doi • 10.5578/tt.59748
Tuberk Toraks 2017;65(4):271-281
Geliş Tarihi/Received: 12.05.2017 • Kabul Ediliş Tarihi/Accepted: 11.12.2017

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Evaluation of nephrotoxicity and prognosis in patients treated with colistin due to hospital-acquired pneumonia

Pervin KORKMAZ EKREN[1]
Zehra Nur TÖREYİN[1]
Huriye BERK TAKIR[2]
Merih KALAMANOĞLU BALCI[2]
Ümmügülsüm GAYGISIZ[3]
Gül GÜRSEL[3]
Begüm ERGAN[4]
Aslıhan YALÇIN[5]
Cüneyt SALTÜRK[2]
Müge AYDOĞDU[3]
Recai ERGÜN[4]
Pınar GÜVEN[5]
Gaye ULUBAY[6]
Aslıhan GÜRÜN KAYA[7]
Aygül ÇELTİK[8]
Hatice ULUER[9]
Feza BACAKOĞLU[1]
Abdullah SAYINER[1]

[1] Department of Chest Diseases, Faculty of Medicine, Ege University, Izmir, Turkey
[1] *Ege Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, İzmir, Türkiye*
[2] Istanbul Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital, Istanbul, Turkey
[2] *İstanbul Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye*
[3] Intensive Care Unit, Department of Chest Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey
[3] *Gazi Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Yoğun Bakım Ünitesi, Ankara, Türkiye*
[4] Clinic of Chest Diseases, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
[4] *Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara, Türkiye*
[5] Intensive Care Unit, Department of Chest Diseases, Faculty of Medicine, Marmara University, Istanbul, Turkey
[5] *Marmara Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Yoğun Bakım Ünitesi, İstanbul, Türkiye*
[6] Clinic of Chest Diseases, Faculty of Medicine, Baskent University, Ankara, Turkey
[6] *Başkent Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Ankara, Türkiye*
[7] Department of Chest Diseases, Faculty of Medicine, Ankara University, Ankara, Turkey
[7] *Ankara Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Ankara, Türkiye*
[8] Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Turkey
[8] *Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, İzmir, Türkiye*
[9] Department of Biostatistic, Faculty of Medicine, Ege University, Izmir, Turkey
[9] *Ege Üniversitesi Tıp Fakültesi, Biyoistatistik Anabilim Dalı, İzmir, Türkiye*

SUMMARY

Evaluation of nephrotoxicity and prognosis in patients treated with colistin due to hospital-acquired pneumonia

Introduction: *Colistimethate sodium (CMS) is frequently used in the treatment of nosocomial multidrug-resistant gram-negative infections. Nephrotoxicity is the most important side effect. The aim of this study is to evaluate the effect of colistin on nephrotoxicity and to assess prognosis in patients treated with CMS due to hospital-acquired pneumonia (HAP).*

Yazışma Adresi (Address for Correspondence)

Dr. Zehra Nur TÖREYİN
Ege Üniversitesi Tıp Fakültesi,
Göğüs Hastalıkları Anabilim Dalı, İZMİR - TURKEY
e-mail: ntreyin@gmail.com

Materials and Methods: *Patients treated with CMS for HAP due to multidrug-resistant Pseudomonas aeruginosa or Acinetobacter baumannii were included in this cohort study.*

Results: *We evaluated 281 patients treated with two different brands of CMS whose administration dose is different: imported (n= 58, low dose/kg) and domestic (n= 223, high dose/kg). Nephrotoxicity developed in 175 patients (62.3%). The median age (73 vs. 66 years, p= 0.004) and mortality rates were higher (66.9% vs. 52.8%, p= 0.022) in patients having nephrotoxicity. The patients receiving high dose/kg had higher nephrotoxicity rate (67.7% vs. 41.4%, p< 0.001). The clinical, bacteriological response and mortality rates of the whole group were 52.0%, 61.0%, 61.6%, respectively. The clinical and bacteriological response rates were similar in the different dose groups. Multivariate analysis showed that nephrotoxicity was associated with domestic brand depending on use of high dose (OR= 3.97), advanced age (β= 0.29, p= 0.008), male gender (OR= 2.60), hypertension (OR= 2.50), red blood cells transfusion (OR= 2.54), absence of acute kidney injury (OR= 10.19), risk stage of RIFLE (OR= 11.9).*

Conclusion: *Nephrotoxicity is associated with the use of high dose colistin, age, gender, hypertension, red blood cells replacement and RIFLE stage. The mortality rate is higher in patients developing nephrotoxicity.*

Key words: *Nosocomial infection; pneumonia; multidrug resistant; colistimethate sodium; toxicity*

ÖZET

Hastane kökenli pnömoni nedeniyle kolistin ile tedavi edilen olgularda nefrotoksisite ve prognozun değerlendirilmesi

