CE 0.5 Pharmacology and 1.5 ANCC Contact Hours

A Most Dangerous Outbreak

New Delhi Metallo-β-Lactamase-1 Carbapenemase-Producing Enterobacteriaceae

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In 2016, a patient with history of travel to India with multiple hospitalizations in India was admitted to an acute care hospital in Nevada. The patient was diagnosed with Carbapenem-resistant Enterobacteriaceae (CRE) with resistance to all available antimicrobial drugs. The patient died of septic shock likely related to an infected hip seroma. Carbapenem-resistant Enterobacteriaceae–*Klebsiella pneumoniae* was isolated from the wound specimen sent to the Centers for Disease Control (CDC) for determination of the source underlying the antimicrobial resistance. Testing confirmed the presence of New Delhi metallo-β-lactamase-1 (NDM-1). No further cases were identified.[1]

In September 2019, health officials in Tuscany, Italy, reported an outbreak of a "superbug bacterium," identified as NDM-1 Carbapenemase-producing Enterobacteriaceae. Between November 2018 and May 2019, 350 cases were documented, with most identified as gastrointestinal track carriage (n = 242), with the remaining found in bloodstream, urine, and respiratory track.[2,3]

Rising antibiotic resistance in Enterobacteriaceae is a worldwide concern. β-Lactams have been the primary agent used to treat these gram-negative infections, with carbapenems used only as the last resort.[4] Carbapenem-resistant Enterobacteriaceae are bacteria resistant to the broad-spectrum carbapenem class of antibiotics owing to production of carbapenemase enzymes that make carbapenem antimicrobials ineffective. Furthermore, carbapenemase genes can be transferred between different kinds of bacteria, which further spreads antibiotic resistance.[4,5]

Carbapenemases appear to widely differ from one another and include enzymes from class B (metallo-β-lactamases [MBLs]), as well as class A and class D (serine carbapenemases). The most prevalent carbapenemase is the *K. pneumoniae* carbapenemase (KPC)–type class-A carbapenemase, *Klebsiella pneumoniae*, especially in the United States followed by Asia, United Kingdom, Israel, and southern Europe. The NDM-1 is a newer type of MBL named after the city of origin.[4]

The rise of KPC in the United States is in part responsible for the increase in CRE infection in the United States. First reported in 2001 in the South East United States, by 2010, KPC was identified in 36 states. Other carbapenemase subtypes such as NDM-1 have also become part of the Enterobacteriaceae group, and like KPC, these enzymes located on mobile genetic material have incredible potential to spread. B metallo-β-lactamases (MBLs) differ from previous carbapenemases because zinc is used to facilitate carbapenem-hydrolyzing activity. Once usually described with the *Pseudomonas* species, MBL-producing Enterobacteriaceae are becoming more common. The New Delhi MBL (NDM-1) was first identified in 2009 in patients who received medical care in India or Pakistan, with a subsequent rise of infectious cases in the United Kingdom related to intercountry travel.[6]

Another related carbapenem-resistant infection of concern is *K. pneumoniae* (CRKP) infections associated with recent organ transplant, stem cell transplant, long-term mechanical ventilation, antimicrobial exposure, poor functional status, and an extended intensive care unit stay. Compared with patients with carbapenem susceptible *K. pneumoniae*, patients with CRKP infections have narrow treatment options with high mortality and longer length of stay. Age, malignancy, and heart disease are also associated with increased mortality in CRKP infection.[6]

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WHY CONCERN IS DEEPENING ACROSS THE WORLD

Since the 1980s, carbapenems have been used as a last defense for multidrug-resistant gram-negative organisms that produce severe and/or high-risk bacterial infections. Carbapenem-resistant Enterobacteriaceae did not emerge until early 2000. In just 2 decades, CRE has become a dangerous group of healthcare pathogens worldwide and in all 50 states. Carbapenem-resistant Enterobacteriaceae is defined by the CDC as organisms nonsusceptible to imipenem, meropenem, doripenem, or ertapenem or a documented isolate that *possesses a carbapenemase*.[7] Members of the Enterobacteriaceae family that have been found with carbapenemases or β-lactamases that render many β-lactams ineffective are described in Table 1.[8] In addition to antimicrobial resistance, carbapenemase-producing CRE, also identified in the literature as CP-CRE, contain mobile resistance elements that facilitate transmission of resistance to other gram-negative bacilli.[9] Early detection and aggressive infection prevention with control strategies are necessary to prevent further spread of these dangerous microbes.

