Carbapenem-resistant Enterobacteriaceae: Deadly superbugs on the rise

BY RAEED DEEN, BA, AND DOROTHY DEBBIE, PhD

Alexander Fleming discovered penicillin in 1928, and in 1946, it became one of the first antibiotics administered to patients with bacterial infections. Not long after this medical milestone, people began to observe bacterial resistance to penicillin.[1] Ever since, bacterial resistance to antimicrobial agents has increased, and it continues to be a menace to patients and the healthcare industry.

Since November 2012, carbapenem-resistant Enterobacteriaceae (CRE), a Gram-negative bacteria that show high levels of resistance to antibiotics, has spread to more than 200 American hospitals in 42 states. This includes a deadly outbreak in Bakersfield, California, in March 2013.[2] For the first time, in September 2013, the Centers for Disease Control and Prevention classified serious threats of bacterial resistance as urgent, serious, and concerning. Currently, CRE is one of only three bacterial infections categorized as an urgent threat.[3]

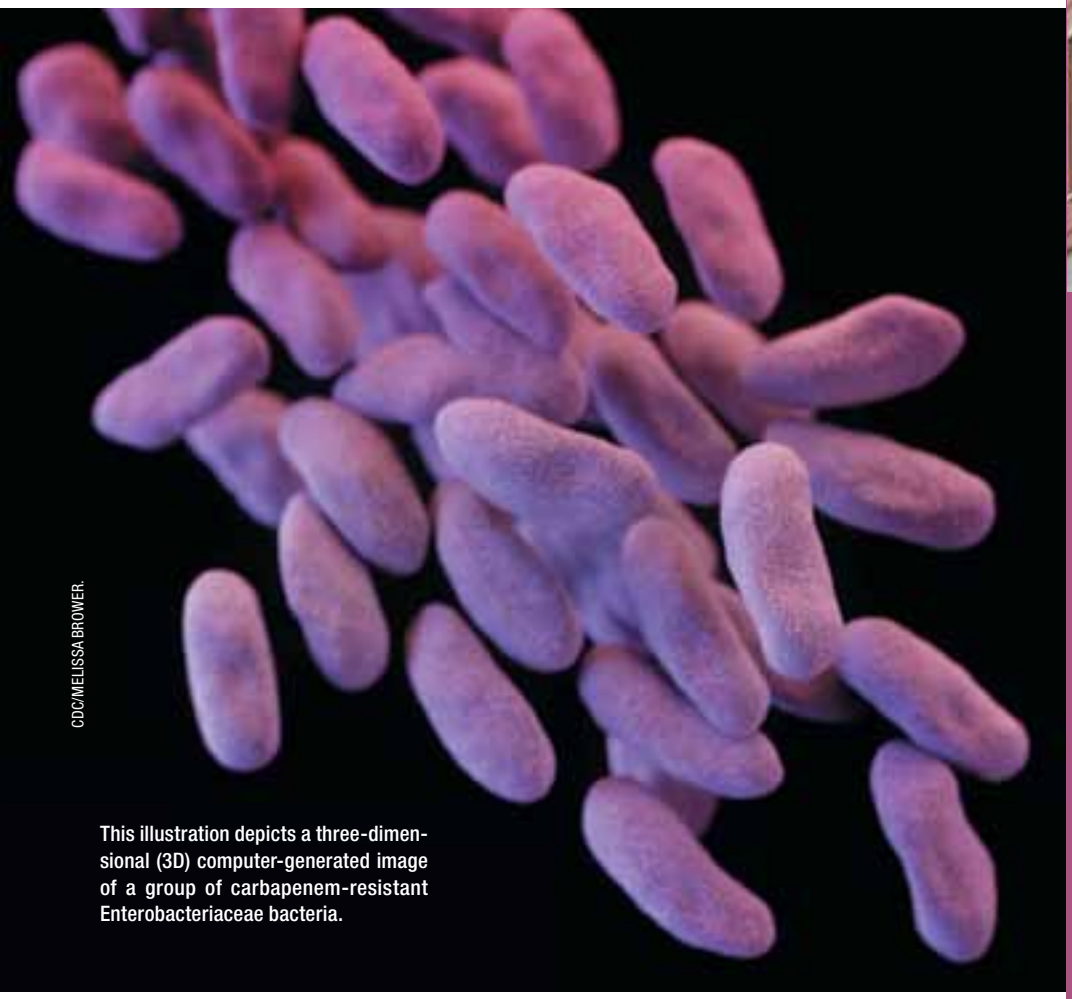
Examples of CRE are the *Klebsiella* species and *Escherichia coli*. Although these bacteria are commonly located in human intestines, in rare instances the bacteria can move out of the gut and cause urinary tract infections, bloodstream infections, wound infections, and pneumonia. People in both healthcare and community settings are susceptible to CRE infection.[4]

