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ORIGINAL RESEARCH
Pediatric Intensive Care

Acinetobacter infections in pediatric intensive care unit: A single-center experience

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ABSTRACT

Objective: The aim of this study is to investigate the risk factors, types of infections, antibiotic resistance patterns, and mortality rates in hospitalized patients with *Acinetobacter* infections in the pediatric intensive care unit.

Material and Methods: The patients who were hospitalized in the pediatric intensive care unit between January 2013 and September 2018 and had *Acinetobacter* infections were evaluated retrospectively.

Results: Eighty-two patients who developed *Acinetobacter* infections were admitted to the study. Fifty-three (64.6%) of the patients were male. The mean age was 68.9±74.6 months. The majority of patients had underlying diseases. Most patients had a history of invasive procedures: mechanical ventilation (95.1%), central venous catheter (86.6%), and urinary catheter (62.2%). Ventilator-associated pneumonia was the most common diagnosis (57.3%). The majority of *Acinetobacter* species were resistant to carbapenems (93.9%). Colistin and meropenem were the most common antibiotics used in the treatment of patients, and 15.8% of the isolates were resistant to colistin. The mortality rate on the 30th day of *Acinetobacter* infection was 35.3%. The most frequent infections in patients who died were ventilator-associated pneumonia and catheter-related bloodstream infection.

Conclusion: *A. baumannii* infections cause high mortality with resistance to antibiotics. When the factors that increase mortality are evaluated and the changeable ones are improved, some of the deaths due to these infections may be decreased. The leading precautions should be avoiding invasive procedures, especially in intensive care units, and the unnecessary use of broad-spectrum antibiotics.

Keywords: *Acinetobacter*; carbapenem resistance; colistin; healthcare-associated infection; pediatric intensive care unit.

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Çocuk yoğun bakım ünitesinde *acinetobacter* enfeksiyonları: Tek merkez deneyimi

ÖZET

Amaç: Bu çalışmanın amacı, çocuk yoğun bakım ünitesinde *Acinetobacter* enfeksiyonu ile yatan hastalarda risk faktörlerini, enfeksiyon tiplerini, antibiyotik direnç paternlerini ve mortalite oranlarını araştırmaktır.

Gereç ve Yöntemler: Ocak 2013-Eylül 2018 tarihleri arasında çocuk yoğun bakım ünitesinde yatan ve *Acinetobacter* enfeksiyonu geçiren hastalar retrospektif olarak değerlendirildi.

Bulgular: *Acinetobacter* enfeksiyonu gelişen seksen iki hasta çalışmaya kabul edildi. Hastaların 53'ü (%64,6) erkekti. Ortalama yaş 68,9±74,6 aydı. Hastaların çoğunda altta yatan hastalık vardı. Hastaların çoğunda invaziv prosedür öyküsü vardı: mekanik ventilasyon (%95,1), santral venöz kateter (%86,6) ve idrar sondası (%62,2). Ventilatör ilişkili pnömoni en yaygın tanıydı (%57,3). *Acinetobacter* türlerinin çoğu karbapenemlere dirençliydi (%93,9). Kolistin ve meropenem hastaların tedavisinde en sık kullanılan antibiyotiklerdi ve izolatların %15,8'i kolistine dirençliydi. *Acinetobacter* enfeksiyonunun 30. gününde ölüm oranı %35,3 idi. Ölen hastalarda en sık görülen enfeksiyonlar ventilatörle ilişkili pnömoni ve kateterle ilişkili kan dolaşımı enfeksiyonuydu.

Tartışma: *A. baumannii* enfeksiyonları antibiyotiklere dirençli olup yüksek mortaliteye neden olmaktadır. Mortaliteyi artıran faktörler değerlendirildiğinde ve değişken olanlar iyileştirildiğinde bu enfeksiyonlara bağlı ölümlerin bir kısmı azaltılabilir. Önlemlerin başında, özellikle yoğun bakım ünitelerinde invaziv işlemlerden ve geniş spektrumlu antibiyotiklerin gereksiz kullanımından kaçınmak gelmektedir.

