ORIGINAL ARTICLE

Nosocomial Transmission of New Delhi Metallo-β-Lactamase-1-Producing *Klebsiella pneumoniae* in Toronto, Canada

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DESIGN.   An analysis of a cluster of New Delhi metallo-β-lactamase-1-producing *Klebsiella pneumoniae* (NDM1-Kp) and a retrospective case-cohort analysis of risk factors for acquisition in contacts of NDM1-Kp-positive patients.

SETTING.   A 1,100-bed Canadian academic tertiary care center.

PATIENTS.   Two index patients positive for NDM1-Kp as well as 45 contacts (roommates, ward mates, or environmental contacts) were investigated.

METHODS.   Retrospective chart reviews of all patients colonized or infected with NDM1-Kp as well as contacts of these patients were performed in order to describe the epidemiology and impact of infection prevention and control measures. A case-cohort analysis was conducted investigating 45 contacts of NDM1-Kp-positive patients to determine risk factors for acquisition of NDM1-Kp. Rectal swabs were screened for NDM1-Kp using chromogenic agar. Presence of $bla_{\text{NDM-1}}$ was confirmed by multiplex polymerase chain reaction. Clonality was assessed with pulsed-field gel electrophoresis (PFGE) using restriction enzyme *Xba*I.

RESULTS.   Two index cases carrying NDM1-Kp with different PFGE patterns were identified. Nosocomial transmission to 7 patients (4 roommates, 2 ward mates, and 1 environmental contact) was subsequently identified. Risk factors for acquisition of NDM1-Kp were a history of prior receipt of certain antibiotics (fluoroquinolones [odds ratio (OR), 16.8 (95% confidence interval [CI], 1.30–58.8); $P =$ .005], trimethoprim-sulfamethoxazole [OR, 11.3 (95% CI, 1.84–70.0); $P = $ .01], and carbapenems [OR, 16.8 (95% CI, 1.79–157.3); $P = $ .04]) and duration of exposure to NDM1-Kp-positive roommates (26.5 vs 6.7 days; $P < .001$).

CONCLUSION.   Two distinct clones of NDM1-Kp were transmitted to 7 inpatient contacts over several months. Implementation of contact precautions, screening of contacts for NDM1-Kp carriage, and attention to environmental disinfection contributed to the interruption of subsequent spread of the organism. The appropriate duration and frequency of screening contacts of NDM1-Kp-positive patients require further study.

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The spread of gram-negative bacteria possessing the New Delhi metallo-β-lactamase-1 (NDM-1) enzyme poses an emerging threat to public health. The NDM-1 enzyme hydrolyzes all β-lactams, including penicillins, cephalosporins, and carbapenems, with the exception of aztreonam.[1] Tigecycline and colistin are often the only remaining active antimicrobial agents, since $bla_{\text{NDM-1}}$-encoding plasmids typically possess multiple resistance determinants.[2]

Since its discovery in a strain of *Klebsiella pneumoniae* isolated from a Swedish patient previously hospitalized in India in 2008,[3] NDM-1 has been identified in multiple genera of gram-negative bacteria and has disseminated worldwide.[4] In Canada, colonization or infection with NDM-1-producing organisms has primarily been associated with importation from medical tourism or hospitalization during travel to an endemic area.[5-8] Autochthonous acquisition of NDM-1-producing *Morganella morganii* has been described in Ontario previously, indicating the potential for local acquisition of $bla_{\text{NDM-1}}$ in Canada.[5]

Infection control guidelines for the prevention of carbapenem-resistant *Enterobacteriaceae* (CRE) have been developed by the Public Health Agency of Canada.[9] Perhaps because of the currently low incidence of CRE in Canada,[10] infection control strategies for CRE are variable, with institutions in various stages of adopting new guidelines.[11] In January 2011, our institution identified an NDM-1-producing *K. pneumoniae* (NDM1-Kp) from a patient who had recently returned from India. We describe the subsequent cluster of nosocomial transmissions, the infection control interventions adopted to prevent transmission, and a case-

cohort analysis of risk factors for nosocomial acquisition of NDM1-Kp.