GEOGRAPHY AND DISEASE

Klebsiella pneumoniae carbapenemase is the dominate carbapenemase in the United States responsible for carbapenem resistance. Carbapenemase production usually confers resistance without additional chromosomal mutations or accessory activities. However, be mindful that carbapenemase genes are carried on mobile genes and can be spread horizontally to naïve bacteria, thus creating further resistance.[10] Consider the expanding fear regarding the potential of widening carbapenem resistance mediated by NDM-1.[11]

The first documented case of infection caused by bacterial producing NDM-1 was in 2008, and it has been reported in 40 countries worldwide. Spread is a complex process by a variety of paths, including interstrain, interspecies, and intergenus transmission of diverse extrachromosomal genetic elements. New Delhi metallo-β-lactamase-1 is now widespread in India, with increasing numbers of reports documenting NDM-1-positive bacteria in persons with epidemiological connections to India, Pakistan, or Bangladesh.

Table 1. Members of the Enterobacteriaceae Family Found With Carbapenemases or β-Lactamases That Render Many β-Lactams Ineffective[7]

Klebsiella pneumoniae
Citrobacter freundii
Escherichia coli
Acinetobacter baumannii
Enterobacter aerogenes

New Delhi metallo-β-lactamase-1 has been identified in Australia, Far East, the United States, Canada, Middle East, and Europe. Increasingly, colonization and infection are believed to be linked to drinking contaminated water with gut colonization.[11]

The Balkans may be an emerging secondary reservoir for NDM-1 with developing strains endemic to Serbia. Medical tourism to Pakistan from Europe and China seeking less expensive organ transplants and other surgeries appears to be driving expansion of cases. Other countries now reporting NDM-1 include Egypt, Iraq, Algeria, China, Libya, and Cameroon. The NDM gene has also been identified in other bacterial strains with known epidemic and pandemic capability.[11]

SO WHAT CAN BE DONE?

In response to rising outbreaks caused by resistant microorganisms related to medical tourism, the Pan American Health Organization/World Health Organization encourages increasing capacity to detect and manage infections. Persons who have traveled outside of country of residence to receive healthcare should be screened and infection control best practices implemented. Needed now are more laboratory personnel with training in the detection of pathogens acquired from international destinations and sharing findings in a timely manner. In this way, outbreaks can be identified early.[12] Second, more surveillance and screening for colonization are required. Third, reliable susceptibility testing, combined with antibiotic stewardship, can make a huge difference in managing and preventing outbreaks. Sadly, these necessary actions are lacking in many parts of the world related to ignorance, poverty, and political unrest.[11] Vigilance is require now as antimicrobial resistance continues to evolve.

As part of national efforts against CRE, the CDC has established the Antibiotic Resistance Laboratory Network at https://www.CDC.gov to provide rapid testing and reporting of carbapenemases that drive resistance to antimicrobials.[13] For further best practices, Table 2 describes the best practices from the CRE Toolkit that should be in place now.[14]

EVIDENCE SUMMARY

Enterobacteriaceae bacteria, including *Klebsiella* species and *Escherichia coli*, are part of normal flora in the human intestine. These bacteria also cause serious infections, such as pneumonia, bloodstream infections, urinary tract infections, wound infections, and meningitis, the most common causes of bacterial infections in hospitals and community settings. Carbapenem antibiotics are frequently used to treat these severe infections.[15]

Resistance to carbapenems can be the function of production of KPC, an enzyme that is produced by some CRE. *Klebsiella pneumoniae* carbapenemase breaks down carbapenems, making them ineffective. In addition to KPC,

