Inhaled Colistin for the Treatment of Tracheobronchitis and Pneumonia in Critically Ill Children Without Cystic Fibrosis

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Summary. Data regarding the role of inhaled colistin in critically ill pediatric patients without cystic fibrosis are scarce. Three children (one female), admitted to the intensive care unit (ICU) of a tertiary-care pediatric hospital in Athens, Greece, during 2004–2009 received inhaled colistin as monotherapy for tracheobronchitis (two children), and as adjunctive therapy for necrotizing pneumonia (one child). Colistin susceptible Acinetobacter baumannii and Pseudomonas aeruginosa were isolated from the cases’ bronchial secretions specimens. All three children received inhaled colistin at a dosage of 75 mg diluted in 3 ml of normal saline twice daily (1,875,000 IU of colistin daily), for a duration of 25, 32, and 15 days, respectively. All three children recovered from the infections. Also, a gradual reduction, and finally total elimination of the microbial load in bronchial secretions was observed during inhaled colistin treatment in the reported cases. All three cases were discharged from the ICU. No bronchoconstriction or any other type of toxicity of colistin was observed. In conclusion, inhaled colistin was effective and safe for the treatment of two children with tracheobronchitis, and one child with necrotizing pneumonia. Further studies are needed to clarify further the role of inhaled colistin in pediatric critically ill patients without cystic fibrosis. Pediatr Pulmonol. 2010; 45:1135–1140.

Key words: Gram-negative infections; polymyxins; Pseudomonas; Acinetobacter; intensive care unit.

INTRODUCTION

The use of inhaled antibiotics for the prevention and treatment of difficult-to-treat infections of the respiratory tract has been investigated over the past years. Inhaled tobramycin and colistin are recommended as an early eradication and maintenance therapy in patients with cystic fibrosis and chronic Pseudomonas aeruginosa infection.1–3 Inhaled pentamidine is suggested as an alternative prophylactic regimen against Pneumocystis jirovecii pneumonia in immunocompromised patients.4 Inhaled ribavirin is also used to treat severe infections of the lower respiratory tract, caused by respiratory syncytial virus (RSV), in children.5 Inhaled zanamivir is considered to be effective for the treatment of influenza infection and the prevention of influenza outbreaks.6,7

The strategy of antimicrobial drug delivery through inhalation has been tested in adult and children population. Specifically, regarding colistin, several studies in adult and pediatric patients with cystic fibrosis have investigated the role of inhaled colistin to eradicate P. aeruginosa, which chronically colonizes the respiratory tract, as well as its adverse events.8–11 Patients on mechanical ventilation constitute a high-risk group for difficult-to-treat respiratory infections, including both ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).12,13 Recent data provide preliminary evidence of inhaled colistin’s value to cure difficult-to-treat infections of the respiratory tract.

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caused by multi-drug resistant Gram-negative pathogens such as *P. aeruginosa*, *A. baumannii*, and *Klebsiella pneumoniae* in the intensive care unit (ICU) setting in patients without cystic fibrosis. On the other hand, in the field of pediatric critical care medicine there is a lack of evidence regarding the role of inhaled colistin to treat such infections. In this regard, in this small case series we present data regarding critically ill pediatric patients hospitalized in the ICU of a tertiary care pediatric hospital in Athens, Greece, who did not suffer from cystic fibrosis and received inhaled colistin for infections of the lower respiratory tract.

**Case Description**

Children who received inhaled colistin (colistimethate sodium) [1 mg equals 12,500 international units (IU) of colistin base activity] in the ICU of the P. & A. Kyriakou tertiary-care pediatric hospital during 2004–2009, were identified by reviewing ICU records. Data presented in this study were extracted from medical charts. Specifically, data regarding the demographical characteristics, underlying disease, reason for ICU admission, length of stay in the ICU and duration of ventilation, type of infection, site of isolation, and susceptibility pattern of each isolated pathogen, whether intravenous colistin was administered prior to inhaled colistin, the device used to deliver inhaled colistin, the type of the ventilator used, and presence of humidification, as well as time of institution, dosage and duration of inhaled colistin treatment, any concomitantly administered antibiotics, quantitative measures of the microbial load, the outcome and any adverse event reported are presented in the Table 1. The collection and report of the data presented in our study was approved from the hospital’s ethical committee. Specifically, this report on inhaled colistin constitutes a nested study within a larger one regarding the toxicity of rarely administered (either intravenously or through inhalation) antimicrobial agents in children.

