ORIGINAL ARTICLE

Use of colistin for the treatment of multi drug resistant isolates in neonates

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Abstract

Objective: To determine the impact of using colistin for multidrug-resistant organisms in neonates.

Methods: This retrospective study was conducted at the Shifa International Hospital, Islamabad, Pakistan, and comprised microbiological data of babies from January 2010 to October 2012.The data was reviewed to identify the babies infected with multidrug-resistant organisms and who had received colistin therapy. SPSS 16 was used for data analysis.

Results: Of the 30 neonates, 24(80%) were males and 6(20%) were females. Besides, 16(53.3%) neonates were preterm babies (≤ 37 weeks gestation). Two or more risk factors for multidrug-resistant organisms were present in 13(44%) babies. Mechanical ventilation was found in 26(87%) neonates and prior prolonged use of antibiotics in 7(23%). The commonest pathogen isolated was Acinetobacter, in 22(73%) cases. All isolates were susceptible to colistin but pan-resistant to multiple antibiotics, including cephalosporins, amikacin, meropenem and piperacillin/tazobactam. Colistin therapy was used for bacteraemia in 2(7%) cases, clinical sepsis 18(60%), pneumonia 2(7%) and tracheitis 8(26.7%). Moreover, 15(50%) neonates received both intravenous and aerosolised colistin while 9(30%) received aerosolised therapy alone.

Conclusion: Colistin therapy was well tolerated in neonates for the treatment of multidrug-resistant organisms.

Keywords: Colistin, Multidrug-resistant organisms, Neonates. (JPMA 67: 1157; 2017)

Introduction

In recent years, there has been an emergence of multidrug-resistant organisms (MDROs) in neonatal intensive care units (NICU) worldwide.[1-3] They present with a wide clinical spectrum of disease, ranging from asymptomatic colonisation to multisystem involvement, including pneumonia, meningitis and septicaemia.[1-3] The resistance to both first- and second-line antibiotics is alarmingly high with limited options for treatment. This has lead to resurgence of old classes of antimicrobials being increasingly used for such difficult infections, including colistin.[4] But the experience of using colistin in neonates remains limited.

The current study was planned to identify the neonatal risk factors for MDROs and to assess the indications of use, efficacy and side effects of colistin.

Materials and Methods

This retrospective study was conducted at the Shifa International Hospital (SIH), Islamabad, Pakistan, and comprised microbiological data of all the babies admitted to the hospital's NICU from January 2010 to October 2012. The data was reviewed to identify the babies infected with MDROs and had received colistin therapy. Their medical records were analysed to collect the relevant data, including risk factors, indications, dose and duration of colistin administration, its adverse effects and outcome. Colistin (colistimethate sodium colistin®) was used in a dose of 25,000 units/kg/day intravenously in 2-3 divided doses and/or 125,000 units twice daily as aerosolised therapy. Automatic blood culture system (BD BACTEC 9240) was used during the entire study period using the manufacturer's paediatric bottles of diagnostic system. Disc diffusion method had been used for susceptibility testing in all organisms except Acinetobacter species where the disc diffusin was not reliable as per the guidelines of Clinical and Laboratory Standards Institute (CLSI) 2010-12.[5] However, all the Pseudomona (P.) aeruginosa isolates were considered sensitive to colistin having the zone of inhibition more than 11mm. The antibiotic panel selected for P. aeruginosa had been as per the CLSI guidelines.[6] Data was analysed using SPSS 16. Demographic, clinical, laboratory features and results were presented as mean ± standard deviation (SD) for quantitative variables (age, birth weight and duration of therapy) and as frequencies and percentages for qualitative variables (gender, gestational age at birth, admitting diagnosis, risk factors for MDROs, pathogens isolated, clinical spectrum of disease, treatment modalities and mortality).

Results

Of the 30 neonates, 24(80%) were males and 6(20%) were

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Table-1: Demographics and clinical spectrum of disease.

