

# Colistin-resistant *Klebsiella pneumoniae* in Surgical Polytrauma Intensive Care Unit of Level-1 Trauma Center: First Case Series from Trauma Patients in India

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## Abstract

**Introduction:** There have been isolated case reports and reports of outbreak of colistin-resistant *Klebsiella* from various parts of the world but only two from India and that too from oncology centers. We report cluster of colistin-resistant *Klebsiella pneumoniae* bloodstream infection cases from our surgical trauma Intensive Care Unit. **Methodology:** The study was carried out in surgical ICU of Level-I trauma center. Retrospective analysis of all the five patients with CRK was done. Demographic data, antibiotic exposure throughout the hospital stay, hospital course, and clinical outcome were analyzed. **Results:** Out of 5 patients, 4 were young males (mean age of 23.5 years) without comorbidities and had undergone exploratory laparotomy following blunt trauma abdomen. 3 patients were chronic patients and had been on carbapenem and colistin 11–20 days before isolation whereas 2 patients had isolation of CRK just within 7 days of admission. Out of the five patients, 3 patients survived and 2 had fatal outcome. **Conclusions:** CRK is an emerging and challenging pathogen in polytrauma victims. There was an outbreak of CRK in our ICU that could be contained with infection control measures.

**Keywords:** Colistin-resistant *Klebsiella pneumoniae*, polytrauma, surgical Intensive Care Unit

## INTRODUCTION

The isolation of multidrug-resistant organisms is increasing day by day in the Intensive Care Unit (ICU) settings and poses a great challenge in treating these patients. Carbapenem-resistant *Enterobacteriaceae* are widespread across various parts of the world and particularly carbapenem-resistant *Klebsiella pneumoniae* are quite common.<sup>[1]</sup> Carbapenem-resistant *Klebsiella* constitute 92% of all carbapenem-resistant in United States.<sup>[2]</sup> Even so, carbapenemase-producing *Klebsiella* are considered endemic in some areas.<sup>[3]</sup> Colistimethate sodium is considered drug of choice and the only option available for treating these infections. However, now a days, there have been many isolated case reports and reports of outbreak of carbapenem and colistin-resistant *Klebsiella* (CRK) from various parts of the world.<sup>[4-7]</sup> The notorious CRK are emerging pathogens in Indian subcontinent also and have been reported from an oncology center in eastern India<sup>[8]</sup> and medical college in southern India.<sup>[9]</sup> These case reports of infection were in immunocompromised patients. We report 5 cases of invasive

blood stream infections due to CRK in immunocompetent patients in our polytrauma ICU of Level-I trauma center in India. In April–June 2016, we had 5 cases of invasive blood stream infections due to CRK. Since incidence of CRK over last year in our hospital and ICU was 0 cases/month, this sudden increase in CRK infections was defined as an outbreak. Here, we describe the epidemiological profile, microbiological investigation, clinical outcome of those cases, and the various infection control practices undertaken to curb the outbreak. To the best of our knowledge, this is one of the initial reported CRK cases of blood stream infections in trauma victims.

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## METHODOLOGY

The study was carried out in surgical ICU of Level-I trauma center in India. Retrospective analysis of all the five patients with CRK was done by medical records' review. Demographic data, antibiotic exposure throughout the hospital stay, hospital course, and clinical outcome were analyzed.

### Microbiological identification and antimicrobial testing

The microbial identification of all Gram-negative bacterial isolates was done by VITEK 2 compact system (Biomérieux Ltd., France). The antimicrobial susceptibility testing of all Gram-negative isolates was done by the disc diffusion method on Mueller–Hinton agar according to the Clinical Laboratory Standards Institute (CLSI) guidelines. *Escherichia coli* ATCC 25922 was taken as control strain.

The following antimicrobials were tested: ampicillin (10 µg), ampicillin/sulbactam (10/10 µg), amoxicillin (10 µg), ceftazidime (30 µg), ceftazidime/clavulanic acid (30/10 µg), cefotaxime (30 µg), ceftriaxone (30 µg), cefoperazone (30 µg), cefoxitin (30 µg), cefpodoxime (30 µg), cefepime (30 µg), aztreonam (30 µg), piperacillin (100 µg), piperacillin/tazobactam (100/10 µg), ticarcillin/clavulanic acid (75/10 µg), cefoperazone/sulbactam (75/30 µg), cefepime/tazobactam (30/10 µg), ceftriaxone/sulbactam (30/15 µg), imipenem (10 µg), meropenem (10 µg), ertapenem (10 µg), amikacin (30 µg), gentamicin (10 µg), netilmicin (30 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), tigecycline (15 µg), polymyxin B (300 U), colistin (10 µg), and chloramphenicol (30 µg).

