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Bacteriological Profile and Antimicrobial Resistance Pattern Among Healthcare-Associated Infections in a Pediatric Intensive Care Unit

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Abstract

Healthcare-associated infections (HAIs) are a global public health issue with clinical and socioeconomic consequences. These infections are important indices for the quality of healthcare services which are serious complications that should be addressed in pediatric intensive care units (PICUs). This study aimed to retrospectively examine the bacterial HAIs, the frequency of isolated pathogen microorganisms, the areas of infection, and the antibiotic susceptibility recorded in the surveillance system in our Pediatric Intensive Care Unit in five years between 01.01.2015 and 31.12.2019. In the study period, 1593 patients were admitted to PICU, and 244 HAIs were detected in 141 patients. A bacterial pathogen was isolated in 190 HAIs of the 99 patients. In those episodes, Gram-negative microorganisms were most commonly seen (160/190). *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella spp*. were the most common bacteria. *Enterococcus spp*. and coagulase-negative staphylococci were the most common Gram-positive microorganisms. The mortality rate of a bacterial HAI was 40.4%. There was no resistance against vancomycin in Gram-positive microorganisms. The resistance rate against methicillin was 100% in coagulase-negative staphylococci and 50% in *S. aureus* strains. The cumulative rate of carbapenem resistance was found as 76.1% in *Pseudomonas aeruginosa*, 45.2% in *Klebsiella spp*. and 0% in *Escherichia coli*. In 2019, the resistance rate against colistin in *Klebsiella spp*. and *Pseudomonas aeruginosa* were 46.2% (6/13) and 20% (1/5), respectively. The resistance rate against carbapenem and colistin was 81.1% and 0% in *Acinetobacter baumannii*. It was observed that the use of carbapenem before an infection episode increased significantly, and the rate of carbapenem resistance reached 100% over the years in *Pseudomonas aeruginosa* and *Klebsiella spp*. A significant proportion of the isolates were multidrug-resistant strains, significantly threatening survival. Implementation of effective preventive strategies to combat the emergence of antibiotic resistance is urgently needed.

Keywords: Healthcare-associated infections, antibiotic resistance, pediatric, intensive care, mortality

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Introduction

Healthcare-associated infections (HAIs), also known as nosocomial infections or hospital-acquired infections, are the most important complications encountered in children, especially in pediatric intensive care units where critically ill patients are hospitalized. HAIs are an important source of morbidity and mortality worldwide.[1–4] In addition to morbidity and mortality, it prolongs hospital stay, increases antibiotic use and the risk of multi-antibiotic resistance to pathogens, and increases care costs.[1,5,6] The microorganisms isolated as causative agents in pediatric intensive care units and their antibiotic susceptibility and following the changes that occur over the years guide in planning the empirical antibiotic treatment on a case-by-case basis and ensuring the rational use of antibiotics in the unit. With this study, we aimed to examine the characteristics of bacteria isolated as the causative agent of HAIs in our pediatric intensive care unit over five years and the changes in our antibiotic use during the same period.

Highlights

- The most common bacterial HAI agents were Gram-negative bacteria
- The most Gram-negative bacteria were resistant to commonly used broad-spectrum antibiotics such as cefepime, piperacillin-tazobactam, carbapenem, and colistin
- It was observed that 40.4% of the patients diagnosed with bacterial HAI died due to infection
- The resistance to piperacillin-tazobactam, carbapenem, and levofloxacin increased over the years in *Klebsiella spp*. and *P. aeruginosa*. The carbapenem resistance of these two agents was 100% in 2019

