Original Research

Bloodstream Infections Caused by Multidrug Resistant Bacteria: Clinical and Microbiological Features and Mortality

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ABSTRACT

Objectives: Bloodstream infections (BSI) are associated with high morbidity and mortality. The aim of our study is to determine whether there is a relationship between certain risk factors such as the underlying disease, patient's medical history, or interventional procedures and multidrug resistant (MDR) bacterial infection and to determine the risk factors for mortality.

Methods: Two hundred and twenty-two outpatients and inpatients who were diagnosed with bacteremia over a 6-month period were included in the study. 232 agents from 222 patients were isolated and tested for antimicrobial susceptibility. The relationship between patients demographic and clinical data and MDR was analyzed.

Results: The most common microorganisms were Gram-negative bacteria (59.4%), Gram-positive bacteria (36.9%), *Candida* species (2.2%), and anaerobic bacteria (1.35%). The most common isolates were *Escherichia coli* 53 (22.8%), *Staphylococcus aureus* 35 (%15.1), *Klebsiella pneumoniae* 26 (11.2%), *Pseudomonas* spp. (n=17, 7.3%), *Acinetobacter* spp 17 (7.3%), and *Enterococcus* spp 14 (6%). Microorganisms with the highest antimicrobial resistance observed were 82.3% in *Acinetobacter baumannii*, 64.5% in coagulase-negative staphylococci, 60.3% in *E. coli*, 50% in *K. pneumoniae,* and 27.2% in *Enterobacterales* spp. Most patients with BSI caused by MDR bacteria were in the intensive care unit (64%). Sepsis diagnosis, urinary catheter use, history of surgery, and use of broad-spectrum antibiotics as well as risk factors for antibiotic-resistant bacteremia, coronary artery disease, inappropriate empirical therapy, health-care-associated infections, urinary catheterization, and stay in the ICU were determined as risk factors for mortality.

Conclusion: Our study identified the risk factors of BSI caused by MDR bacteria and helped to reveal the relationship between these factors and mortality.

Keywords: Bloodstream infections, multidrug resistance, risk factor

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Bloodstream infection (BSI) is an important condition that causes a significant burden of disease in terms of its consequences.[1] Community-onset BSI must either occur in outpatients or have symptoms defined 48 h before hospital admission. It is otherwise classified as healthcare-associated when it occurs among individuals with health-care

exposure.[2,3] In studies conducted in developed countries, the incidence of community-onset BSI was observed to be approximately 100–150/100,000.[4,5]

Multi-drug resistant infections (MDRI) are an important public health problem today. Because MDRIs are often difficult to treat effectively, they result in longer hospital stays and can lead to adverse outcomes such as complications and death. [6] In recent years, various bacterial pathogens have transformed into MDRI forms. In particular, *Pseudomonas aeruginosa*, *Acinetobacter* spp and *Enterobacterales* have become resistant to almost all antibiotics.[6-8] Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* are common and cause poor clinical outcomes that lead to community-onset or healthcare-associated infections.[9,10] *Acinetobacter baumannii* can cause pneumonia and BSI, which are associated with high mortality and morbidity. Besides, *P. aeruginosa* can cause BSI, pneumonia and urinary tract infections.[7,11]

Antimicrobial resistance is an important concern, which can worsen the outcome, particularly of BSI and healthcare-associated infections.[12] Especially, immunocompromised patients such as neonates and hematology-oncology patients are particularly threatened by MDRIs.[13] Sepsis, a public health problem and a major cause of death worldwide, was recently listed as a global health priority by the World Health Organization.[14] Accurate diagnosis and management of BSI and applying appropriate antimicrobial therapy can reduce the incidence of morbidity and mortality by increasing a patient's survival rate.[15] Fast and convenient treatment plays a critical role in the management of BSI. However, the increasing prevalence of MDRI bacteria complicates the empirical treatment of BSI. Healthcare institutions control guidelines should be customized to each geographical location, and new measures should be implemented to improve antimicrobial management strategies.[16,17] Therefore, in this study, we first aimed to determine the microbiology of BSI in our hospital. Afterwards, we aimed to determine the multidrug resistant (MDR) ratios in microorganisms, to reveal the associated factors that cause MDRI, and to determine the factors affecting mortality in patients with MDRI.

Methods

Ethical Approval

The study was approved by the Instructional Review Board (decision no: 1870/date: January 23, 2018). All procedures were performed in accordance with the ethical standards set by the Declaration of Helsinki, and written informed consent was obtained from all participants.

