ORIGINAL ARTICLE

EFFECTIVENESS AND ADVERSE EFFECTS OF INTRAVENOUS COLISTIN IN NEONATES WITH MULTI-DRUG RESISTANT GRAM-NEGATIVE BACTERIAL INFECTIONS

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ABSTRACT

Background: The global burden of multi-drug resistant gram-negative bacterial (MDR-GNB) infections has been increasing. Neonates are at a particularly high-risk and there is limited treatment option. The use of colistin has been re-introduced for this population. However, data on its use in neonates is scarce.

Objective: To determine the effectiveness and adverse effects of intravenous colistin in neonates with multidrug-resistant gram-negative infections.

Design: This is a retrospective cohort study of the clinical profile and outcome of neonates with MDR-GNB infections given colistin for a minimum of 3 days conducted from April 2015 to April 2019.

Results: A total of 175 pediatric patients had MDR-GNB infections. 75 (43%) neonates met the inclusion criteria and received intravenous colistin. Of the 75 patients with MDR-GNB infections- that included sepsis, pneumonia, urinary tract infection and abscess, 37 (49.3%) were alive and 38 (50.7%) patients died. Nephrotoxicity was seen in 4% if patients and 2.6% patients had hypersensitivity reaction. MDROs isolated were Acinetobacter baumanii, Klebsiella pneumoniae and Pseudomonas aeruginosa.

Conclusion: Intravenous colistin is 50% effective and is relatively safe to use in neonates.

KEYWORDS: *colistin, MDR-GNB, neonates*

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INTRODUCTION

Sepsis is one of the major causes of hospital admission and mortality in neonates. A serious concern in the management of neonatal sepsis is antibiotic resistance. Multi-drug resistance among bacterial organisms are emerging and problematic because treatment options with antimicrobial agents for these strains are often limited. [1]

Multi-drug resistant gram-negative bacteria (MDR-GNB) have been reported in different parts of the world. It is a major threat to neonatal care, carrying a high rate of morbidity and mortality. The presence of MDR-GNB and the lack of new antibiotics to treat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Colistin, mainly colistimethate sodium (polymyxin E), has been predominantly used for infections caused by these organisms before the advent of newer safer antibiotics. While colistin is the treatment of choice, few studies have reported its use in neonates. [2]

Colistin was first introduced in 1952 and was used until the early 1980's for the treatment of infections caused by gram-negative bacilli. In vitro, colistin has demonstrated excellent activity against various gram-negative rod-shaped bacteria, including multidrug-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae. The mechanism of action of colistin is on the bacterial cell membrane. It binds to lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria that leads to disruption of the outer cell membrane leading to the leakage of intracellular contents and eventual bacterial death. [3]

Data on the use of colistin in the pediatric population remain scarce. Safety and effectiveness data regarding colistin in pediatric patients especially in the neonates are limited. The optimal dosage has not been defined. However, according to a multicenter study in recent years, 2.5 - 5 mg/kg/day is safe in the pediatric age group.[4] Some studies reported using 50,000-75,000 IU/kg/day (1 mg colistimethate sodium = 12,500 IU) in newborns and preterm infants. The most frequent adverse effect of intravenous colistin is nephrotoxicity. Toxicity is dose-dependent and reversible on discontinuation of treatment.[3] The exact molecular mechanism of toxicity is, however, not known. Other reported side effects include neurotoxicity, electrolyte imbalances.[4] The 2019 International Consensus Guidelines for the Optimal Use of Polymyxins states that the magnitude of polymyxin exposure is the most important risk factor for polymyxin-associated acute kidney injury. The recommended dose is no more than 5 mg/kg/day (equivalent to ~152,000 IU/kg/day). A risk factor in multiple analysis identified that advanced age is co-related with nephrotoxicity, although the so-called cut-off age for increased risk is inconsistent. Administration of concomitant nephrotoxic agents is also a consistent risk factor for acute kidney injury in patients receiving polymyxin therapy.[5]

In the Philippines, colistin use is limited. However, due to the increasing number of MDR-GNB at a tertiary government training hospital in Manila, the drug has been used since 2015. To date, there are no local studies on the effectiveness and adverse effects of colistin use in neonates. This study aims to determine the effectiveness and adverse effects of colistin in neonates with multidrug-resistant gram-negative bacterial infections. Data on the neonates' clinical characteristics, outcome, and adverse effects, as well as the MDRO antimicrobial susceptibility were collected and analyzed.