Material and Method

The study was carried out by retrospectively examining the information of patients who were hospitalized in the pediatric intensive care unit between 01.01.2015 and 31.12.2019 and were followed up for more than 48 hours and diagnosed with HAI in Erciyes University Pediatric Intensive Care Unit. For the study, an application was made to the Erciyes University Clinical Research Ethics Committee on 12.06.2019, and ethics committee approval was obtained with decision no. 2019/437. The hospitalization-discharge information required for our study was obtained from the hospital data processing unit, the information about the clinical follow-up period of the patients, daily follow-up notes, and surveillance notes made by the hospital infection control committee (antibiotics used before infection, isolated agent and antibiotic resistance profile). Patients hospitalized and diagnosed with HAI clinically and laboratory during the follow-up period and bacteria isolated in sterile field cultures (blood, urine, , cerebrospinal fluid) ,tracheal aspirate and/or wound cultures were included in the study. The study did not include HAI episodes in which culture positivity was not detected. Isolated cathater tip culture positive results excluded from the study. The diagnosis of HAI was made based on the American Center for Disease Control (CDC) 2015 diagnostic criteria.[7] A bacterial HAI was defined as the isolation of a microorganism from a culture of sterile regions (blood, urine, tracheal aspirate, cerebrospinal fluid) or wound cultures of patients who developed signs of infection beyond 48 hours of hospital admission with or without local or systemic symptoms. Endotracheal aspirate cultures considered for colonization were not found to be significant and were not included in the study. Epidemics seen in the unit during the study period were also included in the study if they met inclusion criteria. If the same microorganism was isolated from another infection site and there is clinical evidence that the bloodstream infection is secondary to another infection site, only the culture result of the primary site was evaluated in the records. Some of the patients included in the study had more than one underlying chronic disease. Among the existing diseases, the one with the most clinical importance was selected and included in the study as the primary underlying chronic disease. Patients who died within 14 days of an HAI diagnosis were considered HAI-related mortality. Antibiotic treatments for the cases when the HAI episode developed were also examined. Piperacillin-tazobactam and combined antibiotic regimes, carbapenem, quinolone, and colistin treatments were defined as broad-spectrum antibiotics. Prolonged antibiotic use was also considered as antibiotic use longer than ten days in the last 30 days. Resistance results that were given as intermediate in the evaluation of culture antibiograms were accepted as resistant in our study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 25 (IBM Corp., Armonk, NY, USA). The median (interquartile range-IQR) value of the non-parametric numerical data in the study group was calculated, and the categorical data were given as a percentage (%).

Results

Characteristics of the Cases and Episodes of HAIs

During the five years between January 2015 and December 2019, 1593 patients were hospitalized in our PICU. Two hundred forty-four attacks were detected in 141 patients diagnosed with HAI. Among these attacks, 190 HAI attacks of 99 cases with positivity in a sterile field and/or wound bacterial cultures were included in the study. Demographic and clinical characteristics of 99 cases diagnosed with bacterial HAI are shown in Table 1. The median age of the cases was ten months, and 56% were male. There was no underlying disease in 16% (16/99) of the cases. The most common chronic diseases were neurological (39.4%), cardiovascular (19.2%), malignancies (6.1%), respiratory (5.1%) and metabolic (5.1%) disorders, respectively. Infection-related mortality was 40% (40/99) in cases with bacterial HAI.

Table 1
Demographic and clinical features of the patients with a bacterial healthcare-associated infection in the pediatric intensive care unit

Variables	N=99
Age, month, median (IQR)	10 (33)
Sex, male n (%)	56 (56.6)
Underlying chronic diseases, n (%)	
None	16 (16.2)
Neurological	39 (39.4)
Cardiovascular	19 (19.2)
Malignancies	6 (6.1)
Respiratory	5 (5.1)
Metabolic	5 (5.1)
Primary immunodeficiencies	4 (4.0)
Renal	1 (1.0)
Others	4 (4.0)
Mortality, n (%)	40 (40.4)

While 61.1% (116/190) of the agents were isolated from blood culture, 29.5% (59/190) from tracheal aspirate, 5.3% (10/190) from urine, 3.2% (6/190) from wound, 0.5% (1/190) were isolated from cerebrospinal fluid, and again 0.5% (1/190) from peritoneal fluid cultures. The number of episodes by year was 47, 28, 46, 28, and 41 in 2015, 2016, 2017, 2018, and 2019, respectively. The characteristics of 190 bacterial HAI attacks in 99 cases are shown in **Table 2**.

