ORIGINAL ARTICLE

A RETROSPECTIVE STUDY ON THE OUTCOME OF CHILDREN WITH EXTENSIVELY DRUG-RESISTANT GRAM-NEGATIVE INFECTION TREATED WITH COLISTIN VS OTHER ANTIMICROBIALS

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Introduction: The increasing trend of extensively drug-resistant gram-negative infections led to the reconsideration of colistin as a valuable therapeutic option.

Objectives: To describe the clinical profile and treatment response of children with extensively drug-resistant (XDR) Gram-negative infections given colistin versus other antimicrobials.

Methods: This retrospective descriptive study involved patients treated for XDR Gram-negative infections from January 2014 to June 2017 in a tertiary hospital in Metro Manila. Descriptive statistics were used to summarize clinical characteristics of subjects. Treatment response to colistin versus other antimicrobial agents were compared in terms of success, failure, and toxicity. The Fisher-exact and Mann Whitney U tests were used to assess statistical differences between the colistin and non-colistin groups.

Results: Majority of patients with XDR Gram-negative infections had previous antibiotic exposure. More patients in the colistin group received TPN 43.2% vs 23.7% (p=0.035), had a longer hospital stay prior to the onset of XDR Gram-negative infection, 27 days vs. 15.5 days (p=0.001), and had a longer total hospital stay with a median of 52 days vs 30 days ($p < 0.001$). Treatment success was significantly higher in the colistin group at 70.3%, as against 46.5% in the non-colistin group (p=0.014). There was no difference in the treatment duration of both groups. The colistin group had longer time to clinical response, with a mean of 6.27 ($\pm$ 3.57) days compared with those from the non-colistin group, with a mean of 4.36 ($\pm$ 1.77) (p=0.008). The colistin group had more fungal infections during the course of treatment (p=0.001).

Conclusion: Based on our institutional experience, colistin is considered relatively effective and safe in treating XDR Gram-negative infections in children.

KEYWORDS: *extensively drug-resistant gram-negative infection, healthcare associated infection, colistin*

INTRODUCTION

Antibiotic resistance among Gram-negative bacteria has reached critical levels.[1] The World Health Organization (WHO) continues to warn on the rise of new resistance mechanisms threatening our ability to treat common infectious diseases. This results in prolonged illness, increased cost of therapy, disability, and even death. For these serious infections, carbapenems are usually the recommended treatment. Recently, the emergence of carbapenemases has led to high level antibiotic resistance leaving colistin as the only treatment option. Gram-negative bacteria use two main mechanisms to develop phenotypic resistance to carbapenems: the production of carbapenemases, or a combination of structural mutations and production of other β-lactamase enzymes.[1] The following risk factors have been identified to contribute to carbapenem resistance in children: hospitalization for more than 48 hours, receipt of antibiotics, underlying medical conditions such as pulmonary disease, prematurity, oncologic and cardiac disease, solid-organ or stem-cell transplantation, history of surgery particularly gastrointestinal procedures, intake of immunosuppressants and presence of an indwelling device.

A similar trend is seen locally. Compared to 2015, the 2016 Antimicrobial Resistance Surveillance Program of the Department of Health reported a statistically significant increase in Extended spectrum beta-lactamase producing *Klebsiella pneumoniae* from 27% to 40% while the Carbapanem-resistant *Klebsiella* decreased from 11.9 – 15.3% to 9.1 – 11.4%. There was a slight decrease in *Pseudomonas* MDR and XDR rates from 22% and 18% to 21% and 16% respectively. However, there was a significant increase in resistance to amikacin from 7.3 to 8.6% and ciprofloxacin from 13.14 to 14.9%. *Acinetobacter* MDR rate for 2016 decreased from 66% to 61% but the XDR rate increased from 48% to 50%. There was a significant increase in *Acinetobacter* resistance to amikacin from 31% to 38%.[2]

