Treatment Options for Carbapenem-Resistant Enterobacteriaceae Bloodstream Infections

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Learning Objectives

• Define carbapenem-resistant *Enterobacteriaceae* (CRE)

• Describe the morbidity and mortality associated with CRE bloodstream infections

• Analyze current literature evaluating various treatment options for CRE bloodstream infections
A Patient Case…

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Organism</th>
<th>Klebsiella pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>&lt;=8 R S</td>
<td>Final</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>&gt;16 R</td>
<td>Final</td>
</tr>
<tr>
<td>AMPICILLIN SULBACT</td>
<td>&gt;16 R</td>
<td>Final</td>
</tr>
<tr>
<td>CEFAZOLIN</td>
<td>&gt;16 R</td>
<td>Final</td>
</tr>
<tr>
<td>CEFEPIME</td>
<td>16 I</td>
<td>Final</td>
</tr>
<tr>
<td>CEFTRIAXONE</td>
<td>&gt;32 R</td>
<td>Final</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>&gt;2 R</td>
<td>Final</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>8 I</td>
<td>Final</td>
</tr>
<tr>
<td>MEROPENEM</td>
<td>&gt;8 R</td>
<td>Final</td>
</tr>
<tr>
<td>PIPERACILLIN/TAZOBAC</td>
<td>&gt;128 R</td>
<td>Final</td>
</tr>
<tr>
<td>TOBRAMYCIN</td>
<td>&gt;8 R</td>
<td>Final</td>
</tr>
<tr>
<td>TRIMETH SULFAMETH</td>
<td>&gt;4 R</td>
<td>Final</td>
</tr>
</tbody>
</table>

What are Carbapenem-Resistant Enterobacteriaceae?

• Enterobacteriaceae = large family of Gram-negative bacilli
  – *E. coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp.,
  – Noteworthy exceptions:
    – *Pseudomonas* spp., *Acinetobacter* spp.

• Defining “carbapenem resistance”

  Isolate resistant to ≥ 1 carbapenem  
  OR

  Documented carbapenemase production
Morbidity and Mortality Associated with CRE

• Rate of CRE increased from 1.2% in 2001 to 4.2% in 2011
• National Healthcare Safety Network reports 11-13% of hospital-associated *Klebsiella* infections are carbapenem-resistant

Mechanisms for Carbapenem Resistance

β-Lactam antibiotic

Porin

Efflux pump

Outer membrane

Periplasmic space

Cytoplasmic membrane

Enzyme

Pgp

Cytoplasm

Plasmid

Mechanisms for Carbapenem Resistance

- Carbapenemase production

<table>
<thead>
<tr>
<th>Ambler Class</th>
<th>Spectrum</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Narrow-spectrum</td>
<td>Penicillinase</td>
</tr>
<tr>
<td></td>
<td>ESBL</td>
<td>CTX-M</td>
</tr>
<tr>
<td></td>
<td>Carbapenemase</td>
<td>KPC</td>
</tr>
<tr>
<td>B</td>
<td>Metallo-B-lactamase (carbapenemase)</td>
<td>VIM-1, IMP-1, NDM-1</td>
</tr>
<tr>
<td>C</td>
<td>Cephalosporinase</td>
<td>AMP-C</td>
</tr>
<tr>
<td>D</td>
<td>ESBL/carbapenemase</td>
<td>OXA</td>
</tr>
</tbody>
</table>

Clinical Question

“Carbapenem resistance undermines the established choices for treatment…

How does one make a clinical decision when prospective, randomized, controlled trials do not exist?”

-- Robert Bonomo, MD
Antimicrobials Utilized in CRE Treatment

- Carbapenems
- Aminoglycosides
- Polymyxins
- Tigecycline
- Ceftazidime-avibactam
- Fosfomycin
Carbapenems

• Mechanism of Action
  – Inhibit bacterial cell wall synthesis by blocking peptidoglycan synthesis

• Genotypic vs. phenotypic resistance?