Colistin susceptibility was done by both disc diffusion testing and VITEK 2 compact for all isolates. For bacterial isolates showing resistant minimal inhibitory concentration (MIC) cutoff values, further testing was done using E test in accordance with CLSI guidelines. There is no available colistin breakpoint for *Enterobacteriaceae* as per CLSI guideline, so EUCAST breakpoints were followed (S ≤2; R >2). Bacterial isolates were considered to be pandrug resistant (PDR) if isolates were resistant to all classes of antimicrobial.

## RESULTS

The isolates were isolated in a span of 42 days in our ICU, the first being on April 23, 2016 and last on June 05, 16. All the patients were admitted concurrently or subsequently in the same cubicle of the ICU. The demographic profile of the patients is given in Table 1. Out of 5 patients, 4 were young males (mean age of 23.5 years) without comorbidities and had undergone exploratory laparotomy following blunt trauma abdomen. All had invasive blood stream infection due to CRK and no isolation from any other site. One patient was 55 years old with coexisting hypertension and diabetes, had chest trauma with head injury, and he had concurrent isolation of CRK from blood, bronchoalveolar lavage, and urine. Patient no. 2 and 3 were referred from outside hospital where they had stayed for 7 and 8 days, respectively.

### Timing of isolation

Patient no. 1, 2, and 3 were chronic patients and had isolation of bacteria 25, 57, and 13 days, respectively, after ICU admission and had been on carbapenem and colistin 11–20 days before isolation whereas patient no. 4 and 5 had isolation of CRK just within 7 days of admission. The mean length of colistin use was 12.4 days.

### Antibiotics after isolation

After the isolation of *Klebsiella*, colistin was stopped in all the patients. As patient no. 1, 3, and 4 [mentioned in Table 2] had severe abdominal sepsis and were in septic shock at the time of isolation, tigecycline was added. The extensive search for the source was done and surveillance cultures were sent from all possible sites and drains in all cases. Repeated peritoneal washings were done for patient 1, 3, and 4.

Only patient no. 2 had positive cultures for resistant *Klebsiella* from BAL and urine. He was continued on meropenem only. Patient no. 5 was clinically stable and had no exposure to colistin; he was continued on netilmycin.

All the patients had subsequent microclearance with cultures coming negative and subsequently started growing *Klebsiella* and *Acinetobacter* sensitive to colistin.

**Table 1: Demographic and clinical profile of the patients**

Patient	Age (years)	Sex	Diagnosis	Comorbidities	Referred case	Days of previous hospitalization	Date of admission	Operative procedure done
1	22	Male	Duodenal blowout and biliary peritonitis	No	No	82	April 3, 2016	Laprotomy with peritoneal wash with right intercostal drain
2	55	Male	RTI with frontotemporal contusion with 2 <sup>nd</sup> -7 <sup>th</sup> rib fracture	HTN DM	Yes	7	April 4, 2016	None
3	28	Male	RTI with liver laceration	No	Yes	8	April 10, 2016	Laparotomy + hepatic packing
4	16	Male	RTI with Grade V liver laceration	No	No	0	April 28, 2016	Laparotomy + peritoneal wash
5	28	Male	BTA with fracture pelvis with bilateral facial fracture	No	No	0	May 6, 2016	Laparotomy + internal artery ligation

RTI: Road traffic injury; HTN: Hypertension; DM: Diabetes mellitus; BTA: Blunt trauma abdomen

**Table 2: Microbiological characteristics, treatment, and outcome of the patients**

Patient	Site of isolate	Date of isolation	Days in ICU before isolation	Days of colistin/ carbapenem prior use	MIC		Treatment given	Microclearance	Length of stay in ICU (days)	Outcome
					Carbapenem	Colistin				
1	Blood	April 27, 2016	25	20	64	>16	Cefepime + tazobactam Tigecycline	Yes	39	Died
2	Blood, also in BAL, urine	June 5, 2016	57	26	8	>16	Cefepime + tazobactam	Yes	84	Died
3	Blood	April 23, 2016	13	11	32	≥16	Cefepime + tazobactam Tigecycline	Yes	65	Survived
4	Blood	May 6, 2016	7	5	32	≥16	Tigecycline	Yes	55	Survived
5	Blood	May 13, 2016	6	0	32	≥16	Netilmycin	Yes	9	Survived

BAL: Bronchoalveolar lavage; ICU: Intensive Care Unit; MIC: Minimum inhibitory concentration

### Outcome

Out of the five patients, 3 patients (no. 3, 4, 5) survived and 2 had fatal outcome. Patient no. 1 had multiple intestinal fistulas and biliary peritonitis and patient no. 2 was a chronic patient with comorbidities and head injury who did not improve.

