In the Battle against β-Lactamases, Will Avibactam be our Inhibitor in Shining Armor?

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October 7, 2016

Learning Objectives

1. Discuss resistance mechanism and epidemiology of carbapenem resistant Enterobacteriaceae (CRE)
2. Describe available treatment options for serious CRE infections and the limitations of each regimen
3. Review available ceftazidime/avibactam pharmacokinetic and pharmacodynamic data
4. Develop an algorithm for ceftazidime/avibactam use in CRE bacteremia and pneumonia
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Will Avibactam be our Inhibitor in Shining Armor?

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October 3 and 7, 2016  
University Hospital and McDermott Building

Learning Objectives:  
At the completion of this activity, the participant will be able to:

1. Discuss resistance mechanisms and epidemiology of carbapenem resistant Enterobacteriaceae (CRE)  
2. Describe available treatment options for serious CRE infections and the limitations of each regimen  
3. Review available ceftazidime/avibactam pharmacokinetic and pharmacodynamic data  
4. Develop an algorithm for ceftazidime/avibactam use in CRE bacteremia and pneumonia

Assessment Questions:

Carbapenem resistant infections are associated with higher rates of mortality than carbapenem susceptible infections T F

Colistin has relatively few side effects and results in high success rates when used to treat CRE infections T F

Ceftazidime/avibactam is approved for use in cIAI and cUTI T F

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Faculty (Speaker) Disclosure: Maren has indicated she has no relevant financial relationships to disclose relative to the content of her presentation
1. Antimicrobial resistance burden\textsuperscript{1}
   a. Incidence and mortality due to resistant bacteria
      i. Caused 2,049,442 infections in 2013
      ii. Caused 23,000 deaths in 2013
      iii. Many more die from complications
   b. Costs of treating resistant infections
      i. Estimated $20 billion per year, or $35 billion including productivity loss
      ii. Resistant infections are more expensive to treat
         1. Prolonged or pricier treatments
         2. Extended hospital stay
         3. Cost associated with disability and death
   c. New antibiotic development must be aggressively pursued\textsuperscript{2}
      i. The Generating Antibiotic Incentives Now (GAIN) act passed in 2012
         1. Encourages the development of novel antimicrobials
            a. Qualified Infectious Disease Product (QIDP)
         2. Receive an additional 5 years market exclusivity
         3. Receive fast track and priority review status
      ii. GAIN has already increased the number of new antibiotic approvals
      iii. Most new antibiotics have been approved for Gram-positive bacterial infections

2. Mechanisms of resistance\textsuperscript{4}
   a. β-lactams are susceptible to all four resistance mechanisms
      i. Enzyme inactivation
         1. β-lactamase
      ii. Decreased permeability
         1. OprD protein loss resulting in porin loss in \textit{Pseudomonas aeruginosa}
      iii. Efflux pumps
         1. Multidrug efflux pumps in \textit{Pseudomonas aeruginosa}
      iv. Altered target site
         1. Change in penicillin binding proteins (PBP)
3. **β-Lactamases**\(^1, 4\)
   a. Penicillinase seen around the same time as penicillin’s first document use
      i. Spread via plasmid to *Staphylococcus aureus*
      ii. Only 10% of *S. aureus* isolates are susceptible to penicillin today
   b. Occurs more often in Gram-negative bacteria
      i. Efficiently concentrate in the periplasmic space
   c. The Ambler classification
      i. Four classes separated by amino acid structure

**Figure 3. Evolution of β-lactamase resistance**\(^1\)

TEM: temoneira; SHV: sulfhydryl variable; ESBL: extended spectrum β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase
Table 1. Ambler classification of β-lactamases⁴

<table>
<thead>
<tr>
<th>Classification</th>
<th>Name</th>
<th>Common Genes</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Broad Spectrum</td>
<td>PC1, SHV1, TEM1</td>
<td>Penicillins, 1st generation cephalosporins</td>
</tr>
<tr>
<td></td>
<td>ESBL</td>
<td>SHV derived, TEM derived, CTX-M</td>
<td>Broad spectrum plus 3rd generation cephalosporins, aztreonam</td>
</tr>
<tr>
<td></td>
<td>Carbapenemases</td>
<td>KPC</td>
<td>Extended spectrum plus cephamycins, carbapenems</td>
</tr>
<tr>
<td>Class B</td>
<td>Metallo- β-Lactamases</td>
<td>IMP, VIM, NDM</td>
<td>Extended spectrum plus cephamycins, and carbapenems</td>
</tr>
<tr>
<td>Class C</td>
<td>Cephalosporinases</td>
<td>AmpC</td>
<td>Extended spectrum plus cephamycins</td>
</tr>
<tr>
<td>Class D</td>
<td>Oxacillinases</td>
<td>OXA-48</td>
<td>Penicillins, 1st generation cephalosporins</td>
</tr>
</tbody>
</table>

