Journal of Global Antimicrobial Resistance 15 (2018) 127–135

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

# Prospective, comparative clinical study between high-dose colistin monotherapy and colistin–meropenem combination therapy for treatment of hospital-acquired pneumonia and ventilator-associated pneumonia caused by multidrug-resistant *Klebsiella pneumoniae*

Mohamed Farouk Ahmed Abdelsalam[a,*], Maged Salah Abdalla[b,1], Hanan Salah El-Din El-Abhar[c]

[a] *Clinical Pharmacy Department, The Teachers' Hospital, Al-Jazeera, Cairo, Egypt*
[b] *Anesthesia Department, Faculty of Medicine, Cairo University, Cairo, Egypt*
[c] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt*

ARTICLE INFO

*Article history:*
Received 11 May 2018
Received in revised form 4 July 2018
Accepted 6 July 2018
Available online xxx

*Keywords:*
Multidrug-resistant
*Klebsiella pneumoniae*
Hospital-acquired pneumonia
Ventilator-associated pneumonia
Hospital mortality
Procalcitonin

ABSTRACT

*Objectives:* In clinical practice, colistin is used as combination therapy to improve its antibacterial activity, despite the consequent increase in toxicity. This prospective, comparative study evaluated the effectiveness and adverse effects of using colistin alone at a loading dose of 9 million international units (MIU) followed by 3 MIU every 8 h (q8 h) versus colistin + meropenem 1 g q8 h in treating multidrug-resistant (MDR) *Klebsiella pneumoniae*-induced hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). The primary outcome measure was in-hospital mortality. The secondary measure was the occurrence of colistin toxicity.

*Methods:* A total of 60 patients were divided into two groups (30 patients each); the first group received intravenous colistin at a mean daily dose of 8.304 MIU and the second group received colistin 8.58 MIU combined with meropenem (mean daily dose of 2.88 g for 15 days).

*Results:* The colistin–meropenem combination group showed a significant decrease in mortality versus colistin alone [16.7% (5/30) vs. 43.3% (13/30); $P = 0.047$]. The improved clinical response mediated by combination therapy was not associated with any significant nephrotoxicity, hepatotoxicity or neurotoxicity. Moreover, the 42 surviving patients showed normal procalcitonin values associated with a decrease in SOFA score, whilst 12 of them showed significantly elevated C-reactive protein (CRP) ($P = 0.0002$).

*Conclusions:* This study revealed the superiority of colistin–meropenem combination therapy over colistin monotherapy in the treatment of MDR *K. pneumoniae*-induced HAP or VAP and highlights the advantage of procalcitonin over CRP as a marker for eradication of sepsis and suspension of therapy.


## 1. Introduction

Infections caused by multidrug-resistant (MDR) Gram-negative bacteria, which are resistant to three or more antimicrobial categories, represent an important clinical problem associated with a significant increase in morbidity and mortality worldwide [1,2]. The ability of Gram-negative bacteria to develop resistance to most available antibiotics has encouraged the medical community to reconsider the use of colistin (polymyxin E). Colistin is one of the polymyxins, a group of polypeptide antibiotics consisting of five different chemical compounds, namely polymyxin A, B, C, D and E, among which only polymyxins B and E are of clinical value [3]. Colistin is known to act by binding to lipopolysaccharide and phospholipid molecules in the cell membrane of Gram-negative bacteria, producing a disruptive physiochemical effect that leads to an alteration in cell membrane permeability and eventually leading to cell death [4]. From the 1960s until the 1990s, owing to a high incidence of fetal toxicity, especially nephrotoxicity, colistin use was restricted to the treatment of patients with cystic fibrosis having acute exacerbations of lung infection due to MDR *Pseudomonas aeruginosa* strains [5,6]. However, the revival of

* Corresponding author.
*E-mail address:* farouq.mfa@gmail.com (M.F.A. Abdelsalam).
[1] Principle investigator.

https://doi.org/10.1016/j.jgar.2018.07.003
2213-7165/

colistin use started lately because of its high effectiveness against most Gram-negative bacteria, including MDR *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *P. aeruginosa* strains [7].

Although the minimum inhibitory concentration (MIC) is used as a parameter to assess the therapeutic concentration of antimicrobial agents, several in vitro [8,9] and in vivo [10] studies have reported that the area under the unbound (free) concentration–time curve to MIC ratio (*f*AUC/MIC) or AUC/MIC ratio are more predictive parameters than MIC alone as a measure of colistin activity.

It has been shown that intravenous (i.v.) colistin administration at the standard dose level of 2 million international units (MIU) every 8 h (q8 h) results in a steady-state plasma trough concentration ($C_{trough,ss}$) of 1.03 ± 0.69 mg/L [11]. This concentration is below the required MIC for Enterobacteriaceae (2 mg/L) and *Pseudomonas* spp. (4 mg/L) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [12]. In contrast, the Clinical and Laboratory Standards Institute (CLSI) recommends 2 mg/L as a breakpoint both for Enterobacteriaceae and *Pseudomonas* spp. [13]. Furthermore, Imberti et al. reported an $AUC_{0-24}$/MIC ratio of 17.3 ± 9.3 using a colistin standard dose [11], which is again below the recommended range (25–35) required to achieve optimum bacterial killing both of *A. baumannii* and *P. aeruginosa* in lung infection [9,14].

