ORIGINAL ARTICLE

Establishment of a Statewide Network for Carbapenem-Resistant Enterobacteriaceae Prevention in a Low-Incidence Region

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OBJECTIVE. To establish a statewide network to detect, control, and prevent the spread of carbapenem-resistant Enterobacteriaceae (CRE) in a region with a low incidence of CRE infection.

DESIGN. Implementation of the Drug Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network.

SETTING AND PARTICIPANTS. Oregon infection prevention and microbiology laboratory personnel, including 48 microbiology laboratories, 62 acute care facilities, and 140 long-term care facilities.

METHODS. The DROP-CRE working group, comprising representatives from academic institutions and public health, convened an interdisciplinary advisory committee to assist with planning and implementation of CRE epidemiology and control efforts. The working group established a statewide CRE definition and surveillance plan; increased the state laboratory capacity to perform the modified Hodge test and polymerase chain reaction for carbapenemases in real time; and administered surveys that assessed the needs and capabilities of Oregon infection prevention and laboratory personnel. Results of these inquiries informed CRE education and the response plan.

RESULTS. Of 60 CRE reported from November 2010 through April 2013, only 3 were identified as carbapenemase producers; the cases were not linked, and no secondary transmission was found. Microbiology laboratories, acute care facilities, and long-term care facilities reported lacking carbapenemase testing capability, reliable interfacility communication, and CRE awareness, respectively. Survey findings informed the creation of the Oregon CRE Toolkit, a state-specific CRE guide booklet.

CONCLUSIONS. A regional epidemiology surveillance and response network has been implemented in Oregon in advance of widespread CRE transmission. Prospective surveillance will determine whether this collaborative approach will be successful at forestalling the emergence of this important healthcare-associated pathogen.

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Carbapenem-resistant Enterobacteriaceae (CRE) have disseminated rapidly across the United States and abroad since the first report of *Klebsiella pneumoniae* carbapenemase (KPC) in 2001.[1-3] The rapid spread is particularly concerning, because there are limited therapeutic options for the treatment of CRE infections, and such infections are associated with excess morbidity, mortality, and healthcare costs.[4,5]

Control of the spread of multidrug-resistant organisms (MDROs), including CRE, may require a regional approach.[6,7] In response to multiple CRE outbreaks in Israeli hospitals, the Israeli Ministry of Health implemented a multicomponent national CRE intervention that included mandatory CRE reporting to public health, mandatory isolation of hospitalized CRE carriers, and creation of a multidisciplinary task force.[8]

The first known CRE clinical isolate in Oregon, which ultimately tested positive for KPC, was identified in November 2010. This first isolate provided the impetus to initiate surveillance and response to prevent widespread emergence of CRE within the state. In September 2012, with support from the Centers for Disease Control and Prevention (CDC), we initiated the Drug Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network. The steps taken and the initial results of this effort are described herein.

METHODS

We formed a working group comprised of 2 academic infectious diseases physicians (C.D.P. and J.M.T.), a public health physician (A.T.), an academic epidemiologist (J.P.F.), 2 public health epidemiologists (M.C.C. and T.P.), and the

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Oregon Healthcare Associated Infection program director (Z.G.B.). The goal of the working group was to devise and implement a strategy to detect, control, and prevent MDROs in Oregon with an initial focus on CRE. The group met twice per month and regularly interacted with the CDC to help inform decision making. Initial discussions focused on relevant literature and conference calls with clinical staff, microbiology laboratories, and health department personnel in Oregon and in other states.

As a result of these initial meetings, the subsequent steps were identified as priorities of DROP-CRE: (1) development of an advisory committee composed of statewide infection prevention and microbiology leaders and stakeholders; (2) development of a surveillance plan to identify new CRE cases; (3) design and dissemination of needs assessment surveys to measure capacity and resources for identification and infection prevention and CRE; (4) identification of opportunities for statewide education regarding MDRO prevention with an emphasis on CRE; and (5) development and dissemination of an Oregon-specific CRE toolkit; and (6) design the response plan for when new CRE cases were identified.