PC1: penicillinase; ESBL: Extended spectrum β-lactamase; TEM: temoneira; SHV: Sulphhydryl variable; KPC: Klebsiella pneumoniae carbapenemase; CTX-M: Cefotaxime-β-lactamase Munich; IMP: Imipenemase metallo-β-lactamase; VIM: Verona integrin-encoded metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; OXA: Oxacillinase

Carbapenem Resistant Enterobacteriaceae

1. Enterobacteriaceae species⁴
   a. Gram-negative, facultative anaerobes that ferment glucose, reduce nitrate to nitrite, and produce catalase
   b. Inhabit lower gastrointestinal (GI) tract of humans and animals
      i. Some live exclusively in the environment
   c. The most common species include
      i. Escherichia coli
      ii. Klebsiella pneumoniae and oxytoca
      iii. Enterobacter cloacae and aerogenes
      iv. Proteus mirabilis and vulgaris
      v. Citrobacter freundii and koseri
      vi. Serratia marcescens
      vii. Morganella morganii
      viii. Salmonella enterica
      ix. Shigella spp

2. Carbapenem resistant Enterobacteriaceae (CRE)⁵,⁶
   a. A bacteria in the Enterobacteriaceae family that is resistant to at least one carbapenem
      i. Meropenem, doripenem, imipenem/cilastatin, ertapenem
      ii. Clinical Laboratory Standards Institute (CLSI) breakpoints
         1. Lowered to exclude all carbapenemase producers from susceptibility
Table 2. CLSI breakpoints for carbapenems and Enterobacteriaceae

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>&lt;1</td>
<td>2</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Doripenem</td>
<td>&lt;1</td>
<td>2</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&lt;1</td>
<td>2</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&lt;0.5</td>
<td>1</td>
<td>&gt;2</td>
</tr>
</tbody>
</table>

3. Carbapenem resistance mechanisms
   a. First described as a hyperactive Class C AmpC β-lactamase plus a porin loss or efflux pump
   b. First Class A carbapenemase observed in a *K. pneumoniae* isolate in 1996
      i. *Klebsiella pneumoniae* carbapenemase (KPC)
      ii. Most common carbapenemase
      iii. Plasmid encoded
      iv. Observed in *E. Coli, Citrobacter, and Enterobacter*
   c. Class B metallo-β-lactamases that confer carbapenem resistance include VIM and NDM-1
   d. Class D oxacillinases not typically observed in Enterobacteriaceae but
      i. OXA-48 was observed in a *K. pneumoniae* isolate in 2004

4. Prevalence
   a. 2013 CDC Antibiotic Resistance Threats
      i. Estimated CRE causes 9,000 infections annually
         1. 7,900 due to KPC
      ii. The most common pathogen is *K. pneumoniae* with 11% of isolates reported as carbapenem resistant
      iii. CRE infections result in 600 deaths annually
      i. Nationally, 3.5% of Enterobacteriaceae are hospital acquired infections (HAI) resistant to carbapenems

Figure 4. Carbapenem resistance among *K. pneumoniae* from 1999-2010

5. Outcomes
   a. Attributable mortality from CRE infections has been estimated as high as 72%
   b. Most common estimations at 50-60% mortality
      i. Ranges based on differences in age, infection site, and underlying condition
c. The mortality due to CRE is double the mortality of carbapenem susceptible Enterobacteriaceae
   i. Delay in appropriate antibiotics
   ii. Decreased effectiveness of active agents
   iii. Increased toxicity of active agents
   iv. Improper or un-optimized dosing regimens
d. Carbapenem resistance has been independently associated with death

