*Original Article*

# Infection due to colistin-resistant *Enterobacteriacae* in critically-ill patients

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## Abstract

Introduction: This study was conducted in response to the rising incidence of drug resistance observed in the intensive care unit (ICU) of King Fahad Medical City.

Methodology: A retrospective observational study was conducted in the ICU of King Fahad Medical City between October 2003 and April 2012. Data were collected using a structured data sheet.

Results: Nine episodes of infection with colistin-resistant *Enterobacteriacae* were recorded in seven patients. Five were females with an average age of 59.75 years. All patients had multiple co-morbidities; five had diabetes mellitus. In five of the episodes, *Klebsiella pneumoniae* was responsible, *Serratia marcescens* was reported in two, while *Enterobacter aerogenes* and *Providencia stuartii* were responsible for one episode of infection each. Prior colistin use was documented in all but one patient. Colistin resistance was defined by a minimum inhibitory concentration (MIC) of > 4 µg/mL according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint for *Enterobacteriacae*. Various antibiotics were used to treat the patients, with mortality reported in two.

Conclusion: Infection due to colistin-resistant *Enterobacteriacae* is a rising challenge in Saudi Arabia; colistin use is thought to be associated with these infections. This calls for a stricter antimicrobial stewardship program and improved infection control measures to curb the rising trend of antibiotic resistance.

**Key words:** Colistin resistance; Enterobacteriacae; Saudi Arabia

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## Introduction

Members of the family *Enterobacteriacae* are Gram-negative, non-spore-forming, facultative anaerobes that ferment glucose and other sugars, reduce nitrate to nitrite, and produce catalase but (with the exception of Pleisomonas) do not produce oxidase. These bacteria have caused significant challenges to infectious disease (ID) physicians and their patients throughout the world by their resistance to currently available antibiotics. This challenge, unfortunately, has not been paralleled by the development of novel antimicrobials. As a result, there are a growing number of reports on infections caused by Gram-negative bacteria (GNB), for which no adequate therapeutic options exist, with attendant morbidity and mortality [1-3]. This return to the pre-antibiotic era has become a reality in Saudi Arabia [4], where antimicrobials from all classes are prescribed, and the antimicrobial stewardship program is still in its infancy.

The growing resistance among Gram-negative bacteria to commonly used antibiotics has led to the resurgence of previously discarded antibiotics like colistin, a neurotoxic and nephrotoxic agent, as a last-resort treatment option [5-7]. A major concern is that selective pressure due to extensive colistin use may lead to the emergence of resistance. In addition, infection with pathogens intrinsically resistant to colistin, such as *Proteus*, *Providencia*, *Morganella*, *Serratia*, *Edwardsella*, *Aeromonas*, *Vibrio*, and *Burkholderia* have become a matter of concern to clinicians. Despite the toxicity of this relatively old agent, colistin is frequently used to treat infections due to carbapenem-resistant *Enterobacteriaceae* [5,6,8]. In most cases, colistin is the last viable effective option for the treatment of invasive bloodstream infections (BSI) due to carbapenemase-producing Gram-negative bacteria [9]. Overuse of colistin has recently led to the emergence of resistance to this life-saving agent [6].

The mechanism(s) of colistin resistance in carbapenem-resistant Enterobacteriaceae is/are not fully understood. However, the production of carbapenemases, cephalosporinases, and porin loss are thought to play a role. The mechanism of colistin resistance in *Acinetobacter baumannii* has been elucidated [10], but it remains unclear whether the same mechanism(s) is associated with colistin resistance in carbapenem-resistant *Enterobacteriaceae*. Additionally, no interpretative breakpoint has been defined by the Clinical and Laboratory Standards Institute (CLSI) [11]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set the clinical breakpoint for *Enterobacteriaceae*, and resistance to colistin has been defined as a minimum inhibitory concentration (MIC) of 4 μg/mL [12].