Giriş: *Kolistimetat sodyum (KMS) çok ilaca dirençli nozokomiyal gram-negatif infeksiyonların tedavisinde sıklıkla kullanılmakta olup en önemli yan etkisi nefrotoksisitedir. Çalışmamızda hastane kökenli pnömoni (HKP) nedeniyle KMS tedavisi uygulanan olgularda, KMS'nin nefrotoksisite üzerine etkisi ve prognozun değerlendirilmesi amaçlanmıştır.*

Materyal ve Metod: *Çok ilaca dirençli Pseudomonas aeruginosa ve Acinetobacter baumannii ile HKP saptanan ve KMS ile tedavi uygulanan olgular çalışmaya dahil edilmiştir.*

Bulgular: *Araştırmaya iki farklı dozda tedavi uygulanan 281 olgu dahil edilmiş; 58 olguya ithal (düşük doz/kg), 223 olguya yerli (yüksek doz/kg) KMS preparatıyla tedavi uygulanmıştır. Olguların 175 (%62.3)'inde nefrotoksisite izlenmiş olup, nefrotoksisite gelişen grupta median yaşın (73 vs. 66 yıl, p= 0.004) ve mortalite oranlarının (%66.9 vs. %52.8, p= 0.022) daha yüksek olduğu saptanmıştır. Yüksek doz/kg tedavi uygulanan grupta nefrotoksisite oranları daha yüksek bulunmuştur (%67.7 vs. %41.4, p< 0.001). Tüm grup için klinik, bakteriyolojik yanıt ve mortalite oranları sırasıyla %52.0, %61.0, %61.6 olarak saptanmış; her iki doz grubunda da klinik ve bakteriyolojik yanıt oranlarının benzer olduğu görülmüştür. Çok değişkenli analizlerde nefrotoksisitenin; yüksek doz kullanımına bağlı yerli preparat kullanımı (OR= 3.97), ileri yaş (β= 0.29, p= 0.008), erkek cinsiyet (OR= 2.60), hipertansiyon (OR= 2.50), eritrosit replasman tedavisi (OR= 2.54), akut renal hasar bulunmaması (OR= 10.19), RIFLE "risk" evresi (OR= 11.9) ile ilişkili olduğu saptanmıştır.*

Sonuç: *Nefrotoksisite, yüksek doz KMS kullanımı, yaş, cinsiyet, hipertansiyon varlığı, eritrosit replasman tedavisi ve RIFLE evresiyle ilişkili olarak bulunmuştur. Nefrotoksisite gelişen olgularda mortalite oranının daha yüksek olduğu görülmüştür.*

Anahtar kelimeler: *Nozokomiyal infeksiyon; çok ilaca dirençli infeksiyon; pnömoni; kolistin; toksisite*

INTRODUCTION

Nosocomial infections that develop due to multidrug-resistant (MDR) gram-negative bacteria lead to increased morbidity and mortality (1). The increase in the incidence of such infections and the lack of development of new antibiotics have led to reconsideration of colistin as a treatment option. Colistin belongs to the polymyxin group of antibiotics, the use of which was gradually abandoned after 1970's because of its side effects such as nephrotoxicity and neurotoxicity (2). It is currently used via intravenous and inhalation routes in the treatment of infections due to MDR *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* (3,4). The use of colistimethate sodium (CMS) in Turkey has a similar history. An imported brand was used until September 2010. A domestically produced brand was licensed in April 2010 and marketed thereafter.

The safety and efficacy of polymyxins in the treatment of nosocomial infections caused by MDR gram-negative bacteria have been investigated in several studies (5,6). Despite their efficacy, serious side effects such as nephrotoxicity, neurotoxicity, and skin toxicity led to concerns regarding their use (7). The nephrotoxicity has been reported to range widely between 0-53.5% (8).

There are limited reports from Turkey reflecting the clinical experience with CMS. These studies were included few patients with hospital-acquired pneumonia (HAP) (9,10). The primary objectives of this study were to evaluate the frequency of nephrotoxicity and the parameters affecting nephrotoxicity in patients treated with CMS for HAP due to MDR *P. aeruginosa* or *A. baumannii*. The secondary objective was to determine the prognosis in this population.

MATERIALS and METHODS

Patients hospitalized at seven tertiary care centers between February 2007 and November 2013 were included in this retrospective cohort study. Study period was identified according to domestic drug license time to assess equal time for different two drug

brands. The study was approved by the ethics committee of the coordinating center; i.e. Ege University and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

The cases hospitalized and treated with CMS within the given time period were screened and selected from databases of each hospital. Study inclusion criteria: 1) Patients treated with parenteral CMS for HAP associated with MDR *P. aeruginosa* or *A. baumannii*. Study exclusion criteria: 1) CMS administration for less than three days, 2) Administration of inhaled CMS alone, 3) No documentation of *Pseudomonas* or *Acinetobacter* infection, 4) Presence of chronic renal failure, 5) No regular follow-up of renal function tests.

Demographic characteristics, diagnosis at time of admission, underlying conditions, APACHE (Acute Physiology Assessment and Chronic Health Evaluation) II score at the time of diagnosis, presence and severity of hypoxemia and its treatment, and renal functions were recorded (11). In patients who had received CMS for more than one episode, only the data from the first treatment episode was taken into consideration.