The emergence of Gram-negative bacteria resistant to most classes of antibiotics and the lack of effective new antibiotics led to the reconsideration of colistin as a valuable therapeutic option in the early 1990s. In recent studies on the use of colistin in the pediatric population, a favorable outcome was observed in 65% – 89% of patients who received the drug.[3][4][5][6] Nephrotoxicity rates from studies involving pediatric patients including one study on neonates ranged from 1.6% to 22%.[3][4][5][6][7][8] Neurotoxicity is less common and ranged from 0% to 4%.[3][4][5][8][9]. Colistin however is not exempt from antibiotic resistance. The exact mechanism is still unclear but it has been suggested that resistance is related to lipopolysaccharide (LPS) modification.[10] At present, studies and experience on the use of intravenous colistin in extensively drug-resistant Gram-negative infections in the pediatric population are limited and there are no available local data or published research in the Philippine setting. This paper aims to describe the clinical profile and treatment response of children with extensively drug-resistant (XDR) Gram-negative infections given colistin versus other antimicrobials.

METHODOLOGY

Ethical Considerations

The study commenced upon the approval of the Institutional Review Board and Ethics Committee of the institution. The board and committee were likewise

informed of revisions during the research process. All information collected from the laboratory and patients' charts were used for this research only. Confidentiality was maintained during and after the study.

This retrospective descriptive study was conducted in a tertiary hospital in the Philippines from January 2014 to June 2017.

Subject and Sample Size Computation

Inclusion Criteria

Included in the study were children 0-18 years old admitted at the service and pay wards of a tertiary hospital who received colistin or other antimicrobials for the treatment of culture-proven extensively drug-resistant Gram-negative infection.

Exclusion Criteria

Patients 0-18 years old with culture proven extensively drug-resistant Gram-negative infection who received less than 6 doses of antimicrobial therapy, was not admitted, or expired prior to treatment were not included in the study. Patients with XDR Gram-negative culture isolates from the urine or tracheal aspirate but with Gram-positive sepsis or candidemia as the predominant infection in the blood, CNS and other sterile sites were likewise excluded.

Sample Size

A minimum of 346 subjects was required for this study based on a level of significance of 5%, a prevalence of 65.8%, and with a desired width of confidence interval of 10%, as noted from the reference article by Ozsurekci et. al. in 2016. [5] Since, extensively drug-resistant infections are rare, the desired sample size was not attained. The sample size requirement may be precluded by the fact that our primary aim is to describe rather than to estimate prevalence.

Description of the Study Procedure

Data Collection Method

Culture and sensitivity results from the Microbiology Section logbooks were reviewed and charts of patients with extensively drug-resistant cultures were retrieved from the Medical Records for review. Patients with culture proven extensively drug-resistant Gram-negative infection who were treated were included in the study and the following data were obtained:

Microbiologic data which included the culture source, organism and antimicrobial susceptibility of the Gram-negative XDR isolates; patient's demographic data included the age to further qualify if term or preterm if neonate, and sex. Clinical data noted in this study included the type of infection whether community or hospital acquired, the patient's nutritional status, co-morbid illness, surgical intervention and other medical procedures (invasive vascular access, receipt of TPN, use of mechanical ventilator, blood transfusion and foley catheter insertion). Intake of Immunosuppressants were also noted. Receipt of prior antibiotics within the last 90 days prior to XDR Gram-negative infection, and antibiotic regimen and duration were noted. Duration of hospital stay, days of hospitalization prior to onset of XDR gram negative infection, as well as the wards where patients were admitted were also recorded.

Patients were classified into the colistin and non-colistin group based on antibiotics received. The primary outcome was treatment success or failure. Treatment success was based on clinical and/or microbiological response after treatment while treatment failure was demonstrated by poor clinical response, persistence of the organism in the specimens (blood, urine, CSF, tracheal

aspirate, wound or surgical site), relapse or mortality. The secondary outcomes measured were time to clinical response (in days), total treatment duration (in days), occurrence of adverse events (nephrotoxicity, neurotoxicity, others) and occurrence of treatment related infection (example: fungal infection, other Gram-negative or Gram-positive infection)

Data Analysis

Frequency and proportion were used to summarize the number of Gram-negative isolates and the ratio of extremely drug-resistant isolates per year. Descriptive statistics was used to summarize the overall general and clinical characteristics of the subjects in the non-colistin and colistin groups. The number in count and percentages were presented for categorical data. The mean, median, standard deviation, and interquartile range (IQR) were presented for continuous data.

