J Infect Chemother 25 (2019) 909–912

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

# Emergence of NDM-4-producing *Klebsiella pneumoniae* in a Korean hospital due to a patient hospitalized in Vietnam and case review☆

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ARTICLE INFO

*Article history:*
Received 6 November 2018
Received in revised form
1 April 2019
Accepted 13 April 2019
Available online 22 June 2019

*Keywords:*
$bla_{NDM-4}$
Carbapenemase-producing
*Enterobacteriaceae*
*Klebsiella pneumoniae*
Infection control

ABSTRACT

NDM-4-producing *Klebsiella pneumoniae* (NDM-4-KP) was detected from the patient who had previously been injured and hospitalized for 5 days in Vietnam in a neurosurgical intensive care unit (NSICU) of a Korean tertiary-care hospital in December 2016. He admitted with ventilator-associated pneumonia and NDM-4-KP was isolated, which was subsequently detected in two other NSICU patients. All NDM-4-KP isolates from patient and environmental surveillance cultures were sequence type 11. Colonization of three patients persisted for 5–12 months. Dedicated environmental cleaning was added to single room isolation of NDM-4-KP patients and universal chlorhexidine bathing, and no further transmission of NDM-4-KP occurred. This is the first report of NDM-4-KP in a Korean hospital where a patient with a history of hospitalization abroad was the index case initiating an outbreak involving three patients. The spread of newly introduced CPE was controlled using a bundle of infection control.



## 1. Introduction

Since the New Delhi metallo-β-lactamases (NDM) were first identified in 2008 in a Swedish patient hospitalized in India, 21 NDM variants have been described so far [1–4]. NDM-4 was first detected in an *Escherichia coli* isolate from a French patient previously hospitalized in India in 2010 [5]. NDM-4 differs a single amino-acid from NDM-1, but NDM-4 has a greater hydrolytic activity toward cephalothin, ceftazidime, cefotaxime, imipenem, and meropenem [4]. Fifteen isolates of NDM-4 carbapenemase-producing *Enterobacteriaceae* (CPE) have been reported in Europe, Australia, China, India, and Egypt [4–13]. We report here the emergence of NDM-4-producing *Klebsiella pneumoniae* (NDM-4-KP) in a hospital where the index case had previously been hospitalized in Vietnam.

## 2. Case report

From December 2016 to January 2017, carbapenemase-producing *K. pneumoniae* of same phenotypes were isolated from three patients in a neurosurgical intensive care unit (NSICU) of a tertiary care hospital in Seoul, Korea. These isolates produced metallo-β-lactamases as indicated by a positive modified Hodge test and inhibition by EDTA. The isolates were positive for $bla_{NDM}$-specific PCR. For outbreak investigation, we conducted sequencing of PCR product of the $bla_{NDM}$. It yielded 100.0% match to $bla_{NDM-4}$ (GenBank accession number KX470734.1).

The organism was first isolated from an endotracheal suction sample of a 30-year-old male patient on his ninth hospital day in NSICU. He was transferred from the Vietnam hospital, in which he had previously been hospitalized under ventilator care for 5 days due to an accidental cervical fracture in Vietnam. Ventilator-associated pneumonia was diagnosed at admission and

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https://doi.org/10.1016/j.jiac.2019.04.010
1341-321X/

ampicillin/sulbactam, piperacillin/tazobactam, levofloxacin, and vancomycin were administered empirically Initial endotracheal suction specimens yielded ampicillin-susceptible *Haemophilus influenzae*, and carbapenem-resistant *Acinetobacter baumannii* (CRAB), respectively, on conventional sputum cultures. But no growth was detected in the 3 sets of blood cultures. He was under single room isolation due to CRAB since third hospital day and an endotracheal suction specimen for surveillance of CRAB yielded NDM-4-KP on ninth hospital day. NDM-4-KP was also isolated from bronchial aspirate as clinical specimens on thirteenth hospital day. The second and third NDM-4-KP were isolated every three weeks after detection of the index case from sputum specimens of two patients stayed for 20 and 23 days in NSICU (Fig. 1). All three patients were admitted to a bay room first and isolated in a single room after the detection of NDM-4-KP. Forty-two environmental sites were sampled around two bay room beds after NDM-4-KP patients had been moved out and within the room in which the third NDM-4-KP patient had been staying (Fig. 1). NDM-4-KP was detected in the room from a suction table, an oxygen flowmeter, a vital sign monitor, a TV remote controller, and bed linens. NDM-4-KP isolates from clinical and environmental specimens showed identical antibiogram; susceptible to amikacin, fosfomycin, and colistin only on a Microscan NM44 panel (NM44; Beckman Coulter, West Sacramento, CA). All clinical and environmental isolates of NDM-4-KP were ST11. In addition to strict contact precaution and hand hygiene, active surveillance cultures and universal chlorhexidine bathing were applied to all patients hospitalized for more than 3 days in the NSICU. Total of 21 patients in NSICU were tested for active CPE surveillance, which were performed with stool, drainage, sputum, and urine. No positive specimen was found. Ventilator-associated pneumonia of the index patient was improved after colistin treatment for 9 days since isolation of CRAB and was transferred with ventilator weaning to general ward at hospital day 17. He was discharged after negative conversion of sputum and stool specimens 6 months and 10 months later, respectively. The second and third patients were transferred to long-term care hospitals 8 and 5 months later without clearance of NDM-4-KP. There have been no more cases of NDM-carrying *K. pneumoniae* detected in the unit.