Diagnosis of HAP

HAP was clinically diagnosed in patients who had new or progressive pulmonary infiltrates on chest radiographs obtained at least 48 hours post-admission and who was reported two or more of the following symptoms: Fever (> 38°C) or hypothermia (< 36°C); leukocytosis (> 10.000/mm^3) or leukopenia (< 4000/mm^3); presence of purulent tracheal secretions (12,13).

A clinical diagnosis of ventilator-associated pneumonia (VAP) was made if they met the above-mentioned criteria and they had been receiving invasive mechanical ventilation for more than 48 hours (12,13).

Microbiological Evaluation

Sputum, endotracheal aspirate, non-bronchoscopic bronchoalveolar lavage (mini-BAL) or bronchoscopic materials (bronchoscopic aspirates, BAL) were used as respiratory specimens for bacteriologic cultures. Blood cultures were performed in patients with fever or hypothermia; pleural fluid cultures were done when pleural fluid was present.

The threshold values for the quantitative evaluation of lower respiratory tract samples other than sputum were 10^5 cfu/mL for endotracheal aspirates drawn via a protected sterile catheter and 10^4 cfu/mL for mini-BAL and BAL. VITEK 2 automated system (bioMérieux SA, Marcy-l'Etoile, France) and conventional methods were used according to "Clinical and Laboratory Standards Institute (CLSI)" criteria to identify the causative bacteria and their antibiotic susceptibilities (14).

Detection of intermediate susceptibility or resistance to at least three antibiotic groups was accepted as "MDR" (15).

CMS Treatment

The patients were treated with an imported brand of CMS [Colomycin, 1 million international units (MIU), equivalent to approximately 30 mg of colistin base activity (CBA) per vial, Forset Lab., UK] until September 2010 (16). There after, a domestically produced brand (Colimycin, 150 mg CBA per vial, Kocak Farma, Turkey) was used. The dosage of drug used in treatment was calculated according to the manufacturers' recommendations and the patients' creatinine clearance. Thus, for cases with a normal creatinine clearance, the imported drug dose was 90-180 mg CBA/day for those with and ideal body weight > 60 kg, 1.5-2.25 mg CBA/kg/day for those with and ideal body weight ≤ 60 kg, divided into three doses per day. The domestic brand was given at a daily dose of 2.5-5 mg CBA per kg of ideal body weight divided into three doses per day. In patients with impaired renal function, the dose was adjusted according to the creatinine clearance rate. A loading dose was not used in Turkey before June 2013.

In the result section, patients were evaluated in two groups as "high dose/kg" for domestic brand and "low dose/kg" for imported brand according to used colistin dose depending on brand.

Presence of CMS combination with other antibiotics for the treatment of the same HAP episode was also recorded.

Nephrotoxicity Evaluation

Nephrotoxicity was assessed according to the RIFLE criteria (17). In order to determine the "baseline creatinine" level of the patients, their serum creatinine levels were examined from the time of admission to the first day of CMS treatment. These levels were compared to the estimated creatinine level based on age and gender; the lower level was accepted as the patient's baseline creatinine level (18). The serum creatinine levels at the time of admission, initiation of CMS therapy and during hospitalisation were recorded. The patient's RIFLE stage was calculated using the

baseline creatinine level and the levels measured at these time periods (17). Nephrotoxicity was defined as a worsening in the RIFLE stage with respect to the RIFLE stage at the first day of CMS treatment or need for dialysis after the initiation of CMS treatment. In cases who developed nephrotoxicity, changes in the antibiotic dosing and in treatment regimens, use of renal replacement therapy were recorded. The recovery of renal function in response to therapy was categorized as "complete" (improvement in the serum creatinine level, the final creatinine level < 1.5 x baseline level), "partial" (improvement in the serum creatinine level, the final creatinine level ≥ 1.5 x baseline level), or "unresponsive" (no renal function recovery or initiation of renal replacement therapy) based on the latest serum creatinine level of the patients who died and the creatinine levels through the follow-up period of the other patients (19).

Presence of acute renal failure (ARF) before CMS therapy was recorded. This was defined as an abrupt (within 48 hours) reduction in kidney function based on an elevation in serum creatinine level, a reduction in urine output, the need for renal replacement therapy (dialysis), or a combination of these factors. During colistin treatment, the following parameters were recorded as other factors that could potentially have an impact on nephrotoxicity: dehydration, gastrointestinal bleeding, history of cardiopulmonary resuscitation (CPR), administration of diuretics, nonsteroidal anti-inflammatory drugs, contrast agents and other nephrotoxic drugs, presence of septic shock at the time HAP developed (20).