METHODS

Study Site

The study site was a 1,100-bed tertiary care teaching hospital in Toronto, Ontario, Canada. Research ethics board approval was obtained for this study.

Infection Control Practices

Before January 2011, patients infected or colonized with CRE were placed on contact precautions until the patient was discharged. Admission screening for CRE was not routinely performed but was done for contacts of patients with a newly identified CRE. Contacts of CRE-positive patients were preemptively placed on contact precautions and required 3 negative rectal screens over 2 weeks before discontinuation of precautions. Urine, open wounds, indwelling devices, exit sites, and endotracheal tube specimens were also collected for screening, if appropriate. Ward surveillance (screening) once a week for 3 weeks of all patients on a unit was conducted when a new index patient was identified. If the point prevalence surveys were negative, no further investigation was conducted.

Microbiology

Clinical samples were processed using conventional microbiology methods. Antimicrobial susceptibility testing was performed utilizing the VITEK2 automated system (bioMérieux). Colistin and tigecycline susceptibility testing was performed using Etest (bioMérieux). Clinical isolates with an ertapenem minimum inhibitory concentration of 1.0 mg/L or greater underwent confirmatory testing by Etest[12] and in-house polymerase chain reaction (PCR) for the presence of carbapenemases. The multiplex PCR targeted the carbapenemases bla_{NDM-1} and bla_{KPC} using primers NDM1-F (5′ AAA GTC AGG CTG TGT TGC G 3′), NDM1-R (5′ ATC TCG ACA TGC CGG GTT TC 3′),[3] KPC-F (5′ ATG TCA CTG TAT CGC CGT CT 3′), and KPC-R (5′ TTG TCA TCC TTG TTA GGC GC 3′).[13] PCR for other β-lactamases included bla_{CTX-M}, bla_{TEM}, bla_{SHV}, bla_{OXA-1}, and bla_{CMY-2}.[6] The 2011 EUCAST *Enterobacteriaceae* breakpoints were used for colistin,[14] while tigecycline susceptibility was based on the product monograph of tigecycline approved by Health Canada (susceptible, ≤2 mg/L; intermediate, 4 mg/L; resistant, ≥8 mg/L).[15]

Before July 2011, rectal swabs to screen for asymptomatic CRE colonization were planted on MacConkey agar with cefpodoxime (2 mg/L; Oxoid); after this time, these specimens were planted on Colorex CHROMagar KPC (Alere). Suspicious colonies (growth on MacConkey cefpodoxime agar and resistance to ertapenem or any growth on the CHROMagar KPC) were confirmed by PCR assay for carbapenemase-encoding genes.

For environmental samples, gauze moistened with sterile saline was used to swab surfaces. The gauze was then enriched in Letheen Broth (Difco-BBL) for 18–24 hours at 37°C, after which ~50 μL was plated onto CRE screening media using a swab.

Pulsed-Field Gel Electrophoresis (PFGE)

Genetic relatedness of NDM1-Kp was analyzed by PFGE using a CHEF-DR III System (Bio-Rad Laboratories), according to the Centers for Disease Control and Prevention PulseNet protocol with the restriction enzyme *Xba*I.[16]