Operational Definition of terms:

1. Multi-drug resistant organism - is defined as microorganism with non-susceptibility to at least one agent in three or more antimicrobial categories.[2]
2. Extended neonatal period – is defined as corrected gestational age for prematurity plus another 28 days. Age of viability is at 24 weeks thus a maximum of 118 days of life was considered.[6]
3. Nephrotoxicity (drug-induced) - 0.5 mg/dL or 50% rise in serum creatinine over 24–72 h time frame and a minimum 24–48 h of drug exposure or any of

the following: decreased urine output, increased BUN, proteinuria, hematuria or casts in the urine.[4,7]

4. Neurotoxicity – severe neurotoxic effects include seizures, hypertonicity, spasms, change/decrease in sensorium reported during treatment with colistin not explained by any other co-morbidity (meningitis, hypoglycemia, hypoxia, etc.).[4,10]

5. Hypersensitivity reaction – includes but not limited to generalized pruritus, urticaria, rash during or after administration of colistin any time during treatment.

6. Survived – patients who are alive after 14 days of treatment completion with colistin and whose repeat cultures are negative.

7. Died – patients given more than 3 days of colistin treatment and died within 14 days of treatment.

METHODOLOGY

A. Study design and setting

This is a retrospective cohort study of the clinical profile and outcome of neonates with MDR-GNB given colistin that were admitted in the pediatric wards, pediatric intensive care unit (PICU) and neonatal intensive care unit (NICU) from April 2015 to April 2019. The study was done at a tertiary government training hospital with the largest facility and referral center that serves more than 600,000 patients yearly.

B. Study population and sampling plan

A minimum of 57 patients was computed for this study based on a 35.9% prevalence of mortality among neonates with sepsis with 5% level of significance and 12.5% half-width of the confidence interval.[1]

Admitted patients < 118 days of corrected age with MDR-GNB isolates on blood, endotracheal aspirate, urine, cerebrospinal fluid (CSF), abscess on initial or repeat cultures and given colistin for a minimum of 3 days in order to properly assess antibiotic treatment response or failure were included.[6]

Exclusion criteria were as follows:

- Patients beyond 28 days of life or >118 days of age based on an extended neonatal definition of corrected age for prematurity
- Duration of colistin use is < 3 days
- Cultures positive for gram-positive pathogen, fungal infection, and mixed organisms

C. Data collection and procedure

The use of colistin in our center is highly restricted. It requires approval from the Section of Infectious and Tropical Diseases in Pediatrics (INTROP) prior its administration. The list of pediatric patients given colistin was obtained from the section's list and patient records. Medical charts and laboratory data of these patients were reviewed. All information needed was recorded in a case report form.

D. Data processing and analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. Fisher's exact test was used to determine the difference between patients that survived or died in terms of concomitant antibiotics given during colistin administration. Shapiro-Wilk was used to test the normality of the continuous variables. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of mortality. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

E. Ethical Issues

An approval from the Research Ethics Board (REB) was obtained before the conduct of this study. Review of medical records and its anonymity were maintained in accordance with our National Ethical

Guidelines of Health and Health-related Research 2017.

The data was collected solely by the principal investigator. All patient information and data collected in this study were kept confidential.

RESULTS

A total of 175 pediatric patients had MDR-GNB infection from April 2015 to April 2019. 75 (43%) neonates met the inclusion criteria and received intravenous colistin. The median age was 15 days old with a mean weight of 1500 grams. Almost 74% (55) of the patients in this study were pre-term. Sixty-three patients (84%) with MDR-GNB were admitted at the NICU due to sepsis (82.7%). The summary of the other clinical characteristics of patients is presented in Table 1.