Beside the patients' clinical response, bacterial eradication, durations of stay at the hospital and intensive care unit (ICU) and overall mortality at the hospital were evaluated. The clinical response was defined as the presence of at least one of the following criteria following 72 hours of antibiotic treatment: normalization of body temperature, decrease in respiratory secretions (and in the need for suctioning), decrease in the serum CRP level by at least 50%, decrease in the need for inotropic support, significant improvement in oxygenation. Bacteriological response was defined as no growth of the causative pathogen in cultures of lower respiratory specimens obtained at least 72 hours of antibiotic treatment. Additional infections acquired at the hospital that could affect the duration of stay at the hospital and mortality status were recorded.

Statistical Analysis

The data management and analysis were done using SPPS for Windows 16.0 software. Descriptive statistics were used for the demographic data. Mann-Whitney U test was used for non-parametric. Chi-square test was used for comparison of categorical data. Logistic regression analysis with Enter method was performed in order to identify the independent risk factors leading to nephrotoxicity. Sixteen clinically relevant parameters which were identified at univariate analysis were evaluated for this analysis. Hosmer and Lemeshow test was performed to assess the goodness of fit of the model (x^2: 9.303; df: 8; Sig: 0.317). $p< 0.05$ was considered statistically significant.

RESULTS

A total of 281 cases (107 females, median age 71 years) were included in the study. Fifty-one cases (18.1%) had ARF before CMS treatment. Admission diagnoses and APACHE II scores, PaO_2/FiO_2 values,

Table 1. Demographic and clinical characteristics (n= 281)

Parameters	
Number of cases (n, F/M)	107/174
Age (years)*	71 (18-99)
Admission diagnosis, n (%)	
HAP	50 (17.8)
CAP	42 (14.9)
COPD exacerbation	39 (13.9)
Aspiration pneumonia	28 (10.0)
HCAP	27 (9.6)
IPP	13 (4.6)
VAP	10 (3.6)
Cerebrovascular disease	10 (3.6)
Other	62 (22.0)
Comorbidities, n (%)	
Hypertension	116 (41.3)
Neurological diseases	75 (26.7)
Chronic pulmonary disease	65 (23.1)
Heart failure	60 (21.4)
Diabetes mellitus	51 (18.1)
Malignant disease	17 (6.0)
APACHE II*	22 (2-50)
Septic shock, n (%)	64 (22.8)
PaO_2/FiO_2*	185 (28-565)
ARF prior to CMS use, n (%)	51 (18.1)

* Median value (range).
APACHE II: Acute Physiology Assessment and Chronic Health Evaluation, ARF: Acute renal failure, CAP: Community-acquired pneumonia, F: Female, CMS: Colistimethate sodium, HAP: Hospital-acquired pneumonia, HCAP: Healthcare associated pneumonia, IPP: Immunosuppressed patient pneumonia, M: Male, VAP: Ventilator-associated pneumonia (The patients with an admission diagnosis of VAP were transferred from another ICU).

comorbid conditions, presence of ARF prior to CMS therapy are presented in Table 1. CMS was administered to 106 cases for HAP which had developed after a mean of 10 (3-79) days and to 175 cases for VAP that had developed after a mean of 8 (3-95) days following admission. *A. baumannii* was isolated in 79.4% and *P. aeruginosa* was isolated in 13.9% of the patients as a single causative microorganism. The remaining patients had co-infection with *A. baumannii* and *P. aeruginosa*.

CMS Treatment

Until 2010, the imported brand of CMS was used at a relatively lower dose, as recommended by the manufacturer, in the treatment of 58 cases. Thereafter, the domestic brand of CMS was used in the remaining 223 cases at a higher dose, again, as recommended by the manufacturer. Thus, the median CBA of the "low dose/kg" and "high dose/kg" groups for the first day of treatment were 180 (60-180) mg and 300 (75-450) mg, respectively (p< 0.001). In addition to the parenteral route, CMS was administered via inhalation in 69 of the cases and there was no difference between two groups [19 patients (32.8%) and 50 patients (22.4%), who used the imported and domestic parenteral brands, respectively (p= 0.12)].

CMS was combined with other antibiotics in 82.9% of the patients. Combination treatment was used at similar rates in the patients groups treated with the different dose because of CMS brands. The other antibiotics used in combination are shown in Table 2.

Table 2. Antibiotics used in combination therapy

Antibiotics	Imported* (low dose/kg) (n= 47)	Domestic* (high dose/kg) (n= 186)
Tigecycline, n (%)	10 (21.3)	83 (44.6)
Cefoperazone-sulbactam, n (%)	19 (40.4)	20 (10.8)
Carbapenems, n (%)	13 (27.7)	61 (32.3)
Ceftazidime, n (%)	6 (12.8)	3 (1.6)
Aminoglycosides, n (%)	11 (23.4)	3 (1.6)
Sulbactam, n (%)	1 (2.1)	27 (14.5)
Ciprofloxacin, n (%)	2 (4.3)	4 (2.2)

* These antibiotics were grouped according to the used colistin brand.