Table 2
Type of specimen with positive results, isolated organisms, and characteristics of the infection episodes

Variables	N=190
Type of specimen, n (%)	
Blood culture	116 (61.1)
Endotracheal aspirate	56 (29.5)
Urine culture	10 (5.3)
Wound swap	6 (3.2)
CSF	1 (0.5)
Peritoneal fluid	1 (0.5)
Number of episodes by year, n (%)	
2015	47 (24.7)
2016	28 (14,7)
2017	46 (24.2)
2018	28 (14.7)
2019	41 (21.6)
Isolated organisms, n (%)	
Gram-negative	**160 (84.2)**
*Klebsiella spp.**	38 (20)
Escherichia coli	11 (5.8)
Pseudomonas aeruginosa	49 (25.8)
Acinetobacter baumannii	38 (20)
Stenotrophomonas maltophilia	7 (3.7)
Serratia marcescens	10 (5.3)
*Enterobacter spp.***	4 (2.1)
Alcaligenes faecalis	3 (1.6)
Gram-positive	**30 (15.8)**
Enterococcus spp.†	21 (11.1)
CoNS	5 (2.6)
Staphylococcus aureus	2 (1.1)
Streptococcus pneumoniae	1 (0.5)
Leuconostoc spp.	1 (0.5)
Prolonged antibiotic usage in the previous 30 days	159 (83.7)
Broad spectrum antibiotic usage	64 (33.7)
Mortality, n (%)	**40 (21.1)**
Gram-negative infections	34 (21.25)
Gram-positive infections	6 (20)

Klebsiella spp.: Klebsiella pneumoniae, Klebsiella oxytoca
**Enterobacter spp.: Enterobacter aerogenes, Enterobacter cloacae*
†*Enterococcus spp.: Enterococcus faecium, Enterococcus faecalis*
Abbreviations: CoNS, Coagulase-negative staphylococci; CSF, cerebrospinal fluid

Gram-negative bacteria constituted the majority of bacteria isolated, and a total of 160 episodes of HAI due to Gram-negative bacteria were seen (84.2%). The most commonly isolated agents were *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Acinetobacter baumannii*, and *Escherichia coli*, and their ratios among all agents were 25.8%, 20%, 20%, and 5.8%, respectively. Enterococci (21/190, 11.1%) were the most common cause among Gram-positives, followed by coagulase-negative staphylococci (5/190, 2.6%).

For all episodes evaluated, the rate of antibiotic use longer than ten days in the last 30 days was 83.7% (159/190), while the use of broad-spectrum antibiotics before the attack was 33.7% (64/190). When we analyzed the mortality rates according to the agents, the mortality rates due to Gram-positive and Gram-negative HAI episodes were similarly 20% and 21.5%, respectively.

We looked at the distribution of bacteria isolated as HAI agents yearly. The most common bacteria were *P. aeruginosa* in 2015, 2016, 2017, and 2018, and *Klebsiella spp.* in 2019. In **Figure 1**, the yearly distribution percentage of the bacteria is given by specifying the number of detection in the boxes. Considering the distribution of other agents, Serattia marcescens clustered in 2017, and HAIs originating from *A. baumannii* were generally among the top 3 every year.

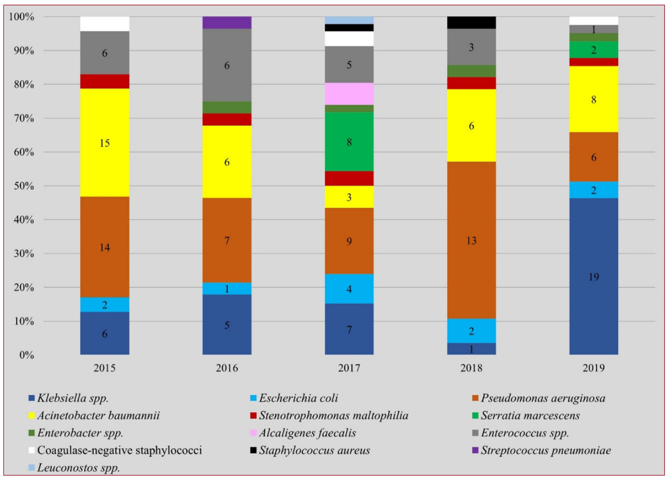

Figure 1. Distribution of the bacterial pathogens by year

Antibiotic Susceptibility Analyses of Bacterial Pathogens

The cumulative rates of antibiotic resistance were analyzed separately for Gram-negative and Gram-positive bacteria. The highest resistance rate was seen against ceftazidime (76.5%) and cefepime (71.9%) in *Klebsiella spp.* On the other hand, *E. coli* had high resistance to levofloxacin (100%) and cefepime (40%). Piperacillin-tazobactam and meropenem resistances in *P. aeruginosa* were 54.2% and 76.1%, respectively. While colistin resistance was not observed in *A. baumannii*, amikacin resistance was 50%, and gentamicin resistance was 81.6%. There was no resistance for trimethoprim/sulfamethoxazole (TMP-SMX) in *S. maltophilia* but 14.3% for levofloxacin. Meropenem resistance was 12.5% in *S. marcescens* strains. Cumulative antibiotic resistance rates of Gram-negative bacteria are shown in **Table 3**.

