Inhaled colistin as monotherapy for multidrug-resistant gram (−) nosocomial pneumonia: A case series

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KEYWORDS
ICU-acquired pneumonia;
Ventilator-associated pneumonia;
Polymyxin;
Acinetobacter baumannii;
Pseudomonas aeruginosa

Summary
Background: Reports of patients with polymyxin-only susceptible gram-negative nosocomial pneumonia treated with inhaled, but without concurrent intravenous, colistin are rare.
Methods: Patients admitted in a tertiary 450-bed tertiary care centre during the period 05/01/2005–05/31/2007 and receiving colistin through nebulization, but not systemically, were included in this retrospective case series.
Results: Five patients (three with ventilator-associated pneumonia and two with nosocomial pneumonia) received colistin through nebulization without concomitant intravenous colistin. The isolated pathogens were Acinetobacter baumannii (three cases), Pseudomonas aeruginosa (one case) and the combination of Klebsiella pneumoniae, A. baumannii and P. aeruginosa (one case). They were susceptible only to colistin (three cases) or to colistin and gentamicin (two cases). Intravenous antimicrobial agents given concurrently were piperacillin/tazobactam, meropenem, ceftriaxone and ciprofloxacin; isolated pathogens were resistant to these agents. Four (80%) out of the five patients were cured, survived and were discharged. One patient died. No colistin-related adverse event was observed.
Conclusions: The experience from this case series and other relevant recent reports suggest that treatment of pneumonia due to polymyxin-only susceptible gram-negative bacilli with inhaled colistin (without concurrent systemic administration) deserves further careful investigation.

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Introduction

Treatment of patients with nosocomial pneumonia due to multidrug-resistant (MDR) gram-negative bacteria is a challenging issue; in such cases, administration of colistin has been advocated. Others and our research group have examined the effectiveness and safety of intravenous colistin given either alone or combined with inhaled colistin for the treatment of such patients.

Administration of inhaled antibiotics (including colistin) as an adjunct to intravenous antimicrobials for the prevention and treatment of nosocomial pneumonia, albeit not generally accepted, has been supported on the basis of comprehensive systematic reviews. In addition, the relevant guidelines by the American Thoracic Society and the Infectious Diseases Society of America note that “aerosolized antibiotics may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy.”

On the other hand, administration of inhaled anti-infective agents without concurrent intravenous antimicrobials is primarily indicated for cystic fibrosis patients with Pseudomonas aeruginosa infection, for prophylaxis (pentamidine) against Pneumocystis jirovecii pneumonia for patients with human immunodeficiency virus intolerant to oral agents, and for patients with respiratory syncytial virus infection (ribavirin). With regard to colistin, administration of inhaled colistin without its concurrent intravenous administration for nosocomial pneumonia has been reported, although very rarely, in the literature. The relevant evidence has been very recently accumulated and critically appraised.

In clinical practice, physicians not rarely face conditions, which discourage the systemic administration of colistin (i.e. due to systemic toxicity), while the implicated pathogen is a polymyxin-only susceptible one. An interesting question is, thereby, arisen: might monotherapy with inhaled colistin be an option in such “desperate” cases? Herein, we present our experience with patients with MDR gram-negative nosocomial pneumonia treated with inhaled (without concurrent intravenous) colistin.

Methods

Study design and data collection

The present retrospective study was carried out at a 450-bed tertiary care centre and was approved by the institutional review board of the hospital. All patients who received colistin for more than 72 h for treatment of MDR gram-negative infections from 05/01/2005 to 05/31/2007 were located from the pharmacy electronic database and their medical records were reviewed. Only patients receiving colistin through nebulization, but not systemically, were included. Demographic, clinical, laboratory and radiological data for these patients were recorded, as previously described.

Administration of inhaled colistin

In patients under mechanical ventilation (MV), 1 million IU colistin was diluted in 2 mL sterile normal saline 0.9% and delivered via the Siemens Servo Ventilator 300 (Siemens-Elema AB, Solna, Sweden). In spontaneously breathing patients, 1 million IU colistin was diluted in 4 mL normal saline and nebulized with 8 L/min oxygen flow.