KPC MIC 16  KPC MIC 8  KPC MIC 4  KPC MIC 2

VS.
Carbapenem Susceptibility Breakpoints

- New breakpoints enhance detection of low-level resistance
  - Additional testing for carbapenemase production not necessary

<table>
<thead>
<tr>
<th>Agent</th>
<th>2009 CLSI</th>
<th>2010-2012</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S I R</td>
<td>S I R</td>
<td>S I R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 4 8 16</td>
<td>≤ 2 4-8 &gt; 8</td>
<td>≤ 1 2 ≥ 4</td>
</tr>
</tbody>
</table>

CLSI. M100 24. 2009
CLSI. M100 24. 2012
CLSI. M100 24. 2015
Carbapenems – PK/PD Principles

• Target %t > MIC: 40%

• Extended interval dosing may assist in overcoming MIC

*1 gram Q8h dose
Aminoglycosides

Mechanism of Action

• Bind to the 30s ribosomal subunit, inhibiting protein synthesis

Dosing

• Conventional or extended interval

Adverse Effects

• Nephrotoxicity (10-25%)
• Ototoxicity (10-20%)
Aminoglycosides – PK/PD Principles

• Target Peak:MIC > 8-10
  – Extended-interval dosing designed to achieve target MIC 2 – 4 for gentamicin and tobramycin and MIC 4 – 8 for amikacin

<table>
<thead>
<tr>
<th>Agent</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤16</td>
<td>32</td>
<td>≥64</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
</tr>
</tbody>
</table>

– If amikacin MIC = 16, goal peak level 128 – 160 mg/mL
MIC Distributions in CRE

Gentamicin MIC breakpoint

Amikacin MIC breakpoint

Percent

MIC

0.5 1 2 4 8 16 32

4 12 20 8 20 44 16 52

Amikacin
Gentamicin

Aminoglycosides as Monotherapy for CRE Infections

• Microbiologic clearance in urinary tract infections

*no mortality difference between groups

Aminoglycosides – In Summary

• Many CRE isolates exhibit resistance to aminoglycosides
• Increasing MICs decrease probability of attaining target PK/PD parameters
• Consider use in bacteremia with urinary source
Polymyxins

- Polymyxin B and colistin (polymyxin E)
  - Cationic detergents – damage bacterial cell wall membrane


CMS = colistimethate sodium

CMS $t_{1/2}$: 2-3 hr  
Colistin $t_{1/2}$: 14.4 hr  
Polymyxin B $t_{1/2}$: 6 hr
Polymyxins

- Susceptibility breakpoints

<table>
<thead>
<tr>
<th>MIC Interpretive Criteria</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

![Graph showing colistin MIC distribution](https://example.com/graph.png)

Heteroresistance to Polymyxins in Subpopulations
Understanding Colistin PK/PD Principles

- AUC/MIC target = 60
  - MIC = 1:
    - Colistin$_{ss}$ concentration of 2.5 mg/L

**Loading dose:**
Colistin$_{ss,avg}$ target x 2.0 x IBW

**Maintenance dose:**
Colistin$_{ss,avg}$ target x ([1.50 x CrCl] + 30)

References:
Balancing Efficacy and Toxicity

PK/PD Target
2.5 mg/L

Nephrotoxicity (18-60%)
2.4 mg/L

Polymyxins for CRE Infection – A Meta-Analysis

• Study Criteria
  – Inclusion criteria:
    – Clinical outcomes of polymyxin therapy for CRE infections
    – Monotherapy or combination therapy
  – Exclusion criteria:
    – Newcastle-Ottawa scale score < 3

• Primary outcome
  – Mortality, as defined by each study
Polymyxins Meta-analysis – Studies Included

• 25 studies included
  – 6 single-arm including total of 175 patients
  – 19 controlled studies including total of 911

Colistin: 20 studies
Polymyxin B: 4 studies
Both agents: 1 study

• *Klebsiella* spp. most common pathogen
• Bacteremia was most common manifestation
Polymyxins Meta-Analysis – Pooled Mortality Results

• Overall Mortality
  – 19 controlled studies: polymyxin vs. control
    – OR: 0.79 (0.58 – 1.08); p = 0.15
    – Pooled polymyxin mortality rate: 33.8%
  – 6 single arm studies:
    – Pooled overall mortality rate: 35.7%