## 3. Discussion

This is the first case report of NDM-4-KP in Korea. The cumulative number of CPE isolates has grown rapidly in Korea [14]. NDM-1 and NDM-5 was the prevalent NDM type which have been the second or third most common carbapenemase detected annually since 2010 [1,14]. NDM-4 CPE are reported in Europe and Australia only if the patients has been hospitalized in Vietnam, Myanmar, India, and Cameroon [4,5,7,8,10] (Table 1). China and Egypt reported the domestic cases [9,12,13] (Table 1). Therefore, NDM-4 CPE seemed to be endemic in the hospitals of certain Asian countries. NDM-4-KP ST11, the type reported here, has been reported as the imported case from Myanmar [10], which isolate exhibited a similar antibiogram as in this case. Therefore, it is a reasonable assumption that the NDM-4-KP of the index case was acquired in Vietnam.

The first NDM-4-KP isolates in this case series were from respiratory specimens. The second and third cases had occupied the bed next to the index case, or the bed occupied by the index patient a 1 month before. These findings suggest two possible transmission routes: droplet transmission and cross contamination. The distance between beds 11 and 13 was over four meters (Fig. 1), which does not support the droplet transmission hypothesis [15]. Although routine tracheal suction is performed with closed circuit, open catheter is often used for the patients producing sticky secretion or specimen collection in this hospital. Therefore droplet transmission is possible as bed-to-bed if the beds are next each other. Environmental contamination around the carbapenem-resistant *Enterobacteriaceae*-carrying patients has been well known [16]. The Centers for Disease Control and Prevention (CDC) in both the United States and Korea emphasize environmental control of CPE, including single room isolation, and daily and terminal cleaning [17,18]. In this study, the room occupied by a NDM-4-KP-positive case was heavily contaminated despite daily cleaning, thus environmental contamination was the most probable source of transmission. Therefore, rigorous cleaning and disinfection are seemed to be crucial measure to prevent cross contamination in addition to contact precaution and hand hygiene [17]. In addition, preemptive isolation of the patients who are “at risk” for carriage of CPE would be the best option to prevent spread of new CPE [17,19], but it is very resource-consuming and recommended at the limited