### Molecular analysis of the isolates

A total of 7 isolates are obtained from these cases. All isolates were resistant to colistin. All isolates had MIC >16 µg/ml. Molecular analysis revealed isolates belong to 2 sequence types—ST 11 and ST 14. These isolates had 3 novel *fosA* variants. They are negative for *mcr-1* gene. Chromosomal-mediated resistance was observed in these strains with mutation in 5 genes.

### DISCUSSION

The emergence and isolation of pandrug-resistant *Enterobacteriaceae* is increasing and posing a great challenge to clinicians. Carbapenem resistance in *Klebsiella* has been increasing and is as high as 44% in India.<sup>[9]</sup> The only drug available for these infections is colistin but rampant use of colistin has led to increased resistance to this drug.<sup>[10]</sup> Case reports and outbreaks have been reported from around the world but few cases only from India. It is difficult to tell in Indian scenario as such cases are highly underreported.

We report five cases of multidrug-resistant *Klebsiella*, resistant to colistin. Sensitivity testing for fosfomycin was not done. Goel *et al.*<sup>[8]</sup> described a series of CRK infection colonization from an oncology center in eastern part of India. The number of patients with positive blood culture was 10.62% of these patients were receiving colistin before isolation as in our case series. The isolates in their series showed intermediate to good susceptibility to tigecycline. Another reporting<sup>[9]</sup> of CRK has been done from India and all the strains isolated were sensitive to tigecycline.

Ghaur *et al.*<sup>[11]</sup> reported isolation of PDR Gram-negative bacteria from 13 patients in a tertiary care oncology and stem cell transplant center in India, but they had reported about all the Gram-negative bacteria and not only *Klebsiella*. They had

five patients infected with resistant *Klebsiella* and were treated with colistin-based regimens with or without combination with carbapenem and tigecycline. However, in our series, colistin was stopped in all cases, and patients with abdominal sepsis were taken on tigecycline.

All the above case reports are from oncology center where patients are immunocompromised. Ours is a trauma center and we have young immunocompetent patients, so isolation of CRK strains is a matter of huge concern.

Isolated reports of isolation of *Klebsiella* resistant to colistin have emerged from Greece, Italy, and South Korea. Three different clones for CRK were detected in Italy<sup>[12]</sup> and South Korea.<sup>[5]</sup>

The risk factors for acquisition of KPC-producing organisms have been cited in various studies. These include prolonged ICU stay, hospitalization, poor functional status, immunosuppression, and posttransplant surgery.<sup>[13]</sup> This seems true for developing colistin resistance infection also. Colistin resistance is mainly mediated by modification of lipopolysaccharide moiety of bacterial wall.<sup>[14]</sup> It can occur *de novo* because of use of colistin or can be transmitted horizontally from one patient to another. The isolation of the colistin-resistant organisms from the same cubicle in ICU and in the same time frame suggested horizontal spread of resistant organisms.

### Infection control measures taken

The isolation of the colistin-resistant organisms from the same cubicle in ICU and in the same time frame suggested horizontal spread of resistant organisms. After 3 consecutive cases, detailed systematic and rigorous hospital infection control practices were undertaken to prevent further spread. We have an intensive, automated ongoing hospital-acquired infection surveillance network and hand hygiene monitoring system. Initially, the infected patient was isolated by means of physical barrier/curtain stand within the cubicle. Each and every cubicle was disinfected by fogging using hydrogen peroxide. Intensive terminal cleaning of cubicles, bed rails, bedside objects was done with quaternary ammonium

compounds. Thorough cleaning of curtains, beddings, and linen was done using appropriate heat disinfection. Hand hygiene with water or alcohol-based hand rub was intensively reinforced and usage of personal protection equipment was encouraged.

All our patients had microclearance though we used different combination of antibiotics in all. We resorted to combination of cefepime–tazobactam and tigecycline in patients with abdominal sepsis, i.e., patients 1, 3, and 4. Patient no. 3 and 4 responded well but patient no. 1 died because of irreversible abdominal biliary sepsis due to multiple intestinal fistulae. Patient no. 1 and 3 were cocolonized with *Acinetobacter baumannii*, so we had to give colistin later on in these patients. Various treatment modalities have been suggested for the treatment of colistin- and carbapenem-resistant *Klebsiella* infection which include colistin-based regimens such as combination of high-dose tigecycline with colistin<sup>[15]</sup> and colistin with double carbapenem regimen.<sup>[16,17]</sup>

## CONCLUSION

CRK is an emerging and challenging pathogen in polytrauma victims in whom several injuries and various surgical interventions lead to prolonged intrahospital stay along with exposure and dependence on various invasive medical devices and use of multiple antibiotics as a prophylaxis or therapeutic regimen. There was an outbreak of CRK in our ICU that was contained with appropriate infection control practices.

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## Conflicts of interest

There are no conflicts of interest.

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