Study Design and Population

This study included 222 adults (≥18 years old) who were hospitalized and treated at training and research hospital

between May 2017 and November 2017. A total of 232 non-duplicated clinical agents were isolated from 222 patients and tested for antimicrobial susceptibility (Table 1). The "resistant bacteria group" (MDRI) included extended ESBL positive *E. coli*, *K. pneumoniae*, *Enterobacter* spp., carbapenem-resistant Enterobacterales species, carbapenem-resistant *Pseudomonas* spp., and *A. baumannii* isolates, methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci, and vancomycin-resistant *Enterococcus* spp. species. The "susceptible bacteria group" (non-MDRI) included non-resistant bacteria. Epidemiological and clinical characteristics of patients with non-MDRI and MDRI bacteremia were compared.

Data Collection and Definitions

Demographic and clinical data were collected through a review of medical records. The clinical data included: Hos-

Table 1. The isolates obtained in the study

Isolates	n	%
Gram-positive bacteria	85	36.6
Staphylococcus aureus	35	15.1
Coagulase-negative staphylococci	31	13.4
S. epidermidis	16	6.8
S. hominis	7	3
S. haemolyticus	4	1.7
S. capitis	1	0.4
S. lugdunensis	1	0.4
S. species	1	0.4
***Enterococcus* spp**	14	6
E. faecalis	8	3.4
E. faecium	5	2.1
E. casseliflavus	1	0.4
***Streptococcus* spp**	5	2.1
Gram-negative bacteria	138	59.5
Enterobacterales	101	43.5
Escherichia coli	53	22.8
Klebsiella pneumoniae	26	11.2
Enterobacter spp	11	4.7
Morganella morganii	4	1.7
Proteus spp	3	1.3
Serratia marcescens	2	0.9
Salmonella spp	2	0.9
Non-fermentative	37	15.9
Pseudomonas spp	17	7.3
Acinetobacter spp	17	7.3
Stenotrophomonas maltophilia	3	1.3
***Brucella* spp**	1	0.4
Anaerop	3	1.3
Bacteroides spp	2	0.9
Clostridium spp	1	0.4
***Candida* spp**	5	2.2
Total	232	100.0

pitalization within the past 3 months, broad-spectrum antibiotic usage, antibiotic usage more than 5 days within the past 3 months, previous health-care assistance, comorbidities, possible sources and risk factors for bacteremia, appropriate empirical antibiotic treatment, and mortality in 30 days.

Bacterial Isolates, Identification, and Susceptibility Testing

The blood cultures were done on BacT/ALERT®3D (bio-Meriéux-France). Microbial identification was performed using standard conventional methods in conjunction with

matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Germany). The antimicrobial susceptibility profile of the bacteria was determined by BD Phoenix™ (Becton Dickinson, USA). European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods and interpretation criteria were used for all antimicrobial agents.

Statistical Analysis

Microsoft Excel was used to collect the data. Continuous variables were recorded as numbers, while categorical variables were recorded as 0 and 1 and transferred to SPSS 17.0

Table 2. Epidemiological, demographic, and clinical characteristics of patients with BSI caused by bacteria in a tertiary referral hospital in Istanbul, Turkey

