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ORIGINAL PAPER

Outcome of ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* treated with aerosolized colistin in neonates: a retrospective chart review

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Abstract Multidrug-resistant (MDR) gram-negative bacteria-related nosocomial infections and ventilator-associated pneumonia (VAP) presents an emerging challenge to clinicians. Older antimicrobial agents such as colistin have become life-saving drugs because of the susceptibility of these pathogens. We report our experience with aerosolized colistin in two preterm and one term neonate with *Acinetobacter baumannii* and *Pseudomonas aeruginosa*-related VAP who were unresponsiveness to previous antimicrobial treatment. All pathogens were isolated from tracheal aspirate. We used 5 mg/kg (base activity) aerosolized colistin methanesulfonate sodium in every 12 h as an adjunctive therapy for VAP. VAP was treated by 14, 14, and 16-day courses of aerosolized colistin in these patients, respectively. No adverse effect such as nephrotoxicity or neurotoxicity was observed. We found that aerosolized colistin was tolerable and safe, and it may be an adjunctive treatment option for MDR gram-negative bacterial VAP in neonates. Further studies are needed to determine appropriate doses for aerosolized colistin and its eligibility as an alternative treatment choice in newborns.

Keywords Aerosolized colistin · Newborn · Multidrug-resistant gram-negative bacilli · *Acinetobacter baumannii* · *Pseudomonas aeruginosa* · Ventilator-associated pneumonia

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Introduction

The emergence of multidrug-resistant (MDR) nosocomial gram-negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has become an important cause of nosocomial infection leading to increasing morbidity and mortality worldwide [24, 38, 40]. Ventilator-associated pneumonia (VAP) is a significant concern in the neonatal intensive care unit (NICU) [43]. No new antimicrobial drugs to treat MDR gram-negative bacterial infections have been approved recently [3]. Therefore, older agents such as colistin have been reevaluated for treatment of these difficult pathogens [7].

Colistin is a member of the polymyxin family and was first discovered in the 1950s [27, 30]. It has a concentration-dependent bactericidal mechanism and binds to the anionic lipopolysaccharide molecule by displacing calcium and magnesium in the outer cell membrane of gram-negative bacteria. Colistin also impedes the production of endotoxins and cytokines [12, 25, 44]. Colistin has a broad spectrum of action against gram-negative aerobic bacilli, including some strains resistant to carbapenems, aminoglycosides, penicillins, cephalosporins, and fluoroquinolones [26]. Low cost of colistin is another important advantage to other antimicrobial agents. Nephrotoxicity and neurotoxicity are limitations of colistin that led to decreased use beginning in the 1980s [8]. Nephrotoxicity, including acute and chronic renal diseases, was reported from 10.5% to 36%, and there were multiple case reports in both children and adults [1, 14, 26, 41]. Neurotoxicity such as paresthesias and respiratory apnea was reported between 7.3% and 27% in the literature [14, 17, 26, 31, 36]. However, intravenous and aerosolized colistin use has increased due to the emergence of MDR gram-negative

bacterial infections and VAP in the last two decades [2, 33, 34]. Colistin administration by inhalation to the lung leads to low systemic absorption and low toxicity [29, 37]. Recently, there have been several reports of successful treatment of MDR gram-negative bacterial VAP with aerosolized colistin in patients without cystic fibrosis [11, 28, 35]. Aerosolized delivery may be less toxic than intravenous colistin, but the available data on the safety and efficacy of aerosolized colistin are mostly from adult patients [8, 9, 23]. Here, we report our experience with aerosolized colistin treatment in two preterm and one term infants with MDR gram-negative bacterial VAP and discuss the new role of this antimicrobial agent in the new era of antibiotics and microorganisms.

Materials and methods

This retrospective study was conducted at the NICU of the Zekai Tahir Burak Maternity Teaching Hospital, the biggest tertiary neonatology unit in Turkey, between January 2010 and December 2010. Our hospital's birth, NICU admission, and patient day numbers are approximately 20,000, 4,000, and 47,000 in a year, respectively. Percentage of documented infection was 3.4% in 2010. The incidence of nosocomial infections due to *A. baumannii* and *P. aeruginosa* were 7.5% and 0.7%, respectively. We use penicillin G and netilmicin as prophylactic antibiotics in conditions such as gestational age <32 weeks, birth weight <1,500 g, prolonged rupture of membranes, chorioamnionitis, maternal positive cervix culture, and urinary infection. We do not routinely perform colonization research. We isolate patients with MDR gram-negative bacterial infection (GNB) until end of treatment and negative culture results. Data regarding demographics, microbiology, risk factors, antibiotic treatment, and prognosis were collected from medical records.