Case-Cohort Analysis

The medical records of all patients with NDM1-Kp were reviewed. Inpatient contacts of these patients who subsequently had at least 1 negative rectal screen culture for NDM-1-producing organisms were identified, and their medical records were also reviewed. Contacts were designated as roommates, ward mates, or environmental contacts. For patients with multiple exposures, categorization was based on the patients' highest level of exposure (roommate > environmental contact > ward mate). Roommates were defined as patients who shared a room occupied by an NDM1-Kp case at the same time, while ward mates were patients who did not share a room with an NDM1-Kp case but were on the same ward as a case patient. Environmental contact was defined as a patient who was admitted to a room directly following the discharge of an NDM1-Kp-positive patient but did not share a room with an NDM1-Kp-positive patient previously. Duration of exposure to NDM1-Kp for contacts was calculated on the basis of the cumulative number of days spent at each exposure level (roommate vs ward mate vs environmental contact). Clinical data including date of admission, location of hospital stay, level of NDM1-Kp exposure (roommate, ward mate, or environmental contact), clinical diagnosis, course in hospital, past medical history, medical interventions (eg, surgery, central line insertions, tracheostomy, Foley catheters), antibiotic history (within 3 months from a positive culture, the first negative CRE screen for contacts, or the earliest exposure date for contacts discharged before being screened for CRE), and history of colonization or infection with other antibiotic-resistant organisms (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum β-lactamase-producing *Enterobacteriaceae*, and *Clostridium difficile*) were recorded. Median time to detection for contacts was calculated on the basis of the date of the first probable exposure to an NDM1-Kp-positive patient to the contact's first positive NDM1-Kp culture (from any site).

Statistics

For categorical variables in the case-cohort study, univariate analysis with the Fisher exact test was utilized. Student t test was used for continuous variables (SAS 9.2). Statistical significance was defined as a P value less than .05.

RESULTS

NDM1-Kp Cluster

Between January 2011 and March 2012, 9 patients were identified with NDM1-Kp. PFGE revealed 2 distinct clones. The index patient for clone 1 had previously received health care in India and was admitted to our institution for 7 days. Urine cultures yielded NDM1-Kp postdischarge; therefore, the patient was not in precautions during his admission. The index case for clone 2 had no previous travel to the Indian subcontinent and was identified only after being discharged from our hospital to a rehabilitation facility. Table 1 summarizes the exposure history and microbiological investigation for NDM1-Kp-positive patients. Nine patients were colonized with NDM1-Kp, of which 4 patients had clinical infections (2 urinary tract infections and 2 bloodstream infections). All isolates of both clones of NDM1-Kp were resistant to all β-lactams, fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole (TMP-SMX) but susceptible to colistin. Clone 1 had intermediate susceptibility to tigecycline, while clone 2 was susceptible. PCR for β-lactamase genes identified bla_{NDM-1}, bla_{CTX-M}, bla_{CMY-2}, and bla_{SHV} in clone 1, while clone 2 possessed bla_{NDM-1}, bla_{CTX-M}, bla_{OXA-1}, and bla_{SHV}. Median time to detection of NDM1-Kp in contacts after their first potential exposure was 53 days.

Environmental contact accounted for transmission to 1 patient. Patient I occupied the same room that had previously been shared by patients E and F for 166 days. Environmental sampling of this room during patients E and F's stay included bed rails, light switches, bedside tables, ventilators, cardiac monitors, supply carts, intravenous poles, and handwashing sinks/faucets. NDM1-Kp was recovered only from culture of the handwashing sinks/faucets in the room and was positive (2/6 samples) on repeat testing 4 and 5 months after the initial positive result. Screening of the bathroom sink in the room was negative (0/14), as were sinks on other units where NDM1-Kp-positive patients occupied (0/12). Repeat testing

of other environmental surfaces was not conducted, since all initial cultures were negative.

Case-Cohort Analysis

In total, 126 patients were identified as contacts of NDM-1-positive patients, with 45 available for follow-up (25 roommates, 15 ward mates, and 5 environmental contacts). Of the 7 patients who subsequently acquired NDM1-Kp, 4 (57.1%) were roommates, 2 (28.6%) were ward mates, and 1 (14.3%) was an environmental contact. Univariate analysis of potential risk factors for NDM1-Kp acquisition identified a history of certain antibiotics (penicillins, fluoroquinolones, macrolides, TMP-SMX, vancomycin, and carbapenems) and mean duration of exposure to NDM1-Kp-positive roommates as significant (Table 2). Duration of exposure to an NDM1-Kp-colonized or -infected patient for roommate contacts was significantly longer in those that acquired NDM1-Kp compared with those that did not (26.5 vs 6.7 days; $P < .001$). A multivariate analysis of potential risk factors for NDM1-Kp acquisition was not done, since the number of cases was too small.

