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# Successful Control of a Colistin and Carbapenem Resistant *Klebsiella pneumoniae* Outbreak in an Intensive Care Unit

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**What is known on this subject?**

There is an ongoing silent endemic of healthcare associated infections leading to patient morbidity and mortality. Outbreaks mainly due to Gram-negative bacterial infections in health-care settings have a major role in the spread of antimicrobial resistant strains.

**What this study adds?**

In this report, an outbreak of OXA-48 producing *K. pneumoniae* with colistin resistance could be controlled with strict infection control precautions. Infusion pump devices may be infection sources. Environmental screening and isolation of colonized patients have a crucial role in the control of multi-resistant Gram-negative bacterial epidemics.

## ABSTRACT

**Objective:** Multi-drug-resistant bacteria burden is rising in both developing and high-income countries. We describe here a cluster of colistin and carbapenem-resistant *K. pneumoniae*, (CCRKP) in an educational and training hospital in Turkey, mainly associated with intensive care unit (ICU) stays.

**Material and Methods:** After CCRKP growth was detected in the microbiological samples of 21 patients who had a history of ICU hospitalization and were admitted to the hospital currently, the situation was classified as an epidemic. Rectal and environmental surveillance cultures were obtained. Carbapenemase production was tested by carbapenem inactivation method, and carbapenemase genes, including blaOXA-48, blaNDM-1, blaKPC, blaVIM, blaIMP and blaGES, were investigated by multiplex polymerase chain reaction (PCR). *mcr1/2* genes associated with plasmid-mediated colistin resistance were investigated by PCR. CCRKP isolated from rectal and environmental screenings were evaluated further for epidemiologic relationships with clinical isolates. Pulsed-field gel electrophoresis was done using Xba-I enzyme for digestion.

**Results:** CCRKP rectal colonization prevalence was 57% (8/14) on the screening day. Five of these eight patients were colonized only, and none of these asymptomatic carriers developed infection. CCRKP was detected on an infusion pump, which was used for some of the previous patients and was suspected to be a cross contamination source. The outbreak isolate was found to be of genotype A; OXA-48 positive,

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## ABSTRACT

NDM negative by PCR. *mCR* gene 1/2 was negative. One of the infected patients and one of the colonized patients isolates were different, and the remaining 22 isolates were indistinguishable. After strict infection control interventions, eight cases were detected in a five month period. Rectal swabbing was stopped after no new cases had been observed for two months. CCRKP hasn't been detected in clinical specimens for one year since then.

**Conclusion:** Environmental screening and isolation of colonized patients have a crucial role in controlling outbreaks of multidrug-resistant Gram-negative bacteria.


**Keywords:** Carbapenem-resistant *Enterobacteriaceae*, infection control, *Klebsiella pneumoniae*, outbreak

## Introduction

Healthcare-associated infections (HAI) are major causes of mortality and morbidity, especially in intensive care units (ICU) of hospitals worldwide. HAIs due to carbapenem resistant bacteria are rising in both developing and high-income countries as a consequence of international traveling (1,2). Crude mortality rates of as much as 70% have been linked to infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) (3). Colistin is usually one of the last treatment options for such infections despite its toxicity (4). Colistin resistance is still relatively uncommon, but published outbreaks or ongoing spread of this multidrug-resistant (MDR) bacterium and the capability of plasmid-mediated resistance transmission are raising concern for worldwide spread in the future (5,6,7,8).

According to the World Health Organization the Central Asian and European Surveillance of Antimicrobial Resistance Network 2023 annual report, Turkey has a carbapenem resistance of 49.1% for invasive Klebsiella strains. The high prevalence of carbapenem-resistant *K. pneumoniae*, as well as the relatively high number of *Acinetobacter* spp. and their high levels of resistance, are a cause for concern and likely reflect the dissemination of resistant clones within healthcare institutions.

To prevent the CRE to become endemic in a hospital, early detection of outbreaks through laboratory based and active surveillance, good communication between infection control team and clinicians, maintaining infection control preventions and continuous education should be provided.