We undertook this retrospective review from a single tertiary care intensive care unit (ICU) in Saudi Arabia to highlight the growing prevalence of infections due to multi-drug resistant (MDR) organisms in our locality and to encourage the medical community to embrace the concept of antimicrobial stewardship in order to curb the trend.

## Methodology

*Study design and setting*

This retrospective cross-sectional study was conducted in the ICU of King Fahad Medical City (KFMC), Saudi Arabia, consisting of 31 beds. All patients admitted to the ICU are cared for by dedicated nurses, with strict infection control procedures to prevent the transmission of infection between patients. The ICU is overseen by a dedicated infection control nurse who goes round daily to ensure strict adherence to hand hygiene and other infection control procedures.

KFMC was commissioned in 2003 with a total bed capacity of 1095. It is one of the largest and most advanced medical complexes in the Middle East. The hospital caters for its primary patients from all regions of the country and also accepts referrals from other health care facilities based on their eligibility. The study was approved by the Institutional Review Board of KFMC.

*Patients and variables*

All patients 13 years of age and older who developed infection due to colistin-resistant *Enterobacteriacae* between October 2003 and April 2012 were identified for inclusion in this study. All infections were acquired during the patient's stay in the ICU. Within the study period, nine episodes of infection due to colistin-resistant *Enterobacteriacae* were reported in seven patients. Infection was confirmed in those with consistent clinical features of infection at a particular site and a positive culture. All patients with colistin-resistant *Enterobacteriacae* were selected for inclusion in this study, and their electronic charts were reviewed. ID specialists diagnosed infection. Data about the patients' demographics, admission sources, co-morbid conditions, prior antibiotic therapies, clinical characteristics, types and sources of isolates, treatments and outcomes were imported into a structured data sheet. Also collected were data about invasive procedures, duration of ICU stays before infection with the colistin-resistant *Enterobacteriacae*, and in-hospital mortality.

*Antimicrobial Susceptibility Testing*

Disk diffusion method

The test was performed by preparing 0.5 McFarland standard suspensions from overnight blood agar cultures. These were swabbed onto the surface of Mueller-Hinton agar plates (Medical Diagnostic manufacturing company, Riyadh, Saudi Arabia). After drying, different concentrations of antimicrobials (Becton Dickinson, San Diego, USA) were placed at the centre, and the plates were incubated at 37$^{o}$C overnight (between 18 and 24 hours). The test was interpreted by measuring the zone size of inhibition according to CLSI guidelines, except for colistin, which was interpreted according to EUCAST guidelines [11,12].

Phoenix

Identification of bacterial species was performed using a Phoenix (Becton Dickinson, San Diego, USA) automated system. Phoenix panels included 45 biochemical agents and 20 antibiotics. Interpretation was done according to CLSI guidelines except for colistin, which was interpreted according to EUCAST guidelines [11,12]. Quality control tests were performed according to the manufacturer's instructions.

**Table 1**: Clinical characteristics and treatment outcomes of patients infected with Colistin-resistant *Enterobacteriacae*

