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ORIGINAL ARTICLE – OPEN ACCESS

The Effect of Aminoglycosides on Colistin-Containing Regimens in the Treatment of Carbapenem-Resistant Gram-Negative Infections in Pediatric Intensive Care Units: A Two-Center Experience

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ABSTRACT

Objective: This study aimed to assess the outcomes including morbidity and mortality of carbapenem-resistant gram-negative (CRGN) infections in pediatric critical care setting. The second aim was to investigate the impact of aminoglycosides on colistin-containing regimen in CRGN-infected pediatric critical care patients.

Materials and Methods: We retrospectively evaluated medical records of 82 patients who had received colistin in combination with an aminoglycoside (CA group) or another antibiotic (CO group) at two reference pediatric intensive care units (PICUs) between February 2011 and February 2016.

Results: We enrolled 82 CRGN-infected patients who were admitted to PICUs of two hospitals. The median age of the patients was 24 (25th–75th percentile; 8–78.75) months, and the median duration of hospital stay was 30 days (25th–75th percentile; 16.7–57.7). No statistical difference was observed in the variables, including microbiological response, attributable mortality, crude mortality, and the duration of achieving first negative culture (p>0.05). Clinical response was significantly more observed in the CA group (85.5% vs. 63.2; p=0.048), and attributable mortality was higher in the CO group (12.7% vs. 31.6%; p=0.055). Nephrotoxicity did not show statistical difference between groups (p=0.357), and neurotoxicity was not observed.

Conclusion: Colistin-containing regimen in combination with an aminoglycoside may be an effective and safe antimicrobial agent without a significant increase in side effects.

Keywords: Pediatric critical care unit, colistin, aminoglycoside, carbapenem-resistant enterobacteriaceae

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INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are becoming more prevalent. They cause numerous outbreaks of severe healthcare-associated infections (1–7). These infections are challenging because of high levels of antimicrobial resistance and limited treatment options. Severe morbidity and mortality are common outcomes (2). Because of difficulties in the treatment and prolonged hospitalization, they also constitute an increased clinical and economic burden (8–11). Carbapenem-resistant Gram-negative bacilli (CRGN) infections, including CREs, *P. aeruginosa*, and *A. baumannii*, are being widely reported in pediatric and neonatal critical care units (12–17). Immediately initiating the appropriate antibiotics can be lifesaving in these infections. Therefore, it is important to predict the antimicrobial susceptibility profile and determinate the local epidemiological data. Recently, the US Food and Drug Administration approved antibiotics for the treatment of CRGN infections, including ceftazidime-avibactam, meropenem-vaborbactam, and ceftolozane-tazobactam. Unfortunately, these are not yet available in Turkey. Therefore, colistin remains a favorable agent in the fight against these infections. Colistin in combination with a non-β lactam agent, particularly an aminoglycoside, tygecycline, or trimethoprim/sulfamethoxazole, have been recommended in the treatment of these infections (6).

This study aimed to assess the outcomes, including morbidities and mortality, of carbapenem-resistant gram-negative infections in the pediatric intensive care settings. We also aimed to investigate the impact of aminoglycosides on colistin-containing regimen in CRGN-infected pediatric critical care patients.

MATERIALS and METHODS

We retrospectively reviewed the records of 82 patients who were admitted to the pediatric intensive care units (PICUs) of two western Turkey reference hospitals because of a CRGN infection between January 2011 and January 2016. Among them, 47 (57.3%) were males and 35 (42.7%) were females. Data on children with CRGN infection were retrieved from hospital records. The choice of colistin-containing treatment depended on the clinician's decision and antimicrobial resistance patterns of the CRGN microorganism. In these hospitals, clinicians preferred to administer colistin-containing combination therapies, particularly with a non-β-lactam antibiotic class (quinolones,

aminoglycosides, trimethoprim/sulfamethoxazole), or a β-lactam antibiotic. This was by virtue of the recommendation of combination therapies to reduce the mortality of CRGN infections (4, 10).