Microbiological testing

An automated broth microdilution method (Vitek 2, bioMerieux, Hazelwood, MO, USA) was used for routine laboratory susceptibility testing to commonly used antibiotics; namely, penicillins (piperacillin, piperacillin/tazobactam), ticarcillin, ticarcillin/clavulanate ampicillin, and amoxicillin/clavulanate), cephalosporins (cefaclor, cefepime, ceftaxime, cefoxitin, ceftazidime, cefuroxime-axetil and sodium, cephalothin, cefprome, cefpodoxime), carbapenems (imipenem, meropenem), monobactams (azactam), quinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin), aminoglycosides (amikacin, gentamicin, netilmicin, tobramycin, isepamicin), and colistin. Susceptibility to colistin was determined by the use of the colistin Etest strip (AB Biodisk, Solna, Sweden). Test results were interpreted as showing susceptibility of a bacterial isolate to colistin when the respective minimum inhibitory concentration was ≤2 µg/mL.

Definitions

Pneumonia

Diagnosis of pneumonia was based on radiological (new or progressive and persistent infiltrate), clinical (fever, purulent respiratory secretions) and laboratory findings (abnormal white blood cell count and gas exchange). All patients should have microbiologically documented pneumonia based on quantitative cultures of bronchial secretions.

Nosocomial pneumonia—ventilator-associated pneumonia (VAP)

Pneumonia occurring at least 48 h after hospital admission or after the initiation of MV was considered nosocomial or VAP, respectively.

MDR

Resistant to all but two antipseudomonal classes of antimicrobial agents (namely antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, and polymyxins).

Polymyxin-only susceptible

Resistant to all antipseudomonal agents except colistin.

Cure/improvement

Defervescence, resolution or partial resolution of presenting symptoms and signs of pneumonia, decrease or disappearance of presenting findings on chest x-ray, and improvement or normalization in arterial blood gases, white blood cell count and C-reactive protein.

Results

Patient population

During the study period, in six patients colistin was given through nebulization only (not systemically) for the
treatment of MDR gram-negative infections. One of these six patients suffered from pneumonia due to \textit{P. aeruginosa}, which was susceptible to colistin and meropenem; this patient was managed with inhaled colistin and intravenous meropenem and, for this reason, was excluded from this case series. The characteristics and outcome data of the five included patients are depicted in Table 1.

Four males and one female were included. The reason of hospital admission was trauma (cranioencebral lesions) in three and medical (one patient with acute myocardial infarction and another with urinary tract and soft tissue infection) in two of them. Three patients developed VAP, one patient nosocomial pneumonia treated in a ward, while the remaining patient suffered from nosocomial pneumonia requiring ICU admission. Thus, four of the five subjects of this case series were admitted in the ICU; mean Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission was 17.5.

Implicated pathogens and susceptibility

In three patients (# 2, 4, 5 of Table 1), the causative pathogen was \textit{Acinetobacter baumannii}. According to the performance standards for antimicrobial susceptibility testing developed by the Clinical and Laboratory Standards Institute (CLSI), \textit{A. baumannii} was polymyxin-only susceptible in one patient (# 2) and MDR (susceptible only to colistin and gentamicin) in the other two patients (# 4, 5). The gentamicin minimum inhibitory concentration of the isolated pathogens in the latter patients (# 4, 5) was 4 \textmu g/mL; a value indicating susceptibility to gentamicin according to the CLSI. \textit{A. baumannii} was polymyxin-only susceptible in one patient (# 2) and MDR (susceptible only to colistin and gentamicin) in the other two patients (# 4, 5). The gentamicin minimum inhibitory concentration of the isolated pathogens in the latter patients (# 4, 5) was 4 \textmu g/mL; a value indicating susceptibility to gentamicin according to the CLSI. \textit{A. baumannii} was polymyxin-only susceptible in one patient (# 2) and MDR (susceptible only to colistin and gentamicin) in the other two patients (# 4, 5). The gentamicin minimum inhibitory concentration of the isolated pathogens in the latter patients (# 4, 5) was 4 \textmu g/mL; a value indicating susceptibility to gentamicin according to the CLSI. From another patient (# 3), a polymyxin-only susceptible \textit{P. aeruginosa} was isolated. Finally, from the remaining patient (# 1) of this case series, \textit{P. aeruginosa}, \textit{A. baumannii} and \textit{Klebsiella pneumoniae}, all susceptible only to colistin, were isolated.

