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Intrapatient transfer of an uncommon carbapenemase in Nebraska

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To the Editor—Carbapenem-resistant *Enterobacterales* are a major medical concern, especially during the coronavirus disease 2019 (COVID-19) pandemic because bacterial superinfections in severe acute respiratory coronavirus virus 2 (SARS-CoV-2)–infected patients have led to poor outcomes.[1] *Enterobacterales* can emerge resistant to carbapenems through multiple mechanisms including the acquisition of carbapenemase genes on mobile genetic elements such as plasmids. These mobile genetic elements are a major concern due to the potential spread of carbapenem resistance and other resistance elements between multiple bacterial species.[2,3] Carbapenemase-producing *Enterobacterales* (CRE) are found worldwide and are widespread in the United States, including in the state of Nebraska.[4] Although KPC is the most commonly identified carbapenemase in the United States, New Delhi metallo-β-lactamase (NDM) carbapenemases have been reported since 2010[5] and have infected patients with and without history of international travel.[3] In Nebraska, routine screening for carbapenem resistance has been recommended since 2017. Phenotypic or genotypic confirmation of carbapenemase production is performed by the Nebraska Public Health Lab.[6] We describe the first documented case of infection with an NDM-7–producing *Enterobacterales* in the state of Nebraska. Furthermore, this case indicates the potential for plasmid spread to multiple species within a single patient.

Bacterial identification and antimicrobial susceptibility testing were performed using MicroScan Walkaway (Beckman Coulter, Brea, CA). Phenotypic determination of carbapenemase production for CRE was performed using the modified carbapenem inactivation method (mCIM) as described by the Clinical and Laboratory Standards Institute (CLSI).[7] According to the Nebraska Department of Health and Human Services protocol, carbapenem-resistant isolates were sent to the Nebraska Public Health Laboratory for genotypic determination of carbapenemase production using Xpert Carba-R (Cepheid, Sunnyvale, CA). Following the initial identification and positive mCIM test, the isolate was sent to our laboratory for further evaluation. Confirmation of the presence of the NDM gene as well as the absence of other carbapenemase genes was determined using the Streck ARM-D β-lactamase identification kit according to manufacturer's instructions. The NDM allele was further identified by Sanger sequencing. Plasmid carriage of NDM-7 was confirmed by Southern blotting using NDM-specific probes.[8]

A middle-aged African-American male presented in the emergency room with a left-foot ulcer associated with poorly controlled diabetes melitus type 2 (Fig. 1A). The patient had a long-standing issue with ulcers in his feet and had been followed by a podiatrist for several years. Patient history was significant for previous foot ulcers positive for methicillin-susceptible *Staphylococcus aureus* and recent travel to the Middle East for work. The diabetic foot ulcer was initially treated in the Middle East with surgical debridement and amputation of the second toe. The patient was prescribed amoxicillin-clavulanate and discharged. While traveling in Nebraska, the patient presented in the emergency room for a wound check. Upon presentation, the left foot had several deep ulcers in stage III and IV that appeared to have good granulation tissue, and no tenderness or purulence was noted. Laboratory tests revealed a normal white blood cell count of 11.8 10^3/mm^3; elevated creatinine at 2.61 mg/dL (baseline 2.0 mg/dL); C-reactive protein (CRP) of 137 mg/L; erythrocyte sedimentation rate (ESR) > 120 mm/hour. Cultures of the foot were obtained, and the patient was discharged with topical bacitracin. Upon consultation with the infectious disease physician several days later, further cultures were obtained, and the patient was started on oral levofloxacin.

Initial cultures were positive for carbapenem-resistant *Enterobacter cloacae* (Figure 1B). Follow-up cultures were positive for carbapenem-resistant *Klebsiella pneumoniae* and methicillin-susceptible *Staphylococcus aureus* (susceptibility not shown). For both *Enterobacterales* isolates, the mCIM test was positive. Real-time polymerase chain reaction (PCR) using the Streck ARM-D β-lactamase identification kit was positive for NDM in both the *E. cloacae* isolate (Entb 348) and the *K. pneumoniae* isolate (Kleb 407). Sanger sequencing of the NDM gene in both isolates identified the NDM-7 carbapenemase gene. Southern blots were performed to determine the location of the NDM-7 gene. Both strains carried a plasmid of the same size encoding NDM-7, suggesting likely conjugative transfer (data not shown).

