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# Outbreak of New Delhi Metallo-Beta-lactamase Carbapenemase Producing Enterobacterales on a bone marrow transplant unit: Role of the environment

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## ABSTRACT

**Background:** Carbapenemase Producing Enterobacterales (CPE) are a global health concern. Nosocomial outbreaks have been reported globally with patient-to-patient transmission felt to be the most frequent route of cross-transmission.

**Aim:** To describe the investigation and control of an outbreak of healthcare-associated New Delhi Metallo-beta-lactamase (NDM) CPE on a haematology ward, over 2 months.

**Methods:** Four patients acquired CPE; all had gastrointestinal tract colonisation with two subsequently developing bacteraemias. The outbreak team performed a retrospective review, prospective case finding and environmental sampling using swabs, settle plates, air and water sampling. Immediate control measures were implemented including appropriate isolation of cases and additional ward cleaning with chlorine disinfectant, ultra-violet light decontamination and hydrogen peroxide.

**Findings:** Following two cases of nosocomial acquired CPE prospective case finding identified two further cases. 4.6% of the initial environmental samples were positive for CPE including from waste water sites, the ward sluice and the ward kitchen. Three of the four CPE isolates were identical on pulse field gel electrophoresis (PFGE) typing. Detection of the CPE from the ward kitchen environmental samples suggests a possible role for cross transmission.

**Conclusion:** This is the first CPE outbreak report to highlight the role of a ward kitchen as a possible source of cross-transmission. In view of this we suggest ward kitchens are reviewed and investigated in nosocomial CPE outbreaks.

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## Introduction

Enterobacterales are gram negative bacteria that colonise the gastrointestinal tracts of humans and animals. They can cause infections at numerous sites including urinary tract

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infections, intra-abdominal infections and bacteraemias. Increasing antimicrobial resistance among the Enterobacterales has seen an increasing reliance upon carbapenems, a group of  $\beta$ -lactam antibiotics often seen as 'antibiotics of last resort'. Some Enterobacterales can render carbapenems ineffective through the production of hydrolysing enzymes known as carbapenemases. These bacteria are referred to as carbapenemase-producing Enterobacterales.

CPE are a cause for international concern. Their clinical infections are associated with an increase in morbidity, mortality and healthcare costs [1,2]. Globally infections due to antimicrobial resistant organisms including CPE result in 700,000 deaths each year and their prevalence continues to increase [3,4]. Treatment of these infections is challenging and hindered by the lack of development of new antibiotic classes [3].

Risk factors for the acquisition of CPE are travel to high prevalence areas, exposure to healthcare and exposure to antimicrobials [4]. Outbreaks of CPE have been reported globally with patient-to-patient transmission thought to be the most important route of acquisition [4,5]. However, intermediate vectors such as equipment, the environment, visitors and healthcare workers should also be taken into consideration [5–8]. There is a body of literature implicating sinks and waste water both as a source and persistent reservoir of infection [9,10]. However, often the source of CPE outbreaks cannot be established [11,12].

In response to the increasing global concern of antimicrobial resistance the UK has created a 5 and 20 year national action plan [3,13]. National and international documents have been published to help address the spread of CPE through increased surveillance and stringent infection prevention and control measures [5,14]. In addition, comprehensive guidance for the treatment of multi-drug resistant gram negative infections has been published [4].

The aim of this study was to investigate an outbreak of CPE on a haematology ward using retrospective review, prospective case finding, patient screening and environmental sampling.

## Methods

### Description of the outbreak

Four patients on a bone marrow transplant unit, at a tertiary referral teaching hospital, were found to be positive for NDM CPE over a two month period (Figure 1). The unit had a CPE screening algorithm which consisted of admission and thereafter weekly, stool or rectal swab samples. CPE detection in the laboratory was performed using a selective agar culture methodology (Colorex mSuperCARBA, E&O Laboratories LTD). Putative colonies were identified using the direct smear method on a Bruker Daltonics MALDI-TOF (matrix-assisted laser desorption/ionisation – time of flight mass spectrometry - software version 3.4) and CPE enzymes detected using Cepheid GeneXpert Carba-R cartridges (blaKPC, blaNDM, blaVIM, blaOXA-48 and blaIMP-1 genes).

The bone marrow transplant unit consisted of eighteen single side rooms with ensuite bathroom/toilet facilities, as well as a lobby for donning/doffing personal protective equipment and a sink for hand hygiene (Figure 2). Some lobbies

served two side rooms whilst other side rooms had their own dedicated lobby. All rooms received HEPA-filtered air.

