Colistin Therapy in a 23-Week Gestational-Age Neonate with Multidrug-Resistant *Acinetobacter baumannii* Pneumonia

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**ABSTRACT**

Multidrug-resistant pathogens are becoming more difficult to treat with significantly increasing infection rates. The lack of new antibiotics to combat these strains has led to the resurgence of older antibiotics. This case highlights the first reported use of colistimethate sodium treatment in a 23-week gestational-age neonate with multidrug-resistant *Acinetobacter baumannii* pneumonia who developed acute renal failure and seizures shortly after initiation of treatment.

**KEYWORDS:** Colistimethate, neonate, extremely low-birth-weight, multidrug resistant

Neonatal infections remain a major cause of morbidity and mortality among extremely low-birth-weight (ELBW) infants. The emergence of multidrug-resistant (MDR) pathogens are increasingly reported and remain a treatment challenge with resistance to standard antimicrobial treatments.1–3 Multidrug-resistant *Acinetobacter baumannii* (MDR-Ab) isolates, one of the most serious therapeutic problems worldwide, are an indicator of poor clinical outcomes and an important cause of ventilator-associated pneumonia, bacteremia, and sepsis in the critically ill patient.1,3–7

**CASE REPORT**

A 535-g female infant was born at 23 weeks' gestational age. She was intubated in the delivery room. Her Apgar scores were 1, 6, and 6 at 1, 5, and 10 minutes. Her neonatal intensive care unit course prior to MDR-Ab was complicated by hyaline membrane disease, electrolyte imbalances, anemia, bilateral grade III to IV intraventricular hemorrhage with infarction of the right cerebral hemisphere, a 7-day course of ampicillin and cefotaxime for suspected early onset sepsis and suppressive chorioamnionitis as diagnosed on placental pathology, and a patent ductus arteriosus that spontaneously closed without treatment. She later developed bronchopulmonary dysplasia, *Enterococcus faecalis* bloodstream infection (on day 67 of life), retinopathy of prematurity, seizures, porencephaly, and posthemorrhagic hydrocephalus requiring placement of a ventriculoperitoneal shunt.

On day of life 11, the patient deteriorated, requiring increased ventilator support and abdominal distension was noted. A full sepsis workup was completed and empiric antibiotic coverage was initiated, which included vancomycin, cefotaxime, and metronidazole. Fluconazole prophylaxis was also initiated per unit protocol. The C-reactive protein and white blood cell count were markedly elevated at 46.66 mg/L and 41.6 K/mm³, respectively, but blood and cerebrospinal fluid cultures...
remained negative. Chest X-ray revealed patchy opacities of both lungs superimposed on granular opacities. Respiratory (sputum) cultures were positive for MDR-Ab. Culture sensitivities revealed a complete resistance to the entire antimicrobial panel, which included cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and beta-lactamase inhibitors. E-test for colistimethate and tigecycline were reported as sensitive (0.5 mCg/mL, 4 mcg/mL respectively). The patient was placed in isolation due to these findings. No other patients were concomitantly positive for MDR-Ab.