Anahtar Kelimeler: *Acinetobacter*; karbapenem direnci; kolistin; pediatrik yoğun bakım ünitesi; sağlık bakımı ilişkili enfeksiyon.

INTRODUCTION

Healthcare-associated infections are the leading ones that cause high rates of morbidity and mortality. Gram-negative bacteria constitute a big part of these infections (1, 2). *Acinetobacter* strains, which are gram-negative non-fermentative coccobacillus, stand as a significant cause of healthcare-associated infections (3–8). They rarely cause community-onset infections, too (1).

The infections caused by *Acinetobacter* types are mostly pneumonia, urinary tract infections, bloodstream infections, and soft tissue infections. They usually cause infections in patients who have been staying in the hospital for a long time, have an underlying disease or are immunosuppressed, and those who underwent invasive procedures. They can survive in dry environments for weeks. Therefore, transmission occurs more easily in healthcare centers (1–3, 9, 10).

One of the significant problems in gram-negative bacteria is that the rate of resistance to antibiotics is high. The management of infections associated with *Acinetobacter* types is hard due to this factor. *Acinetobacter baumannii* is the most commonly seen, and it is resistant to most antibiotics. During the treatment, with various mechanisms, resistance to the antibiotics which *A. baumannii* is sensitive to in the beginning may also appear. Therefore, treatment options are limited, and most of the time, the treatment requires the use of multiple antibiotics. The general resistance of *Acinetobacter* to antibiotics stems in part from the very small number and size of porins in its outer membrane. The reduced outer membrane porin content confers upon *Acinetobacter* a low permeability to antibiotics (1, 2, 6, 7, 11).

The aim of this study is to evaluate the risk factors, types of infections, results of treatments, antibiotics resistance patterns, and mortality rates in critical patients with infections associated with *Acinetobacter* types hospitalized in the pediatric intensive care unit (PICU) of a tertiary pediatric hospital.

MATERIAL AND METHODS

The data of patients between the ages of 0–21 who were hospitalized in PICU between January 1st, 2013 to September 30th, 2018, and diagnosed with *Acinetobacter* infections were retrospectively evaluated. The data of the patients were obtained retrospectively from the patient files.

The following factors were taken into consideration: The patients' gender, age, existence of an underlying disease, the type and location of the infection, whether the patient had effective antibiotics beforehand, whether a change in antibiotics was required or not after reproduction in bacterial cultures, if a change was required, which antibiotics were chosen, C-reactive protein (CRP) and white blood cell count (WBC) examined at the onset of infection, existence of central catheter and urinary catheter, treatment with mechanical ventilation, use of antacids, existence of comorbid infections, and history of former colonization. The cultures taken from the patients during hospitalization were scanned (blood, cerebrospinal fluid, urine, peritoneal fluid, pleural fluid, catheter blood, catheter tip, tracheal aspirate fluid, conjunctiva). Phoenix automated microbiology system (BD Diagnostic Systems, Sparks, MD) was used for bacteria identification. Antimicrobial susceptibility testing of *Acinetobacter* baumannii isolates was also performed by using the Kirby Bauer disc diffusion method, and Phoenix automated microbiology system (BD Diagnostic Systems, Sparks, MD). Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria. The 30-day mortality rate in the patients and the susceptibility of the causing factor to antibiotics

Table 1. Demographic data of the dead and surviving patients with *Acinetobacter* infection, comparison in terms of underlying diseases and performance of invasive procedures