The Fisher-exact test was used to assess statistical differences between the non-colistin and colistin groups. Given the non-parametric distribution of continuous variables in the study population (negatively skewed), the comparative statistical analysis of Mann Whitney U test was performed to determine the differences between the non-colistin and colistin groups.

All complete records were considered valid and were included in the final analysis. Incomplete data and missing charts were excluded. Null hypothesis was rejected at 0.05 α-level of significance. SPSS 22.0 was used for data analysis. [13]

RESULTS

The total number of Gram-negative isolates from January 2014 to June 2017 was 4,571. Among these Gram-negative isolates, 228 XDR isolates were initially identified as potential eligible cases. There were 204 charts available for review. Fifty-three were excluded due to findings of Gram-positive sepsis (5), fungal infection (2), no treatment (6), not admitted (3), expired in less than 48 hours of treatment (4) and MDR infection (33). A total of 151 eligible patients were included in the study. Of the 151 patients with XDR infection, 114 were included in the non-colistin group and 37 in the colistin group.

For the period of January 2014 to June 2017, there was an increasing trend in the proportion of XDR isolates over the total number of Gram-negative isolates. In this study, there were 14 XDR isolates out of 788 Gram-negative isolates for 2014 (1.7%), 36 XDR out of 1,490 isolates for 2015 (2.4%), 66 out of 1,816 isolates for 2016 (3.6%) and 35 out of 477 isolates for the first half of 2017 (7.3%). Table 1 summarizes the microbiologic data of the XDR Gram-negative isolates. The top 3 sources of the isolates were blood (38.4%), urine (19.2%) and tracheal aspirate (18.5%). Sixty (39.7%) out of 151 XDR isolates were sensitive to colistin and amikacin, followed by 47 (31.1%) isolates sensitive only to colistin. (Appendix B) The most common XDR isolate was *Klebsiella* with 53 isolates (35.1%), followed by *Acinetobacter*, 40 isolates (26.5%) and *Stenotrophomonas* and *Pseudomonas aeruginosa* with 16 isolates each (10.6%).

Table 1. Microbiologic Data of Treated XDR Gram-negative Infection

		Overall n = 151 (%)	Non-colistin n = 114 (%)	Colistin n = 37 (%)	p-value
Culture source	Blood	58 (38.4)	42 (36.8)	16 (43.2)	0.347
	Urine	29 (19.2)	18 (15.8)	11 (29.7)	
	Tracheal Aspirate	28 (18.5)	24 (21.1)	4 (10.8)	
	CSF	11 (7.3)	8 (7)	3 (8.1)	
	Wound	11 (7.3)	10 (8.8)	1 (2.7)	
	Peritoneal Fluid	7 (4.6)	5 (4.4)	2 (5.4)	
	Surgical Site	5 (3.3)	5 (4.4)	0 (0)	
	Pleural Fluid	2 (1.3)	2 (1.8)	0 (0)	
Culture and sensitivity	Colistin Only	47 (31.1)	21 (18.4)	26 (70.3)	<0.001
	Colistin + Fluoroquinolone	13 (8.6)	12 (10.5)	1 (2.7)	0.188
	Colistin +Carbapenems	6 (4)	5 (4.4)	1 (2.7)	1.00
	Colistin + Aminoglycosides	60 (39.7)	51 (44.7)	9 (24.3)	0.034
	Others	25 (15.6)	25 (100)	0 (0)	0.001
Culture Isolate	*Klebsiella*	53 (35.1)	36 (31.6)	17 (45.9)	0.066
	Acinetobacter	40 (26.5)	31 (27.2)	9 (24.3)	
	Stenotrophomonas	16 (10.6)	16 (14)	0 (0)	
	Pseudomonas aeruginosa	16 (10.6)	9 (7.9)	7 (18.9)	
	E. cloacae	6 (4)	3 (2.6)	3 (8.1)	
	Elizabeth kingae	4 (2.6)	4 (3.5)	0 (0)	
	E. Coli	4 (2.6)	4 (3.5)	0 (0)	
	Burkholderia cepacia	3 (2)	3 (2.6)	0 (0)	
	E. aerogenes	3 (2)	2 (1.8)	1 (2.7)	
	Serratia	2 (1.3)	2 (1.8)	0 (0)	
	Citrobacter	2 (1.3)	2 (1.8)	0 (0)	
	Chryseobacterium	2 (1.3)	2 (1.8)	0 (0)	

