CRE Infections: A Public Health Issue - Parts 1 & 2

Carbapenem Resistant Enterobacteriaceae (CRE) infections are becoming more common and are a tremendous burden to patients and the healthcare system. The social, economic and personal costs related to them are overwhelming. Many researchers have demonstrated various interventions that decrease infection rates. A multi-faceted approach that includes staff education, minimizing patient risk factors and easy to understand institutional guidelines are needed to prevent these infections. This is an active area of research with advancements to patient care published frequently. In Part 1, we review the definition of CRE infections, the risk factors associated with acquiring CRE infections, identification of CRE infections, and general treatment. In Part 2, we review specific therapies, and we relate how CRE infections can be prevented.

Learning Objectives

**Pharmacist**
1. Define CRE infections
2. List the risk factors associated with acquiring CRE infections
3. Discuss the methods of identifying CRE infections
4. Relate general treatment of CRE infections
5. Discuss specific therapies for treating CRE infections
6. List methods for preventing CRE infections

**Pharmacy Technician**
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**Nurse**
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4. Relate general treatment of CRE infections
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Target Audience
Pharmacists, Pharmacy Technicians, Nurses

Universal Activity Number

<table>
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<tr>
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<th>Pharmacy Technician</th>
<th>Nurse</th>
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<td>0798-0000-19-024-H01-T</td>
<td>0798-0000-19-024-H01-N</td>
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Credit Hours
125 Hour

Activity Type
Knowledge-Based

CE Broker Tracking Number
20-646887

Activity Release Date
February 19, 2019

Activity Offline Date
August 19, 2021

ACPE Expiration Date
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INTRODUCTION

Over the past several years we have addressed a number of challenging infectious diseases. One of these was Carbapenem Resistant Enterobacteriaceae (CRE), and it is a good time to review this specific bacterial infection because these have been occurring in hospitals more frequently over the past several years. Additionally, community pharmacy is often involved with counseling of patients and caregivers.

By using a sample case we will discuss:

1. WHAT IS CRE?
2. WHAT ARE THE RISK FACTORS FOR ACQUISITION OF CRE INFECTIONS?
3. HOW ARE CRE INFECTIONS IDENTIFIED?
4. HOW ARE CRE INFECTIONS TREATED?
5. HOW ARE CRE INFECTIONS PREVENTED?

In this Part 1, we review the definition of CRE infections, the risk factors associated with acquiring CRE infections, identification of CRE infections, and general treatment.

In the Part 2, we review the specific therapies, and we relate how CRE infections can be prevented.

The past several years brought formidable challenges to clinicians in the area of drug resistant bacteria and preventable infectious diseases. The World Health Organization (WHO) recognizes antimicrobial drug resistance as a major public health risk, endangering decades of medical advances. (1) The overuse of antimicrobials in clinical medicine and animal husbandry over several decades has led to the rise in microorganisms that are resistant to common medicines. There are two primary factors that promote the rise of resistant microorganisms: overuse of antimicrobials, and the spread of resistant organisms between individuals, communities and countries.

The focus of this lesson will be on Carbapenem-resistant Enterobacteriaceae (CRE) because it is an emerging public health issue in the United States and worldwide. This challenge requires concerted efforts from pharmacists, microbiologists, infection control practitioners and infectious disease clinicians. Via a patient-related scenario, we will relate this important area of contemporary pharmacy practice.

HERE IS THE CASE SCENARIO:

A 70-year-old woman with diabetes and recent cardiac bypass surgery with decreased mobility due to deconditioning is admitted from a long-term acute care hospital to your hospital overnight. She presents with new confusion, dysuria, fever and tachycardia. White Blood cell count is elevated to 25,000 cell/mm³. Chest X-ray is normal. Blood and urine cultures are sent. Patient reports flank pain.

Urinalysis:

Leukocyte esterase: 3+
WBC – too numerous to count
Bacteria – 3+
Squamous epithelial cells: none

The patient was diagnosed with a complicated urinary tract infection and was started on ceftriaxone 1g IV daily. The next day the urine culture is reported as positive for 100,000 colony-forming units/ml of lactose fermenting gram-negative bacilli. Twelve hours later, the organism is identified as K.pneumoniae.
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<td>Resistant</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>Resistant</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2</td>
<td>Resistant</td>
</tr>
<tr>
<td>Imipenem</td>
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<td>Intermediate</td>
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<td>0.5</td>
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<tr>
<td>Tigecycline</td>
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The lab calls you concerned about Carbapenem-resistant Enterobacteriaceae (CRE). They will be performing additional molecular testing to confirm the production of a carbapenemase. The therapy was changed to colistin and tigecycline. The patient is placed in an isolation room.