Organisms (n=232)		MDRI (n)	%	
Escherichia coli	53	32	60.3	
Klebsiella pneumoniae	26	13	50	
Enterobacterales spp.	11	3	27.2	
Pseudomonas spp.	17	3	17.6	
Acinetobacter baumannii	17	14	82.3	
Staphylococcus aureus	35	6	17.1	
Coagulase-negative staphylococci	31	20	64.5	
Enterococcus spp.	14	3	23	
Comorbidities/Underlying disease		**MDRI**	**Non-MDRI**	**p**
	n	**n (%)**	**n (%)**	
Coronary artery disease	76	32 (34.7)	44 (35.2)	0.949
Chronic renal failure	57	20 (21.7)	37 (29.6)	0.193
Diabetes	54	25 (27.1)	29 (23.2)	0.528
COPD	11	6 (6.5)	5 (4)	0.534
Moderate or severe liver disease	6	1 (1.08)	5 (4)	0.196
Metastatic solid tumor	56	27 (29.3)	29 (23.2)	0.306
Neurological	54	25 (27.1)	29 (23.2)	0.525
Risk Factors				
Dialysis	46	16 (17.3)	30 (2.4)	0.239
Urinary catheter	58	38 (41.3)	20 (16)	**<0.01**
Central venous catheter	6	4 (4.3)	2 (1.6)	0.405
Gastrostomy and jejunostomy tube	4	3 (3.2)	1 (0.8)	0.315
Tracheostomy	5	3 (3.2)	2 (1.6)	0.653
Clinical information				
History of inpatient or outpatient surgery	134	68 (73.9)	66 (52.8)	**0.002**
History of broad-spectrum antibiotic use within 3 months or longer than 5 days	126	63 (68.4)	63 (50)	**0.008**
Hospitalization within 3 months	112	57 (61.9)	55 (44)	**0.009**
Type of BSI Number of patients				
Sepsis	111	60 (65.2)	51 (40.8)	**<0.01**
Pneumonia	40	15 (16.3)	25 (20)	0.488
Urinary system infections	76	37 (40.2)	39 (31.2)	0.169
Bloodstream infections associated with an intravenous catheter	41	14 (15.2)	27 (21.6)	0.235
Surgical site infections	38	19 (20.6)	19 (15.2)	0.296
Complicated skin and soft tissue infections	35	12 (13)	23 (18.4)	0.289
Central nervous system infections	6	3 (3.2)	3 (2.4)	0.7

(SPSS Inc.; Chicago, IL, USA) for analysis. Student's t-test was used to compare continuous variables, and the Pearson Chi-square test was used to compare categorical variables. Logistic regression analysis was performed to identify risk factors for MDRI and mortality. $p<0.05$ was considered statistically significant.

Results

Demographics

During the study period, 232 non-duplicated clinical agents were isolated from 222 patients. The mean age was 64±19 for the total study population, while the median age was 67 (49.7–80). In the study population, 47.3% of the patients were female, and 52.7% were male.

Bacterial Isolates

The most common microorganisms were Gram-negative bacteria (59.4%), Gram-positive bacteria (36.9%), *Candida* species (2.2%), and anaerobic bacteria (1.35%). The most frequently isolated Gram-negative microorganisms were *E. coli* (n=53, 22.8%), *K. pneumoniae* (n=26, 11.2%), and *Pseudomonas* spp. (n=17, 7.3%), respectively. The most frequently isolated Gram-positive bacteria were *S. aureus* (n=35, 15.1%), coagulase-negative staphylococci (n=31,

13.4%), *Enterococcus faecalis* (n=8, 3.4%), and *Enterococcus faecium* (n=5, 2.1%). The resistant bacteria were mostly isolated from the patients in the intensive care unit (ICU) (64%). The epidemiological, demographic, and clinical characteristics of the patients are shown in Table 2.

Microbiological Features

The details of the antimicrobial resistance among the most frequently isolated *Enterobacterales* are shown in Table 3. Gram-negative bacteria (n=138, 59.5%), Gram-positive bacteria (n=85, 36.6%), and non-fermentative bacteria (n=37, 15.9%) constituted the majority of the microorganisms. ESBL positivity rate in *E. coli* isolates was 60.3%. *K. pneumoniae* ESBL positivity rate was 26.9%, and the carbapenem resistance rate was 19.2%. The details of the antibiotic resistance among *Pseudomonas* spp. and *Acinetobacter* spp. are shown in Table 4. The rate of carbapenem resistant *Pseudomonas* spp. was 17.6%, while the rate of carbapenem resistant *Acinetobacter* spp. was 82.3%. The details of the antibiotic resistance among *Staphylococcus aureus*, coagulase-negative staphylococcus, and *Enterococcus* spp. strains are shown in Table 5. The antibiotic-resistant bacteria were mostly isolated from the patients in the ICU (n=32, 64%). Antibiotic-resistance rates were 45% (n=23) in med-

Table 3. Proportions of antimicrobial resistance among Enterobacterales that were most frequently isolated from bloodstream

