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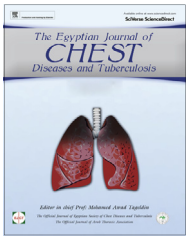

ORIGINAL ARTICLE

Re-emerging of colistin for treatment of nosocomial pneumonia due to gram negative multi-drug resistant pathogens in critically ill patients

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KEYWORDS

Colistin;
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Abstract *Background:* Gram-negative (G-ve) bacilli, particularly *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are important opportunistic multidrug-resistant (MDR) pathogens in hospitalized patients, contributing to their morbidity and mortality. These organisms may still keep their sensitivity to colistin and allowed its use for these selective therapeutic indications.

Objectives: The aim of the present study is to evaluate and compare the effectiveness and safety of both combined intravenous (i.v.) colistin with aerosolized colistin versus i.v. colistin alone in nosocomial pneumonia due to MDR G-ve pathogens in critically ill patients.

Methods: 40 Patients were hospitalized in ICU due to different etiologies. These patients experienced nosocomial pneumonia. The pathogenic organisms were G-ve MDR bacilli and only susceptible to colistin. The first group received both i.v. colistin with aerosolized colistin versus (vs.) the second group who received i.v. colistin alone.

Results: Mortality was less in patients who received i.v. plus inhaled colistin.

Conclusion: Colistin is a reasonable safe last-line therapeutic alternative for pneumonia due to MDR G-ve pathogens. Aerosolized colistin may be considered as a useful adjunctive to i.v. colistin.

1. Introduction

According to data from the Centre for Disease Control and prevention (CDC) and the Nosocomial Infection Surveillance System (NISS), G-ve bacilli are the most common causative organisms for nosocomial pneumonia. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most serious etiologies for nosocomial pneumonia, and more importantly the most common multidrug-resistant (MDR) G-ve pathogens in

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these patients [1]. The increased prevalence of MDR in multiple parts of the world and lack of development of new antibiotics to fight MDR G-ve have created a new antibiotic therapeutic failure, leading to the use and renewed interest of the previously neglected class of polymyxins [2]. Until recently, the polymyxin class was mainly used via inhalation to treat high-density respiratory tract colonization due to MDR *P. aeruginosa* in patients with cystic fibrosis since this class was thought to be unacceptably toxic when administered parenterally. However, in recent years, colistin (polymyxin E) was observed to be less toxic than previously proposed, and to offer an acceptable efficacy for treatment of severe infections due to MDR G-ve bacteria [3]. Colistin is now being used increasingly as a last treatment option for treatment of nosocomial pneumonia with MDR G-ve bacteria [2].

Colistin belongs to polymyxins which were isolated for the 1st time from Bacillus Colistinum in 1949 [4,5]. Polymyxins are a group of polypeptide antibiotics which includes five different chemical compounds (polymyxins A, B, C, D, and E). Only two of them, polymyxins B and E, have been used in clinical practice. Colistin binds to the gram-negative bacterial cell membrane, which leads to its increase in permeability changes and ultimately cell death [4]. Most G-ve microorganisms are susceptible to colistin, including multidrug-resistant *A. baumannii* and *P. aeruginosa, Klebsiella pneumonia and Escherichia coli* strains. However *Proteus* species, *Neisseria* species, *Serratia* species, and *Providencia* species, as well as anaerobic bacteria, are resistant to colistin [6].

Early clinical experience with colistin showed a high incidence of toxicity, namely, nephrotoxicity (acute renal failure), neurotoxicity (facial paresis, dizziness, muscle weakness, vertigo, confusion, neuromuscular blockade and apnea), sometimes with fatal consequences [7–9].

2. Aim of the present study

The aim of the present study is to report and evaluate 2 years experience with the use of colistin and compare the role of combined i.v. colistin and inhaled colistin vs. i.v. colistin alone for treatment of nosocomial pneumonia due to MDR G-ve bacilli in critically ill patients.

3. Patients and methods

This prospective study enrolled patients in ICUs of 300 beds of 3 tertiary specialized hospitals (burns and plastic surgery hospital, orthopedic hospital and organ transplantation center) from May 2011 till August 2012. 40 patients were prospectively followed in this study who suffered from ICU-AP or VAP. The isolated pathogens were MDR G-ve bacilli and were only sensitive to colistin. The primary objective was to compare the treatment outcomes of the pneumonia between different colistin treatment groups (combined parenterally with inhaled colistin therapy "28 patients" or only parental i.v. colistin "12 patients").

All individuals were subjected to the following procedures:

- Thorough medical history and full clinical examination.
- Full data about their age, sex, and smoking status.
- Radiological examinations.
- Routine lab investigations e.g. CBC, ESR, liver and kidney function tests; urinalysis, glucose profile.
- Acute Physiology and Chronic Health Evaluation (APACH II) was scored on admission to the ICU. This score was used as a predictor of hospital mortality risk.
- Administration of i.v. colistin (colistimethate sodium): all patients enrolled in the study had received i.v. colistin as a dose of 1–2 million IU every 6–8 h (62500 IU/kg/day) according to body weight with normal renal function. Treatment continued for 12–15 days with close monitoring for the possibility of nephrotoxicity and neurotoxicity [10].
- Administration of inhaled colistin: in patients under mechanical ventilation (MV), 2 million IU colistin was diluted in 2 mL sterile normal saline 0.9% and delivered via the ventilator every 12 h. In spontaneously breathing patients, 2 million IU of colistin was diluted in 4 mL of normal saline and nebulized with 8 L/min oxygen flow. Treatment continued for 12–15 days [10].
- *Microbiological testing:* identification of all causative pathogens was performed using routine microbiological methods. Susceptibility testing was performed by the disk diffusion method to commonly used antibiotics; namely, penicillins (piperacillin/tazobactam) and amoxicillin/clavulanate), cephalosporins (cefepime, cefotriaxone, ceftazidime), carbapenems (meropenem), quinolones (ciprofloxacin, levofloxacin), aminoglycosides (amikacin, gentamicin) and colistin. Susceptibility to colistin was determined by the use of the colistin Etest strip. Results were interpreted as showing susceptibility of a bacterial isolate to colistin when the respective minimum inhibitory concentration was 2 mg/mL. All patients were sensitive to colistin [11].
- *Pneumonia definition:* Diagnosis of pneumonia "according to the criteria of the American Thoracic Society [12] was based on radiological (new or progressive and persistent infiltrate), clinical (fever > 38Co, purulent respiratory secretions) and laboratory findings (abnormal white blood cell count < 4000/μl "leukopenia" OR > 12000/μl "leukocytosis" and worsening gas exchange) [13]. All patients should have microbiologically documented pneumonia based on quantitative cultures of bronchial sections [14,15]. Microbiological criteria required a quantitative threshold of 106 cfu/ml from tracheal aspirate, and > 104 cfu/ml for bronchoscopic bronchoalveolar lavage (BAL). Reliable induced purulent sputum sample is defined as secretions from lower respiratory tract that contain > 25 neutrophils and < 10 squamous epithelial cells per low power field (100×) with or without alveolar macrophages [16].
- ICU-AP and VAP definitions: pneumonia occurring at least 48 h after ICU admission or initiation of mechanical ventilation respectively [11].
- MDR definition: non-susceptibility to at least six of the following antibiotics: meropenem, amikacin, piperacillin–tazobactam, ceftazidime, cefepime, aztereonam and ciprofloxacin [17].
- Outcome definitions: (1) Cure defined as resolution of presenting symptoms and signs of the infection by the end of colistin treatment. (2)Failed was defined as persistence or worsening of presenting symptoms and/or signs of the infection during colistin administration.