What is a CRE infection?

Carbapenem-resistant Enterobacteriaceae (CRE) is a family of bacteria that produce an enzyme that inactivates carbapenems and other beta-lactams. The Enterobacteriaceae family includes a large group of gram-negative bacteria that normally inhabit the gastrointestinal tract in both humans and animals. (See Table 1) CRE is most commonly isolated from *E. coli* or *Klebsiella* species. The CDC currently defines CRE as an Enterobacteriaceae spp that is resistant to imipenem, meropenem, doripenem or ertapenem or documentation that the isolate possesses a carbapenemase. There are multiple types of carbapenemases known as, KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi Metallo-beta-lactamase), IMP (Imipenemases), VIM (Verona Integron-Mediated Metallo-beta-lactamase), and OXA-48.

Infections caused by CRE are dangerous and represent a serious threat to hospitalized patients. CRE infections are often difficult to treat, spread quickly within an institution, and are associated with high mortality rates. Enterobacteriaceae species are a common cause of community-acquired urinary tract infections. These organisms can also cause a range of healthcare-associated infections including urinary and bloodstream infections in patients with indwelling catheters, pneumonia in patients who are mechanically ventilated, and rarely skin and soft tissue and central nervous system infections. Healthcare associated Enterobacteriaceae infections (*E. coli*, *Klebsiella* and *Enterobacter* species) are reported to the Center for Disease Control National Healthcare Safety Network (NHSN) surveillance system.

Antimicrobial resistance within the Enterobacteriaceae family has increased over the last several decades, leading to increased reliance on the antimicrobial class of carbapenems (imipenem, meropenem, doripenem and ertapenem). Carbapenem-resistant Enterobacteriaceae infections were uncommon in the United States before the year 2000.

The mechanism of resistance is quite complex and can be mediated by several mechanisms. *Klebsiella pneumoniae* carbapenemase (KPC), an enzyme encoded by a highly transmissible gene, was first identified in the year 2000. KPCs are endemic in the United States, Greece, Israel, Italy, Puerto Rico, China and South
America. KPC is the most common carbapenemase found in the United States. (2) It utilizes serine at the active site to hydrolyze beta-lactams. In addition to KPC, additional carbapenemases have emerged outside of the United States, namely New Delhi metallo-beta-lactamase (NDM-1). NDM-1 differs from KPC because it utilizes zinc at the active site to facilitate hydrolysis of beta-lactams. This key difference renders KPCs easier treat with beta-lactamase inhibitors. (25) Both KPC and NDM-1 have been identified in the United States and can easily spread in healthcare settings. The spread of NDM-1 into the United States has begun with cases of travel or hospitalizations in India.(3) In 2013, the CDC published a report stating that 3.9% of short-stay acute-care hospitalizations and 17.8% of long-term acute-care hospitalizations indicated at least one CRE health-care associated infection in 2012.(4) CRE has been isolated in 42 states and the proportion of Enterobacteriaceae that are CRE has increased fourfold over the past 10 years. In 2013, an outbreak of NDM-1 E. coli was identified at a tertiary care hospital associated with contaminated duodenoscopes. The complicated design of the duodenoscopes make cleaning difficult, thus they remain contaminated. Forty-four patients were found to have CRE from the duodenoscopes.

The hospital changed the endoscope reprocessing from an automated high-level disinfection to gas sterilization, which halted the outbreak.(15)

Risk Factors

The risk factors for acquisition of CRE infections include: exposure to health care in general and exposure to antimicrobials. When patients with CRE infections were compared to non-CRE (i.e. patients with Carbapenem-susceptible infections), CRE infections were independently associated with recent organ or stem-cell transplant, recent mechanical ventilation, exposure to antimicrobials and longer length of stay. Long-term acute-care hospitals (LTACHs) are considered to be a reservoir for CRE. A surveillance study of Chicago area LTACHs indicated 30% of the patients were colonized with KPC-producing Enterobacteriaceae compared to 3% of short-stay hospital patients.(16) Increased carbapenem use and differences between infection control practices between healthcare settings and travel patterns have led to a dramatic increase in CRE.

The risk factor for CRE acquisition in the patient in this case is likely due to residing in a long-term acute care hospital.

How are CRE infections identified?