Antimicrobial drug	Enterobacterales spp. (99)				Escherichia coli (53)				Klebsiella pneumoniae (26)			
n (%)	S	I	R	Total	S	I	R	Total	S	I	R	Total
Ampicillin	13 (13.7)	0 (0)	82 (86.3)	95 (100)	13 (26)	0 (0)	37 (74)	50 (100)	*	*	*	*
Ampicillin sulbactam	37 (48.7)	0 (0)	39 (51.3)	76 (100)	21 (45.6)	0 (0)	25 (54.4)	46 (100)	8 (40)	0 (0)	12 (60)	20 (100)
Amoxicillin/Clavulanic acid	36 (39.6)	0 (0)	55 (60.4)	91 (100)	23 (48.9)	0 (0)	24 (51)	47 (100)	10 (40)	0 (0)	15 (60)	25 (100)
Piperacillin	30 (33.4)	2 (2.2)	58 (64.4)	90 (100)	11 (22.9)	1 (2.1)	36 (75)	48 (100)	7 (27)	1 (3.8)	18 (69.2)	26 (100)
Piperacillin tazobactam	73 (74.5)	4 (4.1)	21 (21.4)	98 (100)	39 (75)	4 (7.7)	9 (17.3)	52 (100)	16 (61.5)	0 (0)	10 (38.5)	26 (100)
Cefepime	47 (50.5)	3 (3.3)	43 (46.2)	93 (100)	19 (38.9)	2 (4)	28 (57.1)	49 (100)	13 (50)	0 (0)	13 (50)	26 (100)
Ceftriaxone	52 (78.8)	0 (0)	14 (21.2)	66 (100)	19 (36.5)	1 (2)	32 (61.5)	52 (100)	13 (50)	0 (0)	13 (50)	26 (100)
Cefuroxime	54 (55.6)	5 (5.2)	38 (39.2)	97 (100)	18 (34)	0 (0)	35 (66)	53 (100)	13 (50)	0 (0)	13 (50)	26 (100)
Cefoxitin	47 (47.9)	2 (2.1)	49 (50)	98 (100)	33 (86.9)	0 (0)	5 (13.1)	38 (100)	17 (89.4)	0 (0)	2 (10.6)	19 (100)
Ceftazidime	34 (41.5)	0 (0)	48 (58.5)	82 (100)	24 (47)	5 (9.9)	22 (43.1)	51 (100)	13 (50)	0 (0)	13 (50)	26 (100)
Imipenem	89 (91.8)	4 (4.1)	4 (4.1)	97 (100)	53 (100)	0 (0)	0 (0)	53 (100)	21 (80.8)	1 (3.8)	4 (15.4)	26 (100)
Meropenem	94 (95)	1 (1)	4 (4)	99 (100)	53 (100)	0 (0)	0 (0)	53 (100)	21 (84)	0 (0)	4 (16)	25 (100)
Ertapenem	90 (92.8)	0 (0)	7 (7.2)	97 (100)	52 (100)	0 (0)	0 (0)	52 (100)	20 (76.9)	0 (0)	6 (23.1)	26 (100)
Aztreonam	49 (50.5)	5 (5.2)	43 (44.3)	97 (100)	20 (43.4)	0 (0)	26 (56.6)	46 (100)	13 (50)	0 (0)	13 (50)	26 (100)
Ciprofloxacin	52 (52.5)	3 (3)	44 (44.5)	99 (100)	25 (47.2)	0 (0)	28 (52.8)	53 (100)	11 (42.3)	2 (7.7)	13 (50)	26 (100)
Amikacin	93 (97.8)	1 (1.1)	1 (1.1)	95 (100)	49 (92.5)	1 (1.9)	3 (5.7)	53 (100)	25 (96.1)	0 (0)	1 (3.9)	26 (100)
Gentamicin	68 (68.7)	0 (0)	31 (31.3)	99 (100)	36 (67.9)	0 (0)	17 (32.1)	53 (100)	14 (53.8)	0 (0)	12 (46.2)	26 (100)
Tigecycline	67 (70.5)	20 (21.1)	8 (8.4)	95 (100)	48 (96)	2 (4)	2 (2)	52 (100)	11 (44)	13 (52)	1 (4)	25 (100)
Sulfamethoxazole trimethoprim	61 (61.6)	0 (0)	38 (38.4)	99 (100)	29 (54.7)	0 (0)	24 (45.3)	53 (100)	17 (65.4)	0 (0)	9 (34.6)	26 (100)

*: Naturally resistant.

