New Delhi Metallo-\(\beta\)-Lactamase–Producing Carbapenem-Resistant *Escherichia coli* Associated With Exposure to Duodenoscopes

Lauren Epstein, MD, MSc; Jennifer C. Hunter, DrPH; M. Allison Arwady, MD; Victoria Tsai, MPH; Linda Stein, MPH; Marguerite Gribogiannis, MPA; Mabel Frias, MPH; Alice Y. Guh, MD; Alison S. Laufer, PhD; Stephanie Black, MD; Massimo Pacilli, MS; Heather Moulton-Meissner, PhD; J. Kamile Rasheed, PhD; Johannetsy J. Avillan, BS; Brandon Kitchel, MS; Brandi M. Limbago, PhD; Duncan MacCannell, PhD; David Lonsway, PhD; Judith Noble-Wang, PhD; Judith Conway, RN; Craig Conover, MD; Michael Vernon, DrPH; Alexander J. Kallen, MD

**IMPORTANCE** Carbenapenem-resistant Enterobacteriaceae (CRE) producing the New Delhi metallo-\(\beta\)-lactamase (NDM) are rare in the United States, but have the potential to add to the increasing CRE burden. Previous NDM-producing CRE clusters have been attributed to person-to-person transmission in health care facilities.

**OBJECTIVE** To identify a source for, and interrupt transmission of, NDM-producing CRE in a northeastern Illinois hospital.

**DESIGN, SETTING, AND PARTICIPANTS** Outbreak investigation among 39 case patients at a tertiary care hospital in northeastern Illinois, including a case-control study, infection control assessment, and collection of environmental and device cultures; patient and environmental isolate relatedness was evaluated with pulsed-field gel electrophoresis (PFGE). Following identification of a likely source, targeted patient notification and CRE screening cultures were performed.

**MAIN OUTCOMES AND MEASURES** Association between exposure and acquisition of NDM-producing CRE; results of environmental cultures and organism typing.

**RESULTS** In total, 39 case patients were identified from January 2013 through December 2013, 35 with duodenoscope exposure in 1 hospital. No lapses in duodenoscope reprocessing were identified; however, NDM-producing *Escherichia coli* was recovered from a reprocessed duodenoscope and shared more than 92% similarity to all case patient isolates by PFGE. Based on the case-control study, case patients had significantly higher odds of being exposed to a duodenoscope (odds ratio [OR], 78 [95% CI, 6.0-1008], P < .001). After the hospital changed its reprocessing procedure from automated high-level disinfection with ortho-phthalaldehyde to gas sterilization with ethylene oxide, no additional case patients were identified.

**CONCLUSIONS AND RELEVANCE** In this investigation, exposure to duodenoscopes with bacterial contamination was associated with apparent transmission of NDM-producing *E coli* among patients at 1 hospital. Bacterial contamination of duodenoscopes appeared to persist despite the absence of recognized reprocessing lapses. Facilities should be aware of the potential for transmission of bacteria including antimicrobial-resistant organisms via this route and should conduct regular reviews of their duodenoscope reprocessing procedures to ensure optimal manual cleaning and disinfection.
Carbapenem-resistant Enterobacteriaceae (CRE) are multidrug-resistant organisms isolated predominantly from patients with exposures in health care facilities. Carbapenem-resistant Enterobacteriaceae are a public health concern because treatment options are limited and invasive infections are associated with high mortality. The proportion of Enterobacteriaceae that are resistant to carbapenems has quadrupled in the past decade; however, these organisms still remain an uncommon cause of health care–associated infections in most parts of the United States. Understanding transmission and preventing further spread of CRE is a public health priority.

Although several mechanisms can lead to carbapenem resistance, much of the increase in CRE since 2001 has been driven by the spread of carbapenemase-producing CRE, particularly those producing Klebsiella pneumoniae carbapenemase (KPC). The New Delhi metallo-β-lactamase (NDM) is a carbapenemase that has been infrequently reported in the United States. However, NDM-producing CRE have the potential to add substantially to the total CRE burden. Identification of even a single isolate of NDM-producing CRE has prompted investigation by the Centers for Disease Control and Prevention (CDC) and state and local health departments to prevent transmission.