Administration of inhaled colistin

Daily dosage of inhaled colistin was 1 million IU every 8 h and 500,000 IU every 6 h in four and one patient, respectively. It was administered for 6–11 days. No patient received intravenous colistin. Intravenous antimicrobial agents given concurrently were piperacillin/tazobactam, meropenem, ceftriaxone and ciprofloxacin; isolated pathogens were resistant to these agents. One patient with VAP due to \textit{A. baumannii}, which was susceptible to colistin and gentamicin, received gentamicin intravenously.

Outcome

Four (80%) (patients # 1, 3, 4, 5) out of the five patients of this case series survived. Two (# 3, 5) out of these four patients were discharged from the hospital; the remaining two survivors (# 1, 4) were discharged from the ICU and transferred to another hospital. Cure or improvement of the gram-negative pneumonia episode was achieved in three and one patient, respectively (clinical success: 4/5, 80%). One patient (# 2) died. This patient was admitted in the ICU due to severe acute myocardial infarction requiring implementation of intra-aortic balloon pump. After 27 days of ICU stay and MV, this patient developed VAP due to polymyxin-only susceptible \textit{A. baumannii}. He died 11 days after this VAP episode onset due to cardiogenic shock.

Follow-up cultures were not available for all but one patient. In this patient (# 4), \textit{A. baumannii} persisted in bronchial secretions obtained 5 days after the initiation of colistin administration. This patient was cured and discharged; no repeated cultures were obtained.

Tolerance and safety of inhaled colistin

No patient experienced adverse events from the respiratory system related to the inhalation of colistin, such as bronchoconstriction, chest tightness or apnoea. Serum creatinine level of the five patients was not deteriorated (Table 1).

Discussion

We present a case series of five patients with MDR gram-negative nosocomial pneumonia treated with inhaled (but not intravenous) colistin. The implicated pathogens (mainly \textit{A. baumannii} and \textit{P. aeruginosa}) were polymyxin-only susceptible in three cases and susceptible to colistin and to gentamicin in the remaining two cases (one of these two patients did not receive gentamicin). All but one patient survived and were discharged.

It may be interesting to clarify the reasons why these five patients were not given colistin intravenously. In detail, three of them (namely patients # 1, 4, 5) suffered from recent cranioencebral lesions. Concerns regarding neurotoxicity associated with systematic administration of colistin discouraged physicians from prescribing it in such potentially vulnerable patients. This may be also the case for another patient (patient # 3) with a history of post-traumatic tetraplegia and agyrynodal coma. For this particular patient, the fact that pneumonia due to polymyxin-only susceptible \textit{P. aeruginosa} was not severe (ICU admission was not required) may also contribute to the explanation why care providers considered inhaled colistin as adequate for his management. For the remaining patient (patient # 2) of our case series, his impaired renal function, as indicated by the elevated serum creatinine level (1.7 mg/dL), presumedly discouraged caregivers from administering intravenous colistin for his episode of VAP due to polymyxin-only susceptible \textit{A. baumannii}.

Pharmacokinetics/pharmacodynamics of colistin is currently the subject of intense research. With respect to inhalation therapy, it seems reasonable that the exact delivery of a medication directly to the suffering lung tissue may be beneficial. Indeed, pharmacokinetic studies have shown that a single inhalation of 2 million IU of colistin leads to high sputum concentrations of the drug even 12 h after the administration. Colistin exerts its action through a concentration dependant bactericidal mechanism. It displays the cations of Ca$^{+2}$ and Mg$^{+2}$ that stabilize the outer membrane of gram-negative bacteria and, thus, lead to outer membrane disruption and cell death. Also, colistin reduces the production of endotoxins and cytokines. Finally,
### Table 1  Characteristics and outcome data of the five patients receiving inhaled (but not intravenous) colistin for the treatment of multidrug-resistant nosocomial pneumonia.