Infection Control Interventions

Admission screening for CRE was extended to include patients with a receipt of health care in an endemic region. Following identification of a patient with NDM1-Kp, screening of contacts was done on days 1, 7, 14, and 21. Ward prevalence screens were done when a new case was identified.

Over the course of the investigation, 22 patients were screened within 1 week after suspected exposure; 10 completed 3 weekly screens separated by 1 week, 5 completed 2 weekly screens, and 7 had 1 negative follow-up screen. A flag in the electronic patient record allowed identification of contacts, enabling contact precautions and screening to be initiated for those who were not screened if they were readmitted or seen in clinic. Fifteen patients had a subsequent visit to our hospital (inpatient or outpatient) a median of 165 days

TABLE 1. Clinical Review of Patients with a Positive New Delhi Metallo-β-Lactamase-1 (NDM-1)-Producing *Klebsiella pneumoniae* Culture

| Patient | Presumed contact | Exposure length, days | | | First positive isolate | | Infection (site) | Estimated time to detection, days[a] | Mode of detection | Previous negative CRE screens (dates) | NDM1-Kp |
		R	W	E	Isolate	Date					
A	Index 1	...	...	...	Urine	January 19	Yes (UTI)	...	Clinical	No	1
B	A	0	1	0	Urine	April 18	Yes (UTI)	90	Clinical	No	1
C	B	0	11	0	Blood	July 2	Yes (blood)	111	Clinical	No	1
D	C	29	0	0	Rectal	July 5	No	30	Point prevalence screen	No	1
E	D	31	20	0	Rectal	August 25	Yes (blood)	55	Point prevalence screen	Urine, rectal (July 8, 14)	1
F	E	24	35	0	Urine	August 21	No	24	Point prevalence screen	Urine, rectal (July 25)	1
G	Index 2	...	...	...	Wound	September 14	No	...	Clinical	No	2
H	G	22	8	0	Rectal	October 3	No	53	Contact tracing screen	Urine, rectal (September 22)	2
I	F (room)	0	0	18	Urine	February 2, 2012	No	20	Contact tracing screen	Urine, rectal (January 18)	1

NOTE. CRE, carbapenem-resistant *Enterobacteriaceae*; E, environmental contact; NDM1-Kp, NDM-1-producing *Klebsiella pneumoniae*; R, roommate; UTI, urinary tract infection; W, ward mate.
[a] Based on first probable exposure.

TABLE 2. Univariate Analysis of Potential Risk Factors for New Delhi Metallo-β-Lactamase-1-Producing *Klebsiella pneumoniae* (NDM1-Kp) Acquisition in Inpatient Contacts