Response to Treatment

A clinical response and bacterial eradication were achieved in 52.0% and 61.0% (128 of 210 patients) of the cases, respectively. Control bacteriologic examination could be performed in 74.7% of the patients; thus, the eradication rate reflects the outcome in patients whose data were available. There was no significant difference in clinical response and bacterial eradication rates between monotherapy and combination therapy groups (p= 0.52 and p= 1.0, respectively). The median durations of ICU and hospital stay for all patients were found as 27.5 (0-132) and 34 (9-164) days, respectively. Invasive mechanical ventilation was applied to 247 cases due to respiratory failure.

There was no difference in clinical outcomes in the patients groups classified according to used dose depending on CMS brands (Table 3).

Table 3. Comparison of the clinical outcomes of the patients treated with the two different dose

Parameters	Low dose/kg (n= 58)	High dose/kg (n= 223)	p
Clinical response, n (%)	29 (50)	117 (52.5)	0.88
Bacterial eradication, n (%)*	24/46 (52.2)	104/164 (63.4)	0.18
Combination treatment, n (%)	47 (81)	186 (83.4)	0.70
Nephrotoxicity, n (%)	24 (41.4)	151 (67.7)	**< 0.001**
Additional infection, n (%)	42 (72.4)	132 (59.2)	0.07
IMV duration (days)**	22 (0-132)	17 (0-128)	0.12
NIMV duration (days)**	3 (0-40)	3 (0-34)	0.84
ICU duration (days)**	28.5 (10-132)	26.5 (0-127)	0.53
Hospitalisation duration (days)**	37 (13-141)	33 (9-161)	0.24
Mortality, n (%)	34 (58.6)	139 (62.3)	0.65

* 74.7% of the patients had examination of bacteriological response.
** Median value (range).
CMS: Colistimethate sodium, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation.

Table 4. Clinical and laboratory parameters associated with nephrotoxicity

Parameters	Nephrotoxicity (+) (n= 175)	Nephrotoxicity (-) (n= 106)	p
Age*	73 (20-91)	66 (18-99)	**0.004**
Gender (n, F/M)	60/115	47/59	0.10
APACHE II*	22 (2-44)	21.5 (7-50)	0.57
PaO_2/FiO_2*	188 (41-565)	182 (28-428)	0.37
Weight (kg)*	70 (40-180)	60 (30-170)	**0.017**
Heart failure, n (%)	42 (24)	18 (17)	0.18
Hypertension, n (%)	80 (45.7)	36 (34)	0.06
Diabetes mellitus, n (%)	39 (22.3)	12 (11.3)	**0.025**
Sepsis at admission, n (%)	97 (55.4)	70 (66.0)	0.08
Serum albumin level at admission (g/dl) *	2.9 (1.4-4.8)	2.9 (1.0-4.4)	0.41
Renal dysfunction prior to colistin use, n (%)	29 (16.6)	22 (20.8)	0.43
Nephrotoxic drug use, n (%)	113 (64.6)	74 (69.8)	0.43
NSAID use, n (%)	8 (4.6)	7 (6.6)	0.59
Diuretic use, n (%)	79 (45.1)	51 (48.1)	0.71
Contrast agent use, n (%)	37 (21.1)	23 (21.7)	0.88
Dehydration, n (%)	40 (22.9)	25 (23.6)	0.89
GIS bleeding, n (%)	22 (12.6)	149 (13.2)	1.0
Red blood cell transfusion, n (%)	115 (65.7)	55 (51.9)	**0.017**
CPR, n (%)	33 (18.9)	12 (11.3)	0.13
VAP presence, n (%)	108 (61.7)	67 (63.2)	0.90
HAP related sepsis, n (%)	147 (84)	99 (93.4)	**0.023**
HAP related septic shock, n (%)	97 (55.4)	54 (50.9)	0.32
CMS dose depending on brand, n (%)			**< 0.001**
Imported (low dose/kg)	24 (13.7)	34 (32.1)	
Domestic (high dose/kg)	151 (86.3)	72 (67.9)	
Use of nebulized CMS, n (%)	44 (25.3)	25 (23.6)	0.89
RIFLE score at therapy initiation, n (%)			**0.023**
No AKI	137 (78.3)	81 (76.4)	
Risk	24 (13.7)	8 (7.5)	
Injury	11 (6.3)	8 (7.5)	
Failure	3 (1.7)	9 (8.5)	
Median CBA dose (mg)	300 (60-450)	225 (60-450)	**< 0.001**
Treatment duration (days)*	13 (3-33)	12 (3-26)	0.26

* Median value (range).
AKI: Acute kidney injury, APACHE II: Acute Physiology Assessment and Chronic Health Evaluation, CBA: Colistin base activity, CMS: Colistimethate sodium, CPR: Cardiopulmonary resuscitation, F: Female, GIS: Gastrointestinal system, HAP: Hospital-acquired pneumonia, NSAID: Nonsteroidal anti-inflammatory drug, M: Male, VAP: Ventilator-associated pneumonia.

