

*epi*TRENDS

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Carbapenem-Resistant Enterobacteriaceae: An Emerging Public Health Threat in Washington

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Antibiotics were once considered to be silver bullets, able to cure any bacterial infection. Over the past decades the problem of antibiotic resistance has emerged, first resistance to single antibiotics but eventually multidrug resistance.

Multidrug Resistant Organisms

The problems of healthcare associated infections (HAI), multidrug resistant organisms (MDROs), and antibiotic stewardship (appropriate use of antibiotics) are intertwined. In general, MDROs are bacteria with resistance to one or more classes of antimicrobial agents. The term MDRO can be used to describe bacterial organisms that are frequent causes of HAI such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and gram negative bacilli including those in the family Enterobacteriaceae that are resistant to multiple classes of antimicrobial agents.

Treatment options for patients with infection due to MDROs are extremely limited. Many studies have shown that these patients have longer hospital stays, higher hospital costs, and increased mortality compared to those with infections due to antibiotic-susceptible strains. Patients most at risk for HAIs and MDROs are those who have impaired immune defenses due to serious illness, old age, invasive procedures, and indwelling catheters.

Carbapenem-resistant Enterobacteriaceae (CRE) Microbiology and Epidemiology

Carbapenems (e.g. imipenem, meropenem, ertapenem and doripenem) are used to treat life-threatening infections caused by extremely drug-resistant gram-negative bacteria, and are the antibiotics of last resort for many serious bacterial infections. Carbapenem-resistant Enterobacteriaceae (CRE) are resistant to carbapenems and most other broad-spectrum antibiotics in the medical arsenal. Enterobacteriaceae are intestinal flora and

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include such genera as *Klebsiella*, *Escherichia*, *Enterobacter*, *Morganella*, *Proteus* and *Serratia*.

CRE have been associated with mortality rates of 40-50%. These organisms have spread from patient to patient within healthcare settings via contaminated hands of workers or patient-care items. Transmission can be prevented by appropriate attention to hand hygiene, contact precautions and environmental cleaning. If appropriate preventive measures are not undertaken, CRE can spread quickly within a region by patient movement between acute care facilities and longterm care facilities. Since first being identified in the United States in the late 1990s, certain CRE strains have disseminated widely in some regions, and have become endemic in several eastern states.

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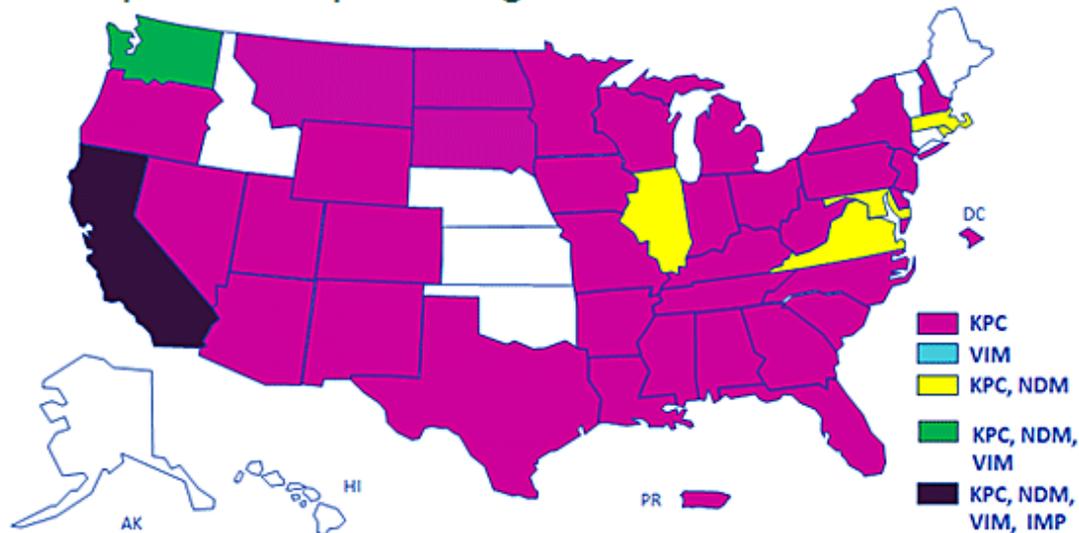
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There are several different mechanisms resulting in carbapenem resistance. The most concerning mechanism for carbapenem resistance results from production of a carbapenemase, an enzyme that hydrolyzes the carbapenems. The most common is carbapenemase production by the *Klebsiella pneumoniae* carbapenase (KPC) gene, (Figure 1) Other mechanisms involving plasmids or integrons fall into three classes (Verona Integron metallo-beta-lactamase [VIM], New Delhi metallo-beta-lactamase [NDM] and Imipenemase metallo-beta-lactamase [IMP]) and are easily transmissible from one species to another, and even between genera of bacteria. Some CRE carry genes encoding for resistance to many other antibiotics, resulting in virtually no treatment options. Carbapenem resistance can also result from a combination of extended spectrum beta-lactamase (ESBL) production with loss of porin proteins (membrane proteins), but porin loss may result in the bacteria being less fit with reduced ability to spread.