Patients undergoing mechanical ventilation for 48 h or more and with a new or progressive infiltrate, consolidation, cavitation, or pleural effusion as shown on chest radiographs were diagnosed as suffering from VAP according to US Centers for Disease Control and Prevention (CDC) guidelines [39]. Additionally, patients who demonstrated one or more of the following: new purulent sputum or a change in the character of the sputum, a microorganism isolated from a blood culture that was not related to another source of infection, and isolation of pathogens from a specimen obtained by transtracheal aspiration of bronchoalveolar fluid after installing 1 mL 0.09% NaCl were diagnosed as VAP.

We used BACTEC 9240 (Beckton-Dickinson, USA) to identify the microorganism. The VITEK 2 susceptibility card AST-N090 (bioMérieux, Marcy l'Etoile, France) containing a colistin susceptibility test was used according to the manufacturer's instructions. Interpretive breakpoints (MIC ≤0.5 μg/mL, susceptible, and MIC ≥16 μg/mL, resistant) were used for the VITEK 2. MDR was defined as antibiotic resistance to three or more antibiotic classes [42].

Colistin methanesulfonate sodium (Colimycin; Kocak Farma, Istanbul, Turkey) was used for the aerosol preparation. Each vial contained 360 mg colistin equivalent to 4.5 million IU or 150 mg colistin base activity diluted with 3 mL of sterile saline 0.9% to give a concentration of 5 mg/kg colistin base activity when administered. Each preparation was completed in approximately 5 min using sterile techniques. The resulting suspension containing 5 mg/kg colistin base activity was aerosolized using a ultrasonic nebulizer (Aeroneb; Aerogen, Galway, Ireland) for 15 min every 12 h to the mechanically ventilated patient (SLE 2000; SLE, South Croydon, UK). Drug options were discussed with the parents, and approval before the drug administration was obtained. Outcomes (e.g., survival, duration of ventilator support, tracheal aspirate cultures) and toxicity were monitored. The primary outcome was successful treatment of VAP. Renal toxicity was defined as decreased urinary output less than 1 mL/kg/h, plasma creatinine level more than 1.5 mg/dL, and elevated blood urea nitrogen [18]. Respiratory and heart rate, blood pressure, and oxygen saturation were monitored during therapy. Intravenous antibiotic treatment was continued during aerosolized colistin therapy.

Results

Case 1 was born at 31 weeks of gestational age, 1,180 g from first pregnancy of 31-year-old mother. He was followed with the diagnosis of meningomyelocele (MMS), respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), grade 4 intracranial hemorrhage (ICH), and perforated necrotizing enterocolitis (PNEC). Diagnosis of VAP was made on 45th day within 25-day course of mechanical ventilation, and *P. aeruginosa* was isolated from tracheal aspirate. He was treated for acute phase reactant positivity with meropenem, gentamicin, and ciprofloxacin before the diagnosis of VAP. Aerosolized colistin was used for 14 days, and VAP was cured. Meropenem and ciprofloxacin were given as concomitant antibiotic therapy for 14 and 10 days, respectively. He died from complications of PNEC.

Case 2 was born at 40 weeks of gestational age, 2,775 g from first pregnancy of 24-year-old mother. She was admitted to the NICU because of metabolic crises of maple syrup urine disease (MSUD) on postnatal sixth day. She had been mechanically ventilated because of pneumonia and heart failure for 10 days before the isolation of *A. baumannii* from tracheal aspirate. She had been treated

with meropenem and amikacin before starting of aerosolized colistin. VAP was resolved after 14-day course of aerosolized colistin. She was treated with meropenem and amikacin for 14 and 6 days during aerosolized colistin therapy. She was discharged without nephrotoxicity and neurotoxicity, and follow-up to 3 months was normal without any complication.

Case 3 was born at 23 weeks of gestational age, 890 g from first pregnancy of 23-year-old mother. He was followed by the diagnosis of RDS and NEC. Ventilator-associated pneumonia was developed on postnatal day 88. *A. baumannii* was isolated from tracheal aspirate. He had been mechanically ventilated for 19 days before VAP diagnosis, and meropenem and ciprofloxacin had been used before aerosolized colistin. After 16-day course of aerosolized colistin, VAP was cured. She took meropenem and ciprofloxacin for 16 days with the course of aerosolized colistin. He died from complications of NEC and brit ileus.