Nephrotoxicity

Nephrotoxicity developed at a mean of 8.4 ± 5.0 days after the initiation of CMS treatment in 62.3% of the patients; of these, 30.9% were in "injury" and 49.7% were in "failure" stage, as defined by RIFLE criteria. The risk factors that were likely to affect the development of nephrotoxicity are presented in Table 4. The patients developing nephrotoxicity had lower RIFLE stages at the time of initiation of CMS therapy than the patients without nephrotoxicity (p= 0.023). In univariate analysis, nephrotoxicity was associated with advanced age (p= 0.004), increased weight (p= 0.017); presence of diabetes mellitus (p= 0.025) and of HAP-related sepsis (p= 0.023), red blood cells transfusion (p= 0.017), the use of high dose colistin measured as colistin base activity (p< 0.001) and the use of the domestic CMS brand (p< 0.001). Renal

Table 5. Comparison of risk factors for nephrotoxicity in patients treated with the imported (low dose/kg) and domestic (high dose/kg) CMS brands

Parameters	Imported brand (n= 58)	Domestic brand (n= 223)	p
Age*	68 (18-87)	71 (19-99)	0.14
Gender (n, F/M)	15/43	92/131	**0.034**
APACHE II*	20 (7-38)	22 (2-50)	0.15
PaO_2/FiO_2*	194 (63-400)	184 (28-565)	0.58
Weight (kg)*	70 (40-90)	65 (30-180)	0.94
Heart failure, n (%)	18 (31.0)	42 (18.8)	**0.049**
Hypertension, n (%)	30 (51.7)	86 (38.6)	0.07
Diabetes mellitus, n (%)	7 (12.7)	44 (19.7)	0.25
Sepsis at admission, n (%)	43 (74.1)	124 (55.6)	**0.006**
Serum albumin level at admission (g/dL)*	3.2 (1.9-4.6)	2.9 (1-4.8)	**0.001**
ARF before colistin, n (%)	12 (20.7)	39 (17.5)	0.57
Nephrotoxic drug use, n (%)	35 (60.3)	152 (68.7)	0.28
NSAID use, n (%)	3 (5.2)	12 (5.3)	1.0
Diuretic use, n (%)	36 (62.1)	94 (42.6)	**0.007**
Radiocontrast agent use, n (%)	13 (22.4)	47 (21.1)	0.86
Dehydration, n (%)	10 (17.2)	55 (24.7)	0.29
GIS bleeding, n (%)	6 (10.3)	30 (13.5)	0.66
Red blood cell transfusion, n (%)	33 (56.9)	137 (61.4)	0.55
CPR, n (%)	6 (10.3)	39 (17.5)	0.23
VAP, n (%)	46 (79.3)	129 (57.8)	**0.002**
HAP-related sepsis, n (%)	55 (94.8)	191 (85.6)	**0.023**
HAP-related septic shock, n (%)	26 (44.8)	125 (56.1)	0.13
Use of nebulized CMS, n (%)	19 (32.8)	50 (22.4)	0.12
RIFLE stage at CMS initiation, n (%)			0.18
No AKI	44 (75.9)	174 (78.0)	
Risk	8 (13.8)	24 (10.8)	
Injury	6 (10.3)	13 (5.8)	
Failure	0	12 (5.4)	
Median CBA dose* (mg)	180 (60-180)	300 (75-450)	**< 0.001**
Treatment duration (days)*	14 (3-27)	12 (3-33)	0.23

* Median value (range).
AKI: Acute kidney injury, APACHE II: Acute Physiology Assessment and Chronic Health Evaluation, ARF: Acute renal failure, CBA: Colistin base activity, CMS: Colistimethate sodium, CPR: Cardiopulmonary resuscitation, F: Female, GIS: Gastrointestinal system, HAP: Hospital-acquired pneumonia, NSAID: Nonsteroidal anti-inflammatory drug, M: Male, VAP: Ventilator-associated pneumonia.

function worsened in 67.7% and 41.4% of patients who used the high and low dose CMS, respectively ($p< 0.001$).

The risk factors for nephrotoxicity in patients treated with high and low doses of colistin were separately examined (Table 5). Multivariate logistic regression analysis showed that the development of nephrotoxicity was independently associated with used brand. Besides, all of the 23 patients required to dialysis because of nephrotoxicity were treated with high dose/kg CMS. The other independent variables associated with nephrotoxicity were increased age, male gender, hypertension, red blood cells transfusion, absence of acute kidney injury and the risk group of RIFLE stage (Table 6).

Nephrotoxicity developed at similar rates in patients with HAP (63.2%) and VAP (61.7%).