CRE are thought to be rare in Washington; only 7 CRE isolates have been reported to DOH since 2010. All reported cases of carbapenemase-producing Enterobacteriaceae were acquired outside the state, including *Klebsiella pneumoniae* with a Verona integron-encoded metallo-beta-lactamase (VIM) carbapenemase in a patient who received medical care in Greece (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5937a4.htm>), several Enterobacteriaceae producing New Delhi metallo-beta-lactamase (NDM-1) carbapenemase in a patient who received medical care in India, and *K. pneumoniae* containing the KPC gene in a patient recently transferred from California. According to CDC, as of June 2012, Washington and California are the only states in the country that have identified all three of these mechanisms of carbapenem-resistance in Enterobacteriaceae. (Figure 1)

Figure 1. Carbapenemase-producing CRE in the United States (June 2012)

Carbapenemase-producing CRE in the United States



Reproduced from Centers for Disease Control (<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>)

Prevention of CRE Transmission

The ultimate goal of public health intervention for CRE is preventing transmission in order to protect patients. Any CRE in a healthcare setting requires prompt control measures to prevent transmission to other patients. Recent guidelines from Centers for Disease Control and Prevention recommend that surveillance should occur to track the emergence of these dangerous organisms, ensure that appropriate prevention and control measures are being implemented, and provide reference laboratory services where needed.

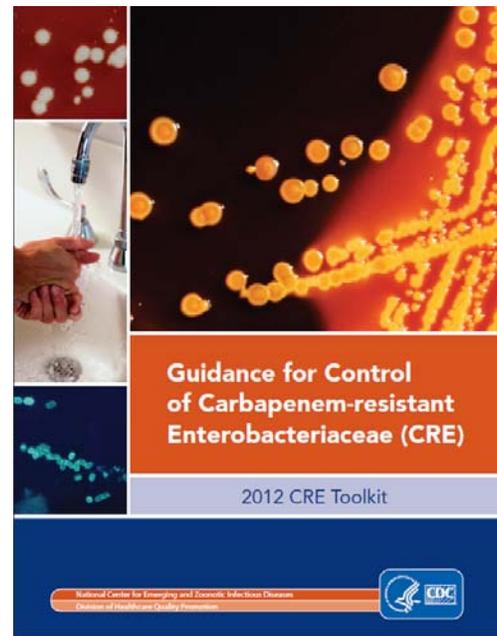
Many interventions effective in preventing other HAIs are similarly effective in the prevention of CRE transmission, but only if uniformly implemented throughout entire regions. No one facility can succeed alone against MDRO. These important interventions include hand hygiene, contact precautions, education on how to prevent transmission, avoiding and discontinuing invasive devices when medically feasible, cohorting patients and staff, active screening cultures, enhanced environmental cleaning, alerting facility staff of the presence of an unusual infection, and antibiotic stewardship.

When a case of suspected CRE is identified in a healthcare setting, the first steps are to assure the patient is placed on contact precautions and the facility infection prevention program is notified. The isolate should be saved by the clinical lab and the antibiotic susceptibility pattern confirmed. Washington State Public Health Laboratories can perform susceptibility testing.

CDC recommends that any patients who are epidemiologically-linked (roommates, patients who shared nursing staff before contact precautions were implemented) to a case with CRE should have screening cultures to detect if transmission has occurred. When a patient known to have a

current or past infection with CRE is admitted to a new healthcare facility, it is essential that appropriate communication occurs so necessary infection control can be implemented by the receiving facility. In addition, facilities accepting transfer patients from CRE-endemic areas should consider preemptively placing these patients on contact precautions until their CRE status is determined.

The phrase “Bad Bugs, No Drugs”^{*} summarizes the ominous situation of CRE in the healthcare setting. DOH Communicable Disease Epidemiology (CDE) is available for consultation regarding MDROs and CRE. Additionally, the DOH HAI Program offers epidemiologic and laboratory assistance in HAI investigations, including consultation on infection control and providing molecular testing, if indicated.



CDE can be reached at (206) 418-5500 and the HAI Program can be reached at (360) 236-4249.

The full CDC guideline entitled **2012 CRE Toolkit - Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)**, is available at <http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html>. For additional CDC reference materials on control and management of highly antibiotic resistant organisms, please see:

Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006
(http://www.cdc.gov/hicpac/mdro/mdro_toc.html)

Investigation and Control of Vancomycin-Intermediate and -Resistant *Staphylococcus aureus* (VISA/VRSA): A guide for Health Departments and Infection Control Personnel
(http://www.cdc.gov/hai/pdfs/visa_vrsa/visa_vrsa_guide.pdf)

2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (<http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf>)

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship 2007
(<http://cid.oxfordjournals.org/content/44/2/159.full.pdf>)

^{*}The term “Bad Bugs, No Drugs” is from an Infectious Diseases Society of America publication of the same name available at:
http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Images/Bad%20Bugs%20no%20Drugs.pdf