In March 2013, NDM-producing Escherichia coli was identified in a 650-bed teaching and referral hospital in northeastern Illinois from a urine culture obtained from a hospitalized patient with no international travel history. Between March 2013 and July 2013, 6 additional patients with a history of admission to this hospital had positive clinical cultures for CRE. In August 2013, we launched an investigation to identify the source and prevent further NDM-producing CRE transmission. A brief notification of the outbreak has been published.

Methods

The activities involved in this investigation were reviewed by the Science Office of the National Center for Emerging and Zoonotic Infectious Diseases (CDC) and were determined to constitute an urgent public health response that did not require submission to the institutional review board.

Case Definition

A case was defined as an NDM-producing E coli isolate with greater than 85% similarity by pulsed-field gel electrophoresis (PFGE) to the outbreak strain, recovered from a patient in northeastern Illinois and confirmed by the CDC between January 1, 2013, and December 31, 2013.

Field Investigation

Initial Case Finding and Case Description

Suspected NDM-producing CRE isolates were initially identified by a clinical laboratory in Illinois that performed screening among CRE isolates for metallo-β-lactamase (MBL) production using carbapenem disks with and without inhibitors (Rosco Diagnostica). Isolates with positive results for MBL were sent to the CDC for confirmation using polymerase chain reaction.

After the identification of the initial case patients from clinical cultures, the hospital performed CRE rectal screening cultures on the patients' roommates who were still hospitalized and on patients admitted to the ward where the first patient was treated. For case patients who had been discharged, the local health departments performed CRE rectal screening on epidemiologically linked patients (eg, roommates either from a long-term care facility or during initial hospitalization). Rectal screening cultures were plated to CHROMagar (HardyCHROM Carbapenemase Agar). Identification and antimicrobial susceptibilities were performed on gram-negative colonies. Screening for MBL production was performed as described above. Electronic medical records were reviewed and abstracted, and details of patient movement within and among local health care facilities during the preceding 8 months were recorded.

Case-Control Study

To identify risk factors for NDM-producing CRE carriage, a case-control study was conducted using all case patients identified from January 2013 to July 2013 with any history of admission to the hospital. To minimize misclassification among control patients, 27 unmatched control patients were randomly selected from the 131 patients in the hospital’s inpatient rehabilitation ward (where CRE screening had occurred) with negative CRE rectal screening cultures during May 2013. Controls were further restricted to patients with (1) a non-elective admission to the hospital immediately prior to admission to the rehabilitation ward and (2) a minimum 5-day length of stay at the hospital.

Infection Control and Environmental Assessment

Interviews were conducted with health care personnel at the hospital. A medical record review revealed that a history of endoscopic retrograde cholangiopancreatography (ERCP) procedures involving the use of a duodenoscope was common among initial cases. Duodenoscope reprocessing procedures were reviewed by the field team and by the manufacturers of the duodenoscope and the automated endoscope reprocessor. Environmental cultures were collected from duodenoscopes, the endoscopy reprocessing area, and procedure rooms.

Duodenoscope Investigation

A subsequent investigation was conducted from August 2013 through December 2013 focusing on duodenoscope exposure as a source of CRE transmission.

Additional Case Finding

Beginning in August 2013, the hospital notified all 226 living patients who underwent a procedure with any duodenoscope.
scope at the hospital between January 1, 2013, and September 30, 2013, of potential exposure to CRE and offered CRE rectal screening and blood-borne pathogen testing.

**Cohort Study**
A cohort analysis was conducted among patients with a history of exposure to 1 duodenoscope (duodenoscope A) to assess whether procedure-specific exposures were associated with an increased risk of NDM transmission. Data were collected from medical and procedure records for patients who either returned for screening cultures or previously had been identified as case patients from January 1, 2013, through June 21, 2013.

**Laboratory Analysis**
Environmental surface samples were collected using premoistened sponge wipes, which were then extracted in phosphate buffer saline containing polysorbate 80. The biopsy channel of duodenoscope A was cultured using the flush-brush-flush method.αβ The channels were flushed with tryptic soy broth and brushed with a duodenoscope cleaning brush; the broth was then collected at the distal end. The distal tip of the duodenoscope, including the elevator mechanism, was submerged in tryptic soy broth and scrubbed with a duodenoscope cleaning brush and subject to mechanical vibration (or sonication). Sponge wipes and duodenoscope extracts were concentrated by centrifugation. All overnight cultures and extracts were either plated onto blood and MacConkey agar plates or submerged in tryptic soy broth for overnight enrichment at 35°C.