**Treatment of Serious CRE Infections**

1. **Introduction**
   a. Limited treatment options available to treat CRE infections
   b. Most available options result in significant toxicity or have limited efficacy
   c. Mortality rates of bloodstream infections and pneumonia caused by resistant Enterobacteriaceae continue to be high, even when treated with antibiotics with *in vitro* activity

2. **Antimicrobial options**
   a. Tigecycline
      i. Bacteriostatic but retains activity against CREs
      ii. Glycylcycline, protein synthesis inhibitor
      iii. Advantages
         1. Large volume of distribution (7-9 L/kg)
            a. Extensive tissue penetration
      iv. Disadvantages
         1. Cannot achieve high concentrations in the blood
            a. $C_{\text{max}}$ after multiple doses of 50 mg every 12 hours: 0.63 mg/mL
            b. FDA breakpoint for Enterobacteriaceae: ≤2 mcg/mL
         2. Tissue penetration in the epithelial lining fluid is poor
         3. A pooled FDA analysis found an increased mortality rate compared to other drugs, when used for pneumonia or bacteremia, resulting in a Black Boxed Warning from the FDA
         4. CRE bacteremia mortality rates in patients treated with tigecycline are 40-80%
   b. Colistin and polymyxin B
      i. Bactericidal against Gram-negative bacteria
      ii. Disrupts cell membrane integrity
      iii. Advantages
         1. Low baseline resistance
            a. Of KPC isolates, 80% are susceptible to colistin
      iv. Disadvantages
         1. Side effect profile
            a. Nephrotoxicity rates as high as 30-50%, potentially resulting in dialysis
            b. Neurotoxicity, including paresthesias and slurred speech, occurs in 7% of patients
               i. Polymyxin B has a Black Boxed Warning for neurotoxicity resulting in respiratory paralysis when combined with anesthesia or muscle relaxants
         2. Dosing
            a. Colistimethate sodium (CMS) is converted to colistin in aqueous solutions such as plasma and urine, instead of metabolized
            b. The conversion rate is widely variable within the population
            c. Therapeutic drug monitoring results in overestimation due to spontaneous conversion in the sample
d. CMS is renally eliminated and can be cleared rapidly before conversion in patients with good renal function

e. Lower total daily doses, as seen in patients with adequate renal function, are associated with higher mortality rates

3. Adaptive resistance\textsuperscript{11}

   a. Lipopolysaccharide binding site modification can develop during therapy
   b. Can increase the MIC above the breakpoint
   c. Failure rates with colistin monotherapy can be 56%

c. Carbapenems\textsuperscript{13}

   i. Used in combination with other agents
   ii. Cell wall agent with bactericidal activity
   iii. In 2010, CLSI dropped carbapenem breakpoints from 4 mcg/mL to 1 mcg/mL to ensure organisms that produce carbapenemases would not be reported as susceptible
      1. Some organisms that do not produce carbapenemases may be reported as resistant based on MIC >1 mcg/mL
   iv. Optimizing pharmacokinetic parameters can result in pharmacokinetic and pharmacodynamic target attainment
      1. Time dependent antibiotics, relying on a concentration above the MIC for >50% of the time to maximize bacterial killing
         a. Extending the infusion time increases time above MIC
      2. Meropenem has a large therapeutic index
         a. Safety data up to 6 grams per day
      3. Monte Carlo simulations demonstrate attainment of 50% T>MIC up to an MIC of 8 mcg/mL with a regimen of 2 grams every 8 hours infused over 3 hours
         a. May be an option when CLSI interpretation is resistant

Figure 5. Probability of target attainment for 50% time above MIC for each meropenem dosing regimen\textsuperscript{13}

3. Combination Therapy\textsuperscript{9,14-16}

   a. Associated with decreased rates of mortality when compared to monotherapy
      i. Retrospective study of 661 patients with KPC infections
         1. 447 bloodstream infections, 84 lower respiratory tract infections
      ii. Overall mortality was lower in the combination group (30.2%) than the monotherapy group (38.4%)
iii. Combination therapy may be most appropriate for critically ill patients with severe infections like pneumonia and bacteremia\(^9\)

1. Mortality was significantly lower in the combination group for blood stream infections (BSI) and lower respiratory infections
   a. BSI combination and monotherapy mortality (32% vs 51.3%, p<0.001)
   b. Respiratory infection combination and monotherapy mortality (25% vs 49.1%, p=0.03)

