CD Summary

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OREGON PUBLIC HEALTH DIVISION • OREGON HEALTH AUTHORITY

DROP EVERYTHING, THE CRE ARE COMING!

Deadly new bacteria that are resistant to all known antibiotics seem to be reported in the media regularly. This *CD Summary* provides background on the classification and clinical importance of carbapenem-resistant *Enterobacteriaceae* (CRE), and describes our efforts to control their spread in Oregon.

CRE

The *Enterobacteriaceae* are a large family of Gram-negative bacilli, many members of which are upstanding residents of the human gastrointestinal tract.* Commonly encountered species include *Escherichia coli, Klebsiella* spp., *and Enterobacter* spp. (*Pseudomonas* spp. and *Acinetobacter* spp. may be multiply resistant but are not in the *Enterobacteriaceae* family.)

Carbapenems are broad-spectrum antibiotics typically used to treat severe hospital-associated infections (HAIs) caused by multi-drug resistant bacteria; currently available carbapenems include imipenem, meropenem, ertapenem, and doripenem. Although related to the β-lactam antibiotics, carbapenems retain antibacterial activity in the presence of most β-lactamases, including extended-spectrum β-lactamases (ESBLs) and extended-spectrum cephalosporinases (e.g., AmpC-type β-lactamases); hence their increasing use in HAIs.

CRE are generally lumped into two categories based on the mechanism of their resistance: carbapenemase producers (CP-CRE) and non-carbapenemase producers. Carbapenemases directly inactivate carbapenem antibiotics. Resistance among non-CP-CRE typically involves the combination of an ESBL or AmpC-type β-lactamase coupled with decreased permeability of the bacterial cell wall.[1,2] CP-CRE have spread rapidly across the nation and around the globe, perhaps because carbapenemases are typically encoded on plasmids that are easily transferred within and among bacterial species.

The list of carbapenemases of global importance reads like alphabet soup: KPC, NDM, VIM, IMP, and OXA-48.[3,4] The first identified in the U.S. was *Klebsiella pneumoniae* carbapenemase (KPC), reported in North Carolina in 2001.[5] KPC-producing bacteria have since become endemic in many hospitals on the East Coast and have spread throughout the world. Of *Klebsiella* isolates submitted in 2011 to the National Healthcare Safety Network (NHSN), 10.4% were CRE — compared to 1.6% reported but a decade earlier.[6] KPC-conferred resistance has also been reported within other *Enterobacteriaceae.*

Reporting CRE in Oregon

Clinicians and laboratories are required to report any bacteria of the *Enterobacteriaceae* family that:

- Are non-susceptible (i.e., intermediate or resistant) to ANY carbapenem antibiotics AND resistant to ANY of the following 3rd-generation cephalosporins tested: cefotaxime, ceftriaxone, or ceftazidime; OR
- Possess a gene sequence specific for carbapenemase(PCR); OR
- Are positive for carbapenemase production by a phenotypic test (e.g., Modified Hodge Test).

Laboratories are required to submit *E. coli, Klebsiella* spp., and *Enterobacter* spp. CRE isolates to the Oregon State Public Health Laboratory (OSPHL) for further testing.

Since 2009, the New Delhi metallo-β-lactamase (NDM) carbapenemase, first reported in a Swedish patient who had been hospitalized in India, has also spread around the globe.[7] Carbapenemases infrequently seen to date in the U.S. include Verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP) metallo-β-lactamase, and oxacillinase-48 (OXA-48).

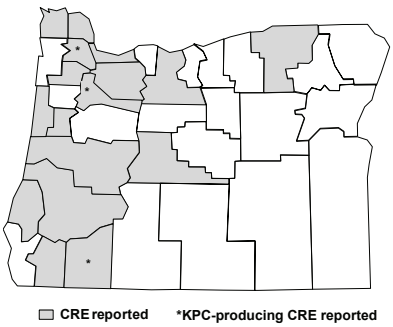
WHY SHOULD WE CARE?