Patients received colistin via intravenous route at a daily dose 3–5 mg/kg every 8 or 12 h. The majority of the patients received colistin in combination with an aminoglycoside such as amikacin (15 mg/kg) or gentamicin (7.5 mg/kg) in accordance with antimicrobial susceptibility and clinicians' preference. The patients who received colistin and an aminoglycoside were defined as the colistin-aminoglycoside (CA) group. Patients who received colistin alone, or in combination with meropenem, ciprofloxacin, or trimethoprim/sulfamethoxazole were classified as colistin-other (CO) group. We retrospectively reviewed all available clinical and demographic characteristics, and laboratory results. The primary infections including ventilator-associated pneumonia, bloodstream infection, urinary tract infection, and central nervous system infection, results of antibiotic treatment, as well as outcomes were also recorded.

Microbiological Methods

Gram-negative pathogens were identified by VITEK MS (bioMérieux, France) using Matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) technology, which is a new technology used for the identification of species according to protein composition of microorganisms.

VITEK 2 isolates automated system (bioMérieux) was used to determine antimicrobial susceptibilities of the microorganisms. For the strains resistant to carbapenems in the automated system, the gradient testing method determined the minimum inhibitor concentration (MIC) values to confirm the carbapenem resistance. The susceptibilities of β-lactam antibiotics such as piperacillin-tazobactam, and non-β-lactam antibiotics were determined by an automated system, disk diffusion, or the gradient test method. The susceptibility testing of colistin was performed by using broth microdilution method, in accordance with The European Committee on Antimicrobial Susceptibility Testing guidelines (EUCAST). For susceptibility tests, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *E. coli* NCTC 13846 were used as quality control strains (18).

Definition

Based on the presence of symptoms and indicators, the attending physicians decided to obtain culture specimens of biological samples. Samples of bronchial secretions were collected using sterile catheter insertion. Then, quantitative cultures were performed. Standard definitions of nosocomial infections were used adhering to the Center for Disease Control and Prevention (CDC) definitions (19). Sepsis diagnosis was made according to the International Pediatric Sepsis Consensus (20). Patients were defined as CRGN if they were having an infection caused by *Enterobacteriaceae* strains or/and non-fermentative *Pseudomonas* spp, and *Acinetobacter* spp. that showed resistance to meropenem or imipenem (18).

Treatment failure was defined as the need of switch to another antibiotic because of a side effect, lack of clinical improvement and microbiological clearance or mortality attributed to CRGN infection. If the infection was completely cleared, clinical response was defined. Microbiological response was defined if the culture did not grow a microorganism. Nephrotoxicity was defined in patients with a blood creatinine level below 1.2 mg/dL and an increase of >50% of the baseline creatinine level compared with baseline or a decline in renal function (2, 6). The administration of additional nephrotoxic agents was reviewed; these included vancomycin, acyclovir, amphotericin, aminoglycosides, cyclosporine, ganciclovir, intravenous contrast, and other chemotherapeutic agents. Attributable mortality was defined as mortality due to treatment failure, and crude mortality was defined as mortality caused by anything other than CRGN infection within 30 days of CRGN bacterial infection.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 22.0; IBM-SPSS, Inc, Armonk, NY). Numerical data was expressed as medians (interquartile range). The Mann–Whitney U test was used for intervariable analysis. Categorical variables were evaluated using the χ^2 test. If the expected count was less than 5, the evaluation was done using the two-tailed Fisher exact test and then presented as percentages in terms of acquiring CRGN infections. Comparisons were referred to as statistically significant if the p values were <0.05.

Ethics

The Ethical Board of İzmir Katip Çelebi University granted permission covering all aspects of this study [ethical decision number: 58/March 24, 2016].