	Number (Percentage)
Total patients	30 (100)
Males	24 (80)
Mean age at admission (days)	2.5±2
Preterm ≤ 37 weeks	16 (53.3)
Shifa Born	19 (63.3)
Admitting Diagnosis	
Prematurity with RDS	11 (36.7)
Sepsis	8 (26.7)
Birth asphyxia	7 (23.3)
Risk Factors	
Two or more	13 (44)
Mechanical ventilation	26 (87.6)
Prolonged antibiotics	7 (23.3)
Central venous catheters	4 (13.3)
Surgical interventions	3 (10)
Clinical Spectrum	
Culture proven sepsis	2 (6.7)
Clinical sepsis	18 (60)
Pneumonia	2 (6.7)
Tracheitis	8 (26.7)
Crude Mortality	5 (16.7)

RDS: Respiratory distress syndrome.

females. The overall mean age at admission was 2.5±2 days (range: 1-17 days). Moreover, there were 16(53.3%) preterm babies (≤ 37 weeks gestation) and approximately two-thirds were born at the SIH. Besides, 13(44%) neonates had 2 or more risk factors for MDROs. The commonest risk factors identified were mechanical ventilation, prolonged antibiotics, central venous catheters and surgical interventions.

Among the positive cultures, 8(26.7%) were tracheitis and 18(60%) were clinical sepsis. Crude mortality was 5(16.7%) (Table-1).

The MDROs pathogens isolated were Acinetobacter in 22(73.3%) cases, Pseudomonas in 9(30%), Klebsiella in 3(10%) and Enterobacter in 2(6.6%), with 2 (6.6%) neonates having polymicrobial infections. The commonest site of isolation was tracheal secretions 27(90%), followed by blood 2(6.7%).

Susceptibility showed 100% resistance to cephalosporins, amikacin, meropenem and piperacillin-tazobactam and 96.7% resistance to ciprofloxacin. All were susceptible to colistin. Colistin therapy was started for culture-proven sepsis (positive blood culture) in 2(6.7%) cases, clinical sepsis (positive tracheal secretion's culture with clinical and laboratory evidence of sepsis) in 18(60%), pneumonia (clinical and radiological evidence of pneumonia along with positive culture of tracheal secretions) in 2(6.7%) and

Table-2: Colistin Therapy.

	Number (Percentage)
Indications	
Culture proven sepsis	2 (6.7)
Clinical sepsis	18 (60)
Pneumonia	2 (6.7)
Tracheitis	8 (26.7)
Mode of Administration	
Intravenous andaerosolised	15 (50)
Aerosolised only	9 (30)
Intravenous only	6 (20)
Dose (units/kg/day)	
Intravenous	25,000
Aerosolised	2,50,000
Mean Duration of Therapy (days)	
Aerosolised	6.6 (1-20)
Intravenous	9 (1-12)

tracheitis (positive tracheal secretion's culture without associated clinical or laboratory findings suggestive of pneumonia) in 8(26.7%) cases. Colistin was used as monotherapy in 4(13.3%) cases and as combination therapy in 26(86.7%) cases with other antimicrobials, including cephalosporins 13(43.3%), amikacin 20(66.6%), meropenem 10(33.3%), ciprofloxacin 1(3.3%), vancomycin and linezolid 2(6.7%) each. The aerosolised therapy with colistin was given for a mean duration of 6.6±2 days and intravenous (IV) therapy for 9±3.5 days (Table-2).

None of the patients had any side effect of colistin. During the course of hospitalisation serum creatinine was serially monitored twice weekly and no colistin related nephrotoxicity was observed. At the cessation of therapy, serum creatinine was normal in all the neonates. Also, there was no evidence of neurotoxicity manifesting as seizures or irritability that could be attributed to colistin.