The Center for Disease Control and Prevention (CDC) defines CRE as an Enterobacteriaceae species that are non-susceptible to 1 of the following carbapenems: (doripenem, imipenem or meropenem, or ertapenem) OR documentation that the isolate possesses a carbapenemase. Detection of the carbapenemases can be difficult because some isolates have MICs (minimum inhibitory concentration) that fall just below the breakpoint for susceptibility.(2) It is important to distinguish the difference between an organism that produces a carbapenemases (enzymes that breaks down all carbapenems) and an organism that offers other combinations of resistance mechanisms (i.e. other beta-lactamases combined with porin mutations) that render carbapenemases resistant. Some Enterobacteriaceae (Proteus spp, Morganella spp, Providencia spp) have intrinsic resistance to imipenem as evidenced by elevated MICs. In order to determine if they are carbapenemase producing CRE, these species must also have resistance to meropenem, doripenem or ertapenem.(2)

In 2010, the Clinical and Laboratory Standards Institute (CLSI) updated the breakpoints for Enterobacteriaceae. The new breakpoints are lower than the original breakpoints, allowing for easier identification of Enterobacteriaceae that are intermediate or resistant to carbapenemases. Since most carbapenemases in the United States are found among Klebsiella and E. coli, some laboratories might choose to apply the CRE definition only to these specific Enterobacteriaceae.

(2) Laboratories may conduct additional phenotypic or genotypic testing for carbapenemases.

(17) Several commercial tests are available for rapid detection of carbapenem-resistance producing Enterobacteriaceae. The tests include either molecular tests that detect the resistance mechanism (i.e. presence of the gene (OXA, NDM, KPC and VIM)) or phenotypic tests that detect in vitro activity of carbapenemase enzymes.
In addition to the MIC tests, the acceptable tests for detecting carbapenemases include: polymerase chain reaction, modified-Hodge test, Carba NP, or metallo-beta-lactamase testing. (See Table 3) Additionally, carbapenemase testing may be performed for infection control purposes, and isolates may be sent through the state public health laboratories or to the CDC for further characterization.

*In the case, the isolate meets the criteria for CRE because of the meropenem and ertapenem resistance. The microbiology department will conduct additional molecular tests to confirm the presence of a carbapenemase and send the isolate to the public health authorities.*

**Table 1: Common Genera of Enterobacteriaceae**

<table>
<thead>
<tr>
<th>Genus</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia</td>
<td>Klebsiella</td>
<td>Providencia</td>
<td>Serratia</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>Proteus</td>
<td>Salmonella</td>
<td>Shigella</td>
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</tbody>
</table>


**Table 2: Interpretive Criteria for Carbapenems and Enterobacteriaceae**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Previous Breakpoints (mcg/ml)</th>
<th>Current Breakpoints (mcg/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Doripenem</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&lt;2</td>
<td>4</td>
</tr>
<tr>
<td>Mipenem</td>
<td>&lt;4</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&lt;4</td>
<td>8</td>
</tr>
</tbody>
</table>

Adapted from References: 2 and 6.

**Table 3: Laboratory tests for the detection of CRE**

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carba NP</td>
<td>Color indicator of imipenem hydrolysis</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Film Array®</td>
<td>Detects presence of KPC gene</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Verigene Gram-negative</td>
<td>Detects presence of KPC, IMP, VIM, NDM and OXA-48</td>
<td>FDA approved</td>
</tr>
<tr>
<td>GeneXpert</td>
<td>Detects presence of KPC, IMP, VIM, NDM and OXA-48 from rectal swabs</td>
<td>FDA approved</td>
</tr>
</tbody>
</table>

**How are CRE infections treated?**

The antibiotic options are limited for CRE infections because the presence of carbapenemases renders resistance to all penicillins, cephalosporins and carbapenems. Beta-lactamase inhibitors such as tazobactam (formulated with piperacillin), sulbactam (formulated with ampicillin) and clavulanate (formulated with ticarcillin) are not stable against the carbapenemases, therefore, cannot be used for treatment. See Table 4. (3,5) The newer beta-lactamase inhibitors, avibactam, relebactam and vaborbactam, will inhibit KPC enzymes but not metallo-beta-lactamases, VIM, IMP and NDM-1. Unfortunately, the gene encoding for carbapenemases are usually found on plasmids or other mobile genetic elements. These genetic elements allow for the organism to acquire genes conferring resistance to other classes of antibiotics, thus most isolates are also resistant to non-penicillin.
antibiotics including: trimethoprim-sulfamethoxazole, fluoroquinolones and aminoglycosides. Additional susceptibilities should be requested from the microbiology lab for polymixins, aztreonam, tigecycline, and fosfomycin (urinary tract infections.) Selection of antimicrobial therapy should be tailored to susceptibility results.(3) Due to complexity of treating these infections, consultation with an infectious disease clinician is highly recommended.