2. Mortality was not significantly lower in intra-abdominal (IAI) and urinary tract infections (UTI)
   a. IAI combination and monotherapy mortality (23.5% vs 32%, p=0.55)
   b. UTI combination and monotherapy mortality (9.1% vs 4.2%, p=0.48)

b. Combination therapy with a carbapenem\(^9\)

i. Most common combination choice, 58% of patients on combination therapy

ii. Significant mortality benefit is seen with meropenem when the minimum inhibitory concentration (MIC) is <8
   1. Combination therapy and monotherapy morality (27.9 % vs 40.4 % p=0.03)

iii. No significant mortality benefit is seen when the meropenem MIC is >16
   1. Combination therapy and monotherapy mortality (32 % vs 37.9 %, p=0.22)
   2. Low probability of attaining those concentrations even with optimized pharmacokinetics
   3. As many as 46-47% of KPC isolates in some studies had a meropenem MIC greater than 8

c. Combination without a carbapenem when the meropenem MIC is >8\(^{14-16}\)

i. Agents appropriate for combination include colistin, tigecycline, and aminoglycosides

ii. Associated with significant mortality benefit in bacteremia, with a mortality rates of around 40%

iii. Not associated with significant mortality benefits in pneumonia, however too few patients were included to discern a true difference

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**Figure 6. 14 day mortality rates of monotherapy vs combination therapy\(^9\)**

![Graph showing 14 day mortality rates of monotherapy vs combination therapy](image)
4. Take home points
   a. Combination therapy, especially with a carbapenem, has the lowest mortality rates in treating CRE bacteremia and pneumonia
      i. Up to half of patients with CRE infections, though, are unlikely to benefit from a carbapenem due to elevated MICs
   b. Mortality rates, even with combination therapy, continue to be high for bacteremia and pneumonia caused by CRE
   c. Treatment options can often result in significant adverse effects

**Ceftazidime/Avibactam (Avycaz®)**

1. Introduction
   a. Approved February 25, 2015
   b. Designated a QIDP under the GAIN act
      i. Evidence based on safety and efficacy phase II trials
   c. Indicated for adults with limited or no alternative treatment options
      i. Complicated intra-abdominal infections (cIAI), in combination with metronidazole
      ii. Complicated urinary tract infections (cUTI) including pyelonephritis

2. Mechanism of action
   a. Ceftazidime
      i. 3rd generation cephalosporin
      ii. Bactericidal effect through cell wall synthesis inhibition
      iii. Binds and inhibits penicillin binding proteins (PBP) responsible for cross-linking peptidoglycan chains, leading to compromised cell wall structure, cell lysis, and death
   b. Avibactam
      i. New non-β-lactam β-lactamase inhibitor
      ii. Contains diaza-bicyclo core which adds hydrogen binding sites and increases rigidity during transition without dramatically increasing size
      iii. Covalently binds to the hydroxyl active site of the β-lactamase, inhibiting the β-lactamase
      iv. Carbamate linkage creates a stronger position in the active site resulting in longer deactivation of β-lactamase
      v. Improved spectrum
         1. Ambler class A carbapenemases, class C, some class D β-lactamases

<table>
<thead>
<tr>
<th>Classification</th>
<th>Name</th>
<th>Clavulanic Acid in vitro susceptibility</th>
<th>Avibactam in vitro susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Broad-Spectrum</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>ESBL</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>KPC</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Class B</td>
<td>Metallo-B-Lactamases</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Class C</td>
<td>AmpC</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Class D</td>
<td>Oxacillinases</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

ESBL: extended spectrum β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase
Table 4. Ceftazidime and ceftazidime/avibactam activity against β-lactamases by Ambler classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Name</th>
<th>Common Genes</th>
<th>Ceftazidime in vitro susceptibility</th>
<th>Ceftazidime/Avibactam in vitro susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Broad-Spectrum ESBL</td>
<td>PC1 SHV1 TEM1 SHV derived TEM derived CTX-M KPC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>ESBL Carbapenemases</td>
<td>IMP VIM NDM</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Class B</td>
<td>Metallo-B-Lactamases</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Class C</td>
<td>Cephalosporinases</td>
<td>AmpC No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Class D</td>
<td>Oxacillinases</td>
<td>OXA-48 Pseudomonas OXA-11, 14, 15 Acinetobacter OXA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

