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

Mohamed Amin a,*, Alaa Rashad b, Assem Fouad a, Amal Abdel Azeem c

a Chest Department, Faculty of Medicine, Fayoum University, Egypt
b Chest Department, Faculty of Medicine, Assiut University, Egypt
c Chest Department, Faculty of Medicine, Zagazig University, Egypt

Received 20 April 2013; accepted 21 May 2013
Available online 22 July 2013

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
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. baumanii 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 parenteral i.v. colistin “12 patients”).

All individuals were subjected to the following procedures:

- 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 (cephem, cefotriaxone, cefazidime), 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 > 38°C, 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 (100x) 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, aztreonam 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.

...
All data were entered into a database and analyzed.

4. Results

4.1. Identified cases

We identified 40 patients who received i.v. colistin for a micro-biologically documented MDR G-ve pneumonia. This study was performed during the period May 2010 to August 2012. 28 patients received both i.v. plus inhaled colistin, whereas 12 patients received i.v. colistin alone.

4.2. Outcomes

Table 1 shows the demographic and clinical features of the studied patients and their outcomes. The bivariable analyses showed that blood transfusion and the duration of administration of i.v. colistin were differentially distributed between the two groups of patients. The outcome of infection was cure for 22/28 patients (78%) who received combined i.v. plus inhaled colistin vs. 7/12 patients (58.3%) who received i.v. colistin alone (p < 0.05). The use of inhaled colistin was the only independent variable significantly associated with the cure of nosocomial pneumonia in the multivariable analysis (OR 3.49, 93% CI 2.0–4.90). Mortality was 8/28 (28%) in patients who received i.v. plus inhaled colistin vs. 5/12 (41%) patients who received i.v. colistin alone (p < 0.05).

The toxicity of colistin was assessed in the present study. However, no serious adverse events of inhaled colistin (such as disturbed renal function, neurological abnormalities, bronchoconstriction chest pains) were recorded.

Table 2 shows the demographic and clinical features of the patients who died compared to those who survived. The bivariable analysis showed that older age, greater APACHE II score, and a lower daily dosage of i.v. colistin were associated with higher mortality. These variables, along with the type of colistin treatment (i.v. plus inhaled vs. i.v. alone), were entered into a multivariable analysis. A higher APACHE II score (OR 2.1, 95% CI 0.89–1.03), and a lower daily dosage of i.v. colistin (OR per million IU 0.79, 95% CI 0.59–0.89) remained statistically significant predictors of mortality in this model.

Also tracheostomy and bronchoscopy procedures were significantly more in the died group. However this may be due to the severity of disease, long duration of MV and poor response to the administered antibiotics.

5. Discussion

The present study demonstrated that the infection outcome of VAP caused by MDR strains of G-ve pathogens was better in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of demographic and clinical characteristics, including outcomes, of patients with VAP treated with colistin i.v. in combination with inhaled colistin vs. colistin i.v. monotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colistin i.v. and inhaled (n = 28)</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>55.6 ± 21.9</td>
</tr>
<tr>
<td>Sex (male) n/N (%)</td>
<td>15/28 (54%)</td>
</tr>
<tr>
<td>Apache II score (mean ± SD)</td>
<td>18.1 ± 5</td>
</tr>
<tr>
<td><strong>Co morbidity n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>11/28 (40%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>6/28 (20%)</td>
</tr>
<tr>
<td>DM</td>
<td>9/28 (30%)</td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>2/28 (5%)</td>
</tr>
<tr>
<td>Hematological</td>
<td>3/28 (8%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>6/28 (20%)</td>
</tr>
<tr>
<td><strong>Previous hospitalization n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization until the 1st day of colistin (mean ± SD)</td>
<td>15.3 ± 9.5</td>
</tr>
<tr>
<td>Duration of ICU stay till 1st day of colistin, (mean ± SD)</td>
<td>9.8 ± 4.5</td>
</tr>
<tr>
<td>Duration of MV till the 1st day of colistin</td>
<td>7.6 ± 4.3</td>
</tr>
<tr>
<td><strong>Special treatment n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>16/28 (60%)</td>
</tr>
<tr>
<td>L-thyroxin</td>
<td>3/28 (10%)</td>
</tr>
<tr>
<td>Urinary catheter n/N (%)</td>
<td>28/28 (100%)</td>
</tr>
<tr>
<td>Tracheostomy n/N (%)</td>
<td>14/28 (50%)</td>
</tr>
<tr>
<td>Bronchoscopy n/N (%)</td>
<td>6/28 (20%)</td>
</tr>
<tr>
<td><strong>i.v. colistin, days (mean ± SD)</strong></td>
<td></td>
</tr>
<tr>
<td>Responsible pathogens, n/N (%)</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>18/28 (65%)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>3/28 (10%)</td>
</tr>
<tr>
<td><strong>Outcomes; n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>22/28 (78%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>8/28 (28%)</td>
</tr>
</tbody>
</table>
patients who received combined inhaled colistin along with i.v. colistin vs. i.v. colistin alone. The use of inhaled colistin was an independent predictor of cure of VAP. Mortality was significantly less in patients who received combined inhaled colistin with i.v. colistin [18]. It has been assumed that the delivery of antimicrobial directly to the site of infection is clinically beneficial by increasing topical drug levels [19,20]. Inhaled antibiotics such as tobramycin, amikacin and colistin have mainly been used to treat patients with cystic fibrosis with generally favorable results [21,22]. In the present study, patients in the i.v. plus inhaled colistin group received i.v. colistin for a longer period of time than patients in the i.v. colistin alone group (Table 1). Because more patients in the i.v. plus inhaled colistin group showed clinical improvement, these patients received the full course of treatment for VAP caused by G-ve pathogens, which is approximately 2–3 weeks [23].

The present study demonstrated statistically significant differences in ICU mortality between patients who received inhaled plus i.v. colistin and those who received i.v. colistin alone, as shown in Table 1. Because more patients in the i.v. plus inhaled colistin group showed clinical improvement, these patients received the full course of treatment for VAP caused by G-ve pathogens, which is approximately 2–3 weeks [23].

The present study demonstrated statistically significant differences in ICU mortality between patients who received inhaled colistin plus i.v. colistin and those who received i.v. colistin alone, which was less in the former group [24]. APACHE II score was predictor of mortality in the study. Colistin is recommended in the latest guidelines of the American Thoracic Society as a last therapeutic resort for the treatment of VAP and is usually administered in patients with the most severe clinical condition [25]. Some studies have shown that the administration of inhaled colistin should not be accompanied with a decrease in the dosage of i.v. administered colistin, which may be performed to prevent dose-related toxicity, particularly nephrotoxicity [26]. Similarly, in the present cohort of patients, a lower i.v. colistin daily dosage was independently related to higher mortality.

The present study has some limitations. Inhaled colistin was usually administered via conventional nebulizers, which do not control the particle size, and therefore the actual amount of the drug delivered to the lungs could not be accurately estimated [27,28].

6. 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 in these patients. However, the severity of these infections in the ICU setting means that treatment just with aerosolized colistin is unlikely to be sufficient. This is in contrast to therapeutic strategies employed in patients with cystic fibrosis, in which initial lung colonization with P. aeruginosa strains is commonly treated with aerosolized colistin alone. Randomized controlled trials studying the possible additional benefits and risks associated with use of nebulized colistin, as an adjunct to intravenous antimicrobial treatment are needed.

References

Re-emerging of colistin for treatment of nosocomial pneumonia


