EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits click on Earn CE Credits under Continuing Education on the left side of the screen.

LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- describe the different mechanisms of resistance for carbapenem-resistant Enterobacteriaceae.
- explain the different methods of laboratory testing to detect carbapenem-resistant Enterobacteriaceae.
- describe the challenges for selection of appropriate treatment for patients with carbapenem-resistant Enterobacteriaceae infections.
- discuss the recommended guidelines for the control of carbapenem-resistant Enterobacteriaceae in acute-care and long-term care facilities.
- recognize the risk factors for colonization or infection with carbapenem-resistant Enterobacteriaceae.

Introduction

The development of antimicrobial agents in the twentieth century has substantially reduced the threat posed by infectious diseases. Antibiotics have prevented many deaths from previously untreatable diseases. Over the past few decades, antibiotics have saved the lives and eased the suffering of millions. By bringing serious infectious diseases under control, antibiotics have helped change the leading causes of death over the last century and led to a gain in life expectancy.

The benefits conferred by antibiotics are now jeopardized by another recent development: the emergence and spread of organisms that are resistant to these antibiotics. The bacterial infections that contribute most to human disease are those in which emerging microbial resistance is most evident: diarrheal diseases, respiratory tract infections, meningitis, sexually transmitted infections, and hospital-acquired infections. Some significant examples include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Streptococcus pneumoniae*, multidrug-resistant *Mycobacterium tuberculosis*, *Clostridium difficile*, *Neisseria gonorrhoeae*, and multidrug-resistant Enterobacteriaceae. Rates of antimicrobial resistance among hospital and community pathogens have increased considerably during the past decade. Antibiotic resistance is becoming a major public health problem, locally, nationally, and worldwide.
EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)

Enterobacteriaceae

Among these pathogens are the Enterobacteriaceae, a large family of gram-negative rods consisting of more than 70 genera. Normal flora of the intestinal tract, Enterobacteriaceae are one of the most common causes of bacterial infections in both hospital and community settings. Although this family includes more than 100 species, health care-associated Enterobacteriaceae infections most commonly reported to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) surveillance system are Escherichia coli, Klebsiella species, and Enterobacter species.¹

Historically, most Enterobacteriaceae species were susceptible to a wide range of antibiotics, including broad-spectrum cephalosporins and penicillins, monobactam, and carbapenem antibiotics.² In the past several decades, however, there has been an increase and spread of Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs) capable of hydrolyzing almost all cephalosporins except carbapenems.³ In March of 2013, the CDC reported that the development of this resistance to broad-spectrum antimicrobials has led physicians to rely on the carbapenem antimicrobial class (imipenem, meropenem, doripenem, and ertapenem) to treat infections caused by resistant organisms possessing ESBLs.⁴

Similar to how the widespread overuse of broad-spectrum cephalosporins led to the emergence of ESBL-producing Enterobacteriaceae, the recent carbapenem overuse has selected for the emergence of carbapenem-resistant Enterobacteriaceae (CRE). Carbapenems are broad-spectrum antibacterial drugs, particularly imipenem, doripenem, and meropenem. Members of the class of β-lactam antibiotics, carbapenems possess a β-lactam ring and share the same mechanism of action, but they are structurally different from penicillins and cephalosporins. Carbapenems should be reserved as a treatment of last resort for drug-resistant infections, including nosocomial infections in patients who have received many classes of antibiotics during their hospital stay.⁵ Antimicrobial stewardship of these agents is necessary, owing to the limited development of new antimicrobials to treat these multidrug-resistant infections.⁶

Resistance

Carbapenem resistance among Enterobacteriaceae was first considered to be caused by overproduction of Amp C-mediated β-lactamases or ESBLs in organisms with porin mutations. Carbapenemases, enzymes produced by the bacteria that are able to hydrolyze nearly all β-lactam antibiotics, are another mechanism of carbapenem resistance among CRE in the United States.⁴ Most carbapenemases are plasmid mediated and have been mainly reported in Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii.⁸ The Ambler molecular classification scheme divides β-lactamases into 4 classes, A-D, with carbapenemases found in classes A, B, and D.⁷ The most common carbapenemase
produced by Enterobacteriaceae in the United States is *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler molecular class A enzyme that utilizes serine at the active site to facilitate hydrolysis of a broad variety of β-lactams. The KPC enzyme is not unique to *K pneumoniae*, but is also found in other Enterobacteriaceae species. KPC-producing Enterobacteriaceae were first reported in North Carolina in 2001 but have spread throughout North America and, more recently, worldwide.

In addition to KPC, other carbapenemases have emerged among the Enterobacteriaceae, including the class B metallo-β-lactamases (MBLs) and the class D oxacillinase-48 enzymes (OXA-48). The MBLs include VIMs (Verona integrin-encoded MBLs), IMP (active on imipenem), and NDM (New Delhi MBL). NDM has spread from the Indian subcontinent to Europe, the Middle East, and Asia. VIM, IMP, and OXA-48 are currently less common than KPC and NDM. VIM and IMP have been reported worldwide, with a higher prevalence in southern Europe and Asia. OXA-48 has been identified mostly in the Mediterranean and European countries and in India. With the exception of KPC, CRE in the United States are primarily associated with patients who have traveled to other countries.