Accordingly, other studies started to use a higher colistin dose. Markou et al. used a colistin dose of 2.8 MIU q8 h, which showed a higher maximum serum concentration ($C_{max}$) (2.93 ± 1.24 mg/L vs. 2.21 ± 1.08 mg/L at the standard dose of 2 MIU q8 h), but with the same $C_{trough,ss}$ and adverse effects [15]. In another prospective study, Plachouras et al. highlighted the advantage of using loading and maintenance doses of colistin to achieve an effective therapeutic level faster than the standard regimen without the loading dose [16]. The authors used a loading dose of colistin (9–12 MIU) in intensive care unit (ICU) patients with subsequent administration of 9 MIU i.v. in two or three divided doses daily. After several studies [3,16,17], such a protocol was approved and updated in 2017 by the University of California, Los Angeles (UCLA) Health System Pharmaceutical Services [17].

Apart from using colistin as monotherapy against MDR Gram-negative bacterial infections, many in vitro and in vivo studies have documented the synergistic effect obtained from combining it with other antibiotics [1,18], e.g. colistin combined with ceftazidime [19], ciprofloxacin [19] or piperacillin [20] against *P. aeruginosa* strains and with meropenem against carbapenem-resistant *K. pneumoniae* [21]. In an in vitro study, Timurkaynak et al. stated that the effect of the colistin–meropenem combination is superior to that of colistin alone [22]. This conclusion was further emphasised by a retrospective study revealing a synergistic effect when colistin was co-administered with meropenem against carbapenem-resistant *K. pneumoniae* infection in ICU patients [23].

Although a recent study was published comparing colistin alone versus colistin plus meropenem for the treatment of carbapenem-resistant Gram-negative bacterial infections including hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), bloodstream infection and urosepsis [24], prospective data are still lacking regarding their possible synergistic effect when both antibiotics are used specifically against MDR *K. pneumoniae*-induced HAP or VAP. The latter has recently been recognised as a spreading MDR micro-organism in ICU patients with either HAP or VAP [25].

Referring to the aforementioned data, the current study is the first prospective study to evaluate the efficacy and safety of the new high doses of colistin as monotherapy versus combination therapy with meropenem in non-cystic fibrosis HAP and VAP patients caused by MDR *K. pneumoniae*.

## 2. Subjects and methods

### 2.1. Study design

This study was a prospective, comparative, single-blind, randomised study conducted on 60 adult patients (age ≥18 years) divided into two equal groups. The first group ($n$ = 30) received colistin as monotherapy and the second group ($n$ = 30) received colistin–meropenem combination therapy. The study was approved by the Ethics Committee of the Faculty of Pharmacy, Cairo University (Cairo, Egypt).

### 2.2. Inclusion criteria

Patients with HAP or VAP caused by MDR *K. pneumoniae*, as defined by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) [26], who were hospitalised in the general ICU during the period from the start of May 2016 to the end of October 2016 and confirmed with carbapenem-resistant *K. pneumoniae*-positive culture results from sputum within the previous 4 days were included in the study.

### 2.3. Exclusion criteria

All patients without a MDR carbapenem-resistant *K. pneumoniae*-positive culture isolated from the sputum were excluded from the study. In addition, the following patients were excluded: patients with a Glasgow Coma Scale (GCS) score of <9 in non-ventilated patients or <6 in ventilated patients; patients with end-stage metastatic malignant cancer; and all terminal patients with Acute Physiology and Chronic Health Evaluation (APACHE) II or Sequential Organ Failure Assessment (SOFA) scores of >34 or >15, respectively, and risk of mortality >85% or >80% on the first day of colistin administration, respectively [27,28]. Moreover, patients who received i.v. colistin therapy for <72 h were excluded from further analysis.

### 2.4. Microbiological testing

Sputum specimens were isolated from all patients before the start and after the end of treatment, and identification of all causative micro-organisms was performed using routine microbiological methods. Antimicrobial susceptibility testing was performed by the disk diffusion method for all antimicrobial agents except colistin. Colistin susceptibility was determined by the broth microdilution method according to the CLSI reference method [13,29]. The breakpoints were those defined by the CLSI [13].

### 2.5. Colistin administration

All patients in the current study received i.v. colistin (colistimethate sodium (CMS); Forest Laboratories UK Ltd., Dartford, UK) as a therapeutic intervention for infection due to MDR Gram-negative bacteria at a dose according to the protocol of the study. One milligram of the colistin base activity (CBA) formulation is approximately equal to 30 000 IU. The colistin preparation contains CMS, which is the active ingredient, as an amount of dry powder equivalent to one MIU (or equal to ca. 80 mg of CMS).

Adjustment of the i.v. dose is based on kidney function after consulting the ICU director or the infectious diseases specialists of the hospital. According to the protocol used [20,30], the loading dose of CBA was a constant single dose of 300 mg (5 mg/kg), whereas the maintenance dose was 100 mg (1.7 mg/kg) q8 h if the creatinine clearance ($CL_{Cr}$) was >50 mL/min. For a $CL_{Cr}$ ranging between 20–50 mL/min the maintenance dose was 150 mg