Advisory Committee

We recruited an interdisciplinary group of experts to assist with a regional MDRO response network, which used local and national resources to review an Oregon CRE Toolkit and develop a strategic plan to limit the potential for spread of CRE in Oregon. The advisory group was comprised of 22 members including infectious diseases physicians, infection preventionists, long-term care representatives, microbiologists, and personnel from Acumentra Health (Oregon's quality improvement organization), the Oregon Patient Safety Commission, and the CDC. This group convened once in person and subsequently via e-mail to assist in the development of a workable statewide CRE definition, the Oregon CRE Toolkit, and recommendations for future MDRO surveillance and response strategies.

CRE Definition

We established a statewide CRE definition as follows: Enterobacteriaceae that are nonsusceptible (ie, intermediate or resistant) to any carbapenem (eg, doripenem, ertapenem, imipenem, and meropenem) and resistant to any of the third-generation cephalosporins tested (cefotaxime, ceftriaxone, and ceftazidime); or possess a gene sequence specific for carbapenemase; or are positive for carbapenemase production by a phenotypic test (eg, modified Hodge test).

CRE Surveillance and Expanded Laboratory Capacity

CRE became reportable in Oregon in December 2011. Available isolates from reported cases were sent to the CDC for additional testing (not real-time testing), which included modified Hodge test and polymerase chain reaction (PCR) testing for KPC and New Delhi metallo-β-lactamase (NDM). For all cases, data from medical records were reviewed and entered into a statewide reportable disease database using a newly developed CRE case report form, which was modeled after the Emerging Infections Program (EIP) Multi-Site Resistant Gram-Negative Bacilli Surveillance Initiative (MuGSI) case report form.

With the advisory committee input, we chose to focus CRE control response efforts specifically for carbapenemase-producing CRE (eg, KPC and NDM), and we realized that rapid molecular identification of carbapenemases would be critically important to facilitate a prompt infection control response. To achieve real-time detection, we developed the capacity of the Oregon State Public Health Lab (OSPHL) to perform both modified Hodge test (available March 2012) and PCR for KPC and NDM (available July 2013). The working group promptly assisted any facility reporting carbapenemase-producing CRE as discussed below.

Needs Assessment Surveys

Needs assessment surveys were created with the intent of understanding the needs, capacities, and resources of key stakeholder groups likely to encounter and respond to cases of CRE. We determined that the 3 primary groups in Oregon were microbiology laboratories, infection preventionists in acute care facilities, and long-term care facilities. Across surveys, not all respondents responded to every question, and nonresponses were dropped from the denominator. Findings informed the development of statewide education and the Oregon CRE Toolkit.

Self-administered needs assessment surveys were tailored to a specific audience and administered November 2012 through January 2013. Web links or copies of the survey were e-mailed; hard copies were mailed upon request. Clinical microbiology laboratory directors completed a 25-question survey focused on MDRO and CRE identification and subsequent notification practices. Acute care infection prevention and control program directors completed a 27-question survey about MDRO and CRE definitions, infection control practices, and surveillance. Long-term care facility administrators and directors of nursing completed a 27-question survey that was based on a CDC long-term care assessment tool.[9] Questions focused on infection control policies, procedures, and resources and MDRO management.

Statewide Education

We coordinated statewide education targeting the infectious diseases, microbiology, infection prevention and control, and long-term care communities. The DROP-CRE working group members gave webinars and presentations across the state to all targeted groups. In addition, national experts came to Oregon to speak and to help inform our own approach. Educational material was also included as an important component of the Oregon CRE Toolkit.

TABLE 1. Clinical Microbiology Laboratory Testing Methods, by Susceptibility System, Oregon

Method of routine susceptibility testing	No. of laboratories (n = 37)	No. (%) of laboratories that used CLSI breakpoints predating 2010 update[19]	No. (%) of laboratories that performed modified Hodge test
Automated system only	25	18 (72)	4 (16)
Manual system only	9	6 (67)	2 (22)
Both	3	1 (33)	1 (33)

NOTE. CLSI, Clinical and Laboratory Standards Institute.