There was no significant difference noted between the colistin and non-colistin groups in terms of age, proportion of preterms among neonates and sex. (Table 2)

Table 2. Demographic Data of Patients Treated for XDR Gram-negative Infection

		Overall	Non-colistin Group	Colistin Group	p-value
Age in years	Mean (SD)	3.9 (± 5.78)	3.4 (± 5.16)	5.4 (±7.26)	0.210
	Median (IQR)	0.69 (0.85-5.55)	0.57 (0.08-4.78)	1.08 (0.10 - 10.95)	
Neonates	neonates	32 (21.2%)	28 (24.6%)	4 (10.8%)	0.104
	Preterm among neonates	8 (25%)	8 (28.6%)	0 (0%)	0.550
Sex	Male	86 (57%)	61 (53.5%)	25 (67.6%)	0.181
	Female	65 (43%)	53 (46.5%)	12 (32.4%)	

Table 3 summarizes the clinical data of patients included in the study. The clinical profile between the non-colistin and colistin groups were not statistically significant except for receipt of TPN which was noted to be higher in the colistin group, 43.2% vs 23.7% (p=0.035).

Table 3. Clinical Data of Patients Treated for XDR Gram-negative Infection

		Overall n= 151 (%)	Non-colistin n =114 (%)	Colistin n=37 (%)	p-value
Nutritional status	Severely wasted	31 (20.5)	24 (21.1)	7 (18.9)	0.371
	wasted	18 (11.9)	13 (11.4)	5 (13.5)	
	normal	91 (60.3)	71 (62.3)	20 (54.1)	
	Overweight	11 (7.3)	6 (5.3)	5 (13.5)	
Co-morbidities	None	23 (15.2)	17 (14.9)	6 (16.2)	0.165
	Malignancy	33 (21.9)	29 (25.4)	4 (10.8)	
	Congenital Anomalies	95 (62.9)	68 (59.6)	27 (73)	
Type of infection	Hospital acquired	122 (80.8)	89 (78.1)	33 (89.2)	0.157
	Community acquired	29 (19.2)	25 (21.9)	4 (10.8)	
Surgical intervention		49 (32.5)	36 (31.6)	13 (35.1)	0.691
Accessory medical	Invasive Vascular access	58 (38.4)	43 (37.7)	15 (40.5)	0.846
	TPN	43 (28.5)	27 (23.7)	16 (43.2)	0.035
	Mechanical ventilator	70 (46.4)	51 (44.7)	19 (51.4)	0.570