Characterization of the carbapenem resistance mechanism was performed using a multiplex real-time polymerase chain reaction assay that detects both the genes for NDM and KPC.4αβ Pulsed-field gel electrophoresis was performed as previously described for E coli using XbaI for single-enzyme digestion of DNA and electrophoresis for 21 hours with switch times of 5 and 40 seconds.7 The PFGE patterns were analyzed using BioNumerics software (Applied Maths). Similarity of patterns was based upon Dice coefficients and a dendrogram was built using the unweighted pairing method.10

**Statistical Analyses**
All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute), or OpenEpi, version 2.3.1 (www.OpenEpi.com). Bivariable logistic regression was used to obtain odds ratios and 95% CIs for the association between case status and each of the exposures; a 2-sided α level of .05 was used for significance. For calculation of odds ratios involving cells with 0 observations, the 0.5 zero-cell correction was applied. For the cohort analysis, risk ratios and 95% CIs were calculated for the association between duodenoscope exposure variables and case status; a 2-sided α level of .05 was used for significance.

**Results**

**Field Investigation**

**Initial Case Finding and Case Description**
Figure 1 illustrates the suspected transmission pathways of NDM-producing E coli among case patients. During the field investigation, 9 case patients were identified (January 2013 through July 2013), including 7 from clinical culture at the hospital, 1 from clinical culture at another health care facility, and 1 from a rectal screening culture at the hospital (case patients C1-C8, S28). Eight (C1-C7, S28) of the 9 case patients were treated at the hospital during this time frame, and 1 of the 9 (C8) had been the roommate, at another facility, of a patient who had been at the hospital during the outbreak; none had a history of international travel. In the hospital, epidemiological tracing of the 8 case patients treated at the hospital revealed no temporal overlap of patient rooms or wards. Six of 8 case patients (C1-C6) who were treated at the hospital (75%) had an ERCP at that facility. Four of these 6 case patients (C1-C4) were exposed to duodenoscope A only, 1 case patient (C6) was exposed to a second duodenoscope (duodenoscope B) only, and 1 case patient (C5) had been exposed to both duodenoscope A and duodenoscope B. Among the 3 case patients (C7, C8, S28) who did not have a procedure with a duodenoscope at the hospital; all were either linked (ie, roommate at another facility) to a known case or were admitted to the hospital during the outbreak. Two of the 8 case patients (C1, C2) with clinical cultures died during their hospitalization but their deaths did not appear related to the CRE infection. No additional case patients were identified through screening of 131 patients admitted to the rehabilitation ward.

**Case-Control Analysis**
Of the 9 case patients identified during the initial field investigation, 8 were treated at the hospital; these 8 case patients and 27 control patients from this hospital were included in the case-control study. These groups had similar demographic characteristics; however, the length of hospital admission was significantly longer for control patients (Table 1). On bivariable analysis, case status was significantly associated with history of ERCP, magnetic resonance cholangiopancreatography, and antibiotic use in the past 3 months (Table 2). Eighty-three percent (5 of 6 patients) of patients who had a history of ERCP had also undergone magnetic resonance cholangiopancreatography.

**Infection Control Practices and Environmental Assessment**
An infection prevention assessment that focused on duodenoscope reprocessing was conducted. No breaches were identified in the reprocessing of duodenoscopes at the hospital. Manufacturer-recommended procedures were followed in all 6 steps of the process: (1) precleaning, (2) manual cleaning, (3) high-level disinfection using an automated endoscope reprocessor, (4) rinsing, (5) drying, and (6) storage. The automated endoscope reprocessor was evaluated by the manufacturer and found to be functioning correctly. The hospital used an enzymatic cleaner and high-level disinfectant, ortho-phthalaldehyde, that were not included on the duodenoscope manufacturer’s list of known compatible agents (ie, they had not been specifically tested by the manufacturer). The enzymatic cleaner is a standard product used for reprocessing, and the high-level disinfectant is listed by the US Food and Drug Administration as identical to a product on the duodenoscope manu-
The hospital also used compatible cleaning brushes, although not the brand recommended by the duodenoscope manufacturer.