Table 3
Antibiotic resistance rates of selected Gram-negative bacteria

Antibiotic	*Klebsiella spp.** (n=38)		*Escherichia coli* (n=11)		*Pseudomonas aeruginosa* (n=49)		*Acinetobacter baumannii* (n=38)		*Stenotrophomonas maltophilia* (n=7)		*Serratia marcescens* (n=10)	
	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %
Amikacin	3/35	8.6	1/11	9.1	16/46	34.8	18/36	50	N/A	N/A	1/10	10
Gentamicin	11/20	55	1/3	33.3	19/42	45.2	31/38	81.6	N/A	N/A	6/9	66.7
Ampicilin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ceftriaxone	4/8	50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cefotaxime	15/24	62.5	3/9	33.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ceftazidime	13/17	76.5	N/A	N/A	23/49	46.9	N/A	N/A	0/3	0	5/8	62.5
Cefepime	23/32	71.9	4/10	40	16/44	36.4	N/A	N/A	N/A	N/A	7/8	87.5
Ciprofloxacin	15/33	45.5	4/7	36.4	10/47	21.3	30/38	78.9	N/A	N/A	7/10	70
Levofloxacin	7/11	63.6	2/2	100	5/15	33.3	20/27	74.1	1/7	14.3	5/8	62.5
Piperacillin-tazobactam	18/38	47.4	2/10	20	26/48	54.2	N/A	N/A	N/A	N/A	3/10	30
Meropenem	14/31	45.2	0/10	0	35/46	76.1	30/37	81.1	N/A	N/A	1/8	12.5
Imipenem	5/27	18.5	0/7	0	32/44	72.7	27/33	81.8	N/A	N/A	N/A	N/A
Colistin	6/19	31.6	0/3	0	1/21	4.8	0/37	0	N/A	N/A	N/A	N/A
Tigecycline	5/17	29.4	0/3	0	N/A	N/A	0/35	0	N/A	N/A	1/5	20
Fosfomycin	2/3	66.7	0/3	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TMP-SMX	12/20	60	0/1	0	N/A	N/A	28/36	77.8	0/7	0	2/8	25

**Klebsiella spp.*: *Klebsiella pneumoniae, Klebsiella oxytoca*, Abbreviations: N/A, not available; TMP-SMX, trimethoprim/sulfamethoxazole

The most common Gram-positive agent was enterococci, and vancomycin resistance was not observed. High-dose gentamicin and ampicillin-sulbactam resistances were 50% and 25%, respectively. Although methicillin resistance was 100% and 50% in coagulase-negative staphylococci and *S. aureus*, glycopeptide resistance was not observed in any of them. *Streptococcus pneumoniae*, which grew in only one peritoneal fluid sample during the study period, was sensitive to penicillin. The resistance rates of Gram-positive agents are shown in **Table 4**.

In our study, we also examined the change over the years besides the cumulative rate of antibiotic resistance. For this purpose, we evaluated the rates of resistance to broad-spectrum antibiotics year-based in the three most common Gram-negative bacteria (*P. aeruginosa*, *Klebsiella spp.*, and *E. coli*), **Figure 2**. The resistance to piperacillin-tazobactam, carbapenem, and levofloxacin increased over the years in *Klebsiella spp.* and *P. aeruginosa*. The carbapenem resistance of these two agents was 100% in 2019. The resistance to cefepime and levofloxacin in *P. aeruginosa* was 100% in 2019, and the resistance to piperacillin-tazobactam was 80%. It was observed that resistance rates in *E. coli* did not increase in 2019, unlike others.