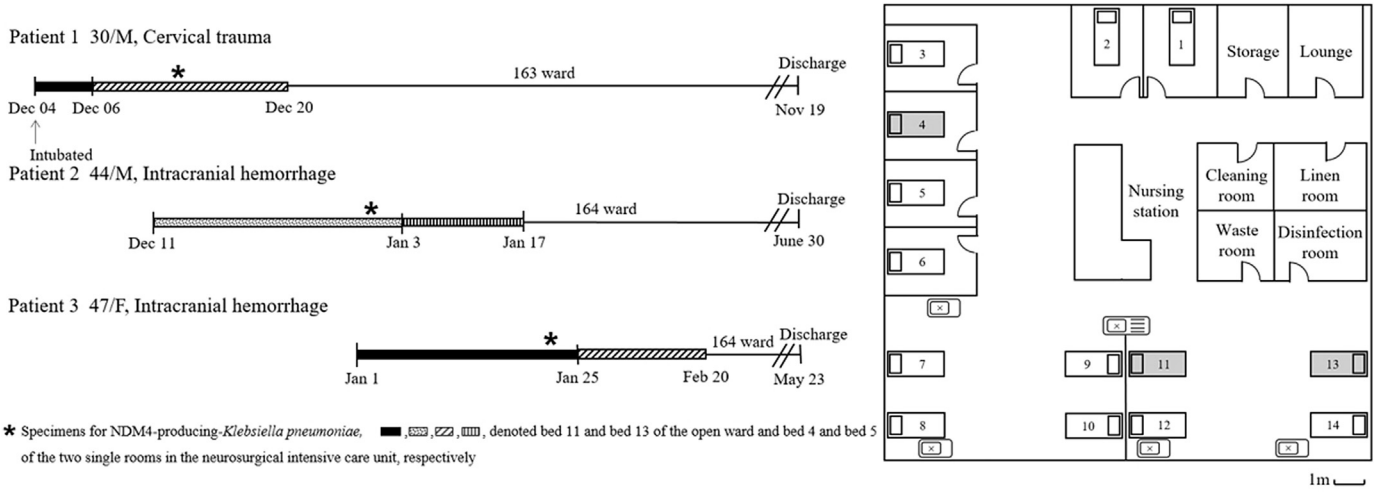


**Fig. 1.** Chronological and spatial details of three patients colonized by NDM-4-producing *Klebsiella pneumoniae*. Bed 11, which was initially occupied by patient 1, is next to bed 13 that was occupied by patient 2 five days after patient 1 was moved to bed 4. Patient 3 was admitted to bed 11 while patient 2 was still in bed 13. Environmental cultures to detect NDM-4-producing *klebsiella pneumoniae* were carried out around beds 4, 11 and 13 (shaded beds).

**Table 1**
Microbiological and Epidemiological features of NDM-4-producing *Enterobacteriaceae* reported in the previous publications and this study.

| Countries of reporting | Endemicity reported.[a] | Study period | Species | Antibiogram | ST | Transmission/Infection type | Ref |
|---|---|---|---|---|---|---|---|
| France | Imported (India) | 2010 | *Escherichia coli* | MDR | 648 | No/NA | [4] |
| France | Imported (Cameroon) | 2012 | *Escherichia coli* | MDR, S to A | 405 | No/NA | [7] |
| Denmark | Imported (Vietnam) | 2012 | *Escherichia coli* | MDR, S to C, T | 405 | No/NA | [8] |
| Italy | Imported (India) | 2012 | *Escherichia coli* | MDR, S to C, T | 405 | Yes/NA | [5] |
| Australia | NA | 2012–2014 | *Escherichia coli* | NA | 167 | NA/NA | [11] |
| Australia | NA | 2012–2014 | *Escherichia coli* | NA | 4450 | NA/NA | [11] |
| Australia | NA | 2012–2014 | *Escherichia coli* | NA | 101 | NA/NA | [11] |
| China | Domestic | 2014 | *Escherichia coli* | MDR, S to A, C, T | 410 | No/NA | [13] |
| China | Domestic | 2015 | *Escherichia coli* | MDR, S to A, C, T | 405 | Yes/NA | [12] |
| India | Domestic | 2016 | *Enterobacter aerogenes* | MD, R, S to C | NA | No/NA | [6] |
| Australia | Imported (Myanmar) | 2015 | *Klebsiella pneumoniae* | MDR, S to A | 11 | No/Endocarditis | [10] |
| Egypt | Domestic | 2014 | *Klebsiella pneumoniae* | MDR | 45 | No/Pneumonia | [9] |
| Korea | Imported (Vietnam) | 2016 | *Klebsiella pneumoniae* | MDR, S to A, C, T | 11 | Yes/Pneumonia[b] | This study |

Abbreviations: ETA, endotracheal aspirates; ST, sequence type; S, susceptible; A, amikacin; C, colistin; T, tigecycline; CRE, carbapenem-resistant *Enterobacteriaceae*; NA, not available; MDR, multi-drug resistant, resistant to β-lactams including carbapenems, quinolone, cotrimoxazole, and aminoglycoside.
[a] Country of hospitalization prior to detection of CRE.
[b] The index case had pneumonia, but the other cases were of endotracheal colonization.

conditions like an outbreak [17,19]. As the previous studies [20], there is a possible reservoir of CPE in waste or disinfection room, especially from biofilm forming in a sink or a sewer. However, those area were not included at the time of environmental cultures and this outbreak has been closed without any control measure targeted to those in this study. Therefore, role of common reservoir seemed to be less likely.

Sputum cultures became negative in all three patients, but stool cultures were positive longer than sputum cultures in the index case and remained positive in the second and third patients for several months after discharge. The CDC of United States does not recommend the cessation of contact precautions and isolation during hospitalization for patients who has been colonized with CPE [17]. Therefore Korean CDC guideline that contact isolation is discontinued following three or more consecutive negative cultures [18] should be applied with caution, and gut colonization surveillance using highly sensitive methods is recommended. The use of a chlorhexidine bathing combined with other control measures can contain a CPE outbreak [21]. However, chlorhexidine bathing did not result in clearance of gut colonization of NDM-4-KP in this study. Its contribution to the control of CPE required further study.

To the best of our knowledge, this is the first report of NDM-4-KP in Korean hospital patients, and it was associated with a nosocomial infection from overseas. Environmental contamination was the most likely source of transmission within NSICU. To prevent outbreaks or the establishment of CPE in hospitals, early detection of the initial introduction and reinforced infection control measures such as active surveillance, single room isolation, and strict environmental control are required.

## Conflicts of interest

None.

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