Infection Control Response and the Oregon CRE Toolkit

To provide a standardized CRE infection prevention and response framework tailored to Oregon healthcare facilities, we created the Oregon CRE Toolkit, a state-specific CRE guide booklet. The contents of the Oregon CRE Toolkit were based on the CDC 2012 CRE toolkit and were informed by our survey data and initial experience assisting facilities with CRE prevention and control.[10]

RESULTS

Initial Surveillance

From November 2010 through April 2013, CRE were reported in 60 patients statewide. The reported CRE species distribution and frequency were as follows: *Enterobacter cloacae* (33), *K. pneumoniae* (10), *E. aerogenes* (8), *Escherichia coli* (3), and other (6). Only 3 carbapenemase-producing CRE were detected; all 3 isolates were KPC-producing *K. pneumoniae*. The KPC-producing case patients were not epidemiologically linked.

Microbiology Laboratories

Among the 48 clinical microbiology laboratories that were sent the survey, 37 (77%) responded, including 1 (3%) commercial reference laboratory, 31 (84%) hospital-affiliated laboratories, and 5 (14%) outpatient laboratories. Results of the susceptibility testing methods used, the Clinical Laboratories and Standards Institute (CLSI) carbapenem breakpoints for *Enterobacteriaceae* applied, and modified Hodge test performance are summarized in Table 1.

Of the 25 laboratories that reported using CLSI breakpoints that predated the 2010 update (which are less sensitive for carbapenemase detection), only 2 (8%) performed the modified Hodge test. No laboratory performed carbapenemase PCR testing. Fifty percent and 78% of laboratories "flagged" carbapenem-resistant organisms and extended spectrum β-lactamase-producing organisms (ESBLs) in the medical record, respectively; 68% of laboratories included minimum inhibitory concentrations (MICs) in the susceptibility report. Actions taken when multidrug-resistant Enterobacteriaceae were encountered included notifying infection control (44%), notifying the nursing station (44%), generating an automated report on the medical record (42%), notifying the ordering physician (33%), or no further action (14%). Similar responses were reported for multidrug-resistant *Pseudomonas aeruginosa* and multidrug-resistant *Acinetobacter baumannii* (data not shown). A minority of laboratories (29%) had definitions for multidrug-resistant Enterobacteriaceae. All respondents expressed interest in CRE educational opportunities; the most desired formats included webinars (89%), printed material (89%), and a dedicated web site (86%).

Acute Care Facilities

Among the 62 infection prevention and control programs queried, 45 (73%) responded. Most programs (82%) had direct physician involvement in infection prevention, and of those, 56% were infectious diseases physicians. Most facilities had a program in place to monitor adherence to hand hygiene (91%), environmental cleaning and disinfection of patient rooms (85%), and isolation precautions (79%).

There was no majority consensus definition for multidrug-resistant Enterobacteriaceae among infection prevention and control programs. Of programs surveyed, 28% and 25% required resistance to 2 or more and 3 or more antimicrobial classes, respectively; 6% required susceptibility to only 2 classes of antimicrobials; and 41% used an alternate definition. There was a similar lack of consensus on facility-wide definitions for multidrug-resistant *P. aeruginosa* and multidrug-resistant *A. baumannii* (data not shown). Furthermore, when defining antibiotic class, most infection preventionists (70%) did not consider cephalosporins and β-lactams to be in the same class, some (21%) were unsure, and very few (9%) considered them to be within the same class.

Eighty-five percent of respondents would use contact precautions with patients who had CRE. Nine percent had encountered CRE in their facility, and no facility had conducted a CRE point prevalence study. Of the 15 facilities (45%) that reported having reviewed microbiology records to detect unrecognized CRE cases, 3 (20%) identified earlier CRE cases as a result of the review.