Table 4: Stability of various beta-lactam and beta-lactamase inhibitors against beta-lactamases in gram-negative organisms.

<table>
<thead>
<tr>
<th>Enterobacteriaceae beta-lactamases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/Compounds</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Inhibitors: Clavulanate</td>
</tr>
<tr>
<td>Sulbactam</td>
</tr>
<tr>
<td>Tazobactam</td>
</tr>
<tr>
<td>Avibactam</td>
</tr>
<tr>
<td>Vaborbactam</td>
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<tr>
<td>Relebactam</td>
</tr>
<tr>
<td>Drugs: Imipenem/Meropenem</td>
</tr>
<tr>
<td>Aztreonam</td>
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AmpC: cephalosporinases encodes on chromosomes of many Enterobacteriaceae; ESBL: extended spectrum beta-lactamases; KPC: Klebsiella pneumoniae carbapenemase; OXA: oxacillinases which hydrolyze a variety of beta-lactams; IMP/VIM/NDM: Imipenem, Verona-integron Metallo-beta-lactamase and New-Delhi Metallo-beta-lactamase. Adapted from Reference 25.

In the next lesson we discuss the specific therapeutic options and also prevention of CRE infections.

Additional information:

http://www.cdc.gov/hai/organisms/cre/

The case discussed represents a typical presentation and course of a patient with a complicated urinary tract infection. Treatment and management of the patient is based on available clinical data at the time of this lesson and the personal opinion of the author.

REFERENCES


INTRODUCTION


In this lesson we describe:

1. Specific treatment options, and
2. Prevention of CRE infections.

The discussions in the previous lesson, and in this lesson, are referenced to the following case & patient information:

HERE IS THE CASE SCENARIO AGAIN:

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**Polymyxins**

Polymyxin E (also known as colistimethate sodium or colistin) and polymyxin B are cyclic peptides. The polymyxins are polycationic and have both hydrophilic and lipophilic moieties. Their mechanism is not fully understood, but they interact electrostatically with the outer membrane of gram-negative bacteria and displaced divalent cations, thus disrupting the permeability of the membrane. Ultimately, this leads to cell lysis and death. Polymyxin E and polymyxin B only differ by one amino acid. They target gram-negative aerobic organisms, namely Enterobacteriaceae spp, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. (5) The polymyxins were introduced in the 1950s, but their use diminished due to excessive toxicities including nephrotoxicity and neurotoxicity. (7) Resistance is rare but can emerge upon exposure to suboptimal polymyxin concentration. (25)

The pharmacokinetics of the polymyxins is an area of intense investigation. Since polymyxins were introduced, modern pharmacokinetic studies are lacking. Colistin is available in two dosage forms, colistin sulfate (topical use) and colistimethate sodium (intravenous use). Colistimethate sodium is a prodrug that hydrolyzes to colistin, the component with antimicrobial activity. Colistimethate has little antibacterial activity on its own. To add to the confusion, there are two formulations of the parenteral product colistimethate sodium. In the United States, the product is supplied in vials containing 150 mg of colistin base; whereas, the product in Europe is provided in vials of 1-2 million international units of colistin. (7) The optimal dosing of colistin remains unclear, but one study suggests a loading dose of 9 MU followed by 4.5 MU every 12 hours. A dose reduction is required in patients with renal dysfunction. Colistimethate undergoes renal clearance and has short elimination half-life (2-3 hours). In contrast, colistin, the microbiologic active drug, has a longer half-life (9-13 hours) and is excreted in the urine. (5) The pharmacokinetics of polymyxin B is less studied, but is not a pro-drug like colistin, nor is it renally eliminated. The toxicities related to the polymyxins include nephrotoxicity and neurotoxicity. The mechanism of nephrotoxicity is unknown, but the incidence ranges from 14% to 53%. Risks factors for nephrotoxicity include longer duration of therapy, concomitant nephrotoxin, and higher total daily dose. Luckily, the renal toxicity is usually reversible after the drug is stopped. (5, 25) The polymyxins can be given via the inhalation route for ventilator-associated pneumonia and cystic fibrosis patients along with systemic antibiotics. Multi-drug resistant organism (MDRO) polymyxins can be used for infections caused by any of the carbapenemases (KPC, NDM, OXA, VIM, or IMP).