The duodenoscopes used by the hospital ranged in age from less than 1 month to several years old. Duodenoscope A was first acquired by the hospital in 2009. In 2013, the hospital performed 315 ERCPs. A review of gastroenterology laboratory records showed that the hospital adhered to the manufacturer's duodenoscope service schedule. The make and model of the duodenoscope and automated endoscope reprocessor were compatible for use according to both manufacturers.

Table 1. Bivariable Comparison of Demographic Characteristics for Case Patients and Control Patients Included in the Case-Control Study

<table>
<thead>
<tr>
<th>Demographic and Clinical Characteristics</th>
<th>Case Patients (n = 8)</th>
<th>Control Patients (n = 27)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>70.4 (13.6) [45-88]</td>
<td>63.3 (19.0) [21-91]</td>
<td>.34</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>6 (75.0)</td>
<td>11 (40.7)</td>
<td>.12</td>
</tr>
<tr>
<td>Days hospitalized at hospital A, medianc</td>
<td>8.5</td>
<td>25.0</td>
<td>.002</td>
</tr>
<tr>
<td>Mean (SD) [range]</td>
<td>13.3 (12.0) [1-37]</td>
<td>30.2 (13.2) [14-65]</td>
<td></td>
</tr>
<tr>
<td>Hospital readmission score, mean (SD) [range]d</td>
<td>6.0 (3.4) [0-10]</td>
<td>6.9 (3.8) [0-14]</td>
<td>.54</td>
</tr>
</tbody>
</table>

- NDM indicates New Delhi metallo-β-lactamase. This diagram illustrates the suspected modes of transmission of NDM-producing *Escherichia coli* among case patients. Each box represents a case patient. Dashed lines connect case patients with a suspected source of NDM-producing *E. coli* (eg, overlapped in the same hospital with a patient with NDM-producing *E. coli*, but did not share a room or ward with that patient). Patient identifiers beginning with *C* were identified through clinical culture and are numbered in order of date of positive culture; those beginning with an *S* were identified through screening culture.

- and are ordered by date of endoscopic retrograde cholangiopancreatography procedure (if applicable). Thirteen case patients had exposure to more than 1 duodenoscope prior to their NDM-positive sample collection date (2 had exposure to >1 duodenoscope associated with the outbreak [C5 and S21]; 1 had exposure to 1 outbreak-associated duodenoscope and to duodenoscopes not associated with the outbreak). Case patients with >1 duodenoscope exposure are included with the patient notification group in which they were first identified.

- A risk prediction score used at the hospital to determine the likelihood of readmission; subsequent interventions at the hospital are based on the score. Components of the score include certain medical conditions (ie, cranial/peripheral nerve disorders, depression, HIV, malignancy, pancreatitis, red blood cell disorder, renal failure, or urinary or kidney infections), previous hospitalization or emergency department visit within 12 months, insulin usage, warfarin usage, Medicare or Medicaid status, and race. The range of possible scores was 0-15; higher scores indicate increased risk.
Duodenoscope Investigation

Additional Case Finding: Clinical Case Patients
In addition to the 9 case patients identified in the field investigation, 2 case patients (C9, C10) were identified from clinical cultures in September 2013; both had a history of exposure to a third duodenoscope only (duodenoscope C; Figure 1). They were both alive at the time of hospital discharge.

Additional Case Finding: Surveillance Case Patients
From August 2013 through October 2013, the facility notified the 226 living patients who were exposed to any duodenoscope (156 exposed to duodenoscopes A, B, or C; 70 exposed to other duodenoscopes); 102 returned for screening. Twenty-seven additional case patients were identified; all were exposed to duodenoscopes A, B, or C (Figure 1). Blood-borne pathogen testing was negative for all patients. Of note, the first known case patients associated with duodenoscopes B (C5) and C (S21) had been previously exposed to duodenoscope A, potentially explaining the route of cross-contamination for duodenoscopes B and C (Figure 1).