We present here a cluster of colistin and carbapenem-resistant *K. pneumoniae* (CCRKP) in an educational and research hospital in Turkey, mainly related to the ICU stay. The epidemiologic and molecular outbreak investigations, and preventive infection control measures that followed are detailed in the study.

## Material and Methods

### Setting

This outbreak investigation took place in a 720-bed educational and research hospital in İstanbul that has a sixteen-bed anesthesiology and critical care ICU. The ICU is a mixed unit that serves level-3 care to critically ill patients with acute emergencies and postoperative patients. The hospital receives referrals from neighboring state hospitals. The ICU is open-plan with twelve patient areas, featuring fixed separators and 2-meter distances between beds. There are four additional single bed isolation rooms with a corridor opening to the common area, of which two also have negative pressure ventilation. The nursing ratio is one nurse to two patients, but it could be one to three during night shifts. The ICU has full-time physician coverage. An infection control nurse and infectious diseases specialist routinely make visits to the unit on weekdays. Infectious diseases residents provide twenty-four-hour, 7-day consultation. Microbiological cultures are taken from potential sites of infection in clinically indicated patients, but there is no active microbiological surveillance for MDR bacterial colonization.

### Patients

A case was defined as any patient newly found to have at least one clinical isolate of *K. pneumoniae* from November 12$^{th}$, 2015 to April 12$^{th}$, 2016 that was resistant to any carbapenem (ertapenem, imipenem, or meropenem) and colistin (CCRKP). CCRKP was detected in clinical samples of twenty-one patients within a five-month period. These patients were either in the ICU or had a history of staying in the ICU during their hospitalization. All antimicrobial susceptibility reports of *K. pneumoniae* isolated from patients in the ICU were reviewed retrospectively to identify CCRKP. Rectal screening was performed on all patients in the ICU to determine asymptomatic fecal carriers.

### Identification and Susceptibility Testing

Identification was done by MALDI-TOF MS (Bruker, Daltonics) and susceptibility tests were carried out using BD-Phoenix automated system and minimal inhibitory concentrations were determined following EUCAST guidelines. *In vitro* susceptibility of the isolates to ampicillin/sulbactam, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, imipenem, ertapenem, meropenem, amikacin, gentamicin, netilmicin, aztreonam, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole was evaluated. Carbapenemase production was tested by the carbapenem inactivation method.

### Detection of Resistance Genes

Carbapenemase genes, including blaOXA-48, blaNDM-1, blaKPC, blaVIM, blaIMP and blaGES, were investigated by multiplex polymerase chain reaction (PCR) (9). The *mcr-1/2* genes associated with plasmid-mediated colistin resistance were examined also with PCR (10).

### Microbiological Screening

Rectal screening samples were inoculated immediately in trypticase soy broth (5 mL) with a 10 µg ertapenem disk (Oxoid, Basingstoke, Hampshire, England), and processed as previously described. Cotton swabs humidified with isotonic serum were used for environmental screening. The surfaces and medical equipment frequently touched by hand were selected for screening. Eighteen CCRKP isolates of fifteen patients' clinical samples, five rectal colonizing isolates, and the isolate detected on the infusion pump were evaluated by arbitrarily-primed-PCR and pulsed-field gel electrophoresis (PFGE) for epidemiologic relatedness. PFGE was performed using the Xba-I enzyme for digestion (11).

### Ethical Approvement

The study was approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee on 29th November 2016, decision number: 720.

### Statistical Analysis

The epidemiological and laboratory characteristics of the patients were recorded using standard descriptive statistics. The Statistical Package for the Social Sciences (version 18, SPSS Inc., Chicago, IL, USA) was used to analyse the data. Descriptive statistics for numerical parametric variables were calculated as the mean ± standard deviation (SD), and for categorical variables as percentages.

## Results

### Patients

CCRKP was detected in the microbiological samples of 21 patients between 12.11.2015 and 12.04.2016. With the exception of amikacin, the isolate demonstrated resistance to all antibiotics that were tested. All these patients were hospitalized in an adult ICU, or the cultures were taken on wards, although they had a history of ICU admission in this period; thus, the situation was evaluated as an ICU outbreak. When the microbiology records were reevaluated, one ICU patient with CCRKP was also detected 10 months before the outbreak started. There were no CCRKP cases in 2014 (Figure 1).