Table 2. Best Practices in Response to CRE Infections[14]

1. Patients with history of CRE, colonization, or infection should be placed in contact precautions.
2. Perform hand hygiene before donning gown/gloves.
3. Donning gown/gloves before entering the affected patient's room.
4. Removing the gown/gloves and performing hand hygiene before exiting the affected patient's room.
5. For patients with CRE able to wash their hands, contain stool and secretions, and need little assistance with ADL, use of gowns, gloves should be a function of the care provided. Gown/gloves should be used when there is a potential for healthcare provider exposure during bathing patients, assisting with toileting, changing briefs or dressings, or manipulating patient devices (eg, catheter).
6. Discontinuation of contact precautions is a difficult decision. CRE colonization can persist for more than 6 months. If surveillance cultures are obtained to decide if a patient remains colonized, collect more than 1 culture to improve sensitivity testing. Regardless of what testing is preformed, be mindful of risk factors for ongoing carriage and CRE exposure before discontinuing contact precautions.
7. Minimize device (endotracheal tubes, urinary catheters, etc) use and discontinue as soon as possible.
8. Dedicated antimicrobial stewardship program is necessary. Prescribed antimicrobials should be narrowest spectrum antimicrobial that is appropriate and the shortest effective duration.
9. Daily environmental cleaning is necessary with particular attention to sinks and areas where splashing occurs. Keep medical equipment away from sinks and splash areas.
10. Cohorting patients colonized or infected is recommended, as well as staff cohorting.
11. Active point prevalence and surveillance are required.
12. Surveillance cultures should be obtained for any patient reporting an overnight stay in a hospital outside the United States in the last 6–12 months.
13. For high-risk settings such as the ICU, consider daily chlorhexidine bathing with 2% liquid chlorhexidine or 2% chlorhexidine wipes. Chlorhexidine is usually not used above the jaw line or on open wounds. When chlorhexidine bathing is used in a high risk setting, consider bathing all patients regardless of CRE colonization status.

Abbreviations: ADL, activity of daily living; CRE, Carbapenem-resistant Enterobacteriaceae; ICU, intensive care unit.

other enzymes, such as NDM-1, can also break down carbapenems, leading to the development of CRE.[15]

A working definition of CRE from the CDC is Enterobacteriaceae are resistant to any carbapenem antimicrobial (ie, minimum inhibitory concentrations of ≥4 μg/mL for doripenem, meropenem, or imipenem *or* ≥2 μg/mL for ertapenem) or are documented to produce carbapenemase.[14] Invasive infections caused by CRE are associated with 40% to 50% mortality. Concomitant with β-lactam/carbapenem resistance, CRE often carry genes that confer resistance to many other antimicrobials which will limit therapeutic options. Panresistant CRE has been reported. Carbapenem-resistant Enterobacteriaceae has spread throughout the United States and has significant potential to spread more widely.[14]

Carbapenemase-producing bacteria, especially NDM-1 and its variants, are a serious worldwide health concern. New Delhi metallo-β-lactamase-1 hydrolyzes a wide range of β-lactam antibiotics and carbapenems, the last available resort of antibiotics for the treatment of infections caused by resistant strains of bacteria. There *will be* continuing evolution of resistant markers spreading among the bacteria through horizontal gene transfer, which is a major threat to hospitals trying to control infections. New and novel drug therapies are needed now.[16]

In addition to antimicrobial development and stewardship with infectious control practices, there are other interventions being explored. New Delhi metallo-β-lactamase-1 and KPC are gene's protein products that confer antibiotic resistance; the protein product itself does not cause disease.[17] Probiotics may offer a solution to antimicrobial resistance. Early evidence suggests that coadministration of probiotics with antibiotics may have the ability to overcome resistance in complex infections. The problem is that probiotics are also bacteria and susceptible to the antibiotics that are also being administered. Early research suggests that transforming probiotic bacteria using biofilm encapsulation may confer protection for the probiotic to work in efforts to overcome resistance.[18]

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