Table 4. Proportion of antimicrobial resistance among non-fermentative Gram-negative bacilli that were most frequently isolated

Antimicrobial drug	*Pseudomonas* spp.[17]				*Acinetobacter* spp.[17]		
	S	I	R	Total	S	R	Total
Piperacillin	13 (86.7)	0 (0)	2 (13.3)	15 (100)	-	-	-
Piperacillin Tazobactam	13 (86.7)	0 (0)	2 (13.3)	15 (100)	-	-	-
Cefepime	13 (86.7)	0 (0)	2 (13.3)	15 (100)	-	-	-
Ceftazidime	16 (94.1)	0 (0)	1 (5.9)	17 (100)	-	-	-
Imipenem	15 (88.2)	1 (5.9)	1 (5.9)	17 (100)	3 (17.6)	14 (82.4)	17 (100)
Meropenem	14 (82.4)	3 (17.6)	0 (0)	17 (100)	3 (17.6)	14 (82.4)	17 (100)
Aztreonam	1 (6.7)	12 (80)	2 (13.3)	15 (100)	-	-	-
Ciprofloxacin	14 (82.4)	0 (0)	3 (17.6)	17 (100)	2 (12.5)	14 (87.5)	16 (100)
Amikacin	14 (93.3)	0 (0)	1 (6.7)	15 (100)	3 (17.6)	14 (82.4)	17 (100)
Gentamicin	14 (87.5)	0 (0)	2 (12.5)	16 (100)	3 (17.6)	14 (82.4)	17 (100)
Sulfamethoxazole Trimethoprim	-	-	-	-	3 (17.6)	14 (82.4)	17 (100)

Pseudomonas spp.: *Pseudomonas aeruginosa*: 14, *Pseudomonas putida*: 3, **Acinetobacter spp.:** *Acinetobacter baumannii*:15, *Acinetobacter putti*:1, *Acinetobacter junii*:1

Table 5. Proportions of antimicrobial resistance among Gram-positive cocci

Antimicrobial drug	*Staphylococcus aureus*[35]			*Coagulase negative staphylococcus*[31]			*Enterococcus* spp.[14]		
	S	R	Total	S	R	Total	S	R	Total
Penicillin (Parenteral)	0 (0)	31 (100)	31 (100)	0 (0)	10 (100)	10 (100)	-	-	-
Ampicillin	0 (0)	23 (100)	23 (100)	0 (0)	24 (100)	24 (100)	9 (64.3)	5 (35.7)	14 (100)
Amoxicillin / Clavulanic Acid	-	-	-	-	-	-	9 (64.3)	5 (35.7)	14 (100)
Cefoxitin	29 (82.9)	6 (17.1)	35 (100)	11 (35.5)	20 (64.5)	32 (100)	-	-	-
Ciprofloxacin	32 (91.4)	3 (8.6)	35 (100)	15 (48.4)	16 (51.6)	32 (100)	-	-	-
Levofloxacin	32 (91.4)	3 (8.6)	35 (100)	15 (48.4)	16 (51.6)	31 (100)	-	-	-
Gentamicin	30 (85.7)	5 (14.3)	35 (100)	20 (64.5)	11 (35.5)	31 (100)	6 (60)	4(40)	10 (100)
Tobramycin	31 (88.6)	4 (11.4)	35 (100)	19 (61.3)	12 (38.7)	31 (100)	-	-	-
Vancomycin	35 (100)	0 (0)	35 (100)	31 (100)	0 (0)	31 (100)	10 (77)	3 (23)	13 (100)*
Teicoplanin	35 (100)	0 (0)	35 (100)	30 (96.8)	1 (3.2)	31 (100)	13 (92.9)	1 (7.1)	14 (100)
Erythromycin	30 (85.7)	5 (14.3)	35 (100)	14 (45.2)	17 (54.8)	31 (100)	-	-	-
Clindamycin	29 (82.8)	6 (17.2)	35 (100)	21 (70)	9 (30)	30 (100)	-	-	-
Quinupristin/Dalfopristin	34 (97.1)	1 (2.9)	35 (100)	28 (9.3)	3 (9.7)	31 (100)	4 (100)	0 (0)	4 (100)
Tetracycline	27 (77.1)	8 (22.9)	35 (100)	18 (62.1)	11 (37.9)	29 (100)	-	-	-
Tigecycline	33 (94.3)	2 (5.7)	35 (100)	31 (100)	0 (0)	31 (100)	8 (88.9)	1 (11.1)	9 (100)
Linezolid	35 (100)	0 (0)	35 (100)	30 (96.8)	1 (3.2)	31 (100)	14 (100)	0 (0)	14 (100)
Daptomycin	34 (97.1)	1 (2.9)	35 (100)	29 (96.7)	1 (3.3)	30 (100)	-	-	-
Fosfomycin	31 (91.2)	3 (8.8)	34 (100)	24 (88.9)	3 (11.1)	27 (100)	-	-	-
Fucidin Acid	33 (94.3)	2 (5.7)	35 (100)	15 (48.4)	16 (51.6)	31 (100)	**	**	**
Sulfamethoxazole Trimethoprim	34 (100)	0 (0)	34 (100)	20 (95.2)	1 (4.8)	21 (100)	1 (7.1)	13 (92.9)	14 (100)

*: *Enterococcus casseliflavus* strain naturally resistant to vancomycin did not participate in the vancomycin resistance rate; **: Naturally resistant.