**Tigecycline**

Tigecycline is a glycyclcline antibiotic that is bacteriostatic and exerts its mechanism by binding to the 30S ribosomal unit, thus inhibiting protein synthesis. (5) Tigecycline was approved by the FDA in 2005 for complicated skin and soft tissue infections, complicated intra-
abdominal infections, and later for community-acquired pneumonia. (8) It is available as a parenteral formulation only. It has a large volume of distribution with good tissue penetration, but the plasma concentrations remain low. The primary route of elimination occurs through the feces via biliary excretion with only 15% excreted in the urine. Due to the low plasma and urine concentrations, tigecycline is not appropriate for bloodstream infections or urinary tract infections, respectively. The Clinical Laboratory Standards Institute (CLSI) does not have published breakpoints for Enterobacteriaceae and tigecycline, but the FDA has a breakpoint of 2 mcg/ml.

The FDA breakpoint has been criticized as being too high, thus suggesting higher susceptibility than the achievable pharmacokinetics of the drug. The European Committee on Antimicrobial Susceptibility Testing has suggested lower breakpoints of 1 mcg/ml for Enterobacteriaceae. (9) The elimination half-life is long, approximately 42 hours. Renal or mild hepatic impairment does not affect clearance; therefore, dosing adjustments are not recommended. In patients with severe liver dysfunction (Child-Pugh Score C), a 50% dose reduction is recommended. (10) The most common toxicity is nausea, and rarely pancreatitis and alkaline phosphatase elevations. In 2010, the FDA issued a warning about increased risk of death with the use of tigecycline, based on data from a meta-analysis. (11) Although the cause of excess death in these trials is unknown, the FDA suggests that it is related to progression of the infections.

Tigecycline was evaluated in combination with other antimicrobials for bloodstream infections caused by KPCs (Klebsiella Pneumoniae Carbapenemases). The overall mortality was 41%, but a higher mortality was associated with patients treated with monotherapy compared to those who received combination therapy. The combination of tigecycline, colistin and meropenem was also associated with a lower mortality. (24)

Fosfomycin

Fosfomycin is a phosphonic acid derivative that is bactericidal against both gram-positive and gram-negative microorganisms. (5,21,25) Fosfomycin inhibits the bacterial enzyme, pyruvul transferase, leading to inhibition of bacterial cell wall synthesis. In the United States, fosfomycin is available as a 3g oral powder sachet; whereas, in Europe, both intravenous and oral formulations are available. The oral formulation has limited oral bioavailability. Fosfomycin is primarily excreted unchanged in the urine and persists in the urine for up to 72 hours, thus making it an ideal agent for cystitis. The half-life is prolonged in patients with renal failure, but the optimal dose in this patient population is unknown. A few case reports have indicated that oral fosfomycin can be effective for patients with cystitis caused by KPC and NDM organisms that have in-vitro susceptibility to fosfomycin. Limited clinical data is available for the treatment of CRE cystitis with oral fosfomycin; therefore, should be used with caution. (25)

Aminoglycosides

The aminoglycosides (gentamicin, tobramycin and amikacin) are an option for CRE, if the organism is susceptible. (5) Aminoglycosides inhibit protein synthesis by binding to the 30S
subunit of the ribosome. The pharmacokinetic properties are similar among the aminoglycosides. They distribute well into bone, peritoneal fluid, and urine, but there is limited penetration into the lungs and the central nervous system. The elimination half-life is dependent on age and renal function; therefore, close monitoring of serum concentrations is recommended. The excretion of aminoglycosides is primarily in the urine, making aminoglycosides an ideal agent for urinary tract infections. Similar to colistin, nephrotoxicity is one of the major adverse effects. Often the nephrotoxicity is associated with drug accumulation in the proximal renal tubular cells but is often reversible once the drug is stopped. Ototoxicity is an unfortunate irreversible toxicity that can manifest as vestibular or cochlear damage (3,5) Aminoglycosides are generally used in combination with another antimicrobial.(5)

**Ceftazidime-avibactam**

Ceftazidime-avibactam is a beta-lactam/beta-lactamase inhibitor that was approved by the FDA in 2016. This antibiotic demonstrates in vitro activity against carbapenem resistant Enterobacteriaceae that produce KPC, but not metallo-beta-lactamases (NDM, OXA, VIM and IMP).(18) Ceftazidime-avibactam was evaluated retrospectively in a single-center study for CRE infections. Thirty-seven patients with CRE infections (mainly pneumonia and bacteremia) were treated with ceftazidime-avibactam. Twenty-two patients had clinical success. The overall survival was 76%. The CRE infection recurred in one-fourth of the patients. Almost one-third of the patients had microbiologic failure, defined as isolation of CRE greater than 6 days of ceftazidime-avibactam treatment. Based on the limited data, ceftazidime-avibactam should not be used for CRE infections until more definitive data is available.(22)