Table 1. Clinical profile of patients with MDR-GNB treated with colistin (n=75)

	Frequency (%); Mean ± SD; Median (IQR)
Age (days)	15 (9 to 23)
Term	20 (26.66)
Pre-term	55 (73.33)
Weight (grams)	1500 (940 to 2495)
Sex	
Male	36 (48)
Female	39 (52)
Admission ward	
Ward 9	7 (9.33)
Ward 11	4 (5.33)
PICU	1 (1.33)
NICU	63 (84)
Underlying disease	
Sepsis	62 (82.67)
Pneumonia	9 (12)
Ventriculitis	6 (8)
UTI	3 (4)
NEC III/abscess	1 (1.33)

Clinical manifestations of patients are presented in table 2, the most common signs and symptoms seen in patients with MDR-GNB were poor activity (94.7%), abdominal distention (60%), tachypnea (53.3%), tachycardia (42.7%) and fever (37.3%).

Table 2. Clinical manifestations of patients with MDR-GNB prior to treatment with colistin

Signs and symptoms	**Frequency (%)**
Temperature	
> 38.5^{0}C	28 (37.33)
Normal	30 (40)
< 36^{0}C	17 (22.67)
Respiratory	
Tachypnea	40 (53.33)
Normal	18 (24)
Apnea	17 (22.67)
Cardiac	
Tachycardia	32 (42.67)
Normal	24 (32)
Bradycardia	19 (25.33)
Hypotension	8 (10.67)
Seizure	6 (8)
Decreased urine output	1 (1.33)
Skin and subcutaneous manifestations	
Mottling	8 (10.67)
Rashes	10 (13.33)
Sclerema	10 (13.33)
Normal	47 (62.67)
Gastrointestinal manifestations	
Feeding intolerance	7 (9.33)
Poor suck	0
Abdominal distention	45 (60)
Normal	23 (30.67)
Irritability	4 (5.33)
Poor activity	71 (94.67)

Patients with MDR-GNB in this study presented with thrombocytopenia (90.5%) and leukocytosis (45.3%). Details of the laboratory findings are seen in table 3.

Table 3. Laboratory findings of patients with MDR-GNB prior to treatment with colistin

Laboratory	Frequency (%)
WBC count	
< 4,000 x10^9 cells/L	34 (45.33)
Normal	15 (20)
> 30,000 x10^9 cells/L	26 (34.67)
Platelet count < 100,000 x10^9 cells/L (n=74)	
Yes	67 (90.54)
No	7 (9.46)
CRP (n=21)	
< 12 mg/dL	10 (47.62)
> 12 mg/dL	11 (52.38)
Glucose	
Hyperglycemia	1 (1.33)
Normal	62 (82.67)
Hypoglycemia	12 (16)

There were 83 MDR-GNB isolated from different sites, the top 3 isolates were A. *baumannii* (57.83%), *K. pneumoniae* (26.51%) and *P. aeruginosa* (4.82%). As shown in Table 4, the majority of the MDR-GNB was isolated in the blood (65). Out of the 75 patients, 41(61.29%) neonates had A. *baumannii* and 19 (29.23%) neonates had *K. pneumoniae* in their blood culture. *Acinetobacter baumannii* was also the most common organism seen in the endotracheal aspirate and cerebrospinal fluid culture. Other isolated MDR-GNB were *E. coli*, *S. maltophilia*, and *D. acidorovans*.