30-day mortality	Non-survived		Survived		Mortality (%)	p
	n	%	n	%		
Gender					>0.05	
Male	19	65.5	33	62.3	23.2	
Female	10	34.5	20	37.7	12.2	
Average age (month)	84.6±76.7		60.4±72			>0.05
Underlying disease						0.042
Present						
Neurometabolic disease[a]	7	24.1	16	30.2	30.4	
Cardiac disease	3	10.3	7	13.2	30	
Chronic pulmonary disease	1	3.4	7	13.2	12.5	
Solid tumor	6	20.7	3	5.6	66.6	
Immunodeficiency	5	17.2	1	1.9	83.3	
Hematologic malignancy	2	6.9	3	5.6	40	
Chronic kidney disease	2	6.9	0	0	100	
Chronic liver disease	1	3.4	0	0	100	
Malnutrition	0	0	1	1.9	0	
Prematurity	0	0	2	3.8	0	
Not Present						
Community-acquired pneumonia	1	3.4	4	7.5	20	
Sepsis	0	0	5	9.4	0	
Trauma	1	3.4	4	7.5	20	
Invasive procedure history						
Central catheter	28	96.6	43	81.1	39.4	0.05
Urinary catheter	25	86.2	26	49	49	0.001
Mechanical ventilation	28	96.6	50	94.3	35.9	>0.05
CRP (mg/L)	158±141		74.5±72.3			0.001
WBC (/mm³)	12.819±8.494		14.760±8.118			>0.05
Presence of anti-acid use	20		24			>0.05
Presence of a secondary infection	13		17			>0.05

[a]: CNS disease and HIE included. CNS: Central nervous system; HIE: Hypoxic-ischemic encephalopathy; CRP: C-reactive protein; WBC: White blood cell.

were evaluated. The Ethical Committee and Review Board served as the central ethics committee on May 27, 2019. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Data analysis was carried out with SPSS Statistics V22.0 program. Descriptive statistics were shown as mean±standard deviation for variables with normal distribution, median (min-max) for the variables without normal distribution, and case number and (%) for nominal variables. Chi-square test and Mann-Whitney U test were used for categorical variables. A p value<0.05 was considered as statistically significant.

RESULTS

Eighty-two patients were included in this study. The 63.4% of the patients were male. The average age was 68.9±74.6 months (1 day-256 months old). 19 (23.2%) of the cases were younger than 3 months, 26 (31.7%) of them were between 3–36 months old, and 37 (45.1%) were patients older than 36 months. The most frequently seen underlying diseases were neurometabolic disease, congenital/acquired heart diseases, solid tumors, and chronic pulmonary diseases. The rates of the underlying diseases were similar in all age groups (Table 1). While *A. baumannii* was detected in 80 patients, *A. pittii* was isolated from 2 patients. In 56% of the patients, the causative agent was isolated from

Table 2. Comparison of 30-day mortality rates in terms of infection types

Type of infection	Non-survived		Survived	
	n	%	n	%
Ventilator-associated pneumonia (VAP)	16	55.2	31	58.5
Skin and soft tissue infection	0	0	5	9.4
Catheter-related bloodstream infection (CRBSI)	2	6.9	4	7.5
Catheter-associated urinary tract infection (CAUTI)	0	0	1	1.9
Catheter exit site infection	2	6.9	1	1.9
Bloodstream infection (BSI)	1	3.4	3	5.6
Complicated pneumonia	1	3.4	2	3.8
Peritonitis	1	3.4	0	0
Meningitis	0	0	1	1.9
Conjunctivitis	0	0	1	1.9
Combination of more than one infection	6	20.7	4	7.5
VAP, skin and soft tissue infection	0		1	
VAP, CAUTI	2		1	
VAP, CRBSI	1		1	
VAP, catheter, skin and soft tissue infection	0		1	
CAUTI, BSI	1		0	
Complicated pneumonia, CRBSI	1		1	
VAP, peritonitis	1		0	

the aspirate culture. The most commonly seen infection type caused by *Acinetobacter* was ventilator-associated pneumonia (57.3%). The other *Acinetobacter*-associated infections were catheter-related bloodstream infections (CRBSI) (7.3%), skin and soft tissue infections (6.1%), bacteremia (4.9%), catheter exit-site infections (3.7%), and complicated pneumonia (3.7%). In 95.1% of the patients, mechanical ventilation was performed, and in 86.6% of them had placed a central venous catheter (Table 2).

When the antibiotic resistance of the isolates was analyzed, 95% of the causative strains were extremely-drug resistant, while 15% were pan-drug resistant. Nearly all patients were treated with multiple antibiotics. The isolates' carbapenem resistance was high (93.9%) (Table 3).