PC1: penicillinase; ESBL: Extended spectrum β-lactamase; TEM: temoneira; SHV: Sulphydryl variable; KPC: Klebsiella pneumoniae carbapenemase; CTX-M: Cefotaxime-β-lactamase Munich; IMP: Imipenemase metallo-β-lactamase; VIM: Verona integrin-encoded metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; OXA: Oxacillinase

3. Spectrum of activity
   a. Enterobacteriaceae
      i. Increased susceptibility to nearly 100% of isolates tested in vitro
         1. Including ceftazidime and meropenem non-susceptible isolates
   b. Pseudomonas aeruginosa
      i. Susceptibility increased relative to ceftazidime
      ii. Susceptibility to meropenem non-susceptible strains is poor at 50%
   c. Acinetobacter species
      i. Remain largely resistant
      ii. Species contains Ambler class D OXA β-lactamase plus other resistance mechanisms
   d. Anaerobic and Gram-positive bacteria
      i. No clinically relevant anaerobic activity
      ii. Limited Staphylococcus aureus activity
      iii. Consistent β-hemolytic streptococci activity

4. Resistance mechanisms
   a. Avibactam does not inhibit Ambler class B or most class D β-lactamases
   b. The potential mechanism for resistance to Pseudomonas aeruginosa is diminished permeability and overexpressed efflux pumps
   c. Spontaneous resistance seen in vitro with Pseudomonas aeruginosa isolates growing after 24 hours and an increase in MIC from 8 mcg/mL to >32 mcg/mL
Clinical Safety and Efficacy Trials

1. FDA approved for cUTI and cIAI based on phase II trials, phase III trials have since been published.20-22

Table 6. Ceftazidime/avibactam use in cUTI and cIAI clinical trials20-22

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cUTI Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime/avibactam Imipenem/cilastatin</td>
<td>Microbiologic response at TOC 1 week after end of therapy in the mMITT group</td>
<td>C/A: 67.4% (31/46) I/C: 63.3% (31/49)</td>
<td>Carbapenem resistant isolates excluded</td>
</tr>
<tr>
<td>≥4 days of therapy De-escalation</td>
<td></td>
<td>No difference</td>
<td>Lower dose of C/A used: 500/125 mg infused 30 min</td>
</tr>
</tbody>
</table>

Acinetobacter (321) | 47 | 41.7 | 31.2 |
### cUTI Phase III

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resolution of symptoms and microbiologic eradication at TOC visit 3 weeks after end of therapy</th>
<th>C/A: 70.2% (269/383)</th>
<th>D: 64.5% (269/417)</th>
<th>Carbapenem resistant isolates excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime/avibactam Doripenem ≥5 days of therapy de-escalation</td>
<td></td>
<td>Non-inferior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAZ-NS isolates only C/A: 64% D: 60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### cIAI Phase II

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resolution of symptoms at TOC 2 weeks after end of therapy in the mMITT group</th>
<th>C/A: 82.4% (70/85)</th>
<th>M: 88.8% (79/89)</th>
<th>Carbapenem resistant isolates excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime/avibactam + metronidazole Meropenem 5-14 days of therapy no de-escalation</td>
<td></td>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients unlikely to respond excluded but not described</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluded patients CrCl&lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C/A resistance 6/147 isolates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **cUTI**: complicated urinary tract infection; **cIAI**: complicated intra-abdominal infection; **TOC**: test of cure; **mMITT**: microbiologic modified intent to treat; **C/A**: ceftazidime/avibactam; **I/C**: imipenem/cilastatin; **D**: doripenem; **CAZ-NS**: ceftazidime non-susceptible; **M**: meropenem; **CrCl**: creatinine clearance; **A**: best alternative therapy

### 2. Adverse events

- Most adverse events are mild to moderate
  - Commonly reported adverse events (1-10%)
    1. GI side effects
    2. Anxiety
    3. Headache
  - Serious adverse events seen in trials include diarrhea, acute renal failure, and elevated liver enzymes

### 3. Take home points

- Ceftazidime/avibactam showed equivalent or non-inferior clinical success rates to carbapenems in cUTI and cIAI treatment
- All trials excluded carbapenem resistant isolates which are known to have higher MICs than susceptible isolates
- Clinical success rates may not be similar in CRE infections
- Ceftazidime/avibactam resistant isolates were seen in several trials
- Considered a safe drug with a few non-serious adverse events