| Age/ Sex | Source of patient | Co-morbidities | Risk factors | Isolate | MIC (µg/mL) | Source of specimen | ICU stay before infection | Prior antimicrobial exposure | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69/M | Home | HTN, advanced NPC, Seizure disorder, pulmonary nocardiosis | Chemotherapy, CVC line, IFC, MV, PEG | *Klebsiella pneumoniae* | >4 | Ear swab | 5 weeks | PEN, CEP, CIPRO, CARB, COL, VAN, TMP-SMX, MET | Otitis externa | Ciprofloxacin | Cured |
| 57/F | ICU | DM, HTN, OSA, Hypothyroid, | CVC, IFC, MV, PEG, | *Klebsiella pneumoniae* | >4 | Blood | 5 months | PEN, CEP, CARB, COL, GEN, VAN, AMK | B.S.I. | AMK + CL | Cured |
| 57/F | ICU | DM, HTN, OSA, Hypothyroid, | CVC, IFC, MV, PEG, | *Klebsiella pneumoniae* | >4 | Urine | 6 months | PEN, CEP, CARB, COL, GEN, VAN, AMK, | U.T.I. | AMK + CL | Cured |
| 76/F | LTCF | DM, HTN, IHD, DLP, COPD, Hypothyroid, ESRD | CRRT, CVC, ICD, TPN, | *Serratia marcescens* | >4 | Surgical site | 4 months | PEN, CIPRO, CARB, COL, LIN, VAN, TMP-SMX | S.S.I. | Ciprofloxacin | Cured |
| 77/F | Home | DM, HTN, AF, GB stones, OSA, hypothyroid, CBD stones | ERCP, PICC, IFC, MV, cholecystectomy | *Klebsiella pneumoniae* | >4 | Urine | 5 months | PIP-TAZ, CARB, CEP, COL | U.T.I. | Tigecycline + CL | Died |
| 77/F | Home | DM, HTN, GB stones, OSA, hypothyroid | PICC, TPN, ERCP, MV, IFC, biliary stent | *Serratia marcescens* | >4 | Blood | 1 month | PEN, CEP, CARB, VAN, COL, LIN | B.S.I. | Ceftriaxone | Cured |
| 76/F | LTCF | DM, HTN, IHD, DLP, COPD, Hypothyroid, ESRD | PICC, CVC, cystoscopy bronchoscopy, MV, | *Enterobacter aerogenes* | >4 | Urine | 4 months | PEN, CEP, CIPRO, CARB, COL, VAN, LIN, TMP-SMX, NTF | U.T.I. | Nitrofurantoin | Died |
| 45/M | LTCF | MS, Pseudobulbar palsy | CVC, IFC, PEG, MV, | *Providencia rettgeri* | >4 | Urine | 2 months | PEN, CEP, CIPRO, TIG, PIP-TAZ, GEN, COL | U.T.I. | Cefepime | Cured |
| 53/F | Home | DM, HTN, CVD, Seizure, CNS vasculitis | CVC, IFC, MV, Endoscopy | *Klebsiella pneumoniae* | >4 | Urine | 5 months | PIP-TAZ, VAN, AZIT, CIPRO, METRO | U.T.I. | Cefepime | Cured |

Legend: HTN=hypertension; NPC=nasopharyngeal carcinoma; DM=diabetes mellitus; OSA=obstructive sleep apnea; IHD=ischemic heart disease; DLP=dyslipidemia; COPD=chronic obstructive airway disease; ESRD=end stage renal disease; CBD=common bile duct; AF=atrial fibrillation; GB=gall bladder; MS=multiple sclerosis; CVD=cerebrovascular disease; CNS=central nervous system; CVC=central venous catheter; IFC=indwelling Foley catheter; MV=mechanical ventilation; PEG=percutaneous endoscopic gastrostomy; PICC=peripherally-inserted central catheter; EGD=esophago-gastro-duodenoscopy; ERCP=endoscopic retrograde cholangiopancreatography; MIC=minimum inhibitory concentration; ICU=intensive care unit; PEN=penicillin, CEP=cephalosporin; CIPRO=ciprofloxacin; CARB=carbapenem; COL=colistin; VAN=vancomycin; TMP-SMX=trimethoprim-sulphamethoxazole; MET=metronidazole; AMK=amikacin; GEN=gentamicin; LIN=linezolid; PIP-TAZ=piperacillin/tazobactam; NTF=nitrofurantoin, TIG=tigecycline; AZIT=azithromycin; UTI=urinary tract infection; BSI=blood stream infection