<table>
<thead>
<tr>
<th>Mortality by strategy</th>
<th>14-day OR (95% CI)</th>
<th>p-value</th>
<th>28-day OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy vs control</td>
<td>0.84 (0.35-2.00)</td>
<td>0.69</td>
<td>1.15 (0.66 – 2.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Combination vs. control</td>
<td>0.76 (0.27 – 2.16)</td>
<td>0.60</td>
<td>0.49 (0.31 – 0.75)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Combination vs. monotherapy</td>
<td>0.91 (0.28 – 2.96)</td>
<td>0.88</td>
<td>0.36 (0.19 – 0.68)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Polymyxins – In Summary

• Target AUC/MIC difficult to achieve with increasing MICs
• Bacteriostatic activity more likely than bactericidal
• Breakthrough bacterial growth and heteroresistance make polymyxin monotherapy undesirable
Tigecycline

Glycylcycline

- Binds to 30s ribosomal subunit, inhibiting protein synthesis
- Bacteriostatic activity

Dosing

- Loading dose: 100 mg
- Maintenance dose: 50 mg every 12 hours*

Adverse effects

- Nausea (26%)
- Vomiting (18%)

*hepatic dose adjustments
Tigecycline *in vitro* activity

<table>
<thead>
<tr>
<th>Enterobacteriaceae Breakpoints</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUCAST</td>
<td>≤ 1</td>
<td>2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>FDA</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

Tigecycline PK/PD Principles

- Volume of distribution > 10 L/kg
- Target AUC:MIC = 1
Tigecycline – In Summary

- Wide volume of distribution leads to low serum concentrations
- Increased doses do not lead to sustained serum concentrations
- Use as monotherapy associated with poor outcomes
Monotherapy for CRE Bacteremia

- Systematic review evaluating percent survival in patients with carbapenemase-producing \textit{K. pneumoniae} bacteremia

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Percent survival for different treatments and no active therapy.}
\end{figure}

% Survival

\begin{itemize}
\item Carbapenem (n=34): 68.4%
\item Aminoglycoside (n=24): 62.5%
\item Colistin (n=98): 54.1%
\item Tigecycline (n=36): 52.8%
\item No active therapy (n=50): 54%
\end{itemize}

COMBINATION THERAPY
Combination Therapy in KPC-Producing *K. pneumoniae* – New York and Pittsburgh

• Inclusion
  – First episode of *K. pneumoniae* bacteremia
  – PCR-confirmed KPC-gene

• Primary Outcome
  – Death within 28 days from onset of bacteremia
  – Risk factors for mortality were compared between survivors and non-survivors

• Definitions
  – **Appropriate therapy**: ≥ 1 *in vitro* active agent for at least 48 hours
  – **Combination therapy**: ≥ 2 agents for at least 48 hours, regardless of *in vitro* susceptibility to each agent

Combination Therapy in KPC-Producing *K. pneumoniae* – Results

- Overall 28-day mortality: 16/41 (39%)
  - Combination therapy: 2/15 (13.3%)
  - Monotherapy: 11/19 (57.8%)
  - *p* = 0.01

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 25)</th>
<th>Non-survivors (n = 16)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>13 (60%)</td>
<td>2 (12.5%)</td>
<td>0.13 (0.01-0.082)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (12%)</td>
<td>7 (43.7%)</td>
<td>5.7 (1.98-3.68)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>5 (31.2%)</td>
<td>∞ (1.59 – ∞)</td>
</tr>
</tbody>
</table>
Mortality by Definitive Treatment Strategy - Monotherapy

<table>
<thead>
<tr>
<th>Definitive Treatment</th>
<th>n (%) (n = 19)</th>
<th>Mortality, n (%) (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin</td>
<td>7 (36.8%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>5 (26.3%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>4 (21%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Amp-Sulbactam</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Pip-Tazo</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Carbapenem MICs
  - 3 received imipenem (MIC 2-4), 1 patient died
  - 1 received meropenem (MIC > 8) and died

# Mortality by Definitive Treatment Strategy – Combination Therapy

<table>
<thead>
<tr>
<th>Definitive Treatment</th>
<th>n (%) (n=15)</th>
<th>Mortality, n (%) (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin + Carbapenem</td>
<td>5 (33%) 1 (7%) 1 (7%)</td>
<td>1 (20%) 0 0</td>
</tr>
<tr>
<td>Tigecycline FQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline + Carbapenem Aminoglycoside</td>
<td>3 (20%) 2 (12%)</td>
<td>0 0</td>
</tr>
<tr>
<td>Carbapenem + FQ</td>
<td>1 (7%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Cefepime + Gentamicin</td>
<td>1 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Aztreonam + FQ</td>
<td>1 (7%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary – New York