**Detection**

Detection of infected patients and carriers is necessary to prevent the spread of these organisms. Accurately identifying CRE in the clinical laboratory is an important first step. Cases of CRE are recognized either by clinical cultures from an infected patient or via surveillance screening cultures from a colonized patient. Colonization is commonly detected through rectal and perianal surveillance cultures of patients at risk. The CDC has primarily obtained surveillance cultures for Enterobacteriaceae from the perirectal area and wounds during outbreak investigations. A laboratory protocol for processing of these swabs is available on the CDC’s website at [http://www.cdc.gov/hai/pdfs/labsettings/klebsiella_or_ecoli.pdf](http://www.cdc.gov/hai/pdfs/labsettings/klebsiella_or_ecoli.pdf).

Within the clinical laboratory, there are currently automated and manual methods for detecting CRE, including culture-based and molecular methods. Detection of these organisms is challenging, owing to the wide diversity in resistance levels to carbapenems, which vary depending on the enzyme and the organism. This makes it difficult to set up uniform screening and confirmatory tests for detection of carbapenemase producers.

Traditionally, detection of CRE organisms has relied on antimicrobial susceptibility testing with synergistic methods such as the modified Hodge test (MHT). Historically, manual and automated susceptibility-testing methods were insensitive because many of the resistant organisms had relatively low levels of resistance and the minimum inhibitory concentration (MIC) values were elevated compared with fully susceptible organisms (but still within the susceptibility category). In recent years, both the Clinical
EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)

Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) have modified the interpretive breakpoints to classify ESBL and CRE strains more accurately, although this modification has not been fully integrated in all commercial susceptibility test systems or clinical microbiology laboratories. Published in the CLSI M100 document, the new breakpoints were established in 2010 and updated in 2012 to more accurately predict carbapenem treatment outcomes without the need for a special test to detect carbapenemase production. Until laboratories and commercial systems can implement the current CLSI interpretive criteria, the MHT should be performed to confirm suspected carbapenemase-producing isolates. After implementation of the current interpretive criteria, the MHT does not need to be performed other than for epidemiologic or infection control purposes.

If performing screening cultures, several commercial chromogenic agars are available for carbapenemase production of CRE. There is no universal screening medium able to detect all types of carbapenemase producers with high sensitivity and specificity. These phenotypic detection tests recover high-level resistant CRE harboring KPC, IMP, VIM, and NDM-1. However, OXA-48 producers are difficult to detect via chromogenic agar, owing to wide variations in carbapenem MICs. None of these culture media detect those OXA-48 producers that hydrolyze penicillins and carbapenems, but not extended-spectrum cephalosporins. In addition, a suspected carbapenemase producer isolated via chromogenic agar must be confirmed by either antimicrobial susceptibility testing or molecular techniques, so definitive results may not be available for 2 to 4 days. Despite limitations, chromogenic screening media have performed well and shown good sensitivity when guided by an internal validation study.

The most reliable method for detecting carbapenemase production, including organisms with low-level resistance, is with DNA-based multiplex assays. Advantages of these assays include detection of ESBL production in addition to carbapenemase, detection of all phenotypes including those missed by culture-based tests, and the ability to incorporate new resistance genes and targets to give a comprehensive picture of multidrug-resistant gram-negative bacilli. Currently available molecular methods for detection of ESBLs and carbapenemases are broadly based on DNA amplification followed by amplicon detection, either on a tube microarray or by an enzyme-linked immunosorbent assay. They have primarily been used with isolated organisms to confirm carbapenem resistance and have been used successfully to screen rectal swabs from ICU patients in Europe.

Treatment

Treatment for CRE infections is limited and can be difficult. Treatment of patients with carbapenemase-producing bacteria should be facilitated by an expert in antimicrobial resistance and multidrug-resistant
bacteria, such as an infectious disease physician. Because CRE can be broadly resistant to many antibiotics of different classes, susceptibility testing should be performed. Most carbapenemase producers are almost completely resistant to β-lactam antibiotics; those with OXA-48 alone remain susceptible to several oxyimino-cephalosporins. CRE with MBLs that lack AmpC or ESBLs also remain susceptible to aztreonam. Aminoglycoside resistance is more variable but can be extensive. Strains with NDM enzyme have broad resistance to aminoglycosides, whereas other strains have different arrays of aminoglycoside-modifying enzymes and show variable resistance. Because the presence of KPC or MBL confers resistance to most if not all penicillins, cephalosporins, and carbapenems, the selection of antibiotic therapy should be tailored to the antimicrobial susceptibility results from the clinical microbiology laboratory. The laboratory should perform additional susceptibility testing outside the β-lactam and carbapenem classes to include colistin or polymyxin B, aztreonam, tigecycline, and fosfomycin (particularly for urine isolates).

