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*Original Article*

# Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: Monotherapy or combination therapy?

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## Abstract

**Purpose:** To evaluate the outcomes of the patients who were infected with colistin-only-susceptible (COS) *Acinetobacter baumannii* and treated with either colistin monotherapy or colistin combined therapy. **Materials and Methods:** This retrospective case-control study was conducted in the training and research hospital with an 800 beds between August 2008 and December 2011. The patients, who were infected with COS *A. baumannii* and received either colistin monotherapy or colistin combined therapy, were included into the study. **Results:** In total, 51 patients fulfilling study criteria were evaluated. Colistin monotherapy was found effective as much as colistin combined therapy in terms of clinical and microbiological responses in patients with ventilator associated pneumonia (VAP) and also in patients with blood stream infections. **Conclusion:** Although there is no randomised controlled study yet, colistin monotherapy and colistin combined therapy are likely to achieve similar treatment responses rates. Heteroresistant strains can emerge in patients who receive colistin monotherapy

**Key words:** *Colistin, Acinetobacter baumannii, treatment, mortality, response*

## Introduction

*Acinetobacter baumannii* is a Gram-negative bacterium, non-fermenting and an aerobic coccobacillus. It is found extensively in natural environments. It can be alive in the environment for a long time and also stay alive within disinfectants.[1] It has been a problem in health care facilities spreading by cross-contamination and causing to ventilator associated pneumonia (VAP).[2] It is resistant to most of the antimicrobials, such as aminoglycosides, fluoroquinolones, carbapenems, *etc*., due to rapidly developing acquired resistance mechanisms acquiring resistance mechanisms rapidly.[3] Only polymyxin E, known as colistin, is highly effective against those resistant micro-organisms. Polymyxins were isolated from *Basillus polymyxa* in 1947. Polymyxin B and E were used in the treatment due to concerns about side effects of polymyxins (A, B, C, D, E), which contain mainly nephrotoxicity and neurotoxicity. Intravenous colistin was used between the 1960s and the 1970s.[3,4] Outbreaks and nosocomial infections in healthcare facilities prompted to reintroduction of colistin due to multi-drug resistant (MDR) *A. baumannii* strains. Most of Gram-negative bacteria are sensitive to colistin except *Proteus spp., Providencia spp., Serratia spp., Burkholderia cepacia* and some *Sthenotrophomonas maltophilia* strains. Colistin impairs the cell membrane permeability with a detergent-like mechanism binding to bacterial cell membrane.[4] Due to the fact that rates of MDR Gram-negative bacteria-related infections have been increasing worldwide, colistin has been used as either monotherapy or combination therapy. Carbapenem resistance rates of *A. baumannii* strains in Turkey were reported between 55% and 63%.[5]

The aim of this study is to evaluate the outcomes of the patients who were infected with colistin-only-susceptible (COS) *A. baumannii* and treated with either colistin monotherapy or colistin combined therapy, retrospectively.

## Materials and Methods

This retrospective case-control study was conducted between August 2008 and December 2011 in the training and research hospital with an 800 beds. This study was approved by the local ethic committee. The patients, who were infected with COS *A. baumannii* and received either colistin monotherapy or colistin combined therapy, were included into the study. Patients, who received either colistin monotherapy or colistin combined therapy for less than 24-h or who received antimicrobial regimens without colistin for *A. baumannii* infection, were excluded from

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the study. Either colistin sulphate or colistimethate sodium was given intravenously. Until colistimethate sodium was manufactured as Colimycin® (Colimycin M 150 mg equals to 360 mg colistin base and 4,500,000 units colistimethate; Koçak Farma, İstanbul, Turkey) in Turkey in the last months of 2010, colistimethate sodium was provided by official permission of Ministry of Health from abroad as Colomycin® (Colistimethate sodium 1,000,000 units equal to 80 mg colistimethate and 33.3 mg of colistin base; Forest Laboratories UK Limited, Bexley, United Kingdom). Colomycin was used as 1–2 million units intravenously thrice daily for patients who weighed 60 kg or more with normal renal function. Colimycin was used in the dose of 2.5–5 mg/kg colistin base a day, which equals to 6–12 mg/kg colistimethate sodium per day. For a 60 kg man, therefore, the recommended dose for Colomycin is 240–480 mg of colistimethate sodium, yet the recommended dose for Colimycin is 360–720 mg of colistimethate sodium. Likewise, the recommended "maximum" dose for each compound is different (480 mg for Colomycin and 720 mg for Colimycin). Patients were monitored for renal function during administration of colistin and also after discontinuation.