| | NDM1-Kp | | | | |
| | Positive | Negative | | | |
Risk factor	($N = 7$)	($N = 38$)	OR	95% CI	*P*
Type of exposure to NDM1-Kp					
Roommate	4	21	1.08	0.16–8.38	1
Ward mate	2	13	0.77	0.07–5.58	1
Environmental contact	1	4	1.42	0.02–18.0	1
Duration of exposure to NDM1-Kp					
Roommate	26.5	6.7	...	14.4–25.6[a]	<.001
Ward mate	18.5	27.9	...	−82.0–63.1[a]	.79
Environmental contact	9.5	8.0	...	−17.7–20.7[a]	.85
Healthcare exposures in past year					
Our hospital	4	17	1.65	0.24–12.7	.69
Canadian hospital	2	7	1.77	0.14–13.8	.61
Non-Canadian hospital	0	1	∞	0.01–∞	1
Direct transfer from another hospital	1	5	1.07	0.02–12.5	1
Long-term care facility	1	1	6.17	0.07–496.6	.29
Rehabilitation center	1	1	6.17	0.07–496.6	.29
Past medical history					
Recurrent urinary tract infections	1	1	6.17	0.07–496.6	.29
Diabetes mellitus	1	5	1.07	0.02–12.5	1
Hypertension	3	16	1.03	0.13–7.05	1
Chronic heart condition	2	17	0.49	0.04–3.55	.68
Chronic pulmonary condition	2	7	1.77	0.14–13.8	.61
Chronic renal failure	0	11	∞	0.65–∞	.17
Malignancy	3	16	1.03	0.13–7.05	1
Medical interventions					
Surgery	4	33	0.20	0.03–1.87	.09
Central line	6	20	5.4	0.55–261.9	.21
Intubation	7	30	∞	0.41–∞	.32
Tracheostomy	5	16	3.44	0.47–39.4	.22
Nasogastric tube	5	21	2.02	0.28–23.4	.68
Gastric feeding tube	3	11	1.84	0.23–12.8	.66
Foley catheter	6	25	3.12	0.32–154.4	.41
History of an antibiotic-resistant organism					
MRSA	1	0	∞	0.29–∞	.16
VRE	0	0	...	...	1
ESBL	1	1	6.17	0.07–496.6	.29
Clostridium difficile	0	4	∞	0.16–∞	1
Antibiotic history[b]					
Any antibiotic	7	31	∞	0.34–∞	.57
Penicillin	6	10	16.8	1.61–799.3	.005
Cephalosporin					
First generation	3	10	2.10	0.26–14.7	.39
Second generation	0	1	∞	0.01–∞	1
Third generation	4	19	1.33	0.19–10.3	1
β-lactam/β-lactamase inhibitor	5	17	3.09	0.43–35.4	.24
Carbapenem	3	3	8.75	1.30–58.8	.04
Fluoroquinolone	6	10	16.8	1.79–157.3	.005
Aminoglycoside	0	0	...	...	1
Trimethoprim-sulfamethoxazole	4	4	11.3	1.84–70.0	.01
Azithromycin	4	2	24.0	3.04–189.4	.003
Vancomycin	4	7	5.9	1.07–32.5	.05

NOTE. CI, confidence interval; ESBL, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; VRE, vancomycin-resistant enterococci.
[a] 95% CI of the difference of the means.
[b] Receipt of antibiotics within 3 months before a positive culture, the first negative carbapenem-resistant *Enterobacteriaceae* (CRE) screen for contacts, or the earliest exposure date for contacts discharged before being screened for CRE.

(range, 27–299 days) after suspected exposure. The majority (8 patients) had only 1 follow-up negative screen, while 6 patients had 2 negative screens and 1 patient completed 3 weekly screens. If a patient was transferred to a long-term care home or a nursing home, the receiving institution was advised of the patient's status as a contact. Where possible, CRE screening was then completed at the receiving facility (1 patient).

Routine practices—including hand hygiene, compliance with contact precautions, and cleaning/disinfection standards—were reinforced. Hydrogen peroxide–based disinfectant was utilized for daily room cleaning/disinfection, with a second daily cleaning/disinfection of high-touch surfaces. Specialized equipment or equipment with materials not compatible with hydrogen peroxide were disinfected by steam cleaning. With NDM1-Kp identified in the handwashing sink of a patient room, further investigation identified healthcare workers using this sink to dispose of bath water and other liquids. This practice was stopped, and the sink was subsequently disinfected with hydrogen peroxide at sporocidal concentrations. However, because the sink cultures continued to grow NDM1-Kp, the sink and sink traps were replaced.

DISCUSSION

The cluster of NDM1-Kp cases in our institution was the result of transmission of 2 distinct clones. Autochthonous acquisition of NDM-1-producing organisms has been described in nonendemic countries, including Canada.[5,17] Its identification in our center suggests a potentially higher burden of bla_{NDM-1} in Ontario than previously appreciated, since 1 index case had no travel history to an endemic area. Active surveillance is now recommended by local provincial guidelines that recommend admission screening of any patient with a history of receipt of healthcare in an endemic region.[18] However, these recommendations may change over time as additional risk factors for CRE are identified.