Table 4. Pathogens isolated from specific sites in neonates treated with colistin

	Blood (n=65)	Respiratory (n=9)	Urine (n=3)	Abscess (n=1)	CSF (n=5)	Total (n=83)
	Frequency (%)					
Acinetobacter baumannii	41 (61)	6 (66.)	0	1 (100)	3 (60)	48(57)
Klebsiella pneumoniae	19 (29)	1 (11)	1 (33)	0	1 (20)	22(26)
Pseudomonas aeruginosa	2 (4)	1 (11)	1 (33)	0	0	4(4)
Others	3 (4)	1 (11)	1 (33)	0	1 (20)	4(4)
Total	65(78)	9(10)	3(3)	1(1)	5(6)	

Cultures were obtained from all patients prior to the initiation of intravenous colistin. Figure 1 shows the blood isolates and antibiotic resistance rates. The most common organism isolate was *A. baumannii* with noted high resistance to meropenem, aztreonam, and amikacin. However, it was susceptible to colistin. Nineteen patients had *K. pneumoniae* in their blood culture with noted resistance to aztreonam, piperacillin-tazobactam and high resistance rates to ciprofloxacin, meropenem, and amikacin. Although there were only two *P. aeruginosa* organisms isolated in the blood, it was resistant to all antibiotics except for colistin.

Figure 1.1 Resistance rates of Acinetobacter baumannii isolates (n=41)

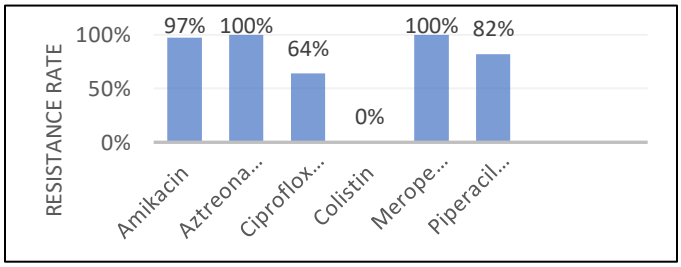


Figure 1.2 Resistance rates of Klebsiella pneumoniae isolates (n=19)

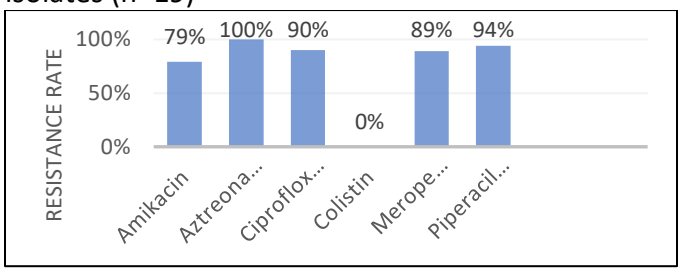
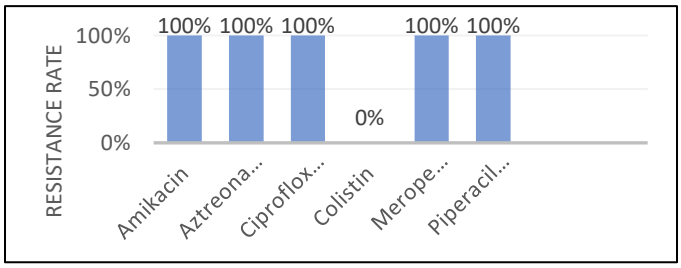


Figure 1.3 Resistance rates of Pseudomonas aeruginosa isolates (n=2)



For the urine isolates, the two most common MDR-GNB isolated were *K. pneumonia* and *P. aeruginosa*. These organisms were sensitive to colistin but were resistant to all other antibiotics. Both patients were term infants born with lumbosacral myelomeningocele with probable concomitant neurogenic bladder.

Antibiotic sensitivity of the endotracheal aspirates was also determined in neonates with severe pneumonia. Standard cultures of the endotracheal aspirates upon intubation were performed and the two most common organisms isolated were *A. baumannii* and *K. pneumoniae*, with similar resistance rate to aztreonam, ciprofloxacin, and piperacillin-tazobactam but colistin showed good activity on these MDR-GNB.

Only three CSF MDR-GNB isolates were recorded in this study, *A. baumannii*, *K. pneumoniae* and *E. coli.* They were resistant to all the listed antibiotics but were sensitive to colistin. Patients who had MDR-GNB ventriculitis have Arnold Chiari II malformation that underwent operative repair of their lumbosacral mass.