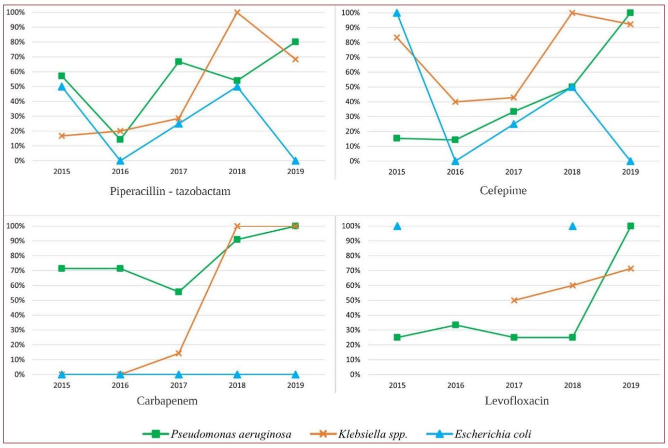

Figure 2. Trends of broad-spectrum antibiotic resistance rates by years in selected Gram-negative bacteria

Evaluation of antibiotic use in PICU

During the study period, treatments of the cases at the onset of the bacterial HAI attack were also evaluated. The use of cefepime, piperacillin-tazobactam, carbapenem, quinolone, and colistin between 2015 and 2019 was examined (**Figure 3**). It has been determined that the use of carbapenems in cases has increased gradually since 2016. While carbapenem was used in

Table 4
Antibiotic resistance rates of Gram-positive bacteria

Antibiotic	*Enterococcus spp.** (n=21)		CoNS (n=5)		*Staphylococcus aureus* (n=2)		*Streptococcus pneumoniae* (n=1)	
	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %	R/(R+S)	R %
Penicillin G	N/A	N/A	N/A	N/A	N/A	N/A	0/1	0
Gentamicin	7/14	50	3/4	75	1/2	50	N/A	N/A
Ampicilin/sulbactam	5/20	25	5/5	100	1/2	50	N/A	N/A
Clindamycin	N/A	N/A	5/5	100	1/2	50	N/A	N/A
Meticilin	N/A	N/A	5/5	100	1/2	50	N/A	N/A
Cefotaxime	N/A	N/A	N/A	N/A	N/A	N/A	0/1	0
Ciprofloxacin	5/21	23.8	N/A	N/A	N/A	N/A	N/A	N/A
Teicoplanin	0/21	0	0/5	0	0/2	0	N/A	N/A
Vancomycin	0/21	0	0/5	0	0/2	0	N/A	N/A
TMP-SMX	N/A	N/A	3/4	75	0/2	0	1/1	100

**Enterococcus spp.*: *Enterococcus faecium, Enterococcus faecalis*, Abbreviations: CoNS, Coagulase-negative staphylococci; N/A, not available; TMP-SMX, trimethoprim/sulfamethoxazole

17.9% of cases during any bacterial HAI attack in 2016, this rate increased to 19.6% in 2017, 28.60% in 2018, and 43.9% in 2019. Similarly, colistin usage gradually increased from 2.2% to 14.6% starting in 2017. During the same period, the use of cefepime and piperacillin-tazobactam declined gradually. While quinolones were not used before a bacterial HAI attack in 2016 and 2017, they were used at 14.3% and 12.2% in 2018 and 2019, respectively.

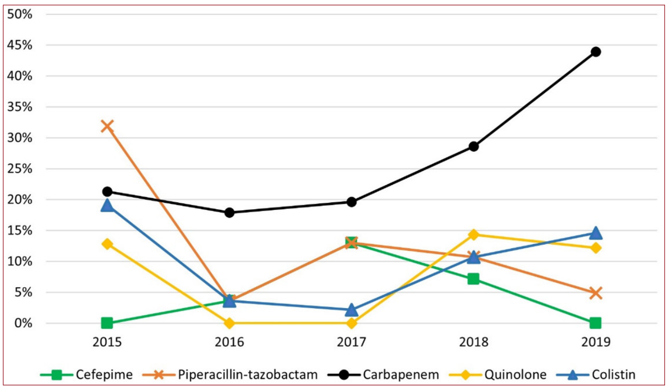

Figure 3. The rate of use of broad-spectrum antibiotics before an infection episode by years

Discussion

HAI is common in developed and developing countries. The World Health Organization (WHO) reported that 8.7% of hospitalized patients developed HAI in a study conducted in 55 hospitals located in 4 regions (Europe, Eastern Mediterranean, Southeast Asia, and Western Pacific).[1] The PICU environment has a high rate of HAI (up to 23%) due to frequent invasive procedures and use of medical devices (central lines, endotracheal tubes) and patient factors (immature immune system, immune deficiencies).[8] In our study, 8.8% of inpatients had at least one HAI attack, and the rate of those who had a bacterial HAI was 6.2% among all patients hospitalized in the PICU.