<table>
<thead>
<tr>
<th>Data</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Male/75</td>
<td>Male/26</td>
<td>Male/18</td>
<td>Male/27</td>
<td>Male/27</td>
</tr>
<tr>
<td>Sex/age (years)</td>
<td>Cardiac valvuloplasty</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
<td>Post-traumatic tetraplegia; coma agrypnodal; tracheostomy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Medical history</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
<td>Coronary disease; arterial hypertension; diabetes mellitus</td>
</tr>
<tr>
<td>Type/reason of hospital admission</td>
<td>Trauma/craniocerebral lesions; subdural hematoma; femoral fracture (^a)</td>
<td>Medical/acute myocardial infarction; acute pulmonary edema</td>
<td>Medical/UTI; SSTI</td>
<td>Trauma/multitrauma patient due to car accident; craniocerebral lesions</td>
<td>Trauma/multitrauma patient; craniocerebral lesions</td>
</tr>
<tr>
<td>Diagnosis of discharge</td>
<td>Craniocerebral lesions; nosocomial pneumonia</td>
<td>Acute myocardial infarction; cardionic shock; VAP</td>
<td>UTI; SSTI; nosocomial pneumonia</td>
<td>Craniocerebral lesions; VAP</td>
<td>Craniocerebral lesions; multiple rib fractures; scapula fracture; VAP</td>
</tr>
<tr>
<td>APACHE II score at ICU admission</td>
<td>27</td>
<td>20</td>
<td>Was not admitted in ICU</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Episode of pneumonia</td>
<td>0</td>
<td>27(^b)</td>
<td>Did not receive MV</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Duration of hospital and ICU stay before pneumonia onset (days)</td>
<td>Hospital: NA; ICU: 0</td>
<td>Hospital: 27; ICU: 27</td>
<td>Hospital: 3</td>
<td>Hospital: 8; ICU: 8</td>
<td>Hospital: 8; ICU: 8</td>
</tr>
<tr>
<td>Site of infection</td>
<td>Nosocomial pneumonia requiring MV and ICU admission</td>
<td>VAP</td>
<td>Nosocomial pneumonia (ward); UTI; SSTI</td>
<td>VAP</td>
<td>VAP</td>
</tr>
<tr>
<td>Isolated gram-negative pathogen(s) (culture)</td>
<td><em>Pseudomonas aeruginosa</em> (bronchial secretions, central venous catheter tip); <em>Acinetobacter baumannii</em> (bronchial secretions, central venous catheter tip); <em>Klebsiella pneumoniae</em> (bronchial secretions)</td>
<td><em>A. baumannii</em> (bronchial secretions)</td>
<td><em>P. aeruginosa</em> (bronchial secretions); <em>K. pneumoniae</em> (urine); <em>Proteus mirabilis</em> (urine, soft tissue abscess)</td>
<td><em>A. baumannii</em> (bronchial secretions)</td>
<td><em>A. baumannii</em> (bronchial secretions)</td>
</tr>
<tr>
<td>Susceptibility of the gram-negative pathogen(s) isolated from respiratory specimens</td>
<td>POS</td>
<td>POS</td>
<td>POS</td>
<td>MDR (susceptible to colistin and gentamicin)</td>
<td>MDR (susceptible to colistin and gentamicin)</td>
</tr>
</tbody>
</table>

\(^a\) Includes patient who died due to disease progression on day 27 of hospitalization

\(^b\) Received mechanical ventilation immediately after admission to ICU

MDR = Multidrug resistant
<table>
<thead>
<tr>
<th>Duration/dosage of inhaled colistin</th>
<th>Administration of intravenous colistin</th>
<th>Duration/dosage of concurrent intravenous antimicrobial treatment</th>
<th>Outcome of patient</th>
<th>Outcome of infection</th>
<th>Duration of MV after pneumonia onset (days)</th>
<th>Duration of ICU/hospital stay after pneumonia onset (days)</th>
<th>Safety</th>
<th>Adverse events from respiratory system</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 days/1 million IU q8h</td>
<td>No</td>
<td>Piperacillin/tazobactam: 7 days/4.5gr q6h</td>
<td>ICU discharge</td>
<td>Improvement</td>
<td>3</td>
<td>ICU: 11</td>
<td>0.5/0.5 (0)</td>
<td>None</td>
</tr>
<tr>
<td>6 days/1 million IU q8h</td>
<td>No</td>
<td>Meropenem: 5 days/1gr q12h</td>
<td>Death</td>
<td>Deterioration</td>
<td>11</td>
<td>ICU: 11</td>
<td>1.7/1.3 (−0.4)</td>
<td>None</td>
</tr>
<tr>
<td>7 days/1 million IU q8h</td>
<td>No</td>
<td>Piperacillin/tazobactam: 11 days/4.5gr q8h</td>
<td>Hospital discharge</td>
<td>Cure</td>
<td>Did not receive MV</td>
<td>Hospital: 10</td>
<td>0.6/0.5 (−0.1)</td>
<td>None</td>
</tr>
<tr>
<td>11 days/0.5 million IU q6h</td>
<td>No</td>
<td>Meropenem: 13 days/1gr q8h</td>
<td>ICU discharge</td>
<td>Cure</td>
<td>0</td>
<td>ICU: 24</td>
<td>0.5/0.5 (0)</td>
<td>None</td>
</tr>
<tr>
<td>6 days/1 million IU q8h</td>
<td>No</td>
<td>Gentamicin: 7 days/80 mg q8h; piperacillin/tazobactam: 8 days/4.5gr q8h</td>
<td>ICU discharge</td>
<td>ICU discharge</td>
<td>3</td>
<td>ICU: 6</td>
<td>0.6/0.6 (0)</td>
<td>None</td>
</tr>
</tbody>
</table>