Discussion

The empirical choice of antibiotics for suspected and proven serious gram-negative bacterial infections is being debated.[1] The goal is to optimise the delivery of effective antibiotics to the site of infection and at the same time to minimise the spread of antimicrobial resistance. Third generation cephalosporins may be the initial drugs of choice but with increasing cephalosporin resistance, carbapenems may be used as initial therapy. Gray et al. noted that with emerging carbapenem resistance neonatologists may have to switch to colistin whose safety and clinical efficacy in neonates is not well defined so far.[1]

Colistimethate is an antimicrobial agent produced by

Bacillus colistinus. It became commercially available in 1959 and was approved by the Unites States Food and Drug Administration (FDA) for treatment-susceptible gram-negative bacteria. Colistimethate is hydrolysed to colistin, a cationic agent that acts by increasing permeability of cell membrane and leading to cell death.[2] Colistin has a half-life of 1.5 to 8 hours and is eliminated via kidneys. The recommended dose and units of measurement, however, remain variable. The most common dose of colistimethate sodium is IV 50,000-75,000 units/kg/day in two divided doses, for patients with normal renal function.[2] We used a lower dose for neonates with good results. The major adverse effects include nephrotoxicity, neurotoxicity and pulmonary toxic effects. Dosages and interval adjustments are required for patients with creatinine clearance less than 75 mL/min.[2] Neurological toxicity, mostly manifests as meningeal irritation, is dose-dependent and reversible.[2]

Acinetobacter baumannii has emerged as a serious challenge in Pakistan as well.[3] Of the 90 Acinetobacter isolates 87 were multidrug-resistant collected from different hospitals in Pakistan. Tigecycline was the most effective drug with susceptibility of 85%, followed by colistin 50%.[3] In our study as well, Acinetobacter was the commonest pathogen but was 100% susceptible to colistin.

Colistin has also been used successfully in the treatment of central nervous system (CNS) infections caused by multidrug-resistant Acinetobacter. In these patients, IV colistin is used in combination with intrathecal colistin[4] with increased cerebrospinal fluid (CSF) concentrations of colistin in children with meningitis.[7] Colistin has emerged as a useful drug in managing a variety of gram-negative infections. Researchers in Saudi Arabia used minimum inhibitory concentration (MIC) to document that colistin was active against 100% of Acinetobacter species, 84% of P. aeruginosa and 79% of Stenotrophomonas (S.) maltophilia.[8]

Nakwan N. et al. conducted a study on eight neonates (three preterm and five term neonates), with ventilator associated pneumonia (VAP) caused by Acinetobacter, who received aerosolised colistin. Six of them received aerosolised colistin without concomitant IV colistin. All the babies were cured leading the researchers to conclude that aerosolised colistin alone may alone be a useful therapy in treatment of VAP.[9]

In another study, thirteen patients (meanage 5 years; range 22 days to 14 years) received 19 courses of colistin for treatment of pneumonia, CNS infection, bacteraemia or complicated soft-tissue infection.[10] The isolated pathogens included Acinetobacter baumannii, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa and Stenotrophomonas maltophilia. Daily dose of colistin (colistimethate sodium) ranged between 40,000and 225,000 international units (IU)/kg and it was administered for duration of 1 to 133 days. Only one patient had an increase of serum creatinine, possibly due to co-administration of colistin and gentamicin. Only two patients died. Colistimethate sodium thus appears effective for the treatment of severe MDROs infections caused in paediatric patients. In our study, Acinetobacter and Pseudomonas were the commonest pathogens isolated and colistin administered.

Falagas et al. found cure rate of 235(86.7%) in children who received colistin with mortality of 20(7.4%).[11] Nephrotoxicity was seen in 2.8% of the cases, thus concluding that systemic colistin is an effective and safe drug for the treatment of children with MDROs. Pintado et al. reported similar results in 2008.[12]

Karaiskos et al. treated 83 episodes on Acinetobacter meningitis and/or ventriculitis (including 10 children and neonates) with colistin administered intraventricular and intrathecal for a mean duration of 18.5 days.[13] The overall success rate was 89%. Colistin induced reversible chemical meningitis and/or ventriculitis in 11% cases.