**Case 1**

Case 1 was a 10-year-old male suffering from acute disseminated encephalomyelitis attributed to infection with influenza B virus. This child stayed in the ICU for 7 months and developed five episodes of septicemia and two episodes of septic shock for which he received various antibiotics. Polymyxin-only-susceptible *A. baumannii* was isolated in one blood culture, and the infection was cured with the administration of intravenous colistin. The child’s clinical manifestations were suggestive of tracheobronchitis and it also had a high microbial load, with a high microbial load of *A. baumannii* and *P. aeruginosa* in cultures of tracheobronchial secretions (the susceptibility pattern of these isolates is presented in the Table 1). In this regard, inhaled colistin was administered alone at a dosage of 75 mg diluted in 3 ml of normal saline twice daily (this equals to a daily dosage of 1,875,000 IU of colistin, administered in two divided doses) for 25 days. At day 21 of inhaled colistin treatment, a culture of tracheobronchial secretions with normal flora was obtained. Bronchoconstriction, attributed to the tracheobronchitis, was present before the initiation of inhaled colistin and was unsuccessfully treated with bronchodilators (specifically, salbutamol and ipratropium). Bronchoconstriction did not worsen during treatment. The outcome of the infection was favorable. However, the child exhibited serious neurological deficiencies that led to the need of permanent tracheostomy and gastrostomy.

**Case 2**

Case 2 was a 7.5-month-old female with no underlying disease, nor immunodeficiencies, who was admitted at the ICU with septic shock due to necrotizing pneumonia caused by *P. aeruginosa*, which was isolated in blood and bronchial secretions cultures obtained at the day of admission in the ICU. The susceptibility pattern of the *P. aeruginosa* is presented at the Table 1. The child received various intravenous antibiotic agents. Inhaled colistin was initiated 3 days after the acquisition of the index cultures at a dosage of 75 mg diluted in 3 ml of normal saline twice daily (a daily dosage of 1,875,000 IU of colistin), administered in two divided doses) for 32 days. Concomitant to inhaled colistin administration of intravenous antibiotic regimens included piperacillin/tazobactam and gentamicin for the first 10 days of administration of colistin and meropenem plus vancomycin (due to the isolation of *Staphylococcus* coagulase-negative from blood culture) for the following 11 days. During the course of the infection the child developed bilateral pleural effusions. Culture of the pleural fluid led to *P. aeruginosa* isolation, as well. At day 32 after the institution of inhaled colistin a culture consisting of normal flora was obtained. Bronchoconstriction was not observed at anytime during treatment. The child was cured from the infection, extubated, and discharged from the ICU.