Carbapenems are the most effective and powerful Beta-Lactam antibiotics, and they are prescribed to patients as a last resort to combat some bacterial infections.[4,5] The antibiotic inhibits transpeptidases—enzymes that produce peptidoglycan, a structural component of bacteria—resulting in bacterial cell lysis. At the time of their development in the 1980s, carbapenems were effective against nearly all Enterobacteriaceae.[6] However, in the 1990s, the bacteria developed resistance to less powerful antibiotics, such as cephalosporin. Inevitably, the prescription rates of carbapenems increased.[7] Between 2002-2006, the use of carbapenems increased by 59 percent in a sample of 35 university hospitals.[8] As with any antibiotic, CRE developed resistance as a result of the increased usage. CRE's resistance to a multitude of antibiotics has earned it the name 'deadly superbugs.'[9]

Bacteria transfer its genetic material with relative ease, resulting in a diversity of CRE bacteria—*Klebsiella oxytoca, Enterobacter, Serratia,* and *Salmonella* species. Additionally, the transfer of genetic material led to the rapid spread of CRE. In 2001, North Carolina reported the first case of *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae in the United States. The following year, a surveillance study in New York found of the 602 known types of *Klebsiella pneumoniae* isolates, nine of them produced KPC. In 2004, there were two hospital outbreaks in New York, and an additional 20 KPC-producing isolates were identified.[10] In the United Kingdom, between 2003 and 2011, 657 carbapenemase-producing Enterobacteriaceae were identified; the number of isolates showed a marked increase during the latter years.[11]

TRANSMISSION

CRE is transmitted through direct contact with either infected people or contaminated surfaces and excrements. CRE can spread not only from patient-to-patient but also through the hands of healthcare personnel. Healthcare settings are often the prime locations for the spread of CRE. In addition to invasive medical devices like urinary catheters, there are many reservoirs for CRE. A study in Colombia found that stethoscopes and sinks were most likely to harbor CRE.[12] Where as in Melbourne, Australia, it was found that hand-washing stations in the intensive care unit were the main



CDC/MELISSA BROWER.

This illustration depicts a three-dimensional (3D) computer-generated image of a group of carbapenem-resistant Enterobacteriaceae bacteria.

CRE reservoirs.[13] An interesting finding from another Australian study showed that resistant bacteria were found on healthcare workers' lanyards and badges, with lanyards harboring a ten-fold increase of bacteria compared to badges.[14] Post-acute care and long-term care facilities are large reservoirs of both colonized patients and contaminated surfaces. Studies have shown that 50–75 percent of CRE-infected patients were admitted from post-acute care facilities.[15, 16]

RISK FACTORS

CRE primarily infects patients in acute and long-term healthcare settings. Often, patients' weakened immune systems, in addition to invasive devices, such as urinary catheters and central venous lines, constitute risk factors for CRE infection. Furthermore, CRE has been found to infect other populations, such as the elderly, critically ill children, and burn patients.[15]

Another risk factor for CRE is the exposure to broad-spectrum antibiotic therapy. Due to the ever-developing resistance of CRE, treatment regimes for affected patients could be difficult to compose and are usually decided on a case-by-case basis. The general treatment procedure involves a combination of antibiotics such as colistin, aminoglycosides, polymyxins, tigecycline, fosfomycin, and temocillin. However, these antibiotics are extremely potent. As a result, they may have adverse side effects, such as neurotoxicity, that further complicate the physician's job.[15,17] Not surprisingly, CRE infections are associated with high mortality rates. Patients with non-bacteremic infections have a 30 percent mortality rate, and those with bloodstream infections have a 72 percent mortality rate.[17]