Only 58% of respondents agreed that their facility is made aware of patient MDRO status at admission to the hospital. In contrast, 82% believed that the receiving facility was made aware of patient MDRO status at discharge from the hospital. When asked to rank the top 3 MDRO priorities in their facility, CRE was rarely selected (15%), as were multidrug-resistant *P. aeruginosa* (6%) and multidrug-resistant *A. baumannii* (3%). The top priorities were methicillin-resistant

TABLE 2. Reported Long-Term Care Facility Infection Control Practices Implemented for 59 Patients Infected or Colonized with Multidrug-Resistant Organisms (MDROs), Oregon

Variable	No. (%) of patients (n = 59)	
	Implemented for active infection	Implemented for colonization
Private room	42 (71)	16 (27)
Contact precautions	56 (95)	31 (52)
Dedicated equipment	52 (88)	19 (32)
Follow-up testing for MDRO status	47 (81)	26 (44)

Staphylococcus aureus (97%), *Clostridium difficile* (97%), vancomycin-resistant Enterococci (61%), and ESBLs (42%). Most respondents were aware of the CDC CRE toolkit (94%). All respondents expressed interest in CRE educational opportunities; most desired formats included printed material (100%), presentations (97%), and webinars (91%).

Long-Term Care Facilities

Among 140 long-term facilities that were sent the survey, 59 (42%) responded. The median daily census of responding facilities was 48 residents (interquartile range [IQR], 38–68). Facility ownership was primarily private (73%). Forty-two facilities (61%) were affiliated with a multifacility organization (eg, chain or corporation), 24 (36%) were independent, and 1 (2%) was part of a hospital system. Most facilities delivered both long-term custodial care (97%) and skilled nursing or short-term rehabilitation (87%); none managed ventilator-dependent residents.

The median staff time per week devoted to infection prevention and control was 5 hours (IQR, 3–9). The director of nursing was the individual primarily responsible for infection control at most facilities (75%); overall, registered nurses were responsible for 95% of the programs. Responses to questions on practices implemented for patients known to be infected or colonized with MDROs are displayed in Table 2.

Less than half of respondents (48%) were aware of CRE, and none had encountered a CRE-positive patient. When selecting up to 3 healthcare-acquired infections as the most difficult to prevent, 59% cited catheter-associated urinary tract infection, 21% chose *C. difficile* infection, 12% selected norovirus infection, and 20% stated that they had no current infection prevention difficulties.

Seventy-nine percent of respondents stated that their transfer documents indicated MDRO infection or colonization status upon release to other levels of care, and 75% said MDRO status was documented for residents transferred into their facility.

Infection Control Response and the Oregon CRE Toolkit

The Oregon CRE Toolkit was published in April 2013. This toolkit was distributed statewide to all microbiology laboratories, infection control programs in acute care facilities, and long-term care facilities and is available online.[11] The toolkit includes (1) the Oregon CRE definition with reporting and isolate submission instructions; (2) an educational reference guide about CRE, including our rationale to focus on carbapenemase-producing CRE; (3) detailed CRE prevention strategies and response algorithms for acute care, long-term care, and ambulatory care settings; (4) CRE screening protocols for clinical staff and the laboratory; (5) an MDRO interfacility transfer tool; (6) an environmental cleaning monitoring tool; and (7) CRE educational material for patients and staff.

For all CRE cases, we recommend increased attention to core infection control measures, including adherence to and monitoring of hand hygiene, environmental cleaning, and contact precautions. When carbapenemase-producing organisms are encountered, the facility receives rapid written and phone consultation from our working group on the recommended infection control response, which includes notifying relevant groups (local health department, infection prevention and control programs, facilities management service, antibiotic stewardship program, infectious diseases and other pertinent clinician groups, and hospital administration), educating patients and staff, communicating CRE status to the receiving facility upon patient transfer, and intervening with core infection control measures. Depending on the scenario, additional recommendations may include surveillance cultures of high-risk patient contacts and patient and staff cohorting. At the time of writing, only 1 case of a carbapenemase-producing CRE had been identified since DROP-CRE was initiated. For that case, we assisted the facilities involved with the infection control response and, through high-risk contact screening and follow-up upon patient transfer, we found no additional indication of spread.