Infections caused by CRE occur most commonly among people with chronic medical conditions, frequent or prolonged stays in healthcare settings, invasive medical devices, or prolonged courses of certain antibiotics. CRE have caused pneumonia, bloodstream infections, urinary tract infections, intra-abdominal infections, and surgical-site infections. CRE may also be resistant to quinolone, sulfa, and even aminoglycoside antibiotics. Treatment options may be limited to tigecycline or colistin. CRE infection case-fatality rates exceeding 40% have been reported.[8]

CRE IN OREGON

CRE, and particularly CP-CRE, have been rare in Oregon, and we'd like to keep it that way. In December 2011, isolation of CRE became reportable here (Box).† To date, 45 cases of CRE infection or colonization have been reported (Map). The median case age was 65 (range, 7–94) years; 28 (62%) were female. Twenty-nine (64%) were hospitalized for an average of 17 days. No attributable deaths have been reported. *Enterobacter* spp. accounted for 73% of the isolates (Table, *verso*). Only three of the isolates were KPC producers — all *Klebsiella pneumoniae* — and the three patients all had extensive histories of hospitalization outside of the Pacific Northwest.

CRE sightings, by county
Oregon, December 2011–March 2012.



WHAT ARE WE DOING ABOUT CRE?

Patients with CRE infection are complex, often severely ill and frequently transferred from one hospital to another and to long-term or rehabilitative care

* for a complete list, see: http://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/CRE/Documents/genera_list.pdf.

† Oregon Administrative Rule 333-018-0015.

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settings. To coordinate infection control across healthcare settings, we collaborated with epidemiologists from Oregon Health & Science University, Portland VA Medical Center, and Oregon State University to create a Drug-Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network. Its primary objective is to detect and contain CRE so that it doesn't establish a beachhead in Oregon.

The DROP-CRE Network is promoting CRE education throughout Oregon and developing a statewide CRE database. The Network will provide real-time outbreak assistance to Oregon facilities with CRE cases and track them as they are transferred between facilities. The Oregon State Public Health Laboratory is developing PCR capacity to test for KPC and NDM genes to inform the infection control response.

DROP-CRE will release an "Oregon CRE Toolkit" this Spring. The Toolkit is intended to be a practical aid to health-care professionals involved in the detection, treatment, and prevention of CRE. Modeled after the 2012 CDC CRE Toolkit,[9] Oregon's Toolkit includes Oregon-specific definitions, recommendations, protocols, and educational material.

See the Oregon CRE website (*http://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=108*) for the Oregon CRE Toolkit (when available) and additional information about these organisms.

Lastly, think "NICE" if you encounted CRE:

- **Notify** the county health department, pertinent clinical groups, and your antibiotic stewardship program that CRE has been spotty. If it's CP-CRE, also notify hospital administration.
- **Intervene** in all cases with core infection control activities: hand hygiene, contact precautions, private rooms, and optimized environmental cleaning. Reduce unnecessary antibiotics and use of invasive devices. Additionally, for CP-CRE, screen patient contacts, and cohort staff and patients.
- **Communicate** CRE infection or colonization status to the receiving facility upon patient transfer.
- **Educate** patients, staff, and visitors about CRE.

Reported CRE, by species and carbapenemase testing results (n=45)

Organism	Number reported No. (#)	Modified Hodge Test Positive	PCR positive for KPC No. (%)
Enterobacter aerogenes	5 (11)	3 (60)	0
Enterobacter cloacae	25 (56)	16 (64)	0
Enterobacter spp.	1 (2)	0	0
Escherichia coli	2 (4)	n/a*	0
Klebsiella pnemoniae	9 (20)	4 (44)	3 (33)
Proteus mirabilis	1 (2)	n/a*	0
Citrobacter spp.	1 (2)	1 (100)	0
Serratia marcescens	1 (2)	0	0
Total	**45**	**24 (53)**	**3 (7)**

*isolate unavailable for testing

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