Patients' characteristics, clinical and laboratory data that contain antimicrobial susceptibilities of *A. baumanii* isolates, treatments and dosages, side effects of drugs, duration of mechanical ventilation (MV), Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, length of stay before and after infection with *A. baumanii*, concurrent other infections, renal function tests were recorded using a detailed case evaluation form. The patients were also followed up with active surveillance. Susceptibility testing of *A. baumanii* isolates was performed using an automated broth microdilution method (Vitek 2; bioMérieux, Marcy-l'Etoile, France) and then confirmed with E test method (AB BIODISK, Solna, Sweden). Mueller-Hinton agar (Oxoid, İstanbul, Turkey) was used in the testing procedure of disc diffusion test and also for E test. Disc diffusion testing was performed with 10 µg colistin disc (Oxoid, İstanbul. Turkey). The breakpoints used were those defined by the Clinical and Laboratory Standards Institute (CLSI).[6] Interpretive breakpoints (MIC ≤ 2 µg/ml, susceptible, and MIC ≥ 4 µg/ml, resistant) were used for the Vitek 2. The colistin E test (AB Biodisk, Solna, Sweden) was performed and interpreted according to the manufacturer's procedures. Colistin susceptibility was defined as if an *A. baumanii* isolate had inhibition zone that was ≥ 11 mm. It was defined as resistant if the inhibition zone was ≤ 10 mm according to National Committee for Clinical Laboratory Standards (M2–A2 S2) An isolate was defined as only colistin sensitive and multi-drug resistant, if it was susceptible to polymyxins but resistant to agents from the six anti-pseudomonal antimicrobial classes including anti-pseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones and aminoglycosides.

Infection was differentiated from colonisation by the infectious diseases physicians who treated the patients at wards. Infection cure, mortality and colistin-associated nephrotoxicity were the main outcomes of this study. Nephrotoxicity was defined by an increase in serum creatinine level of more than>2 mg/dL or two-fold increase over the baseline level in patients with a history of a renal failure.[7]

Response to colistin treatment was defined as defervescence in 48–72 h after initiation of colistin, recovery of elevated C reactive protein (CRP) level, leukocytosis or leukopenia, vital signs and clinical symptoms associated with infection (diminishing of aspiration frequency in a day and recovery of symptoms and signs regarding VAP, improvement in arterial blood-gas values, radiological improvement, negative urine culture for urinary system infection, negative cerebral spinal fluid culture three times subsequent to initiation of colistin for nosocomial meningitis and negative culture of sample related with infection). Infections were defined based on the guidelines of Centers for Disease Control and Prevention.[8] If there was at least one of comorbid factors including malignancy, hypertension, heart dysfunction (acute or chronic), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), renal failure (acute or chronic), neurological diseases, haematological disorders, gastrointestinal disorders and trauma, patient was defined to have comorbidity. Concurrent infections were defined as Gram-positive bacteria-related infections or fungal infections or both of them. Drug choice was based on antimicrobial susceptibility of micro-organisms or probable agents of relevant infections. So concurrent infection did not affect the choice of antimicrobial. Combination therapy was based on articles and recommendations. Monotherapy and combination therapy were choosen randomly.

## Statistics

Statistical analysis was done using SPSS, version 13.0 (Chicago, IL, USA). Continuous variables were described as mean ± standard deviation and range. Dichotomous variables were compared by Fisher's exact test for two by two comparisons or Pearson $\chi^2$ for greater than two responses. Logistic regression analysis was conducted to obtain unadjusted odds ratios and revealed as [Odd ratio (OR); 95% confidence interval (CI); *P* value]. Statistical significance was defined as $P < 0.05$. The crude mortality rate was calculated as all causes of death in patients who received colistin for more than 24-h.

## Results

In total, 51 patients fulfilling study criteria were included into the study. Mean age was 51.71 ± 18.82 years (range:14–87 years), 31 patients (70%) were male [Table 1]. Colistin monotherapy was initiated to 20 patients,. Comorbid conditions were reported in 20 patients; and