Abscess isolates were obtained in two patients, one patient was a full-term infant who had ruptured myelomeningocele upon delivery who underwent surgical repair and developed multi-drug resistant *K. pneumoniae* sepsis and soft tissue abscess on the left forearm secondary to burn. Incision and drainage of the abscess were done revealing multi-drug resistant *K. pneumoniae* on culture. The second patient was a 27-week old infant admitted due to respiratory distress secondary to prematurity, later had necrotizing enterocolitis III-B with abdominal abscess formation. The culture of the abdominal abscess revealed multi-drug resistant *A. baumannii*.

Table 5 presents the antibiotics used prior to colistin administration, the two most common antibiotics were ciprofloxacin (41%) and meropenem (41%). These antibiotics were mostly used in combination with an aminoglycoside (amikacin). Before the utilization of colistin in our institution in 2015, combination therapy with meropenem + ciprofloxacin (8%) were given to MDR-GNB infections.

Table 5. Antibiotics used prior to Colistin treatment

Antibiotics	**Frequency (%)**
Ciprofloxacin	31 (41.33)
Meropenem	31 (41.33)
Meropenem+Ciprofloxacin	6(8.00)
Piperacillin-Tazobactam	4 (5.33)
Cefepime	1 (1.33)
Cefotaxime	1 (1.33)
Meropenem+Vancomycin	1 (1.33)

Table 6 shows the outcome of patients with MDR-GNB treated with colistin. Of the 75 patients with MDR-GNB infections, 37 (49.3%) survived and completed the course of their colistin treatment while the other 38 (50.7%) patients died. The majority of the deaths were attributed to severe sepsis (29) despite adequate antimicrobial treatment. Other causes of death were respiratory

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failure (6) and multiple organ dysfunction syndrome (3).

Table 6. Outcome of patients with MDR-GNB treated with colistin

Outcome	Frequency (%)
Died	38 (50.67)
Survived	37 (49.33)

Univariate analysis on factors associated with mortality including sex, weight, location of admission, underlying disease, isolated organism, and adverse effects was performed. The only factor that was associated with mortality was the duration of intravenous colistin in days this is shown in table 7. The result of the univariate analysis showed that for every day increase in the duration of colistin treatment, the odds of mortality decreases by 19.56%. Since there is only one variable that was significant on univariate analysis, multivariate analysis was no longer done.

Table 7. Univariate analysis of factors associated with mortality (n=75)

Variable	Crude odds ratio	95% CI	P-value
Duration of IV colistin treatment in days	0.8044	0.7187 to 0.9002	**<0.001**

Combination therapy with colistin and another antimicrobial was based on the organism isolated and their culture susceptibility results. Since the most common MDR-GNB isolated was *A.baumannii*, intravenous colistin was given in combination with ampicillin-sulbactam (44%) because of its synergistic in-vitro activity to *A.baumannii*. Table 8 shows the antibiotics given in combination with colistin. Concomitant antibiotics given during colistin administration were analyzed and revealed no statistical association with the outcomes. The mean duration of intravenous colistin treatment was 11.45 ± 5.81 days.

Table 8. Concomitant antibiotics given with colistin and their outcomes

Antibiotics	Total (n=75)	Expired (n=38)	Alive (n=37)	P-value
	Frequency (%)			
Amikacin	3 (4)	0	3 (8.11)	0.115
Ampicillin-Sulbactam	33 (44)	19 (50)	14 (37.84)	0.355
Meropenem	11 (14.67)	8 (21.05)	3 (8.11)	0.191
Ciprofloxacin	17 (22.67)	9 (23.68)	8 (21.62)	1.000
Aztreonam	21 (28)	7 (18.42)	14 (37.84)	0.075

Renal function tests that includes blood urea nitrogen, serum creatinine and urine output monitoring were done prior to and during colistin treatment. It was repeated every 3 to 5 days while ongoing colistin administration until the completion of treatment. Acute kidney injury manifestations were seen in 3 patients, two of which had an increase in serum creatinine as early as the 3rd day and the other patient had decreased urinary output. These patients were referred to a pediatric nephrologist and appropriate adjustment on the colistin dose was done based on their creatinine clearance. In this study, two neonates developed maculopapular rashes after colistin administration typical for hypersensitivity reaction (2.7%). Desensitization to colistin was done on both patients. These adverse effects are shown in table 9.