RESULTS

Eighty-two CRGN-infected patients admitted to PICUs of two hospitals were included in this study. The mean age of the patients was 56.2 (2–204) months, and duration of hospital stay was 40.7 (1–300) days. The median age of the CA group (24 months; interquartile range [IQR] 104) was similar to the CO group (28 months; IQR, 45) (Table 1). Age and gender did not show statistical difference when the CA and CO groups were compared (p=0.771 and p=0.614). The underlying disease etiology did not differ between the CA and CO groups (p=0.055); however, chronic neurological/neuromuscular disorder (17.5%) was the most common underlying disease in the CA group; while hematopoietic stem cell/solid organ transplantation (316%) was the most prevalent in the CO group. Sepsis and septic shock were the most frequent causes of PICU admission in both CA and CO groups, 41.3% and 63.2%, respectively. The most common isolated pathogens were A. baumannii and *P. aeruginosa* in both groups, followed by *Klebsiella pneumoniae* and *E. coli* (Table 2). The antimicrobial susceptibilities of the pathogens have been summarized in Table 3. The antimicrobial susceptibility results according to treatment groups did not show significant difference between groups other than amikacin (p=0.039) (Table 1). The p values were for gentamicin, tygecycline, ceftazidime, trimethoprim/sulfamethoxazole, cefepime, and cefaperazone-sulbactam 0.412, 0.209, 0.363, 0.847, 0.363, and 0.929, respectively. The duration of prior PICU stay, length of stay from infection to discharge, treatment duration, and length of PICU stay did not show significant difference between groups (p=0.741, p=0.091, p=0.763, p=0.110, respectively). No statistical difference was observed between groups in relation to underlying disease, and in the case of PICU admission, P values were 0.055 and 0.191, respectively. Medication history and medical devices that existed at the beginning of infection, including mechanical ventilation, central venous catheter, tracheostomy, Foley catheter,

Table 1. The comparisons of demographic and clinical characteristics of patients received colistin and an aminoglycoside with colistin and an antibiotic other than an aminoglycoside

	CA (n=63)		CO (n=19)		p
	n	%	n	%	
Demographic and clinical characteristics					
Age, months, median	24	104	28	45	0.771
Gender, male	29	46	10	52.6	0.614
Treatment duration (days), median	14	7.75	17	7.0	0.763
Prior PICU stay	10	21.2	9	16	0.741
Total length of stay from infection to discharge (days), median	20	33	7	30	0.091
Total PICU stay (days), median, IQR	31	42.2	24	28	0.110
Co-morbidities					0.055
Chronic neurological/neuromuscular disorders	11	17.5	1	5.3	
Chronic lung diseases	7	11.1	4	21.1	
Hematopoietic stem cell/ olid organ transplantation	3	4.8	6	31.6	
Congenital heart disease	8	12.7	1	5.3	
Chronic liver diseases	4	6.3	1	5.3	
Hematologic/solid malignancies	3	4.8	1	5.3	
Primary immunodeficiency	2	3.2	1	5.3	
Other	2	3.2	1	5.3	
Cause of PICU admission					0.191
Sepsis/septic shock	26	41.3	12	63.2	
Respiratory failure	24	38.1	6	31.6	
Trauma	10	15.9	0	0	
Status epilepticus	2	3.2	0	0	
Cardiac failure	1	1.6	1	5.3	
Medication history and medical devices existed at the beginning of infection					
Mechanical ventilation	63	100	19	100	1.000
Central venous catheter	58	92.1	19	100	0.585*
Tracheostomy	17	27	1	5.3	0.058*
Foley catheter	54	85.7	15	78.9	0.479
External ventricular drainage catheter	12	19	2	10.5	0.503*
Amikacin (R or I)	33	52.3	15	78.9	**0.039**
Gentamicin (R or I)	40	63	14	73.6	0.412
Tigecycline (R or I)	46	73	11	57.8	0.209
Ceftazidime (R or I), n (%)	62	98.4	18	94.7	0.363
Trimethoprim/sulfamethoxazole (R or I)	51	80.9	15	78.9	0.847
Cefepime (R or I)	62	98.4	18	94.7	0.363
Cefoperazone–sulbactam (R or I)	60	95.2	18	94.7	0.929

CA: Colistin and aminoglycoside treatment group; CO: Colistin and other antibiotic treatment group; I: Intermediate; IQR: Interquartile range; PICU: Pediatric Intensive Care Unit; R: Resistant; *: Two-tailed Fisher exact test

and external ventricular drainage catheter, did not show statistical difference (p>0.05). The most common co-administered antibiotic was meropenem (57.8%), followed by a quinolone (15.7%) and trimethoprim/sulfamethoxazole (5.2%) and colistin alone (15.7%).