The 30-day mortality rate associated with *Acinetobacter* infection was 35.4%. The patients' average age was 84.6±76.7 months for those who died and 60.4±72 months for the ones who survived. There was no significant difference between mortality, gender, and age distribution ($p>0.05$). Also, no significant difference was found in the mortality rate through the years ($p>0.05$). Mortality was found significantly high ($p=0.04$) in patients with an underlying disease when compared to the patients who were healthy beforehand. Mortality due to *Acinetobacter* infection in patients with an immunosuppressive condition was 83.3%. While this rate was 66.7% in patients with solid tumors, it was 42.9% in those with neurometabolic diseases. All 3 patients who had chronic kidney and chronic liver disease were lost.

Table 3. Comparison of antibiotic resistance of *Acinetobacter* strains in survived and non-survived patients

Antibiotic	Non-survived		Survived	
	n	%	n	%
Ceftazidime	29	100	51	96.2
Tetracycline	29	100	51	96.2
Amikacin	27	93.1	50	94.3
Ampicillin-sulbactam	29	100	49	92.5
Levofloxacin	29	100	49	92.5
Meropenem	29	100	48	90.6
Piperacillin-tazobactam	29	100	49	92.5
Cefoperazone-sulbactam	29	100	49	92.5
Cefepime	29	100	49	92.5
Tigecycline	27	93.1	48	90.6
Ticarcillin-clavulanate	29	100	49	92.5
Trimethoprim-sulfamethoxazole	29	100	49	92.5
Gentamicin	29	100	44	83
Colistin	5	17.2	8	15

Mortality rate in isolated ventilator-associated pneumonia was 34%, mortality rate in isolated CRBSI was 33.3%, and there were no cases of death in isolated CAUTI.

Table 4. Comparison of 30-day mortality in patients that taking appropriate antibiotics when *Acinetobacter* infection develops and those who had a change of antibiotic therapy after starting *Acinetobacter* infection

	Non-survived		Survived		p
	n	%	n	%	
Taking appropriate antibiotics when *Acinetobacter* infection develops					>0.05
No	9	31	28	52.8	
Yes	20	69	25	47.2	
Meropenem	4	13.8	4	7.5	
Colistin	8	27.6	6	11.3	
Colistin + Meropenem	6	20.7	8	15.1	
Other	2	6.9	7	13.2	
Changing antibiotic treatment when *Acinetobacter* infection starts					>0.05
No	14	48.3	12	22.6	
Yes	15	51.7	41	77.4	

When the laboratory findings of the patients who survived were compared to those of the ones that died, the CRP level was higher in the latter group (p=0.001). There was no significant difference between the two groups in terms of average WBC (p>0.05).

Whereas mechanical ventilation treatment, use of antacid, age, and the existence of a bacterial co-pathogen were not influential on mortality, mortality was significantly higher in patients with central venous catheters and urinary catheters (p<0.05 and p<0.001, respectively).

In patients who developed *Acinetobacter* infection while taking meropenem or colistin, mortality was higher than those who were not taking any antibiotics or who were taking any other antibiotics other than meropenem and colistin (Table 4). Use of antibiotics beforehand was higher in the ones who died, but there was not a statistically significant difference (p>0.05). The duration of antibiotic use before the onset of *Acinetobacter* infection was determined as a week longer in the patients who died than those who survived.

Resistance to meropenem was 93.9%. All the patients who died were infected with carbapenem, amikacin, ampicillin-sulbactam, cefoperazone-sulbactam, cefepime, ticarcillin-clavulanate, tetracycline, *trimethoprim*-sulfamethoxazole (TMP-SMX), and piperacillin resistant strain. Use of multiple antibiotics was required in the treatment of patients due to the problem of resistance. The causative strain was susceptible to tigecycline in only 6.8% of patients who died. Colistin was the most effective antibiotic and the rate of resistance to this drug was 15.8% (Table 3).

