, surgery, and antimicrobial use were risk factors associated with MDR bacteremia in trauma patients. Open fractures are commonly related to high kinetic energy trauma, such as RTA.

Mechanical ventilation is required when there is reduced level of consciousness (eg, TBI and/or hypovolemic shock).

MRSA cohort

In our cohort of 1528 patients, the frequency of bacteremia by MRSA was 1.83% (n=28). Mean SAPS III value, use of mechanical ventilation, use of CVC, use of SVD, need for RRT, and use of antimicrobials were associated with MRSA bacteremia in bivariate analysis. However, in the multivariate analysis, the only independent factor associated with MRSA bacteremia was the need for RRT (OR 3.22; 95% CI 1.32- 7.83; p < 0.0099). This agent was responsible for 59.57% (n = 28) of bloodstream infections. The mean length of hospital stay until the diagnosis of bacteremia was 15.67 days and the mean length of hospital stay was 25.9 days. In our cohort, few patients underwent hemodialysis (9.11%), possibly chronic and acute dialysis patients with dialysis emergency (with the exception of shocked patients who would not tolerate hemodialysis). For hemodialysis, there is usually a need for another deep vein puncture, since the availability of a triple-line catheter (or dialysis catheter with an accessory route) in our service is quite variable. Therefore, the need for dialysis would be linked to two central venous accesses,

which would increase the possibility of primary bloodstream infection.

Conclusion

In a sample of 1528 patients, the use of mechanical ventilation, renal replacement treatment, and surgical procedure were all independently associated with an increased risk of MDR bacteremia. Trauma did not appear to be a risk factor for MDR bacteremia. In this cohort, the prevalence of MDR bacteremia was 4.3% (n = 62), and the mortality rate was 75%. MRSA (28 strains) and *K. pneumoniae* (26 strains) were the most common MDR agents

in this cohort. All MRSA strains tested positive for the *mecA* gene, with 67% being SCCmec type II. *blaKPC* was found in 83.3% of *K. pneumoniae* strains, which is thought to be the main mechanism of carbapenem resistance in India. The most common causes of trauma in this cohort were car accidents (38%), followed by falls (24%), with a trauma cohort mortality rate of 30%. In this cohort, the prevalence of MDR bacteremia was 4.3%, and the mortality rate was 46%. Renal replacement therapy was the only independent risk factor for MDR bacteremia in a cohort of 302 trauma patient.

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