### Pharmacokinetic (PK) and Pharmacodynamic (PD) Data

1. **PK and PD for antibiotics**
   - Determines effective antibiotic dosing regimens
   - PK parameters
     - Volume of distribution
       1. Determines dose required to achieve certain plasma concentrations
     2. Plasma concentrations over time are critical when determining if drug concentration to MIC ratio are achievable
   - Clearance
     1. Determines how often the drug must be dosed
c. **PD parameters**
   i. Describes the relationship between drug concentration and organism inhibition or death using three possible parameters
      1. Duration of time the free drug concentration remains above MIC (T>MIC)
      2. Area under the curve (AUC) to MIC ratio (AUC/MIC)
         a. Commonly referred to as total 24 hour drug exposure above the MIC
      3. Peak serum concentration to MIC ratio (Peak/MIC)

\[\text{Figure 7. Antibiotic pharmacodynamic parameters}\]

![Antibiotic Pharmacodynamic Parameters](image)

   ii. The pharmacodynamic parameter guides the plasma concentration goal to achieve optimal effect
   iii. PD goals for enzyme inhibitors, such as a β-lactamase inhibitor, are dependent on the inhibitor to antibiotic ratio since the inhibitor has no antibacterial activity
      1. Concentration ratio and a time above designated ratio that adequately protect the antibiotic are determined

d. **Monte Carlo simulations**
   i. Runs simulations to determine probability of attaining the PD goal based on the PK parameters using multiple dosing regimens
   ii. If simulation show a low probability of attaining goal concentrations, successful infection treatment is unlikely

2. **Ceftazidime/avibactam Pharmacokinetics\textsuperscript{19}**
   a. PK parameters are usually based on healthy volunteers
      a. Linear without accumulation
      b. Similar as a single dose or multiple doses
      c. Similar alone or in combination
   b. Absorption
      a. Not applicable
      b. Intravenous only
   c. Distribution
      a. Ceftazidime and avibactam have a large volume of distribution indicating good tissue penetration
   d. Metabolism
      a. Insignificant
   e. Elimination
      a. Renally eliminated and renal function based dosing adjustments are recommended
3. **Pharmacodynamics**
   a. β-lactams are time dependent antibiotics
      a. The PD goal for ceftazidime is time above MIC of 50% (50% T>MIC)
   b. β-lactamase inhibitors require time above threshold concentration (Ct) of the β-lactam
      i. The PD goal for avibactam is bacteria specific
         1. Enterobacteriaceae: 0.25-0.5 mg/L for 50% of the dosing interval
         2. *Pseudomonas aeruginosa*: 1 mg/L for 40% of the dosing interval
   c. Monte Carlo simulation in patients with cIAI have determined a 98% probability attaining target concentrations using the free drug fraction (ceftazidime: 85%, avibactam 92%) 2.5 g every 8 hours infused over 2 hours
      ii. Targets were conservatively set
         1. Ceftazidime concentration above MIC for >50% of the time
         2. Avibactam concentration of 1 mg/L (Ct) for >50% of the time
            a. Probability of target attainment
               i. 98% for MIC of 8 mcg/mL
               ii. 51% for MIC of 16 mcg/mL
               iii. 1% for MIC of 32 mcg/mL,

<table>
<thead>
<tr>
<th>MIC (mcg/mL)</th>
<th>40% ft&gt;MIC</th>
<th>50% ft&gt;MIC</th>
<th>40% ft&gt;Ct</th>
<th>50% ft&gt;Ct</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>98.9</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>98.9</td>
</tr>
<tr>
<td>8</td>
<td>99.8</td>
<td>98.3</td>
<td>99.8</td>
<td>98.1</td>
</tr>
<tr>
<td>16</td>
<td>75.4</td>
<td>50.8</td>
<td>75.4</td>
<td>50.8</td>
</tr>
<tr>
<td>32</td>
<td>5.1</td>
<td>1.3</td>
<td>5.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Table 7. Pharmacokinetics of ceftazidime/avibactam 2.5 g every 8 hours as a 2 hour infusion for 11 days**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ceftazidime</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>90.4</td>
<td>14.6</td>
</tr>
<tr>
<td>AUC (mg-h/L)</td>
<td>291</td>
<td>38.2</td>
</tr>
<tr>
<td>T1/2</td>
<td>2.76</td>
<td>2.71</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>6.86</td>
<td>13.1</td>
</tr>
<tr>
<td>Vss (L)</td>
<td>17</td>
<td>22.2</td>
</tr>
<tr>
<td>Protein Binding, %</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Elimination, %</td>
<td>83 urine</td>
<td>&gt;97 urine</td>
</tr>
</tbody>
</table>