**Case 3**

Case 3 was a 4-year-old female with no underlying disease who was admitted in the ICU with acute respiratory distress syndrome due to thermal burn of the airway requiring tracheostomy. The child received a variety of intravenous antibiotics before the administration of inhaled colistin because of three episodes of septicemia due to *P. aeruginosa*, *Escherichia coli*, and coagulase negative *Staphylococcus* spp., respectively.
### TABLE 1—Characteristics and Outcomes of Critically Ill Children Without Cystic Fibrosis Who Received Inhaled Colistin (Colistimethate Sodium) for the Treatment of Tracheobronchitis and Pneumonia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Reason for ICU admission</th>
<th>Length of stay (LOS) in the ICU</th>
<th>Length of time on the ventilator</th>
<th>Type of infection</th>
<th>Isolated pathogen(s)</th>
<th>Site of isolation</th>
<th>Susceptibility pattern of the isolated pathogen(s)</th>
<th>Prior administration of intravenous colistin</th>
<th>Concomitant antibiotic treatment to inhaled colistin</th>
<th>Time of institution of inhaled colistin</th>
<th>Dosage of inhaled colistin</th>
<th>Duration of treatment with inhaled colistin</th>
<th>Delivery of inhaled colistin</th>
<th>Type of ventilator</th>
<th>Humidification</th>
<th>Quantitative change of the microbial burden of the isolated pathogen(s) (cfu/ml)/days after institution of inhaled colistin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 y</td>
<td>M</td>
<td>ADEM</td>
<td>Encephalomyelitis</td>
<td>≈7 mo</td>
<td>≈1.5 mo (followed by tracheostomy)</td>
<td>Tracheobronchitis</td>
<td><em>Acinetobacter baumannii</em>, <em>Pseudomonas aeruginosa</em></td>
<td>Bronchial culture</td>
<td><em>Acinetobacter baumannii</em></td>
<td>Yes2</td>
<td>None</td>
<td>Day 206 after ICU admission (while on tracheostomy)</td>
<td>75 mg diluted in 3 ml of normal saline twice daily</td>
<td>25 d</td>
<td>Via a nebulizer apparatus connected to the tracheostomy circuit</td>
<td>Siemens Servo-i Ventilator3</td>
<td>On</td>
<td><em>Acinetobacter baumannii</em> Day 1: &gt;100,000</td>
<td>Cured from the infection</td>
</tr>
<tr>
<td>2</td>
<td>7.5 mo</td>
<td>F</td>
<td>None</td>
<td>Septic shock, necrotizing pneumonia</td>
<td>≈1.5 mo</td>
<td>≈1.5 mo</td>
<td>Necrotizing pneumonia</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Bronchial culture</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>No</td>
<td>i.v. (piperacillin-tazobactam plus gentamicin for 10 d, meropenem plus vancomycin for the following 11 d)</td>
<td>75 mg diluted in 3 ml of normal saline twice daily</td>
<td>32 d</td>
<td>Via a nebulizer apparatus connected to the ventilation system</td>
<td>Siemens Servo-i Ventilator5</td>
<td>On</td>
<td><em>Pseudomonas aeruginosa</em> Day 1: &gt;100,000</td>
<td>Cured from the infection</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 y</td>
<td>F</td>
<td>None</td>
<td>Respiratory burn, respiratory distress</td>
<td>≈3 mo</td>
<td>11 d (followed by tracheostomy)</td>
<td>Tracheobronchitis</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Bronchial culture</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Yes4</td>
<td>None</td>
<td>Day 27 after ICU admission (while on tracheostomy)</td>
<td>75 mg diluted in 3 ml of normal saline twice daily</td>
<td>15 d</td>
<td>Via a nebulizer apparatus connected to the tracheostomy circuit</td>
<td>Siemens Servo-i Ventilator3</td>
<td>On</td>
<td><em>Pseudomonas aeruginosa</em> Day 1: &gt;100,000</td>
<td>Cured from the infection</td>
</tr>
</tbody>
</table>

(Continued)
P. aeruginosa septicemia was treated successfully with intravenous colistin. P. aeruginosa was also isolated from cultures of tracheobronchial secretions. The susceptibility pattern of this isolate is presented in Table 1. However, due to the child’s clinical manifestations, that were suggestive of tracheobronchitis, and the persistence of a high microbial load of P. aeruginosa in tracheobronchial secretions (>100,000 cfu/ml), inhaled colistin alone was administered at a dosage of 75 mg diluted in 3 ml of normal saline twice daily for 15 days (a daily dosage of 1,875,000 IU of colistin, administered in two divided doses). At day 11 of the administration of inhaled colistin a culture of tracheobronchial secretions consisting of normal flora was obtained. Bronchoconstriction, attributed to the tracheobronchitis, was present before the initiation of inhaled colistin and was unsuccessfully treated with bronchodilators (specifically, salbutamol and ipratropium). Bronchoconstriction did not worsen during treatment. The child recovered from the infection but could not overcome the need for permanent tracheostomy and tracheal dilatations.

DISCUSSION

We report a case series of pediatric critically ill patients who received inhaled colistin for the treatment of tracheobronchitis (two children) and pneumonia (one infant). Cases 1 and 3 of tracheobronchitis were caused by P. aeruginosa, while case 1 was co-infected with a multidrug resistant A. baumannii isolate. Both these two cases recovered from the infections with the administration of inhaled colistin alone. The remaining child had pneumonia caused by P. aeruginosa. This patient was treated concurrently with intravenous antibiotics depending on susceptibility results for the 2/3 of the total duration of inhaled colistin treatment. The outcome was cure for this case also. Bacteriological eradication of the responsible pathogen was confirmed by quantitative cultures of tracheobronchial secretions in all three cases.