Management of Nephrotoxicity

Among the 175 patients that developed nephrotoxicity; the CMS dose was decreased in 88 and CMS therapy was discontinued in 40. For renal recovery treatment,

Table 6. Logistic regression analysis for development of nephrotoxicity and univariate analysis

	Multivariate analysis					Univariate analysis
Parameters	**B**	**S.E.**	**Odds ratio**	**95% CI**	**p**	**p**
Gender			2.60	1.26-5.39	**0.01**	0.10
Age	0.29	0.01	_	-	**0.008**	**0.004**
Heart failure			1.03	0.39-2.70	0.96	0.18
Weight	0.007	0.01	_	-	0.61	**0.017**
Hypertension			2.50	1.03-6.08	**0.043**	0.06
Diabetes mellitus			1.33	0.48-3.68	0.58	**0.025**
ARF before colistin treatment			1.81	0.73-4.52	0.20	0.43
Sepsis at admission			1.16	0.51-2.37	0.68	0.08
Serum albumin level at admission	-0.249	0.27	-	-	0.35	0.41
Diuretic use			1.10	0.50-2.020	0.981	0.71
VAP presence			1.54	0.77-3.08	0.227	0.90
HAP-related sepsis			3.76	0.93-15.17	0.063	**0.023**
Red blood cell transfusion			2.54	1.24-5.18	**0.011**	**0.017**
RIFLE stage at CMS initiation*						
No AKI			10.19	1.69-61.58	**0.011**	
Risk			11.90	1.69-83.97	**0.013**	
Injury			8.36	0.92-75.78	0.59	
CMS brand			3.97	1.08-14.66	**0.038**	**< 0.001**
CBA dose	0.01	0.003	-	-	0.739	**< 0.001**

* Reference: RIFLE-Failure.
ARF: Acute renal failure, VAP: Ventilator-associated pneumonia, HAP: Hospital-acquired pneumonia, AKI: Acute kidney injury, CMS: Colistimethate sodium, CBA: Colistin base activity.

Table 7. Comparison of the patients with and without developed nephrotoxicity with regards to clinical course and prognosis

Parameters	**Nephrotoxicity (+) (n= 175)**	**Nephrotoxicity (-) (n= 106)**	**p**
Clinical response, n (%)	84 (48)	62 (58.5)	0.09
Bacterial eradication, n (%)*	84/135 (62.2)	44/75 (58.7)	0.66
Combination treatment, n (%)	146 (83.4)	87 (82.1)	0.87
Additional infection in follow up, n (%)	113 (64.6)	61 (57.5)	0.26
IMV duration (days)**	18 (0-128)	16 (0-132)	0.12
NIMV duration (days)**	3 (0-32)	2 (0-40)	0.84
Length of ICU stay (days)**	28 (0-127)	27 (0-132)	0.53
Length of hospital stay (days)**	35 (10-164)	31 (9-141)	0.24
Mortality, n (%)	117 (66.9)	56 (52.8)	**0.022**

* There was no data on bacteriologic response in all of the patients.
** Median values (range).
ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation.

twenty-three patients needed to dialysis, and 86 cases received hydration or diuretic treatment depending on their fluid condition. As a result of these interventions; 23.2% of the cases fully recovered, 20.0% had partial recovery, whereas renal function did not recover in 45.7%. No information could be retrieved regarding the outcome of the remaining patients (11.1%).

Effect of Nephrotoxicity on Clinical Outcomes

When patients were compared in terms of developing nephrotoxicity during follow up for their clinical prognosis, the mortality rate was found to be higher in the group having nephrotoxicity (p= 0.022). There was no difference between two groups for other outcomes (Table 7).

Mortality and Risk Factors

The overall mortality rate was found as 61.6%. Multivariate logistic regression analysis showed that the mortality was associated with advanced age [OR= 1.05 (95% CI 1.02-1.07), p< 0.001], lack of clinical response to treatment [OR= 11.5 (95% CI 4.86-27.03), p< 0.001] and the presence of HAP-related septic shock [OR= 2.23 (95% CI 1.07-4.64), p= 0.032]. APACHE II score at hospitalisation, the CMS brand, the CBA dose on first day of treatment, CMS-related nephrotoxicity, bacteriologic response to treatment, presence of sepsis, additional infection, bacteremia due to HAP, serum albumin level at hospitalisation, HAP or VAP diagnosis were not related to mortality.

DISCUSSION

This study showed that CMS therapy was associated with relatively high clinical and bacteriologic response rates in patients with HAP due to MDR *P. aeruginosa* or *A. baumannii*, but that it also led to the development of nephrotoxicity in a significant percentage of the patients. Importantly, the use of high dose/kg CMS depending on the brand was found to be one of the risk factors for nephrotoxicity. Besides, advanced age, male gender, presence of hypertension, red blood cells transfusion and low RIFLE stages were other risk factors. Although the mortality was found to be higher in the patients who developed nephrotoxicity; after adjustment, nephrotoxicity was not found to be an independent risk factor for mortality.

CMS is excreted primarily via renal route and its most important side effect is nephrotoxicity. Renal toxicity due to CMS is mainly manifested as acute tubular necrosis (7). It has been shown to depend on the drug concentration and duration of treatment; a significant association has been found between cumulative doses and increased creatinine levels (21-23). Additionally, the use of higher mean colistin doses per ideal body weight, simultaneous use of rifampin and co-administration of three or more nephrotoxic agents were reported as other nephrotoxicity risk factors (24).