• Conclusion:
  – Antimicrobial combinations associated with improved outcomes

• Considerations:
  – All KPC isolates
  – Small sample size
  – Dose and duration of therapy not specified
  – Definition of combination therapy – agents regardless of *in vitro* activity
Combination Schemes with Carbapenemase-Producing \textit{K. pneumoniae} Bacteremia – Greece

• Inclusion
  – Patients with carbapenem resistant \textit{K. pneumoniae} bacteremia
  – PCR gene + carbapenemase production

• Primary outcome
  – 28-day all-cause mortality
  – Risk factors for mortality were compared between survivors and non-survivors

• Definitions
  – \textbf{Inadequate treatment}: administration of agents with no \textit{in vitro} activity and/or treatment < 48 hours
  – \textbf{Combination treatment}: treatment with $\geq 2$ \textit{in vitro} active agents

Combination Schemes – Association with Mortality

- All-cause 28-day mortality
  - 82 / 205 (40%)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total</th>
<th>Survivors (n = 123)</th>
<th>Non-survivors (n = 82)</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>103</td>
<td>75</td>
<td>28</td>
<td>27.2%</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>72</td>
<td>40</td>
<td>32</td>
<td>44.4%</td>
</tr>
<tr>
<td>No active therapy</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

p = 0.018 between combination vs. monotherapy

Factors Associated with Mortality in Carbapenem-Producing *K. Pneumoniae* Bacteremia

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of underlying disease</td>
<td></td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>3.25 (1.51-7.03)</td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>4.2 (2.19-8.08)</td>
</tr>
<tr>
<td>Severity of sepsis</td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>1.63 (0.74-3.59)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>2.15 (1.16-3.96)</td>
</tr>
<tr>
<td>ICU</td>
<td>1.36 (0.72-2.57)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>2.08 (1.23-3.51)</td>
</tr>
</tbody>
</table>
Outcomes of Patients Treated with Carbapenems Stratified by Carbapenem MIC

*High-dose carbapenem strategy

Summary - Greece

• Conclusion:
  – Supports combination therapy over monotherapy
  – Carbapenem combinations associated with improved mortality

• Considerations:
  – Majority KPC isolates
  – Moderate sample size
    – Subgroups too small to show true differences
  – High-dose carbapenem strategy – extended vs. traditional infusion?
  – Duration of antimicrobial therapy not addressed
Predictors of Mortality in Carbapenemase-Producing *K. pneumoniae* Bacteremia – Italy

• Inclusion
  – Adult patients with carbapenemase-producing *K. pneumoniae* bacteremia
  – Confirmed by PCR

• Primary Outcome
  – Death within 30 days of the first positive blood culture
  – Risk factors for mortality were compared between survivors and non-survivors

• Definition
  – **Adequate treatment**: at least 1 *in vitro* active agent
  – **Combination therapy**: treatment with ≥ 2 *in vitro* active agents
Mortality Outcomes: Monotherapy vs. Combination

- Overall 30-day mortality: 52/125 (41.6%)
  - 54.3% monotherapy
  - 34.1% combination therapy
  - p=0.02
### Multivariable Analysis – Risk Factors for Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation with septic shock</td>
<td>.008</td>
<td>7.17 (1.65–31.03)</td>
</tr>
<tr>
<td>Inadequate initial antimicrobial treatment</td>
<td>.003</td>
<td>4.17 (1.61–10.76)</td>
</tr>
<tr>
<td>High APACHE III score</td>
<td>&lt;.001</td>
<td>1.04 (1.02–1.07)</td>
</tr>
<tr>
<td>Postantibiogram therapy with tigecycline + colistin + meropenem</td>
<td>.01</td>
<td>0.11 (.02–.69)</td>
</tr>
</tbody>
</table>
Stratifying Mortality Outcome by Meropenem MIC in Patients Receiving Carbapenem Therapy

*Meropenem administered by extended infusion at 2 g Q8h

Summary – Italy

• Conclusion:
  – Supports combination therapy over monotherapy
  – Carbapenem combinations associated with improved mortality
    – Colistin + tigecycline + meropenem