**Table 2**:Complete susceptibility profiles of isolates to all tested antibiotics

| Age/ Sex | Source of specimen | Isolate | AMP | AUG | CPL | CXM | CRO | CIP | CPE | GM | SXT | TZP | IMP | MER | TIG | NIT | COL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **69/M** | Ear swab | *Klebsiella pneumoniae* | R | R | R | R | R | S | NT | R | R | R | R | R | NT | NT | R |
| **57/F** | Blood | *Klebsiella pneumoniae* | R | R | R | R | R | R | R | R | R | R | R | R | INT | NT | R |
| **57/F** | Urine | *Klebsiella pneumoniae* | R | R | R | R | R | R | R | R | R | R | R | INT | R | R | R |
| **76/F** | Surgical site | *Serratia marcescens* | R | R | R | R | R | S | R | S | S | R | R | R | NT | NT | R |
| **77/F** | Urine | *Klebsiella pneumoniae* | R | R | R | R | R | R | R | R | R | R | R | R | S | S | R |
| **77/F** | Blood | *Serratia marcescens* | R | R | R | R | R | S | S | S | NT | R | R | R | NT | NT | R |
| **76/F** | Urine | *Enterobacter aerogenes* | R | R | R | R | R | R | R | R | R | R | R | R | R | INT | R |
| **45/M** | Urine | *Providencia rottgeri* | R | R | R | R | R | R | S | R | R | R | R | R | INT | R | R |
| **53/M** | Urine | *Klebsiella pneumoniae* | R | R | R | R | R | R | S | R | R | R | R | R | INT | R | R |

Abbreviations for antibiotics:
Amp=Ampicillin; Aug=Augmentin;, CPL= Cephalothin; Cxm=Cefuroxime; CAZ= Ceftazidime; CRO= Ceftriaxone; FOX=Cefoxitin; CIP= Ciprofloxacin; AN= Amikacin; GM= Gentamicin; SXT=Trimethoprim–Sulfamethoxazole; TZP=Piperacillin/Tazobactam; IMP=Imipenem; MER=Meropenem; CPE=Cefepime; NIT=Nitrofurantoin; TGC=Tigecycline; CL=Colistin; S=sensitive, R=resistant, NT=not tested, INT=intermediate sensitivity

## Results

The mean age of the patients enrolled in this study was 59.75 years. Five out of the seven patients were females. Three were admitted from home, three were referrals from Long Term Care Facilities (LTCF), and one came from another ICU. Table 1 summarizes the characteristics of the cases presented in this study that included clinical and epidemiological information, and the outcome of the infections. All cases had multiple co-morbidities; the majority had diabetes mellitus.

There were nine episodes of infection from seven critically ill patients in the ICU of KFMC in Riyadh, Saudi Arabia. Urinary tract infections (UTI) occurred in five (three due to *K. pneumoniae*, one each due to *Enterobacter aerogenes* and *Providentia rottgeri*). Blood stream infections (BSI) were recorded in two of the nine episodes; *K. pneumoniae* and *Serratia marcesecens* were responsible for these infections. Malignant otitis externa was recorded in a patient with advanced nasopharyngeal carcinoma who was on palliative chemotherapy and had a background of diabetes mellitus. A second infection of *S. marcescens* was identified from the surgical site of one patient. Among the factors thought to be associated with infection with colistin-resistant *Enterobacteriacae* were prolonged ICU stay, mechanical ventilation, invasive procedures such as central venous catheter (CVC) line insertion, percutaneous endoscopic gastrostomy (PEG) tube, peripherally-inserted central catheter (PICC) line, indwelling Foley's catheter (IFC), esophago-gastro-duodenoscopy (EGD), cystoscopy, bronchoscopy, endoscopic retrograde cholangiopancreatography (ERCP), and biliary stent insertion.

The average length of stay (LOS) for cases before acquiring infection with colistin-resistant *Enterobacteriacae* was 14.78 weeks with a range of four weeks to 24 weeks. Colistin MIC for all reported isolates was greater than 4 μg/mL. Various antibiotics, either singly or in combination, were used to treat the infections with varying responses (Table 1). Two patients died; overwhelming sepsis was thought to have contributed to their deaths. A complete susceptibility profile of all the isolates is presented in Table 2.