Table 6. Binary logistic regression analysis for predictors of MDRI in patients with Blood Stream Infection

Variables	Test Statistics	
	p	HR (95% CI for HR)
Sepsis	0.003	2.365 (1.334–4.191)
History of inpatient or outpatient surgery	0.014	2.133 (1.169–3.892)
History of broad-spectrum antibiotic use within 3 months or longer than 5 days	0.021	1.973 (1.107–3.515)
Healthcare-Associated Infections	0.020	1.948 (1.110–3.418)
Hospitalization within 3 months	0.034	1.846 (1.049–3.250)
Urinary Catheter	<0.001	3.428 (1.792–6.555)

Table 7. Binary logistic regression analysis for predictors of mortality in patients with Blood Stream Infection

Variables	Test Statistics	
	p	HR (95% CI for HR)
Sepsis	0.002	3.662 (1.639–8.204)
Surgical Wound Infection	0.009	2.898 (1.298–6.475)
Coronary Artery Disease	0.029	2.218 (1.085–4.536)
Inappropriate Empirical Therapy	0.040	2.143 (1.034–4.442)
Hospitalization within 3 months	0.038	2.200 (1.043–4.644)
Healthcare-Associated Infections	<0.001	4.283 (1.912–9.592)
Urinary Catheter	0.033	2.286 (1.071–4.878)
Intensive Care Unit Stay	<0.001	6.513 (3.041–13.948)

ical clinics, 42.8% (n=12) in surgical clinics, 30.1% (n=22) in the emergency department, and 15% (n=3) in hemodialysis/outpatient clinics.

Risk Factors for MDRI Bacteremia

Table 6 shows binary logistic regression analyses of MDRI estimators of BSI patients. As a result of binary logistic analysis, sepsis (p=0.003; HR 2.3, CI 1.3–4.1), history of inpatient or outpatient surgery (p=0.014; hazard ratio [HR] 2.1, confidence interval [CI] 1.1–3.8), history of broad-spectrum antibiotic use within 3 months or longer than 5 days (p=0.021; HR 1.9, CI 1.1–3.5), healthcare-associated infections (p=0.020; HR 1.9, CI 1.1–3.4), hospitalization within 3 months (p=0.034; HR 1.8 CI 1.0–3.2), and the presence of urinary catheter (p<0.001; HR 3.4, CI 1.7–6.5) were determined as predictors for MDRI.

Risk Factors for Mortality

Table 7 shows binary logistic regression analyses of BSI death predictors. Binary logistic regression analysis revealed sepsis (p=0.002; HR 3.6, CI 1.6–8.2), surgical wound infection (p=0.009; HR 2.8, CI 1.2–6.4), coronary artery disease (p=0.029; HR 2.2, CI 1.0–4.5), inappropriate empirical therapy (p=0.040; HR 2.1 CI 1.0-4.4), hospitalization with-in 3 months (p=0.038; HR 2.2, CI 1.0-4.6), healthcare-associated infections (p<0.001; HR 4.2, CI 1.9-9.5), presence of urinary catheter (p=0.033; HR 2.2, CI 1.0-4.8), and in ICU stay(p<0.001; HR 6.5, CI 3.0-13.9) as predictors for mortality.

DISCUSSION

Dealing with potentially morbidity and mortality infections such as BSI is very important. Accuracy and resistance profile in predicting pathogens are crucial for successful therapy. Therefore, surveillance studies should be performed to understand regional epidemiological and microbiological data.[18,19] BSI surveillance studies are particularly important to identify problems with antimicrobial resistance. In this study, we aimed to determine the epidemiological and microbiological features of MDRI-related BSIs in our hospital.