Cmax: peak concentration; AUC: area under the curve; T1/2: half-life; CL: clearance; Vss: volume of distribution at steady state

**Table 8. Probability of target attainment with normal renal function achieving pre-specified PK/PD targets with 2.5 g ceftazidime/avibactam every 8 hours infused over 2 hours by MIC**

**Pharmacokinetic and pharmacodynamic target definition**

MIC: minimum inhibitory concentration; ft>MIC: time that free fraction of drug is above the minimum inhibitory concentration; ft>Ct: time that free drug is above the concentration threshold; Ct: concentration threshold
1. PK and PD changes in critically ill patients\textsuperscript{11} 
   a. Patients with sepsis experience fluid shifts to extravascular space
      i. Increased Vd for hydrophilic antibiotics
         1. Decreased serum concentrations
   b. Similar changes seen in patients with hypoalbuminemia, postsurgical drains, and burns
   c. Ceftazidime/avibactam is a hydrophilic drug, and may be susceptible to increased Vd and a decrease in serum concentrations
      i. Monte carlo simulation may be an overestimate of the percent chance of target attainment in a critically ill patient
      ii. If target concentration is not met, therapeutic failure is more likely

2. Conclusions
   a. Plasma concentrations necessary to effectively treat Enterobacteriaceae with an MIC of ≤8 are achievable in healthy populations with normal renal function
   b. Critically ill patients may have increased Vd, which can decrease serum concentrations, decreasing the probability the necessary concentrations can be obtained
   c. CLSI has conservatively set the breakpoint at ≤4

**Ceftazidime/Avibactam use in CRE Bacteremia and Pneumonia**

1. Case Reports\textsuperscript{24-26}
   a. Case reports for ceftazidime/avibactam use in CRE bacteremia have been reported on 6 patients

**Table 9. Summary of case reports describing ceftazidime/avibactam use in CRE bacteremia\textsuperscript{24-27}**

<table>
<thead>
<tr>
<th>Age, Sex, Hospital Course</th>
<th>Source, Organism</th>
<th>Susceptibilities</th>
<th>Course of Infection</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>77 y, Female Septic shock</td>
<td>UTI, <em>Enterobacter aerogenes</em></td>
<td>C/A 1.5, Imipenem ≥4, Ertaconem ≥2, Polymyxin B 6, Tigecycline 0.5</td>
<td>Ceftazidime/avibactam monotherapy 15 days</td>
<td>Microbiologic eradication, cure, discharged</td>
</tr>
<tr>
<td>Age</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>C/A</td>
<td>Treatment</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----------</td>
<td>-----</td>
<td>-----------</td>
</tr>
<tr>
<td>89 y, Female</td>
<td>Endocarditis, UTI, Respiratory Failure</td>
<td>Unknown, <em>Klebsiella pneumoniae</em></td>
<td>C/A 1.5</td>
<td>Ceftazidime/avibactam monotherapy 42 days</td>
</tr>
<tr>
<td>72 y, Female</td>
<td>UTI, <em>Klebsiella pneumoniae</em></td>
<td>C/A 0.5</td>
<td>Ceftazidime/avibactam monotherapy 10 days</td>
<td>Microbiologic eradication, cure, discharged</td>
</tr>
<tr>
<td>47 y, Female</td>
<td>Kidney and pancreas transplant, exploratory laparotomy</td>
<td>Intra-abdominal abscess, possible line infection, <em>Klebsiella pneumoniae</em></td>
<td>C/A 0.5</td>
<td>Ceftazidime/avibactam monotherapy 9 days</td>
</tr>
<tr>
<td>62, Female</td>
<td>Splenectomy, Pancreatic cancer, pancreaticoduodenectomy</td>
<td>Intra-abdominal abscess, <em>Klebsiella pneumoniae</em></td>
<td>3 susceptibilities C/A 4, 32, 8</td>
<td>Colistin + EI high-dose meropenem + tigecycline Hospital day 21</td>
</tr>
<tr>
<td>64 y, Female</td>
<td><em>Clostridium difficile</em>, toxic megacolon, total colectomy, small bowel resection, intestinal transplant</td>
<td>Breakthrough bacteremia, <em>Klebsiella pneumoniae</em></td>
<td>Tigecycline &gt;256</td>
<td>Ceftazidime/avibactam + ertapenem</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; UTI: urinary tract infection; C/A: ceftazidime/avibactam; EI: extended infusion; VAP: ventilator associated pneumonia; CLABSI: central line associated blood stream infection; ICU: intensive care unit