28 patients had concurrent infections. History of surgery was recorded in16 patients prior to *A. baumannii*-related infection. Duration of hospitalisation subsequent to infection was 37.17 ± 33.43 days (1–132 days) [Table 1]. Colistin monotherapy was given to 15 patients whereas combination therapy was given in 21 patients due to VAP [Table 2]. Rifampicin was the mostly used combined antibiotic with colistin. There were no significant differences between colistin monotherapy and colistin combination therapy groups in terms of clinical response rates ($P = 0.821$; $P = 1$) and microbiological response rates ($P = 0.113$; $P = 0.667$) associated with VAP and blood stream infections, respectively [Table 2]. Colistin combination therapy did not exhibit clinical response in the treatment of meningitis although microbiological response was observed. Microbiological response was observed in 34 of 51 patients whereas clinical response was achieved in 22 of 51 patients ($P = 0.005$) in overall [Table 2]. There was no correlation between mortality and either presence of comorbid condition ($P = 0.085$) or also concurrent infection ($P = 0.614$). Defervescence occurred between 3 and16 days after treatment in 25 patients. Elevated CRP recovered between 6 and 16 days after treatment. Urea and creatinine increased only in one case (2%) and this patient deceased in the fifth day of treatment. The 10-day crude mortality rates were 40% (8/20) in patients who received colistin monotherapy, and 22% (7/31) in patients who received combination therapy in all cases. There was no significant difference between both groups ($P$=0.182). The 10-day crude mortality rates in VAP cases were 40% (6/15) in patients who received colistin monotherapy, and 28% (6/21) in patients who received combination therapy. There was no significant difference between both groups ($P$=0.475). The 28-day crude mortality rates were found insignificant as 50% (10/20) in patients who received colistin monotherapy, and 32% (10/31) in patients who received combination therapy statistically ($P$=0.244). The 28-day crude mortality rates were insignificant in VAP cases as 40% (6/15) in patients who received colistin monotherapy, and 47% (10/21) in patients who received combination therapy ($P = 0.650$). Mortality rates were found similar in patients that received colistin within 72-h of identification and in patients that received colistin after 72-h of identification (57% versus 58%, $P = 0.651$). Mortality rates were significantly higher in patients who were supported with mechanical ventilation more than 10 days ($n$=22, 62%, OR=5,92; 95% CI 1.06–32.89; $P = 0.027$). There were only seven patients who had no underlying conditions and concurrent infection, hence the attributable mortality could not be calculated. However, 10-day and 28-day mortality rates were found 0% and 14% in seven patients without concomitant infection and underlying conditions who were diagnosed with VAP ($n$=7), wound infection ($n$=1), surgical site infection ($n$=1), meningitis ($n$=1), respectively. Five of them received colistin monotherapy. Only one patient deceased due to meningitis.

**Table 1: Demographic and clinical characteristics of the 51 patients infected with colistin-only sensitive *A. baumannii***

| Demographic and clinical characteristics | No. of patients |
|---|---|
| Mean age | 51.71 ± 18.82 years (14–87) |
| Male | 31 |
| Comorbidity | 20 |
| Malignancy | 4 |
| Heart dysfunction | 12 |
| Chronic obstructive pulmonary disease | 7 |
| Diabetes mellitus | 6 |
| Chronic and acute renal failure | 2 |
| Hypertension | 9 |
| Neurological diseases | 3 |
| Trauma | 12 |
| Haemathological disorders | 3 |
| Gastrointestinal disorders | 8 |
| Prior usage of combined antibiotics | 50 |
| Mechanic ventilation in ICU | 46 |
| Urinary catheter | 42 |
| Central venous catheter | 45 |
| Presence of concomitant other infection | 28 |
| Prosthetic material | 1 |
| Prior surgery | 16 |
| APACHE II score (n=39) | 17.73 ± 6.24 (5–32) |
| Duration of mechanic ventilation (days) | 79.54 ± 62.13 (2–205) |
| Length of stay at hospital prior to infection (days) | 42.49 ± 27.54 (5–105) |
| Duration of hospitalisation subsequent to infection (days) | 37.17 ± 33.43 (1–132) |

## Discussion

It is controversial yet that whether colistin combined therapy is more effective than colistin monotherapy or not. Colistin monotherapy was effective as much as colistin combined therapy in terms of our clinical and microbiological responses rates in the treatment of VAP and blood stream infections. Rifampicin was the mostly combined antibiotic in our study and had better outcome among combination therapies overall [Table 2]. Rifampicin combined therapy was reported to be effective in the treatment of VAP.[9] In the study by Falagas *et al.* study,[10] combination therapy was reported to provide poor survival benefit among patients who were infected with COS-*A. baumannii* overall. Alternatively, in meta-analysis of Kumar *et al.*,[11] combination therapy was reported to reduce mortality rates greater than 25%