Demographic and clinical characteristics are presented in Table 1. Diagnosis of VAP was made by criteria of CDC. Microorganisms isolated from tracheal aspirates were considered to be the causative agents of VAP. Two patients were infected with *A. baumannii* and the third with *P. aeruginosa* without bloodstream infection. Colistin became the only effective antibiotic during the course of imipenem, ciprofloxacin, and amikacin treatment in case 3. The durations of aerosolized colistin administration in our patients were 14, 14, and 16 days, with a dosage of 5 mg/kg every 12 h,

Table 1 Demographic and clinical charasteristics of neonates received aerosolized colistin therapy

	Case 1	Case 2	Case 3
Gestational age (weeks)	31	38	23
Sex	Male	Female	Male
Birth weight (grams)	1,180	2,775	890
APGAR (1, 5 min)	1/3	7/9	7/9
Underlying diseases	RDS, PDA, MMS, ICH, PNEC	MSUD, HF	RDS, NEC
Age of pneumonia onset (days)	45	15	88
Microbiology (tracheal aspirate)	*P. aeruginosa*	*A. baumannii*	*A. baumannii*
Antibiotic susceptibility	Colistin, amikacin, ciprofloxacin, levofloxacin, tigecycline	Colistin, meropenem, amikacin, gentamicin, tigecycline, levofloxacin	Colistin, amikacin, gentamicin (resistance developed)
Antibiotics before VAP diagnosis	Meropenem, gentamicin, ciprofloxacin	Meropenem, amikacin	Imipenem, vancomycin, ciprofloxacin, amikacin
Duration of MV before VAP diagnosis (days)	25	10	19
Time between diagnosis of VAP and aerosolized colistin therapy (days)	12	11	17
Duration of aerosolized colistin (days)	14	14	16
Duration of concurrent intravenous antibiotic therapy	Meropenem 14, ciproloxacin 10	Meropenem 14, amikacin 6	Meropenem 16, ciprofloxacin 16
Hb (g/dL); WBC (/μL); PLT (/μL)	11.1; 11,800; 22,000	14.1; 15,400; 385,000	10.8; 9,800; 179,000
BUN (mg/dL), creatinine (mg/dL)	33.8, 0.67	5.1, 0.25	14.3, 0.07
Blood culture	Negative	Negative	Negative
Outcome			
Outcome of VAP infection	Cure	Cure	Cure
Outcome of patient	Died from complications of PNEC	Discharged	Died from complications of NEC, BI
Duration of MV after colistin administration started (days)	9	8	12
Renal toxicity (between the first day of colistin therapy and 3 days after finishing the therapy)	No	No	No
Neurotoxicity	Could not be evaluated (died)	No	Could not be evaluated (died)

RDS respiratory distress syndrome, *PDA* patent ductus arteriosus, *MMS* meningomyelocele, *ICH* intracranial hemorrhage, *PNEC* perforated necrotizing enterocolitis, *MSUD* mapple syrup urine disease, *HF* heart failure, *NEC* necrotizing enterocolitis, *BI* brit ileus, intestinal obstruction due to adhesion of intestines after surgical operation, *VAP* ventilatory-associated pneumonia, *MV* mechanical ventilation, *Hb* hemoglobin, *WBC* white blood cell count, *PLT* platelet

respectively. After 3 days of colistin treatment, tracheal aspirates from cases 1 and 2 showed no culture positivity; from case 3, it was negative after 5 days. Two of the patients died because of NEC complications despite the treatment of VAP (Table 1).

Aerosolized colistin did not affect respiration or heart rate, blood pressure, or oxygen saturation. Urinary output, serum blood urea nitrogen, and creatinine remained within normal limits during the inhalation treatment and the 72-h follow-up period after aerosolized colistin therapy was stopped. Neurological toxicity could be evaluated in one patient and revealed no neurotoxicity.