DISCUSSION

Acinetobacter types are thought to infect 1 million people every year. Even though it is a pathogen whose virulence is accepted as low, it is reported as a nosocomial pathogen that emerges in respiratory tract, blood, central nervous system, and wound site infections (12–15). In developed countries, while gram-positive factors are in the foreground in nosocomial infections, in developing or underdeveloped countries, the main problems of hospitals are infections that are caused by gram-negatives (16). *Acinetobacter* types have become an important factor whose frequency has gradually increased among those gram-negative factors that are significant pathogens for hospitals; and it progresses with high morbidity and mortality. The fact that it can survive on dry surfaces paves the way to outbreaks. Since it is resistant to antibiotics, various difficulties may arise in treatment (17).

Although there are more than 50 species within the diverse *Acinetobacter* genus, the majority are nonpathogenic environmental organisms (3). The most common species to cause infections are *A. baumannii*, followed by *A. calcoaceticus* and *A. iwoffii* (4). Additional species, including *A. haemolyticus*, *A. johnsonii, A. junii, A. nosocomialis, A. pittii*, *A. schindleri*, and *A. ursingii*, have occasionally been reported as pathogens (11).

Acinetobacter spp. strains cause diseases such as severe pneumonia, bacteremia, catheter infections, urinary tract infections, and skin and soft tissue infections, especially in patients treated in intensive care units, those who have a history of prolonged hospitalization, and immunodeficient patients (18). Several risk factors have been identified in studies related to *Acinetobacter* types. In numerous studies, a history of hospitalization in an intensive care unit, recent operation, central venous catheterization, tracheostomy, mechanical ventilation, enteral feeding, high predicted mortality score, underlying malignancy, recent history of infection, multiple organ failure, and use of antibiotics during a prolonged duration of hospitalization (especially third-generation cephalosporins and carbapenems) were evaluated as risk factors (19–23). In our study, the existence of an underlying chronic disease, existence of central catheter and urinary catheter, and use of broad-spectrum antibiotics, carbapenem, or colistin were found as risk factors for mortality due to carbapenem-resistant *A. baumannii* (CRAB). In a study in Delhi, the factors that increased CRAB risk in neonates were

found to be the duration of ventilation, use of antimicrobial drugs, and prolonged duration of hospitalization, and it was observed that breastfeeding was significantly protective against CRAB. In that study, 60% of *Acinetobacter* strains were identified as resistant to carbapenem, and neonates were observed to be less drug resistant (3). Carbapenem resistance was determined as 93.9% in our study, and the reason why it is so high can be the fact that we were following patients who were complicated and hospitalized for a long time.

Like our study, in a study carried out in Türkiye, the existence of central venous catheter, prolonged hospitalization, prolonged antibiotics use, and the existence of comorbid neurometabolic disease and bacteremia were identified as risk factors. Male gender, use of carbapenems and glycopeptide antibiotics, mechanical ventilation, and existence of gentamicin resistance in isolates were determined as risk factors for the mortality of *Acinetobacter* bacteremia (24). In a study carried out with children in Türkiye, the presence of central venous catheter, prolonged hospitalization, prolonged antibiotics use, comorbid neurometabolic disease, and the presence of bacteremia were determined as risk factors. Male gender, use of carbapenems and glycopeptide antibiotics, mechanical ventilation, and existence of gentamicin resistance in isolates were determined as risk factors for the mortality of *Acinetobacter* bacteremia (25).

In a study conducted by Grupper et al. (26), central venous catheter and the use of mechanical ventilator and antibiotics beforehand were observed to be related to *A. baumannii* bacteremia. In another study carried out by Jang et al. (27), none of the invasive procedures, including recent operation history, were found as a risk factor; yet cardiovascular system surgery and the existence of *A. baumannii* colonization in advance were identified as risk factors.

The duration of hospitalization was stated as a risk factor and found to be associated with the increased mortality of the disease in a study performed in Taiwan. As in our study and several other studies, the most frequent infection caused by *A. baumannii* was identified as pneumonia (27–30). In numerous other studies, the presence of a central catheter, history of antibiotics use, and history of mechanical ventilation were observed to increase the risk. In our study, we considered the reason why we did not identify a relevance between mechanical ventilation and mortality was the fact that we could not make a comparison as most of our patients were under mechanical ventilation (27).