**Table 2: Clinical response rates of colistin monotherapy and combination therapies by sites of infections**

| Site of infection | Therapy | Clinical response | Microbiological response |
|---|---|---|---|
| Ventilator associated pneumonia (*n*=36) | Colistin monotherapy | 7/15 | 10/15 |
| | Colistin + Rifampicin | 5/8 | 8/8 |
| | Colistin + Carbapenem | 1/4 | ¼ |
| | Colistin + Tigecycline + Rifampicin | 0/2 | 0/2 |
| | Colistin + Tigecycline | 1/4 | 2/4 |
| | Colistin + Carbapenem + Rifampicin | 1/2 | 1/2 |
| | Colistin + Sulbactam-Ampicillin | 1/1 | 1/1 |
| Blood stream infection (*n*=6) | Colistin monotherapy | 1/2 | 2/2 |
| | Colistin + Cefoperazone-Sulbactam- | 1/1 | 1/1 |
| | Colistin + Rifampicin | 1/3 | 2/3 |
| Nosocomial pneumonia (*n*=1) | Colistin + Carbapenem | 0/1 | 0/1 |
| Urinary tract infection (*n*=1) | Colistin + Carbapenem+ Rifampicin | 0/1 | 1/1 |
| Surgical site infection (*n*=2) | Colistin monotherapy | 2/2 | 2/2 |
| Meningitis (*n*=2) | Colistin+ Carbapenem+ Rifampicin | 0/2 | 2/2 |
| Surgical site infection + Ventilator associated pneumonia (*n*=1) | Colistin monotherapy | 0/1 | 0/1 |
| Central-line associated blood stream infection (*n*=1) | Colistin + Rifampicin | 1/1 | 1/1 |
| Intra abdominal infection (n=1) | Colistin + Sulbactam-Ampicillin | 0/1 | 0/1 |
| Total (***n***=51) | | 22/51 | 34/51 |

in patients who received monotherapy and had severe illness. Colistin combined therapy is being strongly recommended against monotherapy due to selection of heteroresistant strains during prolonged colistin therapy.[12] In the Rodriguez *et al*. study,[13] heteroresistance strains were reported to be correlated with endemic infections in ICU. Underlying conditions, higher APACHE II score, prolonged mechanical ventilation and prolonged length of stay in ICU, presence of concomitant infection decrease the clinical response rates whereas microbiological response rates were achieved higher . Admission to an ICU, bloodstream infection, dyspnoea, shock, coagulopathy, renal or hepatic failure, immunosuppression, fewer antibiotic use and initiation of inappropriate antimicrobial regimen were described as significant predictors for poor outcome [14]. Renal failure, bloodstream infection and initiation of an inappropriate antimicrobial regimen were also described as independent predictors for non-responsiveness to treatment.[14] Aerosolised colistin that was added to intravenous colistin treatment provided clinical response between 57% and 87%.[15] However, Kofteridis*et et al*.[16]reported that added aerosolised colistin to intravenous colistin treatment did not provide significant outcomes compared with single intravenous colistin therapy in 77% of the patients who were infected with *A. baumannii.* It is clear that a randomised clinical trial is needed about this subject.

The 10-day and 28-day crude mortality rates were statistically similar in patients with VAP who were treated with either colistin monotherapy or colistin combined therapy, although crude mortality rates were higher in patients who received monotherapy. Attributable mortality rates could not be calculated due to insufficient number of patients who had no underlying condition and concurrent infection. Risk factors as mentioned above were considered to increase the crude mortality, but the duration of mechanical ventilation more than 10 days was determined to be a risk factor for mortality in our study. In the retrospective study by Santimaleeworagun *et al.*,[14] presumptive success rate and mortality rates were reported as 80% and 17% for patients with monotherapy and 85% and 12% for patients who received combination therapy, respectively. Renal failure and bacteraemia were reported to be related with poor outcome by Katsaragakis *et al.*[17] In the study by Lim *et al.*,[18] 30-day mortality was described as 35.5% in colistin group and 38.5% in the non-colistin group for MDR-*Acinetobacter* species bloodstream infections, respectively. APACHE II score ≥ 21 was determined to be associated with poor outcome for 30-day mortality in that study. Mean APACHE II score of our study that was reported to have 25% attributable mortality rate was closely related with higher mortality rates.[19] Only one patient who developed nephrotoxicity due to colistin treatment recovered on the fifth day of the treatment. Colistin-induced nephrotoxicity rates were reported as generally mild and reversible with rates from 0% to 53.5%.[20]

Consequently, severity of patients and presence of risk factors are related withpoor prognosis in patients who were infected with COS-*A. baumannii*. Although there is no

randomised controlled study yet, both colistin monotherapy and colistin combined therapy are likely to provide similar treatment response rates. Heteroresistant strains can emerge in patients who receive colistin monotherapy

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