### Screening Results

Three of the 14 patients who were hospitalized on the screening day were already infected. Rectal colonization was detected in 8 patients, including these 3 patients. CCRKP rectal colonization prevalence was 57% (8/14). The mean length of ICU stay was 33±22 days (mean ± SD) for colonized patients. Only five patients were colonized, and none of these asymptomatic carriers developed an infection.

During environmental surveillance, CCRKP was detected on an infusion pump, which was used for some of the previous patients. All the other environmental samples taken from high touch equipment, bed environments, and sinks were negative for CRE.

### Molecular Assay Results

One of the infected patients and one of the colonized patients' isolates were different, and the remaining 22 isolates were indistinguishable by both methods (Figure 2). The outbreak isolate was identified as genotype A and was found to be OXA-48 positive but NDM negative by PCR. *mCR* gene 1/2 was negative. The isolate of the unrelated colonized patient was genotype F and OXA-48 positive. The isolate of the unrelated infected patient was of genotype E and positive for OXA-48. This patient was transferred to our hospital from another medical center.

### Infection Control Precautions

Preventive measures were implemented by the hospital infection control committee based on microbiological findings. Terminal cleaning of the unit was performed under the supervision of nurses. The staff was reeducated about resistant microorganisms, transmission routes, and the importance of hand hygiene. Contact isolation precautions