procedure	**Blood transfusion**	**84 (55.6)**	**63 (55.3)**	**21 (56.8)**	**1.00**
	Foley catheter placement	**43 (28.5)**	**28(24.6)**	**15 (40.5)**	**0.092**
Prior Antibiotics	**None**	**12 (7.9)**	**10 (8.8)**	**2 (5.4)**	**0.045**
	Monotherapy	**92 (60.9)**	**71 (62.3)**	**21 (56.8)**	
	Combination therapy (non colistin)	**44 (29.1)**	**33 (28.9)**	**11 (29.7)**	
	Combination therapy with colistin	**3 (2)**	**0 (0)**	**3 (8.1)**	
Immunosuppression	**None**	**111 (73.5)**	**80 (70.2)**	**31 (83.8)**	**0.297**
	Steroids	**27 (17.9)**	**23 (20.3)**	**4 (10.8)**	
	Chemotherapy	**13 (8.6)**	**11 (9.6)**	**2 (5.4)**	
Ward Admitted	**NICU**	**41 (27.2)**	**28 (24.6)**	**13 (35.1)**	**0.669**
	PICU	**25 (16.6)**	**21 (18.4)**	**4 (10.8)**	
	SICU	**7 (4.6)**	**5 (4.4)**	**2 (5.4)**	
	Service ward	**73 (48.3)**	**56 (49.1)**	**17 (45.9)**	
	Pay	**5 (3.3)**	**4 (3.5)**	**1 (2.7)**	

Table 4 shows the temporal data of patients treated for XDR infections. Overall, patients with XDR Gram-negative infections have received antibiotics for a median duration of 15 days with interquartile percentile (IQR) of 6 to 26 days. The median hospital stay prior to developing XDR Gram-negative infection was 18 days with an IQR of 8 – 30 days. The hospital stay of patients with XDR Gram-negative infection was significantly longer in the colistin group with a median of 27 days, IQR of 14.5 – 56.5 days, compared to the non-colistin group with a median of 15.5 days, IQR of 5.8 – 27 days (p=0.001). Among the 49 patients who underwent surgery, a median of 14 days, IQR of 6 – 23 days post op was noted prior to developing XDR Gram-negative infections. Overall, the total hospital stay of patients was at a median of 36 days with IQR of 18 – 71 days. Patients in the colistin group had a statistically significant longer hospital stay with a median of 52 days, IQR of 36 – 123 days compared to the non-colistin group with a median of 30 days, IQR of 15.5 – 53.3 days (p=0.001).

Table 4. Temporal Data of Patients Treated for XDR Gram-negative Infections

		Overall	Non-colistin	colistin	p-value
Prior antibiotic treatment duration (days)	**Mean (SD)** **Median (IQR)**	**20.1 (24.9)** **15 (6-26)**	**16.5 (15.8)** **13 (6-24)**	**31.2 (40.3)** **17 (5.5-48)**	**0.085**
Hospital stay to XDR infection (days)	**Mean (SD)** **Median (IQR)**	**27.42 (44.13)** **18 (8-30)**	**20.63 (33.5)** **15.5 (5.8-27)**	**48.32 (63.23)** **27 (14.5-56.5)**	**0.001**
post Surgery days to XDR infection (49 cases)	**Mean (SD)** **Median (IQR)**	**15.0 (9.44)** **14 (6-23)**	**14.3 (9.36)** **13.5 (6-22)**	**17.2 (9.7)** **19 (9-25)**	**0.395**
Total Hospital Stay (days)	**Mean (SD)** **Median (IQR)**	**57.9 (66.78)** **36 (18-71)**	**46.9 (57.4)** **30 (15.5-53.3)**	**91.9 (81.56)** **52 (36-123)**	**0.001**

Treatment success of XDR Gram-negative infections was significantly higher in the colistin group at 70.3% vs 46.5% in the non-colistin group (p=0.014), but mortality is almost the same at 73.8% in the non-colistin and 72.7% in the colistin group (p=0.010). Persistence of XDR infection was higher in the non-colistin group at 26.2% vs. 9.1% in the colistin group (p=0.010). There was no significant difference in the duration of treatment among those with treatment success with a median of 10 days (IQR 10-14) for the non-colistin and 10.5 days (IQR 10-14) in the colistin group (p=0.279). However, clinical response is noted to be longer by 2 days in the colistin group, with mean of 6.27 (± 3.57) days vs 4.36 (± 1.77) days in the non-colistin group (p=0.008).