A final case patient (S29) was identified through screening of long-term care facility roommates of known case patients bringing the total to 39 case patients identified. This includes 9 from the initial field investigation (January 2013 - July 2013), 2 from clinical cultures in September 2013, 27 from screening cultures of patients exposed to duodenoscopes, and 1 from screening of long-term care facility roommates. Of the 39 case patients, 35 had duodenoscope exposure (Table 3).

Cohort Analysis
Of the 99 patients exposed to duodenoscope A from January 1, 2013, through June 21, 2013 (the date the duodenoscope was permanently removed from service), the 55 patients that had been tested through screening or clinical culture by December 2013 were included in the cohort analysis (Table 4). On bivariate analysis, case status was significantly associated with stent placement (16 of 18 patients with stent placement [89%] vs 12 of 37 patients without [32%]) and brushing (8 of 9 patients with brushing [89%] vs 20 of 46 patients without [43%]); 89% (8 of 9 patients) of endoscopic procedures that involved brushing also involved stent placement. Individuals who had multiple duodenoscope exposures were significantly more likely to have a positive test result for NDM-producing E coli (10 of 14 patients with multiple exposures [71%] vs 18 of 41 patients without [44%]).

Infection Prevention
During October 2013, the hospital changed its duodenoscope reprocessing procedure from automated high-level disinfection to gas sterilization with ethylene oxide. Additionally, the
hospital completed 3 rounds of postreprocessing cultures on all duodenoscopes in service. All cultures were negative for Enterobacteriaceae; as of August 22, 2014, no new case-patients with duodenoscope-associated NDM have been identified among patients who only had a procedure with a duodenoscope following the change to gas sterilization.

Laboratory Analysis
Isolates from all 39 case patients were sent to the CDC for identification and characterization; all were identified as Escherichia coli with blab<sub>NDM</sub> present. Case patient isolates and the isolate recovered from duodenoscope A were highly related (>92%) by PFGE (Figure 2). 12

NDM-producing E coli and KPC-producing K pneumoniae were the only bacteria recovered from the terminal part of the reprocessed duodenoscope A (around the enclosed elevator mechanism) in August 2013, nearly 2 months following last use. Other Enterobacteriaceae were not recovered from any other environmental or duodenoscope samples.

Discussion
To our knowledge, this report describes the largest known cluster of NDM-producing E coli in the United States to date; apparent transmission was associated with exposure to duodenoscopes. The large number of exposed patients that ultimately had NDM-producing CRE isolated from clinical or screening cultures suggests that duodenoscopes were an efficient source of transmission. Unlike previously reported outbreaks of bacterial transmission related to these devices, there were no reprocessing breaches or duodenoscope defects identified. The complicated design of duodenoscopes makes cleaning difficult. It appears that these devices have the potential to remain contaminated with pathogenic bacteria even after recommended reprocessing is performed.

Difficulties with duodenoscope reprocessing and the potential for bacterial contamination and transmission of infectious agents have been well documented. However, previous reports of bacterial transmission via duodenoscopes involved lapses in infection control, reprocessing deficiencies, or a detectable device defect. 13-26 In contrast with other endoscopes, duodenoscopes have an additional channel (elevator channel) that allows for the use and manipulation of a guide wire. At the terminal end of the elevator channel is a mechanical piece containing a cantilevered elevator mechanism; the intricate design surrounding the elevator mechanism makes accessing all surfaces during manual cleaning difficult. In addition, older models of duodenoscopes with an open elevator wire channel may not be adequately reprocessed in an automated endoscope reprocessor, and manual flushing may be required. 21 To address the issue, newer duodenoscope models, like the one in the investigation, have an enclosed elevator wire channel that is not exposed to patient material and does not require manual flushing. Review of duodenoscope A by the manufacturer did not identify defects or evidence that material had entered the enclosed channel that would have resulted in persistent contamination.