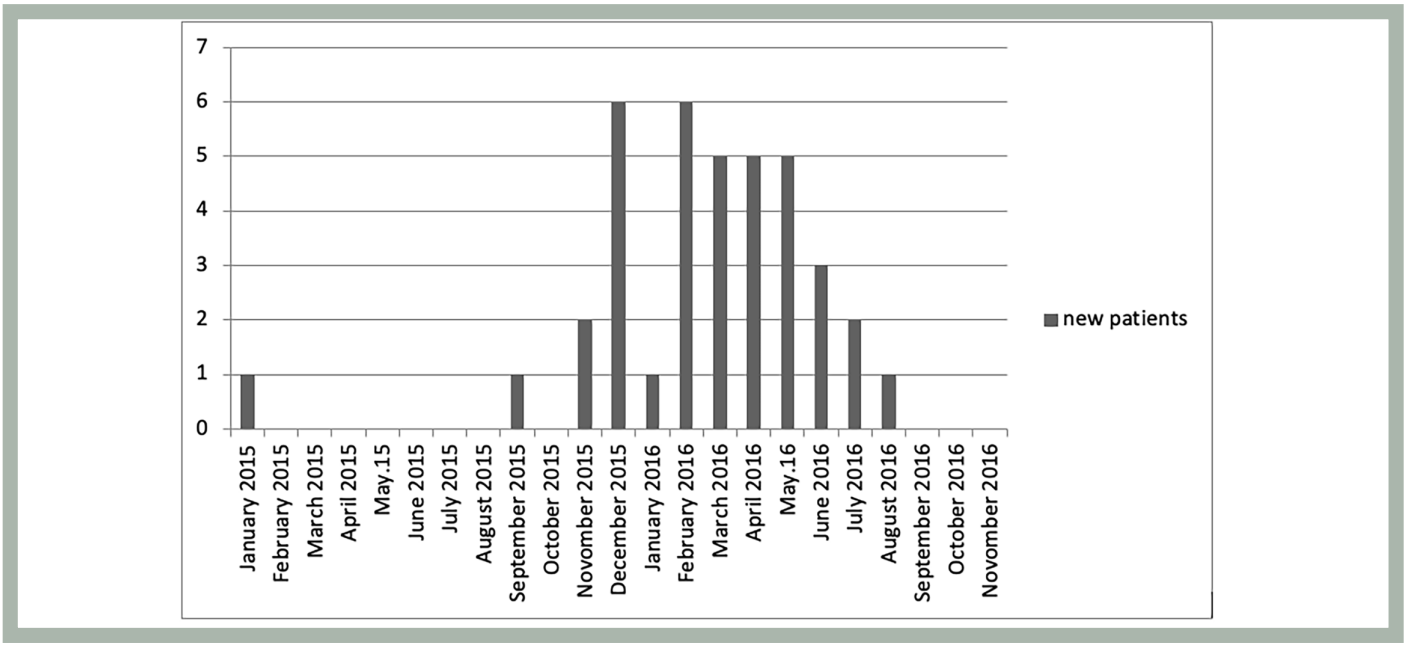


**Figure 1.** Colistin and carbapenem resistant *Klebsiella pneumonia* outbreak timeline

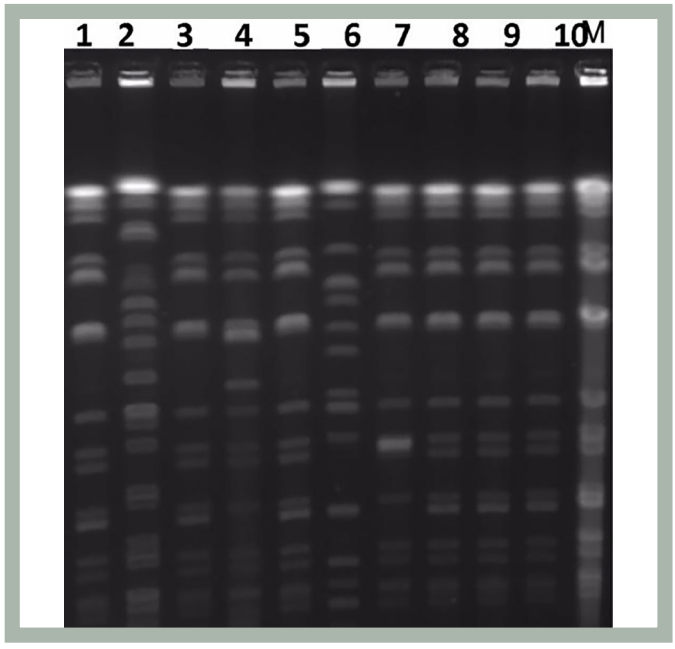


**Figure 2.** Epidemiologic relatedness of isolates by PFGE
*2, 6: Epidemiologically different isolates, 1,3-5,7-9: Epidemiologically indistinguishable cluster isolates, PFGE: Pulsed-field gel electrophoresis*

were taken for all the infected and colonized patients. Patients colonized/infected with CCRKP were transferred to single rooms when possible. The ICU had four isolated rooms, so the remaining patients and nurses giving care were cohorted. Sharing of medical equipment was restricted. All the medical staff and hospital directors were informed at a mortality-morbidity meeting, during which cases of CRE-related mortality were presented. surgical clinics, especially, were informed about the ongoing outbreak since they could postpone their elective cases that would need prolonged postoperative ICU stay. The importance of hand hygiene was emphasised throughout the hospital, particularly in the ICU. The manual buttons at the entrance of isolation rooms were relocated to knee level to decrease hand contact. The manual hand washing spouts were replaced with non-touch ones. The infusion pump detected as contaminated by the outbreak strain was cleaned, disinfected twice with bleach, and then microbiologically sampled. After microbiological confirmation of sterility, it was put back into use in the ICU.

### Follow-up

In 14 patients, the 30-day mortality rate (6/14) was found to be 43%, whose bacterial isolate was available for molecular study and were shown to have been infected with the OXA-48 producing outbreak strain. No mortality occurred in five patients who received amikacin combined with meropenem or tigecycline. Bacteremia was present in these patients. There were two patients who received a combination of colistin and meropenem; both were bacteremic and died. One patient with rectovesical fistula and one patient managed with a cystofix device had positive urine cultures; antibiotics were not administered to these patients and no mortality occurred. In 2016, CCRKP growth was detected in the clinical samples of 30 patients and in the rectal swabs of 5 patients. After

interventions, eight cases were detected in a five-month period. The number of cases gradually decreased, and no new cases were observed for two months; then rectal swabbing was stopped. No CCRKP has been detected in clinical specimens since then for one year.