The microorganisms identified in this study of frequency were Gram-negative bacteria, Gram-positive bacteria, Candida species, and anaerobic bacteria. The most frequently isolated Gram-negative microorganisms were E. coli, K. pneumoniae, and P. aeruginosa and the most frequently isolated Gram-positive bacteria were S. aureus, coagulase negative staphylococci, and Enterococcus spp. The ESBL positivity rate was 60.3% in E. coli isolates and 26.9% in K. pneumoniae isolates. Carbapenem resistance was observed in 19.2% of K. pneumoniae isolates, 17.6% in Pseudomonas spp. isolates, and 82.3% in Acinetobacter spp isolates. MDRIs were mostly isolated from patients in the ICU (n=32–64%). In studies on the epidemiology of BSI, there are studies in which gram-positive cocci predominate, as well as studies in which Gram-negative bacilli predominate.[20,21] In a study conducted in Greece, it was observed that 24.5% of all BSIs were caused by infections due to Gram-positive cocci.[22] According to the results of the EPIC II survey, staphylococci predominate among Gram-positive cocci in BSI, followed by enterococci and streptococci.[23] In a recent systematic review, it was reported that gram-negative bacteria predominate, especially in catheter-related BSIs.[24] E. coli was the most isolated microorganism in BSI in our study.

Despite the increasing occurrence of MDRI organisms, the inability to discover new and effective antibiotics at the same rate has resulted in an increased prevalence of Gram-negative bacteremias, urinary tract, and pulmonary system infections, and the increasing prevalence of *P. aeruginosa and A. baumannii*.[25] It was reported that early diagnosis of BSI and associated sepsis, rational application of empirical antibiotic therapy, and correct antibiotic management significantly reduce morbidity and mortality rates.[26] Therefore, it is very important to determine the risk factors, comorbidities, and associations that adversely affect the prognosis of both MDRI and BSI.

To determine all etiologies of BSI, results with regional variation were obtained in population-based cohorts. As a result of studies conducted in Denmark; kidney failure, diabetes, and liver disease have been documented as important risk factors for the development of BDI.[27,28] HIV infection, cancer, chronic lung disease, dementia, and cerebrovascular accidents have been reported to be risk factors for BIS in studies in the Canadian population.[4] In a study conducted by Marra et al.[25] in 2011, 2563 cases were examined and malignancies (24.2%), neurological diseases (12.1%), and coronary artery disease (11.4%) were found among the most common comorbid diseases in patients with BSI. In the same study, the researchers found that the rate of central venous catheter insertion was 70%, the rate of urinary catheterization was 40%, and the rate of mechanical ventilation was 33%. In a study conducted by Garrouste-Orgeas et al.[29] in 2002 in France, diabetes (13%) and chronic obstructive pulmonary disease (6%) were found to be the most common comorbid diseases. In a study on the epidemiology of BSI, it was determined that most infections were primary (55.9%) and the most frequent foci of secondary infections were the urinary tract (20.3%) and respiratory tract (11.8%). It was also observed that 65.0% of BSIs were health care associated, and 30.8% were community-onset-healthcare associated. Hemodialysis, prior invasive procedure, prior admission, chemotherapy, and home care have been reported as risk factors for BSIs.[30] Ergonul et al.[31] examined patients hospitalized in 17 ICUs in 2016. They found that 65% of patients with BSI had used antibiotics in the last 3 months and 39% had a history of surgery. Researchers also detected central venous catheter intervention as 58%, and this rate was associated with mortality. In our study, the most common comorbid diseases with BSI were coronary artery disease (35%), metastatic solid tumors (26.1), and diabetes (24.8%). The differences in the proportion of comorbid diseases may be related to distinct patient profiles of different hospitals, as well as regions, the development, and socioeconomic status of the countries. Furthermore,

in our study, antibiotic use in the past 3 months was 50%, a history of surgery was 60%, and a history of antibiotic use longer than 5 days was 56%, and the rate of urinary catheterization was 26%.