Patients with various underlying diseases are hospitalized in intensive care units. These underlying diseases may also pose a risk for the development of infection. In our study, neurological and cardiovascular disorders were the most common underlying diseases. It should be kept in mind that the patients in this group will have a high risk of bacterial HAI.

The two most frequent forms of HAI are catheter-associated bloodstream infections (CA-BSI) and pneumonia.[5,9,10] Other HAI encountered in the PICU include surgical-site infections and catheter-associated urinary tract infections. In a study conducted in the USA, the incidence of HAI types was found to be 28% for bloodstream infections, 21% for ventilator-associated pneumonia, and 15% for urinary tract infections.[2] The incidence of HAI types in a national point prevalence study conducted by Kepenekli et al.[4] including 50 pediatric intensive care units; ventilator-associated pneumonia was reported in 55%, bloodstream infection in 27%, and urinary tract infection in 7%.Compatible with other studies, bacterial agents were most commonly isolated from blood, tracheal aspirate, and urine in our study.

Our study observed Gram-negative bacteria more frequently during the five years. In a 5-year prospective and multicenter study from Spain, in the evaluation of the causative microorganism of 99 patients diagnosed with HAI and culture growth; 63 (63.6%) were Gram-negative, 19 (19.2%) Gram-positive, and 17 (17.2%) resulted in fungal positivity.[3] The most common microorganisms isolated in a study from Italy were respectively; Gram-negative (54%), Gram-positive (32%), fungal (7%), and viruses (7%).[11] In our study, the most common Gram-negative agents were; *P. aeruginosa*, *A. baumannii*, and *Klebsiella spp*. In a study from a PICU in Brazil, Gram-negative bacteria were most frequently observed, and *A. baumannii* and *Klebsiella pneumoniae* were reported most frequently among them.[12] We did not evaluate fungal agents in our study, but the frequency of Gram-negative bacteria was similar to the studies in the literature.[13,14] In addition, increasing the rates of Gram-negative bacteria, mainly *P. aeruginosa*, *A. baumannii*, and *Klebsiella spp.*, draws attention. It was seen that the rate of Gram-positive microorganisms in bloodstream infections decreased over the years. We think the sending of control cultures caused this by excluding false positivity after the first growth of coagulase-negative staphylococci.

In our study, it was observed that 40.4% of the patients diagnosed with bacterial HAI died due to infection. The mortality rate was similar in Gram-negative and Gram-positive infections. In a 5-year retrospective study conducted in the pediatric intensive care unit of Adana Numune Training and Research Hospital, the mortality rate was 9%.[6] In a 3-year retrospective study in Israel, mortality was 6% for patients admitted to the pediatric intensive care unit, while mortality was 52% for those who developed bloodstream infections.[15] Various studies from Turkey have mortality data ranging from 2.4% to 27.6%.[16,17] Our mortality rate was found to be higher compared to other studies from Turkey. This may be because patients needing intermediate intensive care are being followed up in the wards, and patients who come with more severe clinics are taken to the pediatric intensive care unit. In addition, patients with chronic neurological disorders, cardiovascular diseases, and postoperative cardiovascular surgery are followed up mostly in our PICU. A large proportion of the patients we follow have a history of prolonged hospitalization due to their underlying chronic diseases. All these factors increase the risk of developing HAI and the associated mortality.

Resistance rates of bacterial pathogens detected in intensive care units are gradually increasing. This leads to treatment failure and increases in mortality. It is considered one of the biggest global health threats, expected to result in 10 million attributable deaths by 2050.[5] Tackling antibiotic resistance has become a priority for the WHO. While studies conducted in the past 15-20 years have targeted Gram-positive agents, recent developments show that Gram-negative bacteria have come to the fore.[18] Increased antibiotic resistance among Gram-negative microorganisms, especially in intensive care units, has limited treatment options.[13]

In our study, most Gram-negative bacteria were resistant to commonly used broad-spectrum antibiotics such as cefepime, piperacillin-tazobactam, carbapenem, and colistin. We also found that carbapenem resistance was widespread among Gram-negative bacteria. The WHO report on pathogen prioritization in 2017 declared extended-spectrum beta-lactamase *Enterobacteriaceae* (especially *Klebsiella spp.*), carbapenem-resistant *A. baumannii*, and *P. aeruginosa* as priority pathogens according to the spectrum of resistance to antimicrobial agents.[19] These top three multidrug resistance bacteria (*Klebsiella*, *Acinetobacter*, and *Pseudomonas*) acquired from PICUs worldwide were the same in recent studies.

