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

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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.[1–3] Others and our research group have examined the effectiveness and safety of intravenous colistin given either alone[4–7] or combined with inhaled colistin[8–10] for the treatment of such patients.

Administration of inhaled antibiotics (including colistin) as an adjunctive 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.[11–13] 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''.[14]

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,[15] 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).[16] 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.[10,17,18] The relevant evidence has been very recently accumulated and critically appraised.[19]

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.[10]

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[9]; namely, penicillins (piperacillin, piperacillin/tazobactam, ticarcillin, ticarcillin/clavulanate ampicillin, and amoxicillin/clavulanate), cephalosporins (cefaclor, cefepime, cefotaxime, cefoxitin, ceftazidime, cefuroxime-axetil and sodium, cephalothin, cefpirome, 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 $\leq$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.[9,10]

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