Table 5. Outcome of Patients Treated for XDR Gram-negative Infection

		Overall n =151	Non-colistin n = 114 (%)	Colistin n = 37 (%)	p-value
Treatment outcome	**Success**	**79 (52.3%)**	**53 (46.5%)**	**26 (70.3%)**	**0.014**
	Failure	**72 (47.7%)**	**61 (53.5%)**	**11 (29.7%)**	
Clinical response (days)	**Mean (SD)** **Median (IQR)**	**4.99 (± 2.64)** **4 (3-6)**	**4.36 (± 1.77)** **4 (3-5)**	**6.27 (± 3.57)** **5 (4-7)**	**0.008**

	Median (IQR)				
Success treatment duration (days)	**Mean (SD)** **Median (IQR)**	**12.27 (± 4.96)** **10 (10-14)**	**11.5 (± 3.03)** **10 (10-14)**	**13.8 (± 7.34)** **10.5 (10-14)**	**0.279**

Table 5 shows the treatment outcome of patients included in the study. Treatment in the non-colistin group comprised of meropenem + aminoglycoside (22.8%), meropenem as monotherapy (13.2%), ciprofloxacin as monotherapy (14%) or combined with aminoglycoside (14%), and cefepime (3.3%). A total of 26 out of 37 patients (70.3%) in the colistin group were given colistin + meropenem, colistin + ciprofloxacin (16.2%), colistin + amikacin (2.7%), and colistin + piperacillin tazobactam (2.7%), (Appendix D). The dose of colistin had a median of 4mg/Kg/day, IQR of 1.58 – 4.44 mg/Kg/day. The treatment duration was a median of 10 days with IQR of 10 – 14 days.

No adverse event was noted with the administration of colistin but fungal infection during the course of treatment was significantly higher at 18.9% in patients treated in the colistin group compared to 1.8% in the non-colistin group (p=0.001). Nephrotoxicity was noted in one patient in the non-colistin group. The patient was a 16-year-old female with Non-hodgkins Lymphoma who received meropenem, vancomycin, amikacin and amphotericin B simultaneously for 12 days prior to the development of acute kidney injury**.** (see Table 6)

Table 6. Treatment Related Adverse Events

		Overall n = 151 (%)	**Non-colistin n = 114 (%)**	**Colistin n = 37 (%)**	**p value**
Post Treatment Infection	**None**	**135 (89.4)**	**107 (93.9)**	**28 (75.7)**	
	Gram-positive (blood)	**1 (0.7)**	**1 (0.9)**	**0 (0)**	
	Fungal (blood)	**9 (6)**	**2 (1.8)**	**7 (18.9)**	**0.001**
	HCAP	**1 (0.7)**	**0 (0)**	**1 (2.7)**	
Toxicity	**none**	**113 (.99)**	**112 (0.98)**	**0**	
	Nephrotoxicity	**1 (0.88)**	**1 (0.88)**	**0**	
	Neurotoxicity	**0**	**0**	**0**	

DISCUSSION

The problem of increasing antibiotic resistance continues to be a threat with catastrophic consequences. There is a rising trend of extensive drug-resistance among Gram-negative isolates in our institution. The top XDR Gram-negative isolates *Klebsiella* (35.1%), *Acinetobacter* (26.5%), *Pseudomonas aeruginosa* (10.6%) with the addition of *Stenotrophomonas* (10.6%), were

consistent with XDR species identified by the WHO and the 2016 Antimicrobial Resistance Surveillance Program of the Philippines. [2]

In this study, 92.1% of the patients received antibiotics for a median duration of 15 days with interquartile percentile (IQR) of 6 to 26 days. The patients were receiving Meropenem ± aminoglycoside and Ciprofloxacin prior to developing XDR Gram-negative infection. Current studies have identified that the selective pressure of broad-spectrum antibiotics was a major risk factor for developing XDR Gram-negative infections. [4] [5] [6]