The rationale justifying the choice of inhaled colistin or other appropriate inhaled antibiotics as monotherapy for the treatment of patients with tracheobronchitis is that tracheobronchitis represents a topical inflammatory process that could be controlled with locally administered antibiotics. A placebo-controlled study in critically ill patients with VAP showed that inhaled antibiotics decreased the signs of respiratory infection and the use of systemic antibiotics. In our cases the only active antibiotic agent for inhalation was colistin based on the in vitro susceptibility pattern of the isolates. In addition, based on preliminary evidence, adjunctive inhaled colistin to intravenous antibiotic treatment improved the outcome of pneumonia. On this ground, inhaled colistin was selected as a therapeutic regimen for case 2.

The dosage administered to the three children presented in our study was 75 mg of colistimethate sodium diluted in 3 ml of normal saline, twice daily. This equals to a daily dosage 1,875,000 IU of colistin, administered in two divided doses. According to the national formulary, the recommended dosage of inhaled colistimethate sodium for children older than 2 years and adults with cystic fibrosis is 1–2,000,000 IU, 2–3 times a day. Regarding the 7.5-month-old infant in our report, the dosage of the 1,875,000 IU per day was chosen due to her critical condition. All three children were closely monitored for adverse events. No adverse event related to colistin treatment was noted in our cases.

In order to achieve the most of the benefits conferred by inhaled antibiotics in mechanical ventilated patients several conditions should be met. The device used for inhalation (nebulizer), the ventilator and the ventilator circuit, the inhaled agent and patient characteristics are aspects of major significance. Nebulizers are placed at a distance from the endotracheal tube in the inspiratory limb of the ventilator circuit and their deliverance of small

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**TABLE 1—(Continued)**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urea/creatinine</td>
<td>(23/0.7 – 25/0.6)</td>
<td>(47/7 – 15/0.3)</td>
<td>(30/0.5 – 35/0.5)</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

F. female; M, male; ADEM, acute disseminated encephalomyelitis; y, year(s); mo, month(s); d, days; S, susceptibility; I, intermediate susceptibility; R, resistant; i.v., intravenous.

1mg/dl.

2Administered for the treatment of Acinetobacter baumannii bacteremia.

3Prior to colistin treatment.

4Administered for the treatment of Pseudomonas aeruginosa bacteremia.

5While on colistin treatment.
particles of the drug is achieved at the maximum with high gas pressure and flow and low humidity as well as low gas density. In addition, nebulizers should be operated intermittently to avoid waste of the drug during exhalation time. Recently, a new electronic nebulizer the pulmonary drug delivery system (PDDS) utilizes information from a pressure sensor to generate the aerosol during a specific time of the respiratory circle and that leads to delivery of the 50–70% of the nominal dose of the drug.23 Patient-related factors such as severity of airway obstruction if any, dynamic hyperinflation of the lung and synchronization with the ventilator are important for drug delivery, as well. Specifically, evidence from published studies suggests that colistin can be successfully nebulized with more than one of the commercially available nebulizers.24

One fact of major importance in all three cases is that the adjunctive use of inhaled colistin or inhaled colistin alone succeeded in the reduction and finally the total elimination of the microbial load in respiratory secretions. When treating vulnerable pediatric patients, issues of safety are of major concern. The administration of inhaled colistin reduces the risk of systemic adverse events. On the contrary, the main worry of physicians regarding inhaled colistin is the provocation of serious bronchoconstriction.25,26 However, even though bronchoconstriction pre-existed in two of our cases, it did not deteriorate with the initiation of inhaled colistin.

In conclusion, inhaled colistin was effective for the treatment of two children with tracheobronchitis and one infant with necrotizing pneumonia, while no adverse events were observed. Accumulating data on inhaled colistin use in the adult critical care population support its safety profile. This may provide the ground for further research in the pediatric critical care setting regarding inhaled colistin and its use in pediatric patients without cystic fibrosis.

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