DISCUSSION

Initial surveillance efforts suggested that clinical CRE cases are uncommon in Oregon as of April 2013. Using this information, we developed a comprehensive program with the necessary infrastructure to quickly identify and respond to CRE to prevent CRE emergence.

A critical component to the response plan was rapid, accurate carbapenemase detection. At the time of the survey, most laboratories applied the pre-2010 CLSI breakpoints, few performed the modified Hodge test, and none tested for carbapenemases using PCR. These results identified areas for improved CRE identification. Thus, we developed the capacity at OSPHL to perform the modified Hodge test and carbapenemase PCR in real time to support the statewide control effort. A limitation to this strategy is that PCR testing only detects KPC and NDM. We plan to develop the capability to rapidly test other carbapenemases, including Verona integron-encoded metallo-β-lactamase, imipenemase metallo-β-lactamase, and oxacillinase-48. However, molecular detection will be a moving target, because the epidemiology of global and local carbapenemases evolves.[12]

Before the DROP CRE Network, the lack of a clear CRE definition hampered reporting and confused microbiologists and clinicians. Agreeing on a definitive, clear, well-publicized CRE definition for Oregon was crucial to establishing reproducible CRE surveillance. We encountered several other potential communication gaps that require additional study. First, laboratories did not often "flag" carbapenem-resistant isolates or specifically notify infection preventionists and clinician providers about multidrug-resistant gram-negative bacilli. On the other hand, acute care facility's definitions of multidrug-resistant gram-negative bacilli varied widely and were not always known in the microbiology laboratory. Although the Oregon CRE definition is now uniform throughout Oregon, a consensus definition for other multidrug-resistant gram negative bacilli remains elusive and would help simplify laboratory-infection prevention communication.

Of note, over 40% of acute care infection preventionists and 25% of long-term care respondents did not agree that patient MDRO status was communicated at the time of transfer into their facility. Lack of communication regarding MDRO status during interfacility transfer may delay appropriate infection control interventions and thereby represents an opportunity to intervene and prevent spread of MDROs.[13] The Joint Commission and Council for State and Territorial Epidemiologists both released statements supporting the reporting of MDRO patient status between facilities upon transfer to ensure prompt initiation of infection control measures.[14,15] In response, we are planning collaboratives to support MDRO prevention across the state with a goal of establishing interfacility teams to foster best practices and effective communication. Maryland reported their statewide long-term care infection control improvement efforts, which involved regulatory, educational, and financial initiatives;[16] Oregon could potentially use that experience to inform a cohesive statewide approach to MDRO and CRE prevention. Although not unique to Oregon, the limited infection control training and resources in our long-term care facilities pose challenges in this regard.[17,18]

The needs assessment surveys indicated that targeted education was required; in long-term care, over half of survey respondents were unaware of CRE. The microbiologists and acute care infection preventionists were enthusiastic about CRE education, and the survey responses helped us to create customized training for each target audience. Future anticipated work includes an overhaul of and regular updates to Oregon's CRE web site.

We observed an opportunity to potentially limit the spread of CRE in a low-prevalence region, and implementation of the DROP-CRE Network has created the necessary infrastructure to quickly detect and respond to CRE cases. Critical to the success of the project is the central role of public health, which is in a unique position to coordinate a regional approach to CRE detection, control, and prevention. With the community's collective interest in MDRO prevention, we were able to facilitate interdisciplinary collaboration between otherwise unconnected healthcare systems and levels of care. Prospective surveillance will determine whether this regional, collaborative approach at prevention will be successful at forestalling the emergence of this important healthcare-associated pathogen.

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