**Meropenem-vaborbactam**

Meropenem-vaborbactam is another beta-lactam/beta-lactamase inhibitor that was recently approved by the FDA in 2017. This beta-lactamase inhibitor was designed to inhibit serine carbapenemases (especially KPCs). In vitro data suggest that this new agent to be highly active against KPC Enterobacteriaceae, but clinical data is limited. Meropenem-vaborbactam was compared to best-available therapy in a non-randomized study evaluating treatment of complicated UTI, acute pyelonephritis, hospital-acquired pneumonia, ventilator-associated bacterial pneumonia, bacteremia or complicated intraabdominal infection due to CRE.(19,20) Best-availabletherapies included carbapenem(eitheraloneorincombination), aminoglycoside, polymyxin B, colistin, tigecycline or ceftazidime-avibactam (used as monotherapy.) Only patients with CRE defined by culture or molecular testing were included. Patients infected with Enterobacteriaceae with NDM-1, VIM, OXA beta-lactamases were excluded. Clinical cure at the end of treatment was 64% (18/28) in the meropenem-vaborbactam group and 33.3% (5/15) in the best available therapy group. The mortality at 28 days was 18% in the meropenem-vaborbactam group compared to 33.3% in the best available treatment group. Meropenem-vaborbactam seems like a promising option for CRE infections.(23)
Combination therapy

There are some retrospective and observational reports that indicate higher survival rates in patients with CRE infections that are treated with combination therapy rather than monotherapy. (3,12) In a retrospective study of 41 cases of bacteremia due to KPCs, investigators found that survival improved with combination therapy rather than monotherapy. Successful combinations included colistin/polymyxin or tigecycline in combination with a carbapenem. (12) This data is consistent with a cohort study in bacteremic patients recently published from Greece, where higher failure rates were seen with monotherapy. (13) The mechanism that colistin and the carbapenem are synergistic is unknown, but this correlates to the in-vitro observation of the combination. In addition, there are in-vitro studies suggesting the use of combination carbapenem therapy with ertapenem and doripenem. The theory is that ertapenem has a higher affinity for the carbapenemase so it will bind up the enzyme allowing for higher concentrations of doripenem in the vicinity of the organism. (14) The role of dual carbapenem combination therapy in clinical practice is unknown at this time.

The optimal duration of therapy is also unknown for CRE infections, but experts suggest using the typical durations for the specified syndrome. For example, seven to 14 days of therapy for complicated urinary tract infections, or two weeks of therapy for bacteremia (from first day with negative blood cultures and source control) and eight to 14 days for pneumonia are appropriate. (3,25)

The patient’s molecular testing from our case has returned:
The patient has a complicated UTI with KPC. Because we are treating a complicated urinary tract infection, it may be prudent to use an aminoglycoside to take advantage of the high concentrations in the urine in addition to meropenem-vaborbactam. Unfortunately, colistin and aminoglycoside both have the risk of nephrotoxicity, so the colistin should be stopped. The patient will be treated for a total of 14 days with antibiotics.

How are CRE infections prevented?

Proper Infection Control is the key to prevention of CRE. The acquisition of CRE is similar to other nosocomial infections including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and *C. difficile*. Risk factors include residence in a long-term care facility, an intensive care unit stay, use of in-dwelling catheters and antibiotic exposure. In addition, travel or hospitalizations in areas where CRE are endemic are risk factors. Standard Infection Control measures including isolating patients with resistant pathogens, diligent hand-hygiene and environmental cleaning are necessary to prevent the transmission and acquisition of CRE. (2, 3)

Infection prevention is essential in both long-term facilities and acute-care centers. The CDC has developed a series of strategies for facilities to prevent CRE transmission: (2)
1. Hand Hygiene.
Hand Hygiene is the key part of preventing multi-drug resistant transmission within a healthcare system. Infection Control departments should provide education for healthcare personnel to ensure proper technique. In addition to policies promoting hand hygiene, facilities should monitor adherence rates of the front-line staff and provide feedback. Additional information can be found on the CDC website (www.cdc.gov/ handhygiene/).

2. Contact Precautions.
Patients in acute care facilities who are colonized or infected with CRE should be placed in Contact Precautions, as defined by the CDC. Contact precautions require healthcare workers to use sterile gowns and gloves for all patient contact or infective material. Gowns and gloves should be removed prior to exiting isolation rooms as well as hand hygiene must be performed immediately after patient contact. Medical equipment should be dedicated to a single patient, if possible. Otherwise, equipment must be cleaned and disinfected prior to use for another patient. Contact Precautions are also required for patients with history of MRSA or VRE infections or colonization. Also, facilities should have mechanisms to identify patients with a history of CRE colonization or infection at admission so that prompt isolation occurs. In addition, algorithms should be in place to notify infection control practitioners when CRE is isolated. Some institutions may opt to use preemptive Contact precautions for patients that are transferred from high-risk settings (i.e. patients from hospitals in countries or areas in the United States where CRE is common) while the results of screening cultures are pending.