None of the patients developed neurotoxicity. However, nephrotoxicity was observed in 7 (8.5%) of the 82 patients. Three patients had baseline increased levels of creatinine. One of these patients died because of sepsis and multiorgan failure, and another required hemodialysis to return creatinine levels to normal, and the colistin was then switched to tygecycline. Nephrotoxicity was observed in one patient between the first and the third day of treatment, in five

Table 2. Isolated microorganisms and isolation site of infections in the CA and CO groups

The site of infection	*P. aeruginosa* (CA/CO)	*A. baumanni* (CA/CO)	*K. pneumoniae* (CA/CO)	*E. coli* (CA/CO)	Dual infection (CA/CO)	Total
Blood/catheter tip (n)	2/1	8/5	3/2	1/0		23
Tracheal aspirate fluid (n)	16/2	27/8	2/1	–	3/0	59
Urine (n)	2/0	4/2	2/0	1/0	–	11
Cerebrospinal fluid (n)	1/0	1	1			3
Wound site (n)	–	2/0	–	–	–	2

A. baumannii: Acinetobacter baumannii; K. pneumoniae: Klebsiella pneumoniae; E. coli: Escherichia coli; P. aureginosa: Pseudomonas aureginosa; CA: Colistin and aminoglycoside treatment group; CO: Colistin and other antibiotic treatment group

Table 3. Antimicrobial susceptibility of isolated microorganisms in the CA and CO groups

	Susceptible		Intermediate		Resistant		Total	
	n	%	n	%	n	%	n	%
Amikacin	34	41.5	6	7.3	42	51.2	82	100
Gentamicin	28	34.1	7	8.5	47	57.3	82	100
Ceftazidime	2	2.4	3	3.7	77	93.9	82	100
Cefepime	2	2.4	2	2.4	78	95.1	82	100
Ciprofloxacin	9	11	1	1.2	72	87.8	82	100
Imipenem	1	1.2	5	6.1	76	92.7	82	100
Meropenem	3	3.7	5	6.1	74	90.2	82	100
Trimethoprim sulfamethoxazole	16	19.5	–	–	66	80.5	82	100
Tigecycline	25	31.6	17	20.3	40	36.5	82	100
Colistin	82	100	–	–	–	–	82	100

CA: Colistin and aminoglycoside treatment group; CO: Colistin and other antibiotic treatment group

Table 4. The comparison of outcomes and side effects according to antimicrobial therapy regimen received for CRGN infection

Side effects and outcomes	CA (n=63)		CO (n=19)		p
	n	%	n	%	
Neurotoxicity	0	0	0	0	N/A
Nephrotoxicity	4	6.3	3	15.8	0.357*
Nephrotoxicity (Day 3) (n=82)	0	0	1	5.3	0.232*
Nephrotoxicity (Day 7) (n=66)	3	5.9	2	13.3	0.318*
Nephrotoxicity (Day 14) (n=44)	1	3.6	0	0	1.000*
Microbiological response	48	76.2	12	63.2	0.261
Clinical response	53	85.5	12	63.2	0.032
Attributable mortality	8	12.7	6	31.6	0.055
Crude mortality	15	23.8	7	36.8	0.261
Time to first negative culture (n=59) [median(IQR)]	8	3.75	10	5	0.549

CA: Colistin and an aminoglycoside; CO: Colistin and other antimicrobials; CRGN: Carbapenem-resistant Gram-negative; *: Two-tailed Fisher exact test

patients between the third and the seventh day of treatment, and in one patient between the seventh and the fourteenth day of treatment, nephrotoxicity did not show statistical difference between groups (p=0.357) (Table 4). No statistical differences were observed in the outcome variables, including microbiological response, attributable mortality, crude mortality, and the time duration for achieving first negative culture (p=0.261, p=0.055, p=0.261, p=0.549) (Table 4). The multiple logistic regression analysis of outcome

Table 5. Multiple logistic regression models for outcome

CA group	OR (95% CI)	p
Clinical response	2.208 (0.185–26.394)	0.531
Attributable mortality	0.667 (0.48–9.189)	0.762

CA: Colistin and aminoglycoside treatment group; OR: Odd ratios; CI: Confidence interval

variables revealed no significant difference in attributable mortality (OR, 0.667; 0.48–9.189; p=0. 0.762) and/or clinical response (OR, 2.208; 0.185–26.394; p=0.531) (Table 5).