In Taiwan, 8 preterm infants (with gestational age of 25-36 weeks) were treated with inhaled colistin as monotherapy for VAP due to Acinetobacter baumannii.[14] All of them were cured and no adverse effects were reported. Similar results were reported by Celik et al. for aerosolised colistin as being tolerable and safe and used as an adjunctive treatment option for MDROs VAP in neonates.[15] Our patients also had multiple presentations ranging from tracheitis to pneumonia and septicaemia. Most of them were successfully treated with no major side effects.

Conclusion

Colistin therapy was well tolerated in neonates for treatment of MDROs infections, such as Acinetobacter and Pseudomonas.

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Conflict of Interest: None.

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References

1. Gray JW, Ubhi H, Milner P. Antimicrobial treatment of serious gram-negative infections in newborns. Curr Infect Dis Rep 2014; 16: 400.
2. Manchanda V, Sanchaita S, Singh NP. Multidrug Resistant

Acinetobacter. J Glob Infect Dis 2010; 2: 291-304.
3. Hasan B, Perveen K, Olsen B, Zahra R. Emergence of carbapenem-resistant Acinetobacter baumannii in hospitals in Pakistan. J Med Microbiol 2014; 63: 50-5.
4. Dalgic N, Ceylan Y, Sancar M, Telhan L, Kafadar I, Cavusoglu H, et al. Successful treatment of multidrug-resistant Acinetobacter baumannii ventriculitis with intravenous and intraventricular colistin. Ann Trop Paediatr 2009; 29: 141-7.
5. CLSI 2010: Performance standards for antimicrobial susceptibility testing; twentieth information supplement. Page 54-55
6. CLSI 2010: Performance standards for antimicrobial susceptibility testing; twentieth information supplement. Page 52-53.
7. Antachopoulos C, Karvanen M, Iosifidis E, Jansson B, Plachouras D, Cars O, Roilides E. Serum and cerebrospinal fluid levels of colistin in pediatric patients. Antimicrob Agents Chemother 2010; 54: 3985-7.
6. Somily AM. Comparison of E-test and disc diffusion methods for the in vitro evaluation of the antimicrobial activity of colistin in multi-drug resistant Gram-negative Bacilli. Saudi Med J 2010; 31: 507-11.
7. Nakwan N, Wannaro J, Thongmak T, Pornladnum P, Saksawad R, Nakwan N, et al. Safety in treatment of ventilator-associated pneumonia due to extensive drug-resistant Acinetobacter baumannii with aerosolized colistin in neonates: a preliminary report. Pediatr Pulmonol 2011; 46: 60-6.
8. Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, et al. Colistin administration to pediatric and neonatal patients. Eur J Pediatr 2010; 169: 867-74.
9. Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents 2009; 33: 503.e1-503.e13.
10. Pintado V, San Miguel LG, Grill F, Mejía B, Cobo J, Fortún J, et al. Intravenous colistinsulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. J Infect 2008; 56: 185-90.
11. Karaiskos I, Galani L, Baziaka F, Giamarellou H. Intraventricular and intrathecalcolistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: a literature review. Int J Antimicrob Agents 2013; 41: 499-508.
12. Kang CH, Tsai CM, Wu TH, Wu HY, Chung MY, Chen CC, et al. Colistin inhalation monotherapy for ventilator-associated pneumonia of Acinetobacter baumannii in prematurity. Pediatr Pulmonol 2014; 49: 381-8.
13. Celik IH, Oguz SS, Demirel G, Erdeve O, Dilmen U. Outcome of ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosatreated with aerosolized colistin in neonates: a retrospectivechart review. Eur J Pediatr 2012; 17: 311-6.