Patient A had leukaemia and had developed graft versus host disease following bone marrow transplantation resulting in severe diarrhoea. The admission CPE stool screening sample, obtained on the third day of admission, was negative. However, a repeat sample on day 10 was positive for New Delhi Metallo-beta-lactamase (NDM) *Enterobacter cloacae*. They were isolated in an appropriately ventilated side room with CPE precautions.

Patient B had lymphoma and was admitted to the same ward forty two days after Patient A (who remained on the ward). *Enterobacter cloacae* with NDM was detected from their first stool screening sample sent 11 days after admission; no admission or 7 day screening sample had been sent. Following identification of this second case an outbreak was declared and initial control measures were implemented.

Eight days later an NDM *E.coli* was identified from the first stool CPE screen from Patient C, 25 days after admission. Again, no admission or weekly CPE screen had been sent. Patient C had leukaemia and had been admitted 36 days after Patient A.

Four days after the detection of Patient C, *E.cloacae* with NDM was detected from a screening rectal swab of Patient D. Patient D had undergone a bone marrow transplant for leukaemia. Patient D was an inpatient prior to patient A and had six prior negative CPE screens. The CPE screen was positive eighty six days into admission.

During their current admission Patients A, B and C had gastrointestinal tract colonisation without clinical infection. Patient D developed a bacteraemia which was treated with targeted antibiotic therapy. All cases were subsequently well enough to be discharged.

In response to the linked cases, an outbreak team was convened to identify any common exposures or variables, and to instigate control measures.

### Investigation and control measures

The outbreak team collected data on inpatient journeys, reviewed patient records for commonalities and performed a retrospective review of NDM CPE on the haematology unit and throughout the hospital.

A number of immediate control measures were implemented. Cases were isolated in appropriately ventilated side rooms with CPE precautions which consisted of barrier nursing the patients with personal protective equipment including long sleeved gowns and gloves. Dedicated equipment, such as blood pressure cuffs and stethoscopes, were introduced for CPE positive patients. Ward cleaning was increased through a combination of 1% sodium hypochlorite solution (1,000ppm chlorine), hydrogen peroxide vapour and ultraviolet (UV) light room decontamination upon patient discharge. Stool sample/rectal swab surveillance CPE screening on the Haematology Unit was increased from weekly to twice weekly. Environmental sampling for CPE was performed. Clinical infection prevention and control audits were implemented to monitor clinical practices and environmental standards. There were daily ward visits from the Infection Prevention and Control Team throughout the outbreak and antibiotic stewardship activity on the ward was increased supported by pharmacy and microbiology teams.

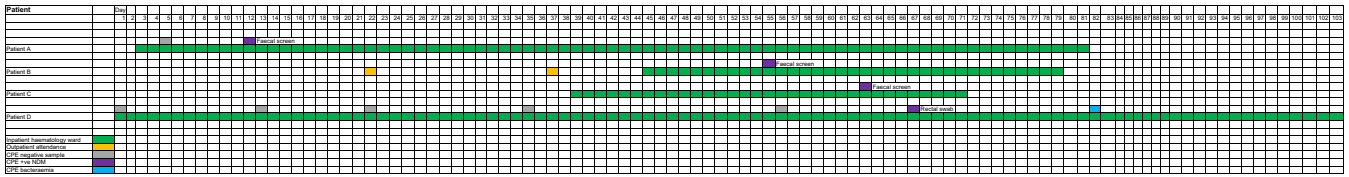


Figure 1. Timeline of CPE cases.

**Environmental sampling**

Environmental sampling was undertaken following identification of the outbreak. Initially 130 sites on the ward were sampled (Table 1) using the following methods:

- Charcoal swabs. These were either directly inoculated on to chromogenic CPE agar (Colorex mSuperCARBA, E&O Laboratories LTD) and incubated at 37°C for 24 hours or inoculated in brain-heart infusion broth, incubated at 37°C for 24 hours and then sub-cultured.
- Commercial premoistened sterile sampling sponges (Polywipe, Medical Wire and Equipment <https://www.mwe.co.uk/microbiology-lab-supplies/environmental-infection-control/polywipe-range/>). These were used to sample larger surface areas such as kitchen counters. They were immersed in brain-heart infusion broth and incubated at 37°C for 24 hours before sub-culturing on to chromogenic CPE agar as above.

- Settle plates. Chromogenic CPE agar plates were placed on the floor at various locations and exposed to the air for 4 hours. They were then incubated at 37°C for 24 hours.
- Air samples: Using an air sampling device, one litre of air was collected directly onto chromogenic CPE agar and incubated at 37°C for 24 hours.
- Water samples: 500ml water was collected into sterile containers. A 100ml aliquot was filtered through a 0.45µm filter. The filter was aseptically placed on to chromogenic CPE agar and incubated at 37°C for 24 hours.