DISCUSSION

This study represents the largest series of pediatric CRGN infections at an ICU. There are few choices in the treatment of CRGN bacterial infections, and colistin is still the most common administered agent. Current recommendations are based on previous reports, and available data support a combination therapy for the reduction of mortality resulting from CRGN bacterial infections (21–23).

Daikos et al. (24) reported that a single antimicrobial agent containing treatment was an independent risk factor for mortality of CRGN infections. The lowest mortality occurred in patients who received therapy including meropenem. We actually observed a lower rate of mortality in the regimen of colistin and an aminoglycoside (12.7% vs 31.6%) when compared with other colistin-containing regimens. We think that we might not show the significant difference between groups because of the limited number of the patients. And also nearly all patients in our study received combination therapy, to compare combination therapy with monotherapy was not statistically significant.

Gutiérrez-Gutiérrez et al. (25) concluded that CRE infections occur most frequently in patients with severe underlying diseases. The severity of underlying conditions might hide the impact of antibiotic therapy (25). They also found lower mortality rates in patients who received combination therapy including colistin, tigecycline, and aminoglycosides when compared to patients receiving colistin monotherapy. In this study, nearly all patients had an underlying disease, and it was beyond the scope of this study to assess the influence of each underlying disease. Despite in-vitro susceptibility, a higher mortality rate of 66.7% was reported in patients with carbapenemase-producing *K. pneumoniae* infections who received monotherapy than the patients that received colistin-polymyxin B, or patients administered with tigecycline combined with a carbapenem [13.3%] (26). The association between combination therapy and improved survival is controversial, and the inclusion of a carbapenem in the combination has been only suggested if the meropenem MIC was 8 mg/L or lower (26). The majority of the patients in our study (64.6%) had been receiving meropenem when a CRGN bacterial infection was observed; however, the MIC values of CRGN bacteria were above 8 µg/L in the majority of episodes (83%).

The major side effects of treatment with colistin tend to be neurotoxicity and nephrotoxicity. Previous studies have observed nephrotoxicity at a rate of 0% and 12.5% (17, 27–30). Seven (8.5%) patients in our study developed nephrotoxicity. The addition of an aminoglycoside that has been known to be a nephrotoxic did not significantly increase the incidence of nephrotoxicity. No neurotoxicity was observed in our patients.

There are several advantages of this study. Primarily, it is the largest series to date in a pediatric critical care setting, while also being the first study to evaluate the impact of adding an aminoglycoside to a colistin-based regimen.

The prominent limitations of this study were the retrospective design and the lack of genotypic analysis.

In conclusion, we demonstrated the rate of clinical response to be higher in the CA group without statistical significance. And also, the attributable mortality was nearly three-fold higher in the CO group with a limit of statistical significance retrieved from logistical regression analysis. Because the incidence of side effects, including nephrotoxicity and neurotoxicity, did not differ between groups, colistin and an aminoglycoside combination treatment regimen may be a safe and effective combination in CRGN-infected PICU patients without a significant increase in the incidence of side effects. No rigorous, in-depth studies are available in the literature to date. Proven therapeutic protocols for CRGN infections in children remain elusive, and the current options are generally based on adult studies. Studies such as the one here do provide some insight; however, further, larger, prospective designed studies are needed if we are to address this continually increasing problem head on.

Ethics Committee Approval: The Ethical Board of Izmir Katip Celebi University granted permission covering all aspects of this study (Ethical decision number: 58/March 24, 2016).

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