## Discussion

We present, to the best of our knowledge, the first case series among critically ill patients from Saudi Arabia that focuses on clinical information and outcome of infection due to colistin-resistant *Enterobacteriacae*. Most of the cases were females; all had multiple co-morbidities and had undergone various invasive procedures either in the ICU or prior to ICU admission. The main association among all (but one) patients with documented infection was their receipt of colistin. The duration of the colistin treatment appeared to be an important factor in the emergence of resistance. A recent study revealed that patients colonized by colistin-resistant isolates had previous colistin exposure compared to those who did not [13]. In addition, patients with a longer ICU stay had an increased risk, although this may reflect a higher frequency of colistin use in patients with long ICU admissions, a finding shown in other studies [14,15]. These findings demonstrate an urgent need for enhanced antimicrobial stewardship in the ICU, with coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewardship seeks to achieve optimal clinical outcomes related to antimicrobial use, to minimize toxicity and other adverse events, to reduce the costs of health care for infections, and to limit the selection for antimicrobial-resistant organisms.

As reported previously, colistin treatment was an independent risk factor for infection with pathogens known to be intrinsically resistant to colistin such as *Proteus*, *Serratia*, *Providencia*, and *Morganella* [16,17].

This report is unique in that it is the first from Saudi Arabia, where high rates of infections due to MDR GNB requiring salvage therapy with colistin have been reported [4,18,19]. Infections with MDR- or pandrug-resistant GNB is not always synonymous with a bad outcome, as occasionally these resistant isolates may exhibit decreased virulence compared to other more sensitive organisms of the same species [3]. Although a 10-year review by Littlewood et al. [20] in 2000 reported that colistin resistance was rare, its increased use has been followed by reports describing clinical isolates of colistin-resistant *K. pneumoniae* from fecal and bronchial flora in critically ill patients [21]. Similarly Matthaiou et al. reported on the burden posed by colistin-resistant isolates and stressed that the common denominator fuelling resistance was colistin use [14].

It can be inferred that the growing threat of colisitin resistance is due to the increased exposure of patients to colistin as a result of infections with carbapenem-resistant *Acinetobacter spp*, carbapenem-resistant *Pseudomonas spp*., and carbapenem-resistant

*K. pneumoniae* [22]. This has led to an increase in the use of colistin, an antibiotic previously discarded due to its high rates of toxicity, to treat these patients. As might be expected, the increased use of colistin has resulted in the emergence of pathogens that are resistant to this agent due to selective pressure, although some infections with colistin-resistant *Enterobacteriacae* have occurred without prior colistin use [23].

The appearance of Gram-negative bacteria with intrinsic resistance to polymyxins, (including species of *Proteus*, *Serratia*, and *Stenotrophomonas*), has been documented in patients receiving these agents [16,17]. In a recent study by Kontopidou et al., 51 (34%) patients were colonized by pathogens with an intrinsic resistance to colistin. The majority of these patients (64%) had been exposed to colistin with a median length of colistin treatment of 26 days, compared with 14 days in patients exposed to colistin but not colonized by pathogens with an intrinsic resistance to colistin ($p = 0.02$) [13].

Four out of the nine episodes of infection recorded in this study were due to organisms with intrinsic resistance to colistin, notably *Serratia*, *Enterobacter*, and *Providentia*., These three bacterial species, with *A. baumannii* and *Citrobacter freundii*, are often referred to as "SPACE."

## Conclusion

Colistin has been extensively used to treat MDR GNB, and this might lead to the development of resistance towards this agent. Multiple co-morbidities, invasive procedures, ICU stay, and, most importantly, prior exposure to colistin, are likely to be the driving factors fuelling the threat posed by colistin-resistant *Enterobacteriacae*. Pressure from colistin use not only exposed the recipients to infections with colistin-resistant organisms, but it also led to infections with organisms with intrinsic resistance to colistin.

To control this trend, a multidisciplinary approach that involves ID physicians, infection control experts, microbiologists, and ID pharmacists must be implemented. Continued surveillance should be actively encouraged to halt transmission between patients. Antimicrobial stewardship, especially in the ICU, should be strictly monitored and enforced. Further work is needed to elucidate the possible synergistic effects of antimicrobial combinations in the treatment of infections caused by pandrug-resistant or extensive drug-resistant organisms.

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