Although sterilization is the definitive mechanism to eradicate all microorganisms during reprocessing, high-level disinfection is typically used for duodenoscopes. Although

### Table 3. Demographic and Clinical Characteristics of All Case-Patients Found to Have Positive Cultures for New Delhi Metallo-β-Lactamase Escherichia coli (n = 39)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of duodenoscope exposures (n = 39)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (10)</td>
</tr>
<tr>
<td>1</td>
<td>22 (56)</td>
</tr>
<tr>
<td>≥2</td>
<td>13 (33)</td>
</tr>
<tr>
<td><strong>Culture site (n = 39)</strong></td>
<td></td>
</tr>
<tr>
<td>Rectal screening</td>
<td>29 (74)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Abscess</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Blood</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Catheter tip</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Wound</td>
<td>2 (5)</td>
</tr>
<tr>
<td><strong>Time from initial duodenoscope exposure to positive culture, clinical cases, median (range), d</strong></td>
<td></td>
</tr>
<tr>
<td>Overall (n = 8)</td>
<td>30 (5-141)</td>
</tr>
<tr>
<td>Sterile site (n = 3)</td>
<td>40 (17-141)</td>
</tr>
<tr>
<td>Nonsterile site (n = 5)</td>
<td>19 (5-57)</td>
</tr>
<tr>
<td><strong>Months of procedure (n = 35)</strong></td>
<td></td>
</tr>
<tr>
<td>January-February</td>
<td>8 (23)</td>
</tr>
<tr>
<td>March-April</td>
<td>12 (34)</td>
</tr>
<tr>
<td>May-June</td>
<td>11 (31)</td>
</tr>
<tr>
<td>July-August</td>
<td>7 (20)</td>
</tr>
<tr>
<td>September-October</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Analysis includes all case patients identified through clinical cultures or screening cultures obtained by December 15, 2013. This includes 9 patients from the initial field investigation (January 2013-July 2013), 2 from clinical cultures in September 2013, 27 from screening cultures of patients exposed to duodenoscopes, and 1 from screening of long-term care facility roommates.

**A** Risk prediction score used at the hospital to determine the likelihood of readmission; subsequent interventions at the hospital are based on the score. Components of the score include certain medical conditions (ie, cranial/peripheral nerve disorders, depression, HIV, malignancy, pancreatitis, red blood cell disorder, renal failure, or urinary or kidney infections), previous hospitalization or emergency department visit within 12 months, insulin usage, warfarin usage, Medicare or Medicaid status, and race. The range of possible scores was 0-15; higher scores indicate increased risk.

2. Patients could have more than 1 New Delhi metallo-β-lactamase- positive culture.
3. Sterile site included blood cultures or central catheters or abscesses; nonsterile sites included urine, sputum, or wounds.
4. Patients could have procedures with more than 1 duodenoscope; therefore, totals exceed the number of cases.
5. Includes only duodenoscopes A, B, and C.
Table 4. Analysis of Indications and Procedure Types for Patients Who Underwent a Procedure With Duodenoscope A (n=55)*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Exposed No. of Cases (%)</th>
<th>Total, No.</th>
<th>Unexposed No. of Cases (%)</th>
<th>Total, No.</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal liver function testb</td>
<td>11 (55)</td>
<td>20</td>
<td>17 (49)</td>
<td>35</td>
<td>1.1 (0.7-2.0)</td>
</tr>
<tr>
<td>Abnormal imagingc</td>
<td>11 (58)</td>
<td>19</td>
<td>17 (47)</td>
<td>36</td>
<td>1.2 (0.7-2.1)</td>
</tr>
<tr>
<td>Biliary stone suspected</td>
<td>13 (54)</td>
<td>24</td>
<td>15 (48)</td>
<td>31</td>
<td>1.1 (0.7-1.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (55)</td>
<td>11</td>
<td>22 (50)</td>
<td>44</td>
<td>1.1 (0.6-2.0)</td>
</tr>
<tr>
<td>Other indication</td>
<td>12 (60)</td>
<td>20</td>
<td>16 (46)</td>
<td>35</td>
<td>1.3 (0.8-2.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedurea</th>
<th>Exposed No. of Cases (%)</th>
<th>Total, No.</th>
<th>Unexposed No. of Cases (%)</th>
<th>Total, No.</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary stent placement</td>
<td>16 (89)</td>
<td>18</td>
<td>12 (32)</td>
<td>37</td>
<td>2.8 (1.7-4.5)</td>
</tr>
<tr>
<td>Brushing</td>
<td>8 (89)</td>
<td>9</td>
<td>20 (43)</td>
<td>46</td>
<td>2.0 (1.4-3.1)</td>
</tr>
<tr>
<td>Multiple ERCP</td>
<td>10 (71)</td>
<td>14</td>
<td>18 (44)</td>
<td>41</td>
<td>1.6 (1.0-2.6)</td>
</tr>
<tr>
<td>Biliary stent removal</td>
<td>3 (50)</td>
<td>6</td>
<td>25 (51)</td>
<td>49</td>
<td>1.0 (0.4-2.3)</td>
</tr>
<tr>
<td>Sphincterotomy</td>
<td>21 (53)</td>
<td>40</td>
<td>7 (47)</td>
<td>15</td>
<td>1.1 (0.6-2.1)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>2 (33)</td>
<td>6</td>
<td>26 (53)</td>
<td>49</td>
<td>0.6 (0.2-2.0)</td>
</tr>
<tr>
<td>Biliary stone removal</td>
<td>12 (52)</td>
<td>23</td>
<td>16 (50)</td>
<td>32</td>
<td>1.0 (0.6,1.8)</td>
</tr>
<tr>
<td>Other procedure</td>
<td>4 (33)</td>
<td>12</td>
<td>24 (56)</td>
<td>43</td>
<td>0.6 (0.3-1.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