Discussion

VAP is becoming an important concern in preterm neonates treated with mechanical ventilation [4, 15]. It may be difficult to diagnose VAP and differentiate from airway bacterial colonization in premature infants especially in very low birth weight (VLBW) infants. Clinical signs of VAP may be nonspecific. Guideline to diagnose VAP was reported by CDC for infants younger than 1 year, but it was not specific for VLBW infants [15, 16, 36]. Cordero et al. reported that isolated positive tracheal culture alone does not distinguish between bacterial colonization and respiratory infection [5]. Clinical and laboratory signs help the diagnosis, but they may be nonspecific. We made the diagnosis of VAP with the combination of clinical, laboratory findings, and tracheal aspirate culture results. Causative bacterial agents with resistance to multiple antibiotics are leading clinicians to use older drugs such as colistin [20]. Most of the isolates are resistant to all antibiotics except colistin and tigecycline. VAP caused by MDR gram-negative bacteria has high morbidity and mortality rates and few treatment options.

We treated our patients with VAP caused by MDR gram-negative bacteria with aerosolized colistin because it is more efficient than intravenous use according to literature. Imberti et al. showed no detectable colistin in bronchoalveolar lavage after administrating colistin intravenously in 13 adult patients with VAP-associated gram-negative bacteria [22]. Lu et al. reported an experimental study with piglets comparing intravenous and aerosolized use of colistin to treat *P. aeruginosa* pneumonia and showed no detectable colistin in lung tissue after intravenous use, and aerosolized colistin was more efficient to treat pneumonia than intravenous use of colistin [32]. Ziv et al. showed that colistin was bounded mostly in skeletal tissues more than lung, kidney, liver, and heart after intravenous route in calves [45].

Nakwan et al. reported a case series using aerosolized colistin in eight newborn patients, including three preterm newborns with VAP due to drug-resistant *A. baumannii* [35]. In this research, they used 4 mg/kg of colistin every 12 h as an adjunctive therapy. All patients were cured with no complications. In our study, we used 5 mg/kg colistin every 12 h in three patients without nephrotoxicity. Falagas et al. showed that aerosolized 75 mg colistin for a duration of 15, 25, and 32 days were effective without complications in three pediatric patients (3.5 months, 4 years, and 10 years of age) with tracheabronchitis and pneumonia [13], Goverman et al. reported the use of intravenous colistin in 14 pediatric burn patients and aerosolized colistin in three pediatric burn patients. Colistin was shown to be effective in treating extensive drug-resistant gram-negative bacterial infections, with a cure rate of 79%. Renal impairment without renal replacement therapy was reported in two patients, and no neurotoxicity was observed [19]. Falagas et al. reported successful use of intravenous colistin in treating MDR gram-negative bacterial infections in seven pediatric patients (ranging from 14 months to 11 years of age) [10]. Adverse effects associated with aerosolized colistin were bronchospasm, chest tightness, and renal impairment, and steroids and beta-2 agonists can be used for treatment of bronchospasm and also for prevention [6, 8]. Nephrotoxicity and neurotoxicity have been rarely observed with aerosolized colistin. In our study, we did not observe any systemic adverse events and also respiratory adverse events such as bronchospasm or chest tightness. We were unable to measure plasma colistin levels Systemic absorption of aerosolized colistin and its distribution in neonates can be determined by measurement of plasma colistin level, and further studies should be of interest in this issue. We did not use colistin intravenously due to potential adverse events and the poor clinical conditions of the three patients in this study. As in previous studies in pediatric and adult patients, we used aerosolized colistin as an adjunctive therapy and adapted the dose used in patients >6 years old with cystic fibrosis to our neonates [21]. It is difficult to decide whether to use aerosolized colistin alone in neonates because of limited data about efficacy, potential side effects, and dose regimen. Although all of our patients who received aerosolized colistin were cured, success of treatment cannot be attributable to aerosolized colistin alone in all cases, because all patients also received other active antibiotics and aerosolized colistin was used as an adjunctive therapy. Aerosolized colistin is not a systemic treatment and will not be able to treat pneumonia due to a systemic infection, which is frequently observed in neonates [37]. The use of aerosolized colistin as an adjunctive therapy in MDR VAP patients in children and adults appears very promising. But, colistin resistance may be developed and superinfection can be seen because of inappropriate use of colistin. There is already little treatment options in the MDR era, and it is important not to lose another possible efficient treatment option in battle to MDR microorganisms.

In conclusion, we found that aerosolized colistin was tolerable and safe and may be an adjunctive treatment for MDR gram-negative bacterial VAP in neonates. Further studies are needed to identify the appropriate dose for aerosolized colistin and to determine its eligibility as an alternative treatment choice.

Conflict of interest We have no conflict of interest.

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