OUTBREAK PREVENTION

To prevent outbreaks of CRE, like the one in Bakersfield, California, and to avoid widespread prevalence similar to the healthcare problem posed by MRSA, implementation of prevention strategies are the need. A study in the *Archives of Internal Medicine* shows that 30 percent of antibiotic prescriptions are deemed unnecessary.[18] Therefore, protocol-based antibiotic stewardship programs must be emphasized and enacted as the principal strategy to combat CRE. To support this, a study from

continued on page 46

STUDY: CRE IS ON THE RISE IN COMMUNITY HOSPITALS

CRE has increased fivefold between 2008 and 2012 in community hospitals in the southeastern United States, according to an August 2014 study in *Infection Control and Hospital Epidemiology*.

The study's authors discovered a total of 301 CRE isolates at 16 of the 25 community hospitals studied. Fifty-nine percent of patients had identifiable CRE infections, and 41 percent of patients were asymptomatically colonized. The authors reported that the most prevalent species of CRE were *Klebsiella pneumoniae*, accounting for 91 percent of the cases. Furthermore, 94 percent of the CRE cases were healthcare-associated.

Thirty-four percent of the CRE cases were discovered while patients were in the community hospital and 60 percent of the cases were evident after the patients had returned home. Fifty-six percent of the CRE cases that were diagnosed after patients left the hospital were associated with nursing home facilities.

The authors noted that their findings may actually underestimate the scope of the actual problem. Per the study, "this point underscores the fact that these organisms are increasingly important and relevant in all areas of healthcare, including small community hospitals."

Read more: Thaden JT, Lewis SS, Hazen KC et al. Rising Rates of Carbapenem-Resistant Enterobacteriaceae in Community Hospitals: A Mixed-Methods Review of Epidemiology and Microbiology Practices in a Network of Community Hospitals in the Southeastern United States. *Infection Control and Hospital Epidemiology*, Vol. 35, No. 8 (August 2014), pp. 978-983. DOI: 10.1086/677157.

Study summary by Janiene Bohannon, APIC associate director of Communications.

continued from page 45

Israel achieved a significant reduction in hospital acquired CRE infection in an acute-care facility utilizing protocol-based antibiotic stewardship.[19] These programs have to be administered not only in hospitals but also in medical schools, where it essential that future doctors are taught to appreciate antibiotic stewardship.[20] Secondly, patients who are colonized with CRE should be placed on contact precautions and be attended to by separate staff.[19] Since direct contact is the mode of transmission, hand hygiene is key. Healthcare workers dealing with CRE patients should ensure proper hand sanitization with hand washing and the use of alcohol-based hand rubs.[4] Thirdly, personal protective equipment should be worn at all times when in contact with a CRE patient. This prevents the healthcare worker from contracting CRE through contaminated body fluids, secretions, or excretions. The same rule should apply to the patient's visitors. Another method of prevention is to perform regular environmental cleaning and disinfection of all surfaces in a healthcare facility, especially intensive care unit sinks and hand-washing stations. In addition, all healthcare personnel should be educated about the risks of CRE and strategies to prevent and control CRE. Access the CDC's CRE toolkit for detailed prevention and control measures (cdc.gov/hai/organisms/cre/cre-toolkit/index.html).

Although CRE is still rare, it has the potential to spread globally. With a mortality rate as high as 72 percent in some infections, it is a serious threat to the safety of patients.[17] Further studies should be carried out to test the efficacy of different treatment regimes, and more finances should be directed to the production of new antibiotics and non-traditional antibacterial treatments. This is now a worldwide priority. We have been presented with a formidable challenge to contain CRE—made possible by implementation of protocol-based antibiotic stewardship programs, effective preventive strategies, education on CRE, and further research into antibacterial treatments. PS

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