*Documented by the clinician in the electronic medical record.

b Defined as elevations in aspartate aminotransferase, alanine aminotransferase, direct bilirubin, or alkaline phosphatase.

c Defined as abnormal findings on a computed tomography scan, magnetic resonance imaging, or abdominal ultrasound of the right upper quadrant.

Figure 2. Pulsed-Field Gel Electrophoresis (PFGE) Dendrogram of Case Patients

This figure provides the results of PFGE analysis for NDM-producing Escherichia coli isolates recovered from 39 case patients and duodenoscope A. All isolates have greater than 92% similarity by PFGE and are considered highly related.
sterilization might have contributed to controlling this outbreak, the limited experience from this investigation does not provide sufficient evidence to recommend that all facilities switch to sterilization. Furthermore, several issues surrounding sterilization potentially limit its widespread use including long processing and aeration time, toxicity of some sterilizing agents for staff and patients, and potential incompatibility with some endoscope devices.26,27

Another option for ensuring adequate duodenoscope reprocessing might be to conduct testing for residual contamination during reprocessing. Many international professional societies recommend periodic microbiological surveillance testing of duodenoscopes after full reprocessing.28-30 In addition to cultures, the use of adenosine triphosphate bioluminescence assays after manual cleaning has been used to detect the presence of persistent organic material following duodenoscope cleaning.30,31 Although nonculture methods using adenosine triphosphate might be faster than culture, more work is needed to validate these methods before they can be widely recommended.

This cluster also demonstrates the challenge associated with identifying and controlling the spread of novel carbapenemases. Although all carbapenemase-producing CRE are epidemiologically important, special attention is afforded to novel carbapenemases, like NDM, to prevent the emergence of these organisms that are rarely identified in the United States. However, at this time, few laboratories regularly perform CRE resistance mechanism testing and are therefore unable to differentiate organisms producing novel carbapenemases from those producing KPC, which is the most common CRE carbapenemase in this region.3,32 The initial cluster of NDM-producing organisms was identified in part because the laboratory serving the hospital performed specialized CRE resistance mechanism testing. Prospectively, improving detection and prevention of CRE will require enhancing laboratory capacities.

Efforts to control dissemination of these organisms will also require a strengthened public health infrastructure. State and local health departments should be capable of responding to CRE in their region to ensure implementation of appropriate infection control practices, improved communication among facilities upon patient transfer, and coordination of infection prevention efforts at regional and state levels.33 In addition, the case-control study identified recent antibiotic use as a risk factor for case status, consistent with previous studies.34-36 Receipt of antibiotics might alter the gastrointestinal flora and facilitate CRE colonization. This finding highlights the fundamental role of antimicrobial stewardship in CRE prevention.