Table 9. Adverse effects of patients with MDR-GNB treated with colistin

Adverse effects	Frequency (%)
Nephrotoxicity	3 (4)
Neurotoxicity	0
Electrolyte imbalance	0
Hypersensitivity	2 (2.70)

DISCUSSION

The increasing global burden of MDR-GNB infections in pediatric patients is emerging. The prevalence of this disease is also seen in our country. Neonates are at the highest-risk for developing MDR-GNB infections. A mortality rate of 78% was documented in pediatric patients with MDR-GNB infections compared to 41% mortality rate among patients with non-MDR-GNB.[9] Treatment options to these infections are limited, because of this, an old drug was re-introduced. Colistin belongs to the Polymyxin group and it was widely used for its efficacy in gram-negative infections both in adults and children but owing to its nephrotoxicity and availability of newer, safer drugs, it was abandoned. Although there are some studies on colistin use in neonates, the effectiveness of this drug is not well established. The efficacy of colistin in those studies range from 50% to 98%.[4,8]

In our study, there was a 49.3% survival rate with intravenous colistin use. The majority of deaths were secondary to severe sepsis. Several confounders like age, weight, co-morbidities, etc. were not found to be significant to their outcome.

In a similar study on the safety and efficacy of intravenous colistin use in neonates by Tekgunduz et.al, the clinical and microbiological response to colistin and its adverse effects were evaluated. Included in that study were 12 neonates with mean 31.8 ± 3.5 weeks gestational age. Eleven (91.7%) patients showed microbiological clearance with intravenous colistin. However, only 6 (50%) patients survived. Despite high microbiological clearance there were 6 (50%) mortalities, contributing factor to mortality was probably secondary to their underlying co-morbidity (congenital cystic adenomatoid malformation, CHARGE syndrome, congenital heart disease, William syndrome, NEC). Although no statistical analysis on the significance of the co-morbidity was done in that study.[4] Comparing this to our study, a similar survival rate (49.3%) was seen. Also, in Tekgunduz study, 91.7% were pre-term with a median birth weight of 1482 grams in contrast to our study of having 73.3% pre-term neonates with MDR-GNB infections with a similar median birth weight of 1500 grams.

A review of neonates who received intravenous colistin admitted to a NICU in India was done in 2012. A total of 62 neonates received intravenous colistin for the treatment of *A. baumannii*, *K. pneumonia* and *P. aeruginosa* infections. Of the total 62 neonates, 41 (66.12%) survived and 21 (33.87%) died. No adverse effect was reported in that study.[10] In that study by Jasani et.al, analysis of variables with the outcome was done. Significant association in mortality was observed in lower birth weight (<1000gm), early pre-term neonates (<32 weeks), duration of colistin use (10 days) and sepsis due to *Klebsiella.* Similar analysis of variables with the outcome was also done in our study, the only similar significant variable in the analysis is the duration of colistin use. In contrast to the study in India, a more specific classification in weight, prematurity, type of sepsis (early or late), timing of initiation and duration of colistin use were analyzed.

A retrospective single-center study was conducted in Turkey in 2018 by Ilhan, et.al, it aimed to compare the efficacy and safety of intravenous colistin among very low birth weight preterm infants and non-low birth weight infants. The efficacy of colistin between the two groups was comparable with 89.3% vs 86.8% efficacy. During colistin treatment, adverse effects were monitored, serum magnesium and potassium levels were significantly lower in the very low birth weight infants than in the non-low birth weight infants during colistin therapy.

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[11] In the study of Ilhan, demographic characteristics and outcome were analyzed, gestational age, weight and apgar score were found to be significant. Clinical characteristics were determined, it was reported that only 27 (40.9%) of 66 patients were intubated probably owing to the low mortality rate (27%) and high efficacy rate (89.3%) in that study. Monitoring of adverse effects including electrolyte imbalance were likewise done in our study but in contrast to the study of Ilhan no abnormalities in electrolytes were documented in our patients.