Different prevalence rates are reported for carbapenem resistance in Gram-negative bacteria. Carbapenem resistance rates reported in *K. pneumoniae* strains are 60% in India, 36% in Italy, and over 15% in some South American countries such as Argentina and Brazil.[20] In a study from Turkey between 2013 - 2016, the rate of carbapenem resistance was found as 100% in *Acinetobacter* spp., 62.5% in *Pseudomonas* spp., 50% in *E. coli*, 36.7% in *Klebsiella spp.*, 33.3% in *Enterobacter spp.*, and 25% in *Serratia spp.*[21] In the CAESAR 2018 report, ertapenem resistance was reported as 43%, and imipenem/meropenem resistance was reported as 38% in *K. pneumoniae* isolates obtained from blood and cerebrospinal fluid samples from Turkey.[22] In our study, it was observed that carbapenem resistance increased from 10% to 100% in the *Klebsiella spp.* group in a short period of 3 years. For *P. aeruginosa*, this ratio increased from 59% to 100% within three years.

Among Gram-positive organisms, antimicrobial resistance has remained consistent. Methicillin resistance has not changed significantly. Vancomycin sensitivity was analyzed in *Enterococcus*, none of which had shown resistance. Although positive cases were detected by surveillance of vancomycin-resistant enterococci (VRE), it was important that vancomycin resistance was not observed in strains causing invasive infection. It would be appropriate to evaluate the use of linezolid in the empirical treatment of infections within this framework.

Since infections occur in a large proportion of PICU patients, the use of broad-spectrum antibiotics is very common in this population. The largest point prevalence study so far, including 38 PICUs (both general and cardiac) in 23 countries, revealed antibiotic usage in 56% of PICU patients, of which the vast majority were treated with parenteral antibiotics and 50% with combination therapy.[23] There is a serious relationship between antibiotic use and drug-resistant microorganisms. In case-control studies, it has been observed that piperacillin-resistant *P. aeruginosa* develops resistance to fluoroquinolones after prolonged antibiotic use, as well as resistance to the antibiotic used or other antibiotics of the same class.[24] Colonization with carbapenem-resistant Gram-negative in the gut microbiome has been documented to occur after only very brief exposure to these antibiotics.[25] In our study, long-term and broad-spectrum antibiotic use rates were high at the onset of an HAI episode. When we look at the five-year period, an increase in the use of carbapenem, colistin, and quinolones has also attracted attention. On the other hand, while the incidence of Gram-negative agents is increasing, the options to treat these agents are rapidly decreasing. The reduction of resistant pathogens is associated with the rational use of antibiotics. In critically ill children, inappropriate antibiotic prescribing ranges up to 60% (mainly overly broad spectrum and wrong dosage), and as such, the PICU represents a major target environment for antibiotic stewardship programs (ASPs).[26]

There are some limitations of our study. In our study, other important risk factors for HAI, such as the presence of a catheter, ventilator support, and length of stay, were not examined. Possible associations between these risk factors and HAI episodes were not the subject of this study. Fungal infections were also excluded. Since the local microbiological data were obtained from the records of the infection control committee, an evaluation of the minimum inhibitory concentration (MIC) values could not be made. Another limitation was that it was a single-center study. It should not be forgotten that there may be different trends in other centers, and each center should approach by examining and criticizing their own epidemiological characteristics.

Conclusion

In our pediatric intensive care unit, like in the world, the most common bacterial HAI agents were Gram-negative bacteria. It was shown that antibiotic resistance increased rapidly in Gram-negative agents, especially in *Klebsiella spp*. It is thought that the use of broad-spectrum antibacterials, both in our unit and in the world, has increased over the years, and this may also contribute to the development of resistance. Effective treatment of frequent ICU isolates is paramount to preventing multidrug resistance. For this, it is necessary to prevent unnecessary antibiotic use and develop and implement antibiotic stewardship strategies

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