• Considerations:
  – KPC isolates
  – Small sample size
    – Subgroups too small to show true differences
  – Extended infusion carbapenem
  – Duration of antimicrobial therapy not addressed
Combination Therapy on Mortality Risk – Cleveland Clinic

• Inclusion:
  – Adult patients admitted to an ICU with a blood culture positive for a carbapenem-resistant Gram-negative organism
    – Defined by 2009 CLSI breakpoints
    – Includes *Pseudomonas* and *Acinetobacter*

• Primary Objective
  – Prevalence of combination therapy

• Definitions
  – **Combination therapy**: concomitant use of ≥ 2 *in vitro* active agents for ≥ 48 h within the first 14 days of blood culture positivity
  – **Multiple agent use**: concomitant use of ≥ 2 agents for ≥ 48 h within the first 14 days of blood culture positivity, regardless of *in vitro* activity
Mortality Outcomes by Treatment Group

• 30-day survival: 78/168 (46.4%)
  – *K. pneumoniae*: 20/36 (55.5%)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Nonsurvivors (n=90)</th>
<th>Survivors (n=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>7 (7.8%)</td>
<td>25 (32.1%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Multiple-agent use</td>
<td>72 (80%)</td>
<td>68 (87.2%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Carbapenem use</td>
<td>43 (59.7%)</td>
<td>41 (52.6%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Appropriate antibiotics</td>
<td>48 (53.3%)</td>
<td>73 (93.6%)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Factors Associated with 30-day Mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.02 – 1.08)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1.15 (1.03 – 1.28)</td>
<td>0.01</td>
</tr>
<tr>
<td>CCI score</td>
<td>1.15 (0.98 – 1.34)</td>
<td>0.08</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>1.67 (0.62 – 4.49)</td>
<td>0.31</td>
</tr>
<tr>
<td>Appropriate antibiotics</td>
<td>0.14 (0.04 – 0.47)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>0.19 (0.06 – 0.56)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Summary – Cleveland Clinic

• Conclusion:
  – Supports combination therapy over monotherapy
    – When *in vitro* active combinations utilized
    – No additional benefit when carbapenem combinations utilized

• Considerations:
  – Included *Pseudomonas* and *Acinetobacter* species
  – Small sample size
  – Strongest definitions utilized
    – Concomitant therapy
Combination Therapy – In Summary

• Across all 4 studies
  – Combination therapy using *in vitro* active agents was associated with decreased mortality
  – Efficacy of carbapenem-containing regimens appear to be MIC- and dose-strategy dependent

• Limitations
  – Retrospective data – difficult to control for confounders
  – Non-standardized study definitions
  – Inconsistent dosing strategies
  – Factors not addressed
    – Time to combination therapy
    – Duration of therapy not addressed
NOVEL AGENTS
Ceftazidime-avibactam

• Novel non-B-lactam B-lactamase inhibitor improves ceftazidime activity against:
  – Ambler Class A – **KPC**
  – Ambler Class C
  – Some Ambler Class D

• Approved by FDA in April 2015
  – Expedited FDA review and approval under Generating Antibiotic Incentives Now (GAIN) Act
  – Unmet medical need

*renal dose adjustments

Lexicomp. Ceftazidime-Avibactam
Ceftazidime-avibactam PK/PD Principles

- %t > MIC: 40-50%

*renal dose adjustments

Dose of 2.5 g every 8 hours

<table>
<thead>
<tr>
<th></th>
<th>CRE MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>2</td>
<td>≤ 8/4</td>
<td>--</td>
<td>≥ 16/4</td>
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</table>

In Vitro Activity of Ceftazidime-Avibactam Against KPC

- Activity in two KPC-2 producing isolates

![Bar graph showing MIC values for VA-361 and VA-406 for CAZ, CAZ-AVI (1 mcg/mL), CAZ-AVI (2 mcg/mL), and CAZ-AVI (4 mcg/mL). The MIC values are as follows:
- CAZ: 512 mcg/mL
- CAZ-AVI (1 mcg/mL): 8, 8
- CAZ-AVI (2 mcg/mL): 4, 2
- CAZ-AVI (4 mcg/mL): 0.25, 0.06]
Ceftazidime-Avibactam in Rat Model with KPC-2
In Summary

• Literature on treatment for CRE bacteremia is heterogeneous with limitations
  – Retrospective
  – Small sample sizes
  – Focused