Isolates were confirmed to be CPE through a combination of sensitivity testing via breakpoint method and EUCAST (European Committee on Antimicrobial Susceptibility Testing) disc diffusion, CPE phenotypic tests, MALDI-TOF and Cepheid GeneXpert Carba-R cartridges. All isolates were sent to reference laboratory (Public Health England) for typing via PFGE.

Over the next 2 months further environmental sampling, using the above methods, was carried out based on risk

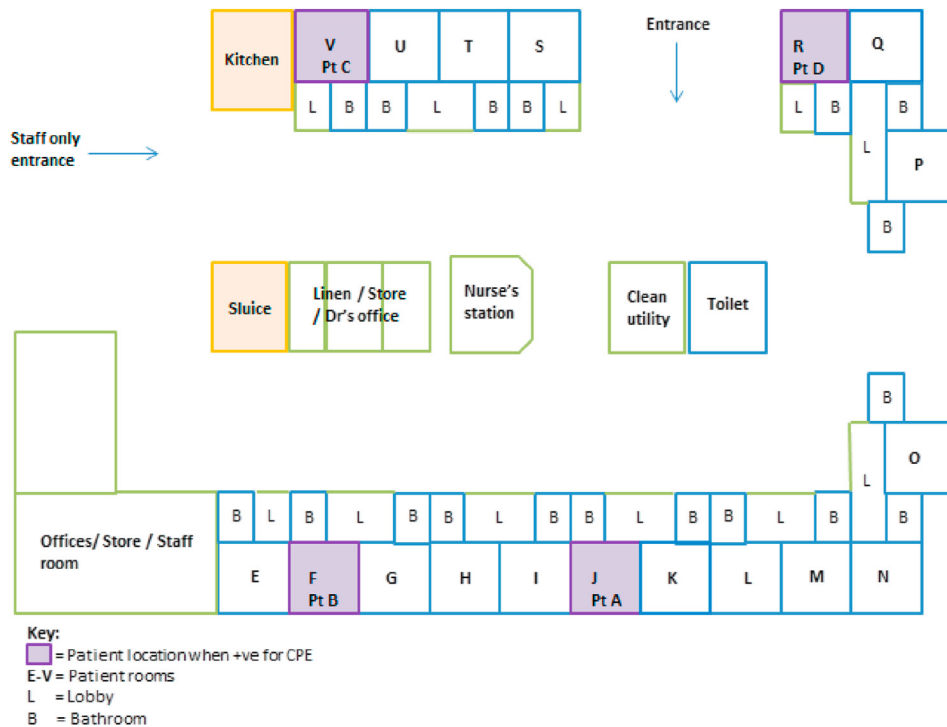


Figure 2. Ward floor plan.

**Table 1**  
Environmental samples

Sample sites	No. of samples	No. (%) of samples positive	Location of positive results
Wash hand basin (WHB) in side room lobby and ensuite toilet and shower drains	58	2 (3%)	Patient A's toilet Patient A's shower drain
Lobby and side rooms of colonised patients (surface sampling, settle plates, air samples)	16	0 (0%)	
Ward WHB and toilet	4	0 (0%)	
Nursing station (Sponges, swabs and settle plates)	12	0 (0%)	
Intravenous therapy preparation room including sink drain (Sponges, swabs, settle plates and air sample)	10	0 (0%)	
Sluice including sink drain (Sponges and swab, settles plates, air sample)	13	1 (8%)	Sluice
Water samples (Showers, kitchen drinking water, IV prep room)	6	0 (0%)	
Kitchen including sink drain (Sponges, swabs, dish cloth, air sample, settle plates)	11	3 (27%)	Draining board and seal around the inset sink unit Top of the bin Food counter

assessment and surveillance requirements (data not shown). There was persisting positivity from the shower drains (from rooms previously occupied by the cases) and the kitchen sink.

## Results

In total four patients were found to have a NDM CPE. All cases were identified through stool sample/rectal swab screening. Three of the isolates were *Enterobacter cloacae* and one was an *E.coli*. Three CPE (*Enterobacter cloacae* isolates) had identical PFGE typing. All cases were initially detected to have gastrointestinal colonisation. Patient C subsequently developed a CPE bacteraemia requiring targeted antibiotic therapy.

Patient A was the first patient to be identified with CPE colonisation on day ten of their admission; they had previously had a negative CPE screen on day three. The patient had been isolated in a side-room, with appropriate personal protective equipment utilised by healthcare workers, prior to the detection of any of the subsequent cases. Forty three days after the identification of Patient A, Patient B was positive for CPE. Eight days later Patient C was identified and then four days later Patient D.