3. Healthcare Personnel Education.
Healthcare professionals taking care of patients with multi-drug resistant organisms, including CRE, should be educated about the prevention of transmission of these organisms.

4. Use of Devices.
As with other nosocomial infections, the use of devices (e.g. central venous catheters, endotracheal tubes, urinary catheters) places patients at risk for associated infections. Minimizing device use is an important method to reduce nosocomial infections, including CRE. In all healthcare settings, device use should be reviewed to determine if they are still required and discontinued when no longer required. Additional information about the appropriate use of devices can be found at www.cdc.gov/hicpac/BSI/BSI-guidelines-2011.html and www.cdc.gov/govhicpac/cauti/002_cauti-toc.html

5. Laboratory Notification.
Laboratories should have protocols in place to rapidly identify and notify the appropriate clinicians and infection control practitioners whenever CRE colonization or infections are identified. Timely implementation of infection control measures is vital to minimize the spread of CRE within an institution.

6. Inter-facility Communication/Identification of CRE patients.
The presence of CRE infection or colonization should not preclude transfer to another facility.
The transferring facility must notify the receiving facility so appropriate infection prevention measures are implemented.

**7. Antimicrobial Stewardship.**
A formalized program to ensure the appropriate use of antimicrobials at an institution, also known as antimicrobial stewardship, is an essential component of the control of multi-drug resistant organisms. Antimicrobial stewardship programs have not been formally evaluated to reduce the incidence of CRE, but stewardship programs have been associated with reduced incidence of other infections, such as *C. difficile*. In addition, carbapenem restriction has been associated with lower incidence of carbapenem-resistant *P. aeruginosa*. Antimicrobial stewardship programs should emphasize antimicrobial use for appropriate indications and durations as well as the selection of the narrowest spectrum antimicrobial for the infection.

**8. Environmental Cleaning.**
The role of environment in CRE transmission is unknown, but CRE outbreak suggests that the environment can serve as a source. In order to decrease the risk of transmission, facilities should perform daily cleaning in all areas around the patient. CRE has been found in sink drains in patient rooms, so the equipment and patient supplies could be contaminated if stored in close proximity. All sinks and surfaces in patient rooms should be cleaned and disinfected regularly.

**9. Patient and Staff Cohorting.**
If patients are colonized or infected with CRE, they should be housed in single patient rooms or cohorted in the same room. During an outbreak, dedicated staff should be used.

**10. CRE Screening.**
Screening cultures or surveillance cultures may be used to identify unrecognized CRE colonization among epidemiologically linked contacts of known CRE colonized or infected patients. In general, stool, rectal or peri-rectal cultures are tested for surveillance cultures. The CDC has published a document to assist facilities with controlling and preventing CRE: [http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf).
The National Institutes of Health (NIH) in Maryland had an outbreak of CRE (*K. pneumoniae*) in 18 patients. The outbreak strain was detected in respiratory and sink drains. The outbreak was contained by detection of CRE through surveillance cultures, strict patient cohorting, and minimal shared medical equipment. Despite these efforts, eleven of the eighteen patients died from CRE related infections.(3)

Our case patient was immediately placed into Contact Precautions. Medical equipment was not shared among other patients. The clinician and microbiology departments contacted the public health authorities to notify them of the case of CRE. The public health authorities notified the long-term care facility of the CRE case so further surveillance and monitoring could be implemented at their facility in order to prevent additional cases.

Carbapenem-resistant Enterobacteriaceae infections are a threat to the safety of hospitalized
patients. Patients infected with CRE have poor outcomes, despite treatment with multiple antibiotics. Prevention of CRE acquisition is of utmost importance but is often difficult as patients transit from various healthcare settings and laboratory detection is often delayed due to complex resistance mechanisms.

Additional studies investigating transmission, molecular characteristics and treatment regimen for CRE are needed immediately.

Additional information:
http://www.cdc.gov/hai/organisms/cre/

Our case represents a typical presentation and course of a patient with a complicated urinary tract infection. Treatment and management of the patient is based on available clinical data at the time of publishing of this CPE lesson and the personal opinion of the author.