Active surveillance of epidemiologic contacts is recommended after the identification of CRE by screening for asymptomatically colonized patients.[9,19] However, the optimal frequency and timing of screening of contacts is unknown. Although there was a long duration between acquisition and detection of NDM1-Kp in our study, this may be an overestimation, since routine screening was not conducted to determine the earliest date that NDM1-Kp could be clinically detected. In our experience, a single rectal swab for contacts was inadequate, since 4 patients (Table 1) were negative on initial screening but developed NDM1-Kp infection or colonization on subsequent screens without ongoing exposure to NDM1-Kp-positive patients. This may be due to a low burden of colonizing organism at the time of acquisition, to inadequately collected specimens, or to use of an imperfect screening test. Currently, there is no gold standard protocol for CRE rectal screening swabs.[20,21] With uncertainty regarding the most sensitive media for the detection of CRE, initial false-negative results may have occurred. Chromogenic media designed for CRE appear to be able to detect CRE with high minimum inhibitory concentrations but may be less sensitive for low-level carbapenem resistance.[21] Further study of screening media, both chromogenic and nonchromogenic, is required to determine the optimal approach for routine laboratory detection of CRE in the absence of molecular detection assays.[21,22]

The role of the environment in transmission of CRE is uncertain, but transmission of *Klebsiella* spp. and *Pseudomonas aeruginosa* through environmental reservoirs has been described.[23-25] Patient I acquired NDM1-Kp colonization after occupying the room of a previously positive patient, with no other NDM1-Kp-positive patient on the ward, suggesting an environmental source for transmission. This highlights the importance of maintaining meticulous cleaning and disinfection standards. Practices such as disposing fluids in handwashing sinks may potentially result in contamination of these surfaces and should be discouraged; biofilm production makes eradication of gram-negative organisms from sinks extremely difficult.[24,25]

Analysis of risk factors for the acquisition of NDM1-Kp in contacts identified a history of recent exposure to certain antibiotics and duration of roommate exposure to be significant. Because the mode of transmission for *Enterobacteriaceae* is primarily through direct contact, patients with close and prolonged exposure would be expected to be at higher risk. Nosocomial clusters of NDM-producing *Escherichia coli* and *K. pneumoniae* have been identified in nonendemic countries,[26,27] including 1 report of transmission between 2 roommates in France.[27] Although roommates represented the highest risk in our study, transmission also occurred in ward mates and environmental contacts presumably via the hands of transiently colonized healthcare workers. We did not attempt to detect staff carriage of NDM1-Kp in this investigation.

A limitation of this study was the small sample size. The majority of NDM1-Kp contacts were discharged from the hospital before screening swabs could be taken, affecting the interpretation of potential risk factors for acquiring NDM1-Kp. This reflects the practical limitations involved in acutely managing a cluster of transmissions. The results, though, reflect previous experience with nosocomial transmission of CRE in nonendemic countries.[27] In addition, there is limited experience with the microbiologic workup of CRE environmental screens, and as discussed previously, the gold standard for CRE screening media has yet to be defined. As institutions acquire more experience with NDM-1-producing bacteria, standardization of practice will develop for the infection control of these organisms.

Although the isolation of NDM-1-producing organisms is currently a rare occurrence in Canadian healthcare settings, this cluster indicates that the prevalence of these organisms is increasing even in nonendemic regions and that prompt initiation of infection prevention and control practices is essential to prevent transmission. Contact precautions for

NDM1-Kp-positive patients are necessary for the duration of admission, since carriage of NDM-1-producing organisms can persist.[28] Further investigation is required to determine the optimal frequency and timing of screening of in-hospital contacts of patients with NDM-1-producing organisms in order to reduce the risk of nosocomial transmission. With the implementation of several interventions—including the use of contact precautions for NDM1-Kp-positive patients, screening of inpatient contacts, flagging contacts for appropriate precautions on readmission, and careful environmental cleaning—no further transmission of NDM1-Kp has been identified in our institution since February 2012.

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