Nephrotoxicity, neurotoxicity, and electrolyte imbalance were the most commonly reported adverse effects of intravenous colistin use. [3,5,11,12,13] In this study, 3(4%) patients developed nephrotoxicity secondary to intravenous colistin. Only 1 patient presented with decreased urine output while the 2 other patients presented with an increase in serum creatinine on serial monitoring after 3 days of intravenous colistin. In other clinical studies, the incidence of colistin-associated neurotoxicity reported was about 7%.[11] In this study, seizure (8%) episodes observed in six patients manifested prior to colistin administration and these were attributed to their underlying CNS disease (meningitis, ventriculitis, hydrocephalus, etc.). Also, important to note was the development of hypersensitivity reaction to colistin on 2 (2.6%) patients presenting as maculopapular rash. Electrolytes were monitored during colistin treatment and no abnormalities were seen.

Studies involving pediatric patients given colistin including one study on neonates reported nephrotoxicity rates that ranged from 1.6% to 22% while neurotoxicity rates range from 0% to 4%.[12] The colistin monograph reports the incidence of reversible renal toxicity with polymyxins ranging from 20 to 60 %, although this wide range depends on several factors including dose, existing renal dysfunction, severity of illness, confounding advanced chronic diseases, and the high use of concomitant nephrotoxins in patients receiving polymyxins. These data are probably the basis why colistin has been used sparingly in the recent years. Our study showed a significantly lower nephrotoxicity profile compared to the ones mentioned in literatures. Hypersensitivity reactions have also been reported in 2% of patients.[13]

Nephrotoxicity rate of concomitant medications used in this review includes amikacin with 10-20%, aztreonam with 6%, ampicillin-sulbactam with <1%. [14] The nephrotoxicity rate reported in literatures for amikacin, a commonly used drug in the population included in this study is higher than the nephrotoxicity rate computed for colistin in this study. It should lead us to question if amikacin use is safer than colistin use in our study population. These relatively low rates of adverse events with the use of colistin would make a physician more comfortable in using this drug in our study population. Especialy important to note is the fact that in most of these patients, only colistin is found to have in-vitro sensitivity to the MDR-GNB isolated.

Efficacy of colistin in MDR-GNB varies in different studies, the organisms involved play a huge factor in the patients' survival. In this study, all MDR-GNB isolates showed high resistance to almost all the antibiotics usually given in the NICU. Perhaps this is one of the reasons why there is only 50% survival of the patients in this study. Prior to colistin use, 41% these patients were on broad-spectrum antibiotics, that may have predisposed them to having MDR-GNB. The different combination of antibiotics that were given, as we have seen in the results of this study, had no significant effect on the outcome of patients. The only significant factor affecting outcome was the days of colistin given. This is probably explained by the fact that the longer you give colistin, bacterial eradication is continued thus probably translates to patient getting better and surviving from the MDR-GNB infection.

Since this is a retrospective study, the lack of a control group and not being able to do a multi-variate analysis of the contributing factors to the outcome are some of the limitations of this study. Likewise, bacterial clearance, long-term effects of colistin were not explored. However, overall, the

result of this study with regards to the effectiveness and adverse effects of intravenous colistin in neonates is quite similar to the other studies.

CONCLUSION

This study showed that neonates with MDR-GNB treated with intravenous colistin had almost 50% effectiveness measured in terms of survival. Although there was note of nephrotoxicity (4%) and hypersensitivity (2.6%), it is within the reported rates based on other studies and is actually much lower.

Neonates are at high-risk to the emerging MDR-GNB infections and with the limited antibiotic options, intravenous colistin is safe and can be used in this age-group until a new drug is available for MDR-GNB organisms.

RECOMMENDATION

Prospective studies are recommended to evaluate efficacy of intravenous colistin in the sterilization of cultures. Likewise, a prospective randomized comparative study on the outcome or efficacy using colistin in combination with different anti-microbials is worthwhile.

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