In a study carried out with pilgrims in Saudi Arabia, it was observed that the antibiotic resistance rate was not that high. Moreover, immunosuppression, invasive procedure (central venous catheter, mechanical ventilation), hospitalization history, history of surgery, and presence of bacteremia were identified as risk factors for resistance. In addition, it was observed that the presence of a drain, nasogastric catheter, arterial catheter, and tracheostomy did not increase the risk (1).

Carbapenem-resistant *A. baumannii* infections were researched in a study, and prematurity, use of mechanical ventilation, and exposure to carbapenem antibiotics were found as risk factors for bacteremia; furthermore, carbapenem resistance, chemotherapy-associated neutropenia, presence of impaired organ function, and history of hospitalization in ICU were determined as risk factors for mortality. In cases in which mortality occurred, the most frequent underlying chronic diseases were prematurity/low birth weight, congenital heart disease, malignancy, and chronic liver disease, respectively. On the contrary, catheter-associated bacteremia and treatment with an antibiotic that contained sulbactam were related to a decrease in mortality among these children (2).

During treatment, with various mechanisms, *Acinetobacter* strains may develop resistance to antibiotics that they were susceptible to at the beginning. In the USA and Europe, 50% of isolates are resistant to multiple antibiotics, including carbapenems. Some of the CRAB strains are extremely resistant and only susceptible to polymyxin and tigecycline. Some of them are pan-resistant; therefore, treatment is hard (17). In multi-drug-resistant carbapenemase-positive gram-negative bacteria, combination therapy with at least 2 agents appears to reduce mortality compared to monotherapy (31). In the USA, aminoglycosides, carbapenems, fluoroquinolones, and ceftazidime have been reported concomitantly in MDR gram-negative infections in children (32). The combination of carbapenem and colistin is a combination that can be tried in resistant strains (31, 33). In our center, we frequently use the combination of meropenem infusion, colistin, and ampicillin-sulbactam in the treatment of multi-drug-resistant carbapenemase-positive *acinetobacter*ial infections.

In a study carried out by Punpanich et al. (2), when antibiotic resistance was analyzed, all were found to be colistin resistant, and the rates of susceptibility to other antibiotics were identified as 63.9% for sulbactam, 49.4% for carbapenem, 42.2% for amikacin, and 40.6% for ceftazidime. Carbapenem resistance was 93.9% in our own study. Treatment with multiple antibiotics was required owing to the resistance problem. When compared to other studies, we had a higher rate of resistance. All the lost patients were infected with strains resistant to carbapenem, amikacin, ampicillin-sulbactam, cefoperazone-sulbactam, cefepime, ticarcillin-clavulanate, tetracycline, TMP-SMX, and piperacillin. Tigecycline resistance was present in 75 patients, while only 6.8% of the lost patients had resistance to this agent. The most effective antibiotic was colistin, and the resistance to this drug was 15.8%.

In various studies, the mortality rate associated with *Acinetobacter* infections in patients hospitalized in intensive care units was identified as between 2–46%, and this rate is similar in our study (13, 23, 34). Prevention is very important in an infection where mortality and drug resistance are so high. Firstly, tight application of hand hygiene, paying attention to contact isolation, avoiding long-term use of antibiotics, and unnecessary invasive intervention are among the basic measures that can be taken (34). Central line bundle (CLB) programs are useful for reducing CLABSIs (35, 36). A typical bundle program includes: training of personnel, strict compliance with asepsis rules when inserting the catheter, daily examination of the entrance site after insertion of the catheter, replacement of the dressing if it is wet or dirty or has

not been changed for 7 days, and withdrawal if the catheter is not needed; if the catheter is to be used, it first includes applications such as rubbing with alcohol for 15 seconds (35).

In conclusion, *A. baumannii* infections cause high mortality with resistance to antibiotics. When the factors that increase mortality are evaluated and the changeable ones are improved, some of the deaths due to these infections may be decreased. The leading precautions should be avoiding invasive procedures, especially in intensive care units, and the unnecessary use of broad-spectrum antibiotics.

Ethics Committee Approval: The Ankara University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 27.05.2019, number: 10-791-19).

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