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2. Case Series

- First study analyzing ceftazidime/avibactam use in CRE infections (n=37)
  - Bacteremia (n=10), pneumonia (n=12)
- Combination therapy with gentamicin, colistin, or tigecycline occurred in 30% (11/37) patients
- Clinical success occurred in 59% (22/37)
  - Bacteremia: 70% (7/10),
    - 59% with primary bacteremia
  - Pneumonia: 50% (6/12)
- Recurrence occurred in 27% (10/37) at 30 or 90 days
- Resistance developed in 3 patients during therapy, leading to failure
  - Resistance occurred on day 10, 15, and 19 of therapy
  - First cases of resistance while on therapy described for ceftazidime/avibactam
3. Comparator trial\textsuperscript{30}
   a. Multicenter, prospective, observational cohort study is currently underway with preliminary data
   b. Compared outcomes of 91 patients treated with colistin (74%), ceftazidime/avibactam (15%), or combination (10%)
   c. Infections included BSI, UTI, wound infection, respiratory tract infection, or abscess
   d. Many patients were receiving combination therapy with other active agents in all three groups
   e. Patients taking ceftazidime/avibactam had increased survival and trend of less nephrotoxicity
      i. Any ceftazidime/avibactam hazard ratio 0.17, 95% confidence interval 0.03-0.62, p<0.01
      ii. Renal failure developed in 8/36 at risk patients
         1. Ceftazidime/avibactam: none
         2. Colistin: 7/23 (30%)
         3. Colistin + ceftazidime/avibactam: 1/4 (25%)

4. Take home points
   a. Very little real world use has been reported
   b. Clinical success rates and mortality rates appear to be similar to other regimens such as combination colistin and meropenem
   c. Combination therapies have been attempted
      i. No evidence to suggest which agent is most appropriate to add to ceftazidime/avibactam
   d. The most alarming result is the 3/37 patients in the case series who developed resistance while on therapy

Recommendations for CRE Bacteremia or Pneumonia Treatment

1. When the patient is not critically ill or rapidly declining I recommend ceftazidime/avibactam
   a. If patient is rapidly declining after 24 hours of therapy refer to next recommendation

2. When the patient is critically ill or rapidly declining use meropenem MIC
   a. If MIC is \( \leq 8 \) I recommend meropenem plus colistin/polymyxin
   b. If MIC is \( >8 \) I recommend ceftazidime/avibactam plus either colistin, tigecycline, or an aminoglycoside

3. Ceftazidime/avibactam should not be used in patients on CRRT at this time
   a. Low success rates (17%) seen in this subgroup
Conclusion

1. Infections caused by CRE are considered an urgent threat due to the lack of clinically efficacious and safe treatment options.
2. Mortality for patients infected with CRE is double that of carbapenem susceptible infections.
3. Best available treatment option is polymyxin/colistin in combination with meropenem when the MIC is ≤8.
   a. Mortality rates remain around 50% in bacteremia.
   b. Many patients experience severe drug related adverse events.
4. Ceftazidime/avibactam is a 3rd generation cephalosporin in combination with a new non-β-lactam β-lactamase inhibitor, which improves spectrum to include KPC.
5. Ceftazidime/avibactam is approved for cUTI and cIAI based on phase II studies in which CRE isolates were excluded.
6. Post approval use in bacteremia and pneumonia CRE infections suggests the mortality rate and clinical success rate is similar to other currently available options.
   a. Baseline resistance and the development of resistance during therapy has been reported.
References