Outcome of infection: Improvement, Deterioration, Cure, Did not receive MV.

Duration of ICU/hospital stay after pneumonia onset (days):
- ICU: 11
- ICU: 11
- Hospital: 10
- ICU: 24
- ICU: 6

Safety:
- Serum creatinine value (mg/dL) at the first day of colistin inhalation/at the end of colistin inhalation (change):
  - 0.5/0.5 (0)
  - 1.7/1.3 (−0.4)
  - 0.6/0.5 (−0.1)
  - 0.5/0.5 (0)
  - 0.6/0.6 (0)

Adverse events from respiratory system:
- None


- This patient was referred from another hospital due to nosocomial pneumonia requiring intensive care unit admission.
- Until the episode of ventilator-associated pneumonia due to polymyxin-only susceptible *A. baumannii*.
- He also received inhaled colistin 0.5–1 million IU q8h for 14 days before the episode of ventilator-associated pneumonia due to polymyxin-only susceptible *A. baumannii*.
- Namely bronchoconstriction, chest tightness, apnoea.
inhaled colistin could demonstrate a unique action against certain pathogen populations’ growth inside biofilms.\textsuperscript{26}

The retrospective design, sample number of patients, and the absence of a control group are limitations of this case series. In addition, we should note that the patients of our report received concurrently intravenous antibiotics; however, the responsible pathogens were not susceptible to intravenous antibiotics (except from patient \# 5). With regard to patient \# 5 (who received both inhaled colistin and intravenous gentamicin for VAP due to \textit{A. baumannii} susceptible to colistin and gentamicin), one might call into question our decision to include him in the present case series. This preservation seems logical. However, there is evidence that aminoglycosides do not penetrate adequately into the lung\textsuperscript{27} and, therefore, monotherapy of nosocomial pneumonia with aminoglycosides is not recommended.\textsuperscript{14} Thus, it seems plausible that administration of inhaled colistin rather than intravenous gentamicin was responsible for the cure of this patient. Furthermore, one might criticize us for establishing the diagnosis of nosocomial pneumonia and VAP on non-invasive (i.e. cultures from bronchial secretions) rather than invasive (i.e. bronchoscopy) diagnostic methods. However, on the basis of a recent randomized controlled trial, non-invasive and invasive diagnostic strategies for VAP did not differ with regard to clinical outcomes (including mortality) and the overall use of antibiotics.\textsuperscript{28} Besides, according to the relevant guidelines by the American Thoracic Society, quantitative cultures of non-bronchoscopic bronchial secretions can reliably guide antibiotic therapy decisions when bronchoscopic sampling is not available.\textsuperscript{14} Finally, one could assume that the organisms treated may not have been the etiology for the nosocomial and ventilator-associated pneumonia in the patients of our report.

In conclusion, we report on five patients with MDR gram-negative nosocomial pneumonia (including VAP) due to polymyxin-only susceptible or MDR gram-negative bacteria treated with inhaled (without intravenous) colistin. The favourable outcome of pneumonia in four out of the five reported cases seems to suggest that this intervention may deserve further investigation in patients with pneumonia due to polymyxin-only susceptible bacteria, especially in patients for whom the possible toxicity of systemic administration of polymyxins is a consideration.

Conflict of interest

None.

Funding

None.

References


Inhaled colistin monotherapy for pneumonia