REFERENCES


Activity Test
CRE Infections: A Public Health Issue - Parts 1 & 2

Activity tests must be completed online at www.freeCE.com. A passing grade of 70 or higher and completion of an online activity evaluation are required to earn credit.

1. Enterobacteriaceae is a family of bacteria that commonly cause which types of infections in the hospital environment?
   a. Urinary tract infections.
   c. Central nervous infections.
   d. A and B.
   e. None of the above.

2. The CDC defines Carbapenem Resistant Enterobacteriaceae as:
   a. Pseudomonas species that are resistant to meropenem and imipenem.
   b. E.coli that is resistant to amikacin.
   c. Klebsiella species that is resistant to imipenem.
   d. Enterobacter species that is resistant to meropenem or imipenem.
   e. C and D.

3. At time of publishing this lesson, how many states have reported CRE infections?
   a. 10 states.
   b. 21 states.
   c. 42 states.
   d. 50 states.
   e. None of the above.

4. Which influences may facilitate an increase in development of resistant microbes?
   a. Aging population.
   b. Excess use of anti-infective agents.
   c. Longer patient hospitalization stays.
   d. Increase of resistant organisms.
   e. B and D.

5. Commercial tests for rapid detection of CRE infections include:
   a. Molecular tests.
   b. Tests that detect presence of the gene (OXA, NDM, KPC and VIM).
   c. Phenotypic tests.
   d. Tests that detect in vitro activity of carbapenemase enzymes.
   e. All of these.
6. The Film Array® test:
   a. Is a color indicator of imipenem hydrolysis.
   b. Detects presence of certain genes from rectal swabs.
   c. Detects presence of KPC gene.
   d. Detects presence of KPC, IMP, VIM, NDM and OXA-8.
   e. None of these.

7. The following is (are) considered to be a “reservoir for CRE.”
   a. LTACHs.
   b. Short term hospital-stay patients.
   c. Increased carbapenem use.
   d. Travel patterns.
   e. A, C and D.

8. Which of these is (are) genera of Enterobacteriaceae?
   a. Proteus.
   b. Serratia.
   c. Escherichia.
   d. Salmonella.
   e. All of these.

9. The most common antibiotic treatment possibilities are limited for CRE infections because the presence of carbapenemases render resistance to all penicillins, cephalosporins and carbapenems.
   a. True.
   b. False.

10. Selection of antimicrobial therapy for CRE infections should be:
    a. Accompanied by trial and error.
    b. Facilitated via consultation with infectious disease clinicians (doctor and pharmacist).
    c. Finalized after expensive interviews with family members.
    d. Tailored to susceptibility testing results.
    e. B and D.

11. What are the toxicities associated with colistin?
    a. Neurotoxicity.
    b. Nephrotoxicity.
    c. Nausea.
    d. A and B.
    e. None of the above.
12. The mechanism of action for colistin is:
   a. Disrupting the cell membrane.
   b. Interacting with the penicillin-binding proteins.
   c. Inhibiting protein synthesis.
   d. Inhibiting cell membrane formation.

13. What are the concerns that the Food and Drug Administration associated with tigecycline?
   a. Increased risk of osteomalacia.
   b. Increased risk of mortality.
   c. Increased risk of nausea.
   d. All of the above.
   e. None of the above.

14. Which agent(s) are ideal for urinary tract infections based on the pharmacokinetics?
   a. Amikacin.
   b. Polymyxin E.
   c. Fosfomycin.
   d. All of the above.
   e. None of the above.

15. Combination therapy for CRE infections may improve survival.
   a. True.
   b. False.

16. If a patient acquires a CRE infection, which infection control measure(s) should be implemented?
   a. Contact Precautions.
   b. Universal Precautions.
   c. Respiratory Precautions.
   d. All of the above.
   e. None of the above.

17. What are some prevention strategies for CRE?
   a. Antimicrobial Stewardship.
   b. Patient Cohorting.
   c. Environmental Cleaning.
   d. Limiting use of devices.
   e. All of the above.

18. Characteristics of polymyxins include:
a. They are polycations.
b. They target gram negative organisms.
c. The target gram positive organisms.
d. They have no known side effects.
e. A & B.

19. Tigecycline is indicated for:
   a. Skin infections.
   b. Soft tissue infections.
   c. Complicated intra-abdominal infections.
   d. Community-acquired pneumonia.
   e. All of these.

20. Properties of aminoglycosides may include:
   a. Excretion mostly in urine.
   b. Nephrotoxicity is a major adverse effect.
   c. Nephrotoxicity may be reversible.
   d. Ototoxicity may be an adverse effect that is irreversible.
   e. All of these.