Prevention

Carbapenemases have been increasingly reported in the past 10 years. KPCs have become endemic in the United States and Greece and the spread of other carbapenemases is worrisome. Although the CDC does not yet perform systematic surveillance for these organisms, as of February 2014 carbapenem-resistant Enterobacteriaceae isolates have been received or identified from 47 states in addition to the District of Columbia and Puerto Rico. Citing increased reports of CRE, the CDC has expanded guidelines aimed at preventing the spread of these difficult-to-treat, multidrug-resistant organisms. The guidelines were made available through a CDC Health Advisory published on February 14, 2013.

The guidelines recommend 8 core measures to control CRE in acute-care and long-term care facilities. They are:

1. Hand hygiene using alcohol-based hand rubs or soap and water before and after contact with a patient;
2. Contact precautions for patients identified as colonized or infected with CRE or patients at increased risk;
3. Education of healthcare personnel about CRE, methods of transmission, and proper use of hand hygiene and contact precautions;
4. Use of devices such as central venous catheters, endotracheal tubes, and urinary catheters should be minimized, or when required, used appropriately;
EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)

(5) patients should be in private rooms, or cohorted with other colonized patients, and staff should be restricted to care of CRE-infected patients if possible;

(6) prompt laboratory notification of positive lab results for CRE to both the patient-care area and infection prevention personnel;

(7) antimicrobial stewardship, including structured guidance for the responsible selection and use of antimicrobial agents; and

(8) CRE screening, including the use of appropriate standardized susceptibility test methods to recognize CRE and the establishment of a screening program to detect colonization in asymptomatic patients.\(^{16}\)

Once a patient with a positive CRE culture has been identified, he or she must be placed in contact isolation precautions within a private room. As mentioned above, some experts have also recommended patient cohorting and use of dedicated staff for these patients.\(^{16}\) If the patient is using a temporary medical device, it is recommended that it be removed as soon as it is no longer needed, because such devices can become colonized with the resistant organism. In addition to this guidance, in 2014 the CDC released new recommendations for patients who have a history of hospitalization outside the United States within the previous six months. First, any time a CRE is identified from a patient, the isolate should be sent to a reference laboratory for confirmatory susceptibility testing and testing to determine the carbapenem-resistance mechanism. Second, facilities should consider performing rectal screening cultures to detect CRE colonization in these patients and placing them under contact precautions while awaiting the results.\(^{15}\)

**Limiting Risk**

Antimicrobial stewardship to ensure appropriate antibiotic use is critical to slowing CRE spread and emergence. Antimicrobial consumption is a specific risk factor for CRE isolation.\(^{17}\) Multiple antimicrobial classes have been identified as possible risk factors for infection or colonization with CRE. Use of broad-spectrum cephalosporins or carbapenems is an important risk factor for colonization or infection.\(^{13,17,18}\) Other predictors for isolation of CRE have been reported in the literature and include advanced age, reduced functional status, residency in a long-term care facility, and invasive procedures.\(^{19}\)

Patients who are infected or colonized with CRE are often cared for in multiple types of health-care institutions throughout their illness. The role of long-term, acute-care facilities (LTACs) with respect to multidrug-resistant, gram-negative organisms has been noted in several studies. One study found that colonization rates with multidrug-resistant, gram-negative organisms were significantly higher among patients admitted from LTACs than among other hospitalized patients.\(^{20}\) Another multicenter study found
EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)

that more than 30% of patients with recent exposure to LTACs were colonized or infected with CRE. In addition, the CDC reported in 2013 that 4.6% of acute-care hospitals performing surveillance for either central-line–associated bloodstream infections (CLABSI) or catheter-associated urinary tract infections (CAUTI) reported 1 or more infections with CRE.

Although much of the effort toward CRE control has been focused on acute-care facilities, nonacute settings also provide care for patients who are infected or colonized. It is important to not limit prevention efforts to acute-care settings and to broaden the approach to prevention across different health-care arenas. A number of states have added, or are considering adding, CRE to their reportable conditions list. Authors in previous studies stressed the importance of coordinated local, regional, and national approaches among acute-care and long-term health care facilities and outpatient clinics to prevent the transmission and emergence of multidrug-resistant Enterobacteriaceae.

Summary

The rise of CRE is important for several reasons. First, invasive infections with CRE are associated with mortality rates exceeding 40%, which is significantly higher than mortality rates for carbapenem-susceptible Enterobacteriaceae. Second, carbapenem-resistant organisms often possess additional resistance mechanisms that make them resistant to most available antibiotics, and the development of new antibiotics is progressing slowly. Third, Enterobacteriaceae are a common cause of community-acquired infections, and CREs have the potential to move from health-care associated infections to community-acquired infections. Fourth, CRE can spread rapidly in health-care settings as documented by recent outbreaks.

The widespread distribution of multidrug-resistant Enterobacteriaceae is a challenge for all patient care providers, including physicians, laboratorians, and public health professionals. Physicians have a limited selection of antibiotics to treat CRE infections, and laboratorians are limited in the diagnostic tools currently available. The combination of screening of high-risk patients, use of infection control practices, and antimicrobial stewardship is critical for preventing the spread of these organisms.

References

EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)


EDUCATIONAL COMMENTARY – THE RISE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (cont.)


© ASCP 2014