The infectious disease team was consulted and in view of worsening findings and marked increase in ventilator support, colistimethate sodium (CMS) was initiated at a dose of 2 mg/kg/dose of colistimethate base activity intravenously (IV) every 12 hours. Synergistic rifampin as reported was added 72 hours later per infectious disease team recommendation. Serum blood urea nitrogen and creatinine prior to initiation of treatment were 34 and 0.8 mg/dL, respectively. The baseline serum blood urea nitrogen and creatinine prior to initiation of treatment were 34 and 0.8 mg/dL, respectively. The baseline urine output was ~4 mL/kg/h. By day 4 of treatment, serum blood urea nitrogen and creatinine increased to 55 and 1.3 mg/dL, respectively, with a significant decrease in urine output. The patient also developed jerking movements, which were suspected to be seizures. She was started on phenobarbital and no further seizure episodes were noted. An electroencephalogram was not feasible at that time due to high-frequency oscillation. Due to signs of nephrotoxicity, the dose of CMS was adjusted to 2 mg/kg IV every 24 hours with close monitoring of renal function. Serum creatinine decreased to 1 mg/dL 2 days later and returned to baseline 5 days later. The patient completed a 10-day course of dose-adjusted CMS and rifampin. The ventilatory support was slowly weaned during the course of treatment, and chest X-ray showed improvement. A repeat respiratory culture after treatment showed no pathogens. The patient also developed an electroencephalogram which was not feasible at that time due to high-frequency oscillation. Due to signs of nephrotoxicity, the dose of CMS was adjusted to 2 mg/kg every 24 hours with close monitoring of renal function. Serum creatinine decreased to 1 mg/dL 2 days later and returned to baseline 5 days later. The patient completed a 10-day course of dose-adjusted CMS and rifampin. The ventilatory support was slowly weaned during the course of treatment, and chest X-ray showed improvement. A repeat respiratory culture after treatment showed no pathogens. The patient also developed a complicated hospital course but was subsequently discharged home at 5 months of age.

DISCUSSION

MDR-Ab is emerging as an important nosocomial pathogen that can cause severe and life-threatening infections and thus increase morbidity and mortality rates in intensive care units. The increase of MDR-Ab strains has rendered traditional antimicrobials ineffective. In addition, due to the decline of new broad-spectrum antibiotics in the pharmaceutical pipeline, combating these MDR strains has prompted the reevaluation of older antibiotics such as the polymyxins.

Polymyxin, a cyclic polypeptide, binds to phospholipids, altering the permeability and causing damage to the cytoplasmic membrane and leakage of intracellular contents. Polymyxins are widely distributed in body tissues such as liver, kidneys, heart, and muscle but do not penetrate into cerebrospinal fluid or synovial fluid or cross the placenta. Reported toxicities associated with polymyxins include renal insufficiency, acute tubular necrosis, and neurotoxicity in the form of apnea, seizures, and neuromuscular blockade. The mechanism of renal toxicity is partly due to its D-amino acid and fatty acid component, which can increase membrane permeability resulting in an increased influx of cations, anions, and water, leading to cell swelling and lysis. Renal toxicity has been reported in up to 11% of cases but is considered to be dose-dependent with previous reports at considerably higher doses used than currently recommended. Recent data on polymyxin-induced toxicity in patients without cystic fibrosis has shown lower and less severe toxicity. The proposed mechanisms of CMS neurotoxicity include a noncompetitive myoneuronal presynaptic blockade of acetylcholine release and hypocalcemia-induced prolongation of depolarization. Reported contributing factors to neurotoxicity have included high doses of CMS, hypoxia, hypocalcemia, and renal disease.

Dosing of CMS in neonates or pediatric patients has varied widely due to the lack of published pharmacokinetic data in this population. Our patient developed signs of toxicity associated with use of intravenous CMS with a Naranjo score of 6 for adverse drug reaction assessment (defined as probable).

Although our patient’s renal function improved with dose adjustments, there are no published studies or recommendations for dosing in ELBW neonates. We suspect that renal compromise induced during CMS treatment was due to extreme prematurity, immature kidneys, and lack of data regarding dosing in the ELBW neonate.

Recent advances in neonatal care have improved the survival and outcomes of ELBW infants. However, infection-related causes of death remain to be a significant issue. Emerging MDR organisms and lack of available drugs to combat these infections has led to the increase in complications. This case report highlights a 23-week gestational-age neonate with MDR-Ab pneumonia who appeared to respond to CMS therapy but who developed suspected CMS-associated nephrotoxicity and neurotoxicity. Due to the paucity of pharmacokinetic data in the neonatal population, toxicities associated with polymyxins must be closely monitored. Further studies in neonates are urgently needed to determine population pharmacokinetics, pharmacodynamics, and efficacy of CMS in this critically ill population.

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