Rates of colistin related nephrotoxicity vary widely, ranging between 0-53.5%. Lower rates have been reported in more recent studies (8). This is possibly due to the use of purified colistin, the use of CMS instead of colistin sulfate, more adequate dose adjustment according to renal function and improvements in treatment and follow-up (specifically the monitoring of hydration) of the ICU patients. Differences in the criteria used for evaluating nephrotoxicity may also explain part of the variance in the rates. RIFLE criteria are more sensitive to changes in renal function. As a result, nephrotoxicity rate has been reported to be higher in studies which used these criteria (25,26).

The rate of nephrotoxicity in this study was 62.3%, well above the previously reported range. This high rate could partly be explained with the use of RIFLE criteria; but when we analyzed the data to determine other contributory factors, the use of the domestic colistin brand with high dose, increased age, male gender, presence of hypertension, red blood cells replacement therapy, absence of acute kidney injury and low RIFLE stage were found to be associated with nephrotoxicity. The increased associated with low RIFLE stage is related to the methodology of RIFLE classification. The classification is done using the basal creatinine value, thus small increases in low baseline creatinine value more easily raise the RIFLE stage.

The association with between used drug brand and nephrotoxicity was unexpected, and patients using the two different brands were compared regarding exposure to other risk factors. The rates of concomitant use of nephrotoxic drugs were similar, and patients who received the imported CMS brand actually had worse risk factors, including higher rates of heart failure, sepsis and diuretic use. On the other hand, the domestic brand was administered at a significantly higher dose, as per the manufacturers' commendations, which is possibly the underlying reason for increased nephrotoxicity. This was an alarming finding and the authorities were immediately informed.

A smaller Turkish study evaluated the efficacy and safety of imported CMS in 24 patients with nosocomial

infections caused by MDR gram-negative bacteria. CMS was administered at daily doses of 90-180 mg CBA. Nephrotoxicity developed in 7.7% and 18.2% of the patients treated with low and high doses, respectively. These difference from our results in nephrotoxicity rates may be explained with the differences in methods used to define nephrotoxicity (0.5 mg/dL increase in level of creatinine), and in patient populations (all cases had normal baseline renal function) (27). Another study by Kalin et al. evaluated nephrotoxicity in VAP cases treated with the domestic CMS (28). They used RIFLE criteria and renal toxicity rate was reported 20-40% depending on the daily dose. It was also found that the risk of nephrotoxicity increased with advanced age, use of high dose and concomitant use of aerosolized CMS. However, their patient population was younger than our patients [50.07 ± 20.47 vs. 71 (18-99) years] and possibly explains the lower rate of nephrotoxicity. Combination therapy with inhaled and parenteral treatment has been reported to cause increased nephrotoxicity (29). This factor was not seen as an important contributing factor to the high rate observed in our study. Balkan et al. have shown that colistin induced nephrotoxicity was more frequently seen in patients older than 60 years of age, with low initial glomerular filtration rate and high Charlson co-morbidity index (30).

The overall mortality rate was high, as expected in a high-risk group with nosocomial pneumonia due to MDR bacteria. Similar rates have been reported in similar patient populations, whereas lower rates were observed in younger patients with less severe disease (9,31). Although the mortality rate was higher in our patients with nephrotoxicity, the only independent risk factors for mortality were older age, lack of response to treatment and presence of HAP-related septic shock. These findings are consistent with previous reports on mortality in patients with HAP and VAP (32,33).

This study has several limitations. First, the data were gathered from a retrospective review of patient charts and thus not all data were obtained from all patients. On the other hand, we were able to collect the data for all parameters (except for the follow-up bacteriology results) from more than 90% of the patients and to reach a high number of patients from seven centers. Second, we could not calculate the cumulative doses of CMS, as the patients' discharge reports did not include daily changes in colistin doses. Besides, serum colistin levels were not monitored in any of the patients, as this analysis is not available in any of the participating centers. Different results might have been obtained, if cumulative doses or serum concentrations had been entered into the analysis. Third, although the use of all potentially nephrotoxic drugs used during the hospitalization period was recorded and analyzed, no reliable data could be obtained regarding the use of these drugs prior to hospital admission. Fourth, comparison of the nephrotoxicity rates in this and other studies is somewhat problematic. Different criteria have been used in evaluating renal function. Besides, even when RIFLE scoring is used, there is still a debate about the creatinine level which should be accepted as the baseline. In previous studies; the pre-ICU, ICU admission and previous hospital discharge creatinine levels have been used for baseline renal function (34,35).

In conclusion, this large, multicenter study showed that a considerable group of patients with HAP due to MDR gram-negative microorganisms could successfully be treated with CMS, but this was associated with unacceptably high rates of nephrotoxicity. The rate of nephrotoxicity was higher than previously reported and associated with older age, male gender, presence of hypertension, red blood cells transfusion, RIFLE stage and the use of colistin doses.

ACKNOWLEDGEMENTS

The authors thank to Husnu Pullukcu for his contributions to the manuscript.

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