There are several limitations to this investigation. Although all patients with duodenoscope exposure were notified, only half returned for screening cultures. Duodenoscope reprocessing was reviewed by the field team after the majority of case patients had been exposed, so we cannot comment on practices that might have occurred prior to this. However, reprocessing was reviewed by several groups prior to the field investigation and at least 2 case patients had duodenoscope exposure after our assessment, suggesting observations during the field investigation likely represented actual hospital practice. Due to the small number of cases, multivariable analyses were not conducted in the case-control and cohort evaluations; these evaluations do not assess independent associations. Finally, the controls were selected during an urgent public health response from a group of patients already known to be CRE-negative (rehabilitation ward). Although this control group may not have been ideal, we did not identify significant differences between cases and controls with respect to demographic characteristics and severity of illness. The controls may not have had equal opportunity for exposure to ERCP compared with cases, which may have biased this analysis.

Conclusions

In this investigation, exposure to duodenoscopes with bacterial contamination was associated with apparent transmission of NDM-producing \textit{E coli} among patients at 1 hospital. Bacterial contamination of duodenoscopes appeared to persist despite the absence of recognized reprocessing lapses. Facilities should be aware of the potential for transmission of antimicrobial-resistant organisms via this route and should conduct regular reviews of their duodenoscope reprocessing procedures to ensure optimal manual cleaning and disinfection.

**ARTICLE INFORMATION**

**Author Affiliations:** Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia (Epstein, Hunter, Guh, Lauffer, Moulton-Meissner, Rasheed, Avillan, Kitchel, Limbago, MacCannell, Lonsway, Noble-Wang, Kallen); Epidemic Intelligence Service, Division of Scientific Education and Professional Development, Centers for Disease Control and Prevention, Atlanta, Georgia (Epstein, Hunter, Arwady); Illinois Department of Public Health, Chicago, Illinois (Arwady, Tsai, Conway, Conover); Advocate Lutheran General Hospital, Park Ridge, Illinois (Stein, Gribogiannis); Cook County Department of Public Health, Oak Forest, Illinois (Frias, Vernon); Chicago Department of Public Health, Chicago, Illinois (Black, Pacilli).

**Author Contributions:** Drs Epstein and Hunter as co-first authors contributed equally to this article, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Epstein, Hunter, Arwady, Guh, Lauffer, Limbago, MacCannell, Kallen. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Epstein, Hunter, Arwady, Frías, Guh, Pacilli, Kitchel, MacCannell. Critical revision of the manuscript for important intellectual content: Epstein, Hunter, Arwady, Tsai, Stein, Gribogiannis, Guh, Lauffer, Black, Moulton-Meissner, Rasheed, Avillan, Kitchel, Limbago, MacCannell, Lonsway, Noble-Wang, Conway, Conover, Vernon, Kallen.

**Statistical analysis:** Epstein, Hunter, Arwady, Tsai, Lauffer, MacCannell, Vernon. Administrative, technical, or material support: Hunter, Arwady, Tsai, Stein, Gribogiannis, Frías, Moulton-Meissner, Avillan, Kitchel, Limbago, MacCannell, Conover, Vernon. Study supervision: Guh, Lauffer, Rasheed, Lonsway, Noble-Wang, Conover, Kallen.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Disclaimer:** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Additional Contributions: We acknowledge Dean Silas, MD, Robert Citronberg, MD, Leo Kelly, MD, Barb Weber, MSA, MBA, MHRM, RN, Lidia Rasliau, RN, Norah Connelly, RN, Evonne Woloshyn, MA, Pam Hyziak, RN, PhD, Cindy Mahal-Van Brenk, RN, BSN, MS, CNOR, Chad Calabria, MHA, MBA, Beth Quinones, RN, Beth Hickey, CPA, Judith Rosenblum, RN, Anthony Armada, MHA, MBA, Valerie Diaz, RN, BSN, and Mike Wiegel, MS, Dusanka Bjelan, Evangeline Feldorean, Marcel Truta, Vicki Marriot, Joanna Welring, and Lee Joesten, MD, BVCC (all from Advocate Lutheran General Hospital), for clinical, epidemiological, and administrative support at the hospital. We also acknowledge Mike Costello, PhD, and Janet Havel, MS, BT (both from Aurora Consolidated Laboratory), as well as Karen Anderson, BS, Tatiana Travis, BS, Thiphasone Kongphet-Tran, MS (all from Centers for Disease Control and Prevention [CDC]), for laboratory support. We also acknowledge Lynne Sehulster, PhD (CDC), for her expertise and advice. These contributors received no compensation for their work other than their usual salary.

REFERENCES


