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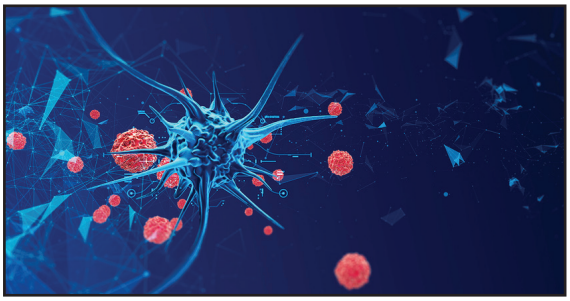
"Part 2: CRE Infections: A Public Health Issue"

August 2018



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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 the last lesson (Part 1), we reviewed the definition of CRE infections, the risk factors associated with acquiring CRE infections, identification of CRE infections, and general treatment.**

In this lesson (Part 2), we review specific therapies, and we relate how CRE infections can be prevented.

This lesson is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 0798-0000-18-224-H01-P for pharmacists, and 0798-0000-18-224-H01-T for technicians.** This lesson furnishes 1.25 (0.125 CEUs) contact hours of credit.

Participants completing this lesson by July 31, 2021 may receive full credit. Release date for this lesson is August 1, 2018. This is knowledge-based continuing pharmacy education. You must answer the questions on the quiz (70% correct required) and return the answers. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call 1-843-488-5550. **Please write your name, NABP eProfile (cpe Monitor) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

The objectives of this lesson are such that upon completion participants will be able to:

For Pharmacists:

1. Discuss specific therapies for treating CRE infections.
2. List methods for preventing CRE infections.

For Technicians:

1. Discuss specific therapies for treating CRE infections.
2. List methods for preventing CRE infections.

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INTRODUCTION

In the previous lesson, "Part 1: CRE: An Emerging Public Health Issue," we discussed: the definition of CRE infections, the risk factors associated with acquiring CRE infections, identification of CRE infections, and general treatment.

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:

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 at 25,000 cell/mm3. Chest X-ray is normal. Blood and urine cultures are sent. Pt 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 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.

The next day, the susceptibilities are reported as follows:

Drug	MIC(mcg/mL)	Interpretation
Ampicillin	*>32*	*Resistant*
Ampicillin/Sulbactam	*32/16*	*Resistant*
Aztreonam	*8*	*Resistant*
Cefazolin	*8*	*Resistant*
Cefotetan	*16*	*Resistant*
Ceftazidime	*16*	*Resistant*
Cefepime	*16*	*Resistant*
Ceftriaxone	*8*	*Resistant*
Ciprofloxacin	*4*	*Resistant*
Ertapenem	*2*	*Resistant*
Imipenem	*2*	*Intermediate*
Meropenem	*4*	*Resistant*
Gentamicin	*1*	*Susceptible*
Tobramycin	*0.5*	*Susceptible*
tigecycline	*0.125*	*Susceptible*

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.

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 displace 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 baumanii*. (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 150mg 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 4.5MU 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 glycylcycline 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-available therapy included carbapenem (either alone or in combination), an 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**). 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.

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August 2018 "Part 2: CRE (Carbapenem Resistant Enterobacteriaceae) Infections: A Public Health Issue"

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does this lesson meet the learning objectives? (Circle your choice).
   - Discuss specific therapies for treating CRE infections.

     Yes-Meets Objectives No-Does Not Meet Objectives

   - List methods for preventing CRE infections.

     Yes-Meets Objectives No-Does Not Meet Objectives

2. Was the program independent & non-commercial? YES NO

3. Relevance of topic Low Relevance 1 2 3 4 5 6 7 Very Relevant

4. What did you like **MOST** about this lesson?_____

_____

5. What did you like **LEAST** about this lesson?_____

_____

6. How would you improve this lesson?_____

_____

MARK CORRECT ANSWER(S)--- "Part 2: CRE (Carbapenem Resistant Enterobacteriaceae) Infections: A Public Health Issue"

1. **What are the toxicities associated with colistin?**
   a. Neurotoxicity.
   b. Nephrotoxicity.
   c. Nausea.
   d. A and B.
   e. None of the above.

2. **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.

3. **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.

4. **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.

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

6. **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.

7. **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.

8. **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.

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

10. **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.