This study noted malignancy, gastrointestinal congenital anomalies, Chiari II malformation, and gastrointestinal surgery as the most common underlying conditions of patients with XDR gram negative infections, compared to Weintstein and Logan's study where pulmonary disorders, prematurity and malignancy were the top co-morbidities. [1] There was no significant difference noted between the colistin and non-colistin groups in terms of demographic and clinical data, consistent with previous studies. [1] [7]

Treatment success of XDR infections was significantly higher in the colistin group at 70.3% vs 46.5% in the non-colistin group (p=0.014). This is comparable with previous studies with colistin success rate ranging from 65 – 89%. [3][4][5][6] There was no significant difference in the duration of treatment among those with successful treatments, with a median of 10 days (IQR 10-14) for the non-colistin and 10.5 days (IQR 10-14) for the colistin group (p=0.279). The patients in our study received colistin for a shorter duration compared to Ozsurekci's study where patients received the drug with a median duration of 17 days IQR 9-14 days. However, clinical response is noted to be longer in the colistin group, with mean of 6.27 (± 3.57) days vs 4.36 (± 1.77) days in the non-colistin group (p=0.008). This finding can guide us in monitoring our treatment of XDR infections.

Previous studies, including one study involving neonates reported nephrotoxicity rates ranging from 1.6% to 22%. There were no reports of nephrotoxicity among patients who received colistin in this study. However, it is worth mentioning that one neonate had an episode of decreased urine output for 6 hours, occurring within 3 days after the last dose of colistin. The patient responded to hydration. There was no recurrence of oliguria noted and no laboratories were requested. One neonate had increased creatinine levels which occurred on the 6th day of colistin. The patient was evaluated by the nephrology service and acute kidney injury was attributed to prolonged shock. This patient received only 20,000 IU/kg/day of colistin. As mentioned earlier, one patient from the non-colistin group had nephrotoxicity and the patient received vancomycin, amphotericin B deoxycholate and amikacin, all known nephrotoxic drugs, and received at the same time. The lower nephrotoxicity rates in recent colistin studies can be attributed to closer monitoring of renal function and advances in intensive care unit monitoring as mentioned by Cagan et al. [3] Fungal infection during the course of treatment was significantly higher in the colistin group at 18.9% vs.1.8% in the non-colistin group (p=0.001). This finding can also be explained by selective pressure but it needs to be further validated since this is not a usual complication of colistin noted in other studies.

As to colistin dosing, the recommended dose of colistimethate for

patients with normal renal function is 2.5 to 5 mg/kg of ideal body weight not to exceed 300 mg daily. [11] A loading dose is recommended in critically ill adult patients. [11] Patients in this study received an average of 3.5 (±2.1) mg or 43,698 (±26,157) units per Kg/day in 3 divided doses, with no loading dose given. The IV infusion rate cannot be determined. The Adult and Pediatric Guideline for South Africa 2016 recommends 50 – 75, 000 IU/kg/day in three divided doses to be infused for 30 minutes for neonates and 50 – 75, 000 IU/kg/day in three divided doses for infants and children. [9] While colistin showed a favorable outcome, determining the optimal dose for the best treatment outcome is of clinical relevance for future studies.

Given the retrospective nature of this study, the authors acknowledge that the major limitation is the small number of subjects in the colistin group. However, to the authors' knowledge, this is the first descriptive study on the use of colistin among children in the Philippines. Similar to other retrospective studies, some clinical variables are uncontrolled and may affect treatment outcome analysis. The authors recommend a prospective study to validate the findings in our study.

CONCLUSION AND RECOMMENDATION

This retrospective comparative study showed that in the treatment of XDR Gram-negative infection in children, colistin, compared to other antimicrobials, is considered relatively effective and well tolerated. Though colistin is now available in our setting, preventive measures against the occurrence of XDR gram negative infections are of prime importance. In this study, majority of patients have previous or current exposure to broad-spectrum antibiotics prior to developing extensively drug-resistant Gram-negative infection. Hence, it is urgent and critical to continue efforts to prevent healthcare associated infections and to implement antimicrobial stewardship while new therapeutic options are evaluated.

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