Each case was reviewed in detail to highlight any risk factors for acquiring CPE. Patient C had travelled abroad to Poland in the previous year but was not hospitalised. Patient A, C and D had received broad spectrum antimicrobials prior to their CPE diagnosis. Patients A, B and C had had recent contact with other hospitals but these were not known to have problems with CPE.

Upon review of the case notes it was noted that the admission and discharge dates for the four cases varied, but that they were all inpatients at the same time on the same ward over a twenty seven day period. However, they stayed in separate side rooms and there was no direct contact. In addition, there was no common piece of equipment used across all cases. Different clinical teams had cared for the patients so there were no commonalities across healthcare worker contacts.

A retrospective review of NDM CPE cases confirmed there had been no previous cases detected on the bone marrow transplant unit. PFGE typing showed that the strain was unique.

Initial environmental sampling detected NDM *E.cloacae* from the ward sluice, the toilet and shower drain in patient A's room and in the ward kitchen from the sink draining board and seal around the inset sink unit, bin lid and food counter worktop.

## Discussion

Patient A was considered as the likely index case for the outbreak. It is unclear how this patient acquired CPE colonisation, however, several mechanisms of acquisition have been considered. One possibility is that the first CPE screening result for patient A could have been a false negative and that subsequent administration of broad spectrum antibiotic therapy then facilitated its detection on a later screening sample. Another possibility is that a preceding undetected CPE positive patient contaminated the environment/equipment facilitating transmission to Patient A. The weekly CPE screening already in place does not support this theory, however, it is acknowledged that not all patients may have been screened. Finally, as Patient A had gastrointestinal colonisation the likely mechanism of transmission was thought to be faeco-oral spread. Upon review the patient had eaten food from both the hospital kitchen and brought in by visitors. This is felt to be the most likely route of acquisition.

Patient A was CPE positive forty three days before the second patient was detected. This suggests Patient A may have been the index case. The route of spread to the subsequent cases despite appropriate isolation of Patient A was investigated. As they all had gastrointestinal tract colonisation, a faeco-oral route of transmission was felt to be likely. Positive environmental samples from the kitchen supported this theory. In view of the diarrhoeal symptoms in Patient A, it may have led to higher levels of environmental contamination of CPE. This may have facilitated

contamination of the ward kitchen and subsequently transmission to the other cases. During the investigation it was noted that the ward kitchen was accessed by both patient visitors and healthcare workers. As a control measure access was subsequently restricted to hospital staff only. Environmental and clinical audits identified requirements for improvements in kitchen practices with regard to hand hygiene and the wearing of PPE when dealing with meal trays from the rooms of CPE cases. Education was provided to staff and meal trays were disinfected in a steam steriliser. A regime of weekly UV decontamination of the kitchen in addition to routine cleaning with 0.1% sodium hypochlorite solution (1000ppm chlorine) was introduced. Following introduction of the above control measures no further cases were detected.

During the investigation the ward sluice was found to be positive. It was noted that the bedpan waste from patient cases was transported to the sluice (which was on the main ward area) and disposed of. Clinical practice was changed so faecal material from positive cases is disposed of within the ensuite facilities to reduce risk of spread through spillages during transport.

The NDM enzyme was detected mostly in *Enterobacter cloacae* species. However, an identical enzyme was detected in an *E.coli* from patient C. This highlights the ease with which CPE enzymes can transfer between species and that vigilance is needed when detecting outbreaks of CPE [15].

This outbreak supports existing literature which found that once CPE enters water traps such as sinks and shower drains it can survive for prolonged periods of time, be difficult to eradicate and serve as an ongoing source of nosocomial transmission [9,10,16]. In response to the positive sampling results the seal around the kitchen sink was removed, the whole unit cleaned with 1% sodium hypochlorite solution and then resealed. After this control measure was instigated, repeat sampling of the kitchen sink and its seal have remained negative. In addition, as a result of this outbreak 1% sodium hypochlorite solution was placed down the shower drains of CPE positive patients to try to suppress the bacterial load and risk of environmental contamination and subsequent patient cross transmission.

All patients were able to be discharged. Patient A was readmitted a short time later with worsening graft versus host disease. At this time the patient developed a CPE bacteraemia which was treated with targeted antibiotic therapy. Patient B, C and D did not need further admissions but continued to be followed up by the haematology team. Patient C continues on therapy for ALL. Patient D was readmitted several times and died a few months later.

A limitation of this outbreak review was the lack of compliance from the Haematology Unit with their CPE screening algorithm. Both Patient B and C did not receive admission or day 7 screens. As a result we can't determine the actual timeline of CPE acquisition for these patients.

To the best of our knowledge this is the first CPE outbreak describing a contaminated ward kitchen environment. In view of this we suggest ward kitchens are reviewed and investigated in nosocomial CPE outbreaks.

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