## Discussion

The presence of MDR-Gram-negative bacteria (GNB) has been linked to severe HAIs over the past ten years, with their prevalence showing a consistent upward trend (12). Plasmid-acquired carbapenemases in *Enterobacteriaceae* are now being identified all over the world in an increasing trend (13).

The types of carbapenemases vary among countries, but some factors like international travel, transportation of food products, and migrations are responsible for introducing these resistant microorganisms to countries far beyond their origin (14).

Asymptomatic CRE colonization of the gastrointestinal tract may occur before infection, constituting an unidentified reservoir within hospitals (15,16). In our routine, CRE surveillance was not performed before the outbreak. Within the first two months of the cluster, the infection control team educated the unit about CRE, and contact isolation precautions were taken for the infected cases. Hand hygiene compliance was observed continuously. As these preventive measures were not sufficient, 'Facility Guidance for Control of Carbapenem Resistant *Enterobacteriaceae* (CRE) November 2015 Update' recommendations were implemented (17). By rectal screening, we detected that more than half of the patients were colonized, and by further evaluation, we found that all isolates but one were related. None of these colonized patients became infected, so without screening, contact precautions would not be taken for these patients and there would be an ongoing spread in the unit. Landelle et al. (18) have published a protracted outbreak of MDR *Acinetobacter baumannii* caused by intercontinental transfer of colonized patients and could be terminated by cohorting all colonized or infected patients in a separate isolation unit with dedicated healthcare personnel. It is well known that *Klebsiella pneumoniae* can spread via healthcare workers' hands from colonized patients or environmental reservoirs to other patients in both endemic and epidemic situations (15). We did not screen healthcare personnel's hands, as it is not recommended by guidelines, but we reinforced their hand hygiene practice and cohorted the colonized/infected patients' nurses (15).

Contaminated sinks have been shown to be a reservoir for *Klebsiella oxytoca* outbreaks (19). In a study from China, whole-genome sequencing and analysis revealed that one sink was the source of ST 16 high risk clone *Klebsiella pneumoniae*, acquisition in two patients (20). In environmental screening, we did not isolate any CRE in the sinks, monitors, bed rails, and isolation room buttons. It was determined that some of the automatic hand washing units were replaced by manual units during previous renovations. In terms of outbreak control, all the manual hand washing taps were replaced with automatic faucets. During the outbreak period, isolation room doors were operated using manually operated buttons. Although the buttons didn't carry CRE on screening, this could cause intermittent breaks in hand hygiene and contact isolation, so the buttons were moved to knee level.

Environmental cleaning has an important role in outbreak control. Recent reports suggest that GNB may exhibit greater survivability than Gram-positive organisms. It has been shown that survival for more than a year under certain conditions can be achieved by *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas* spp. (21). The household personnel were reeducated, and cleaning and disinfection with chlorine tablet solutions (500 ppm) was performed twice a day.

Medical equipment that is used for patients can be contaminated, and after inadequate cleaning or disinfection, can become a source of outbreaks. Yan et al. (22) found that 31.34% (21/67) of bed units occupied by CRKP patients had positive results for one or more surrounding surfaces. Additionally, 7.99% (49/613) of environmental samples and 3.57% (4/112) of ICU staff samples tested positive for CRKP (22). In our outbreak investigation, only an infusion pump that was used previously for some of the infected patients was found to be contaminated with the outbreak isolate, and thought to be the probable cause of cross-contamination.

## Conclusion

"This outbreak demonstrates the critical need for active surveillance, environmental screening, and strict infection control measures in limiting the spread of OXA-48, producing *K. pneumoniae*." A contaminated infusion pump was suspected to be the contamination source. Environmental screening and isolation of colonized patients has a crucial role in the control of multi-resistant Gram-negative bacterial epidemics.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee on 29th November 2016, decision number: 720.

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: İ.O.B., Z.K.Ç., B.O., Concept: A.A.H., N.U., Design: A.Ö., M.E.B., Data Collection or Processing: İ.O.B., Z.K.Ç., B.O., Analysis or Interpretation: A.A.H., N.U., B.O., Literature Search: A.Ö., D.Y.S., Writing: A.Ö., D.Y.S., M.E.B., E.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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