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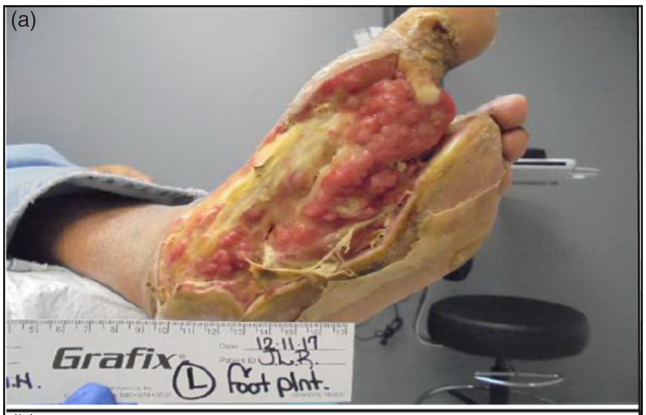
(a)



(b)

Antibiotic	MIC µg/mL (S/I/R)	
	Entb 348	Kleb 407
Amikacin	≤8 (S)	
Ampicillin	>16 (R)	≥32 (R)
Ampicillin/Sulbactam	>16/8 (R)	
Aztreonam	≤4 (S)	≤1 (R)
Cefazolin	>16 (R)	≥64
Cefepime	>16 (R)	≥64 (R)
Ceftriaxone	>8 (R)	≥64 (R)
Ciprofloxacin	>2 (R)	≥4 (R)
Ertapenem	>4 (R)	≥8 (R)
Gentamicin	>8 (R)	≤1 (S)
Levofloxacin	2 (S)	≥8 (R)
Meropenem	>8 (R)	
Piperacillin/Tazobactam	>64 (R)	≥128 (R)
Tetracycline		16 (R)
Tobramycin	>8 (R)	
Trimethoprim/Sulfamethoxazole	>2/38 (R)	2/38 (S)

Fig. 1. Two NDM-7–producing *Enterobacterales* were isolated from a diabetic foot ulcer. (A) The left-plantar diabetic ulcer at the initial presentation. (B) Susceptibilities of the *Enterobacter cloacae* (Entb 348) and *Klebsiella pneumoniae* (Kleb 407) isolates indicate carbapenem resistance mechanisms.

The infectious disease physician elected to continue the levofloxacin because of clinical improvement despite apparent resistance in the *K. pneumoniae*. Tissue cultures obtained at wound care visits a few weeks later were positive for methicillin-resistant *S. aureus*, but no resistant gram-negative organisms were detected at that time. The patient was switched from levofloxacin to linezolid for the *S. aureus* and was scheduled for further debridement and flap. The patient had a split-thickness graft placed several weeks later over the left-foot ulcers, and the infections resolved.

NDM-7 was initially identified in Germany in 2012. This NDM variant is of particular concern due to greater hydrolytic activity against carbapenems than other NDM variants and high potential for horizontal gene transfer.[9] To date, NDM-7 has only been identified in the United States in patients with a history of international travel.[10] To our knowledge, this case represents the first identification of NDM-7–producing *Enterobacterales* in Nebraska. Although this patient's history is significant for international exposure, the incidence of NDM-producing *Enterobacterales* infection without international travel has been increasing.[3] Thus, the identification of NDM β-lactamases is a cause for concern, regardless of patient history. The spread of the NDM-7 β-lactamase between *E. cloacae* and *K. pneumoniae*, as well as evidence of plasmid carriage of the gene, highlights the mobile nature of this resistance determinant. Swift action of the ID team and the outpatient setting can prevent transfer of the NDM-7 plasmid to other patients. Robust surveillance for these uncommon β-lactamases and appropriate precautions upon identification are necessary to ensure that their presence remains limited.

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