Because of the high morbidity and mortality in MDRI-induced BSIs, it is essential to identify patients at risk of MDRI, administer appropriate broad-spectrum empirical antibiotics, and improve patient outcomes. Therefore, the development of a predictive model, albeit at a local level, and the easy application of this predictive model at the bedside is crucial to improving outcomes. Of course, risk factors for MDRI BSI should be determined well. In a study focusing on patients with acute leukemia and BSI, it was revealed that inadequate empirical antibiotic therapy was associated with MDR *P. aeruginosa*. MDR *P. aeruginosa* was the only independent risk factor associated with mortality in patients with BSI.[32] Leal et al.[30] found MDRI-gram negative bacilli in 41 (28.7%) of 143 BSI episodes. They observed that risk factors for BSI caused by MDRI are liver disease, male gender, age ≥60 years, previous antimicrobial use, and *K. pneumoniae* bacteremia. However, they documented that especially *K. pneumoniae*-induced bacteremia and liver disease were 4.6 and 4.9 times more likely to show MDRI infection than those without. Studies have shown that antibiotic use 30 days before BSI infection is an independent risk factor for ESBL-producing *E. coli* BSIs.[33,34] It has been reported that the presence of a urinary catheter in cancer patients is an independent risk factor for MDRI-induced BSI.[35] In another study, it was documented that patients with liver cirrhosis were 10 times more likely to develop bacteremia than the general population.[28] Multivariate analysis by Addo Smith et al.[36] showed that the biliary etiology of cirrhosis, non-white race, recent hospital admission, and blood cultures taken >48 h after hospitalization were independent predictors of MDRI-related bacteremia. In a study conducted in China, hospitalization in the ICU within 30 days, transfer from other hospitals, tracheal cannula or tracheotomy in the past 30 days, central vein catheterization and changes in antibiotic treatment after culture positivity was associated with BSI caused by carbapenem-resistant *K. pneumoniae*.[37] In a recent study, significant associations were found between skin-soft tissue infection, surgery as a source of infection, inadequate empirical antibiotic therapy, history of hospital stay before ICU, history of surgery before ICU admission, and duration of ICU stay and MDRI.[38] In our study, it was determined that the risk factors for MDRI were the diagnosis of sepsis, the use of a urinary catheter, the history of surgery, the use of broad-spectrum antibiotics for more than 5 days in the past 3 months, and the hospitalization in the past 3 months. Binary logistic regression analyzes of MDRI predictors in BSI patients revealed that

urinary catheter presence increased 3.4-fold and sepsis 2.3-fold increased MDRI development.

Many factors affecting mortality in patients with BDE have been described. In retrospective studies, inappropriate empirical therapy, septic shock, mechanical ventilation, neutropenia, Charlson comorbidity index ≥3, high APACHE III and SAPS II scores, parenteral nutrition, and corticosteroid administration were determined as mortality predictors.[39,40] In the Cox regression analysis for BSIs caused by vancomycin-resistant enterococci, it was reported that age, chronic kidney disease, oncological disease, and ICU admission were risk factors independently associated with 30-day mortality, and early effective treatment was associated with survival.[41] In their study, Kuo et al.[42] observed that sepsis, malignancy, age >65 years, inadequate empirical antimicrobial therapy, kidney disease, cardiovascular disease, catheter placement in the internal jugular vein, infection with fungi or resistant strains were associated with 14-day mortality. In contrast, patients who received adequate definitive antimicrobial therapy, infected with gram-negative bacteria and admitted due to burn were more likely to survive within 14 days. In their study, Abubakar et al.[43] revealed that sepsis/septic shock, admission to the ICU, female gender, thrombocytopenia, and high creatinine levels were significantly associated with in-hospital mortality as a result of logistic regression analysis. In our study, logistic regression analysis determined sepsis, surgical wound infection, coronary artery disease, and inappropriate empirical therapy, as well as hospitalization in the past 3 months, healthcare-associated infections, urinary catheterization, and ICU stay as predictors of mortality in a 30 days. All the predictors we obtained from the study are consistent with the results of previous studies. However, there is no study in which all predictors accurately match. This situation depends on the differences in different hospitals, geographical regions, development levels, and socioeconomic status.

The limitations of our study are that it is single-centered and short-term. However, we think that the results of our study will shed light on future studies.

Conclusions

In this single-center study, the epidemiological and clinical features of MDRI-associated BSIs were investigated. The most frequently observed microorganism was Gram-negative bacteria, the highest ESBL positivity rate was in *E. coli* isolates and most of the patients with MDRI were ICU patients. Sepsis, surgical wound infection, coronary artery disease, inappropriate empirical therapy, hospitalization in the past 3 months, healthcare-associated infections, urinary catheterization, and ICU stay were determined as risk fac-

tors for mortality. We consider that the determination of risk factors for both MDRI development and mortality will contribute to both our hospital database and MDRI literature. However, our results need to be supported by studies with longer follow-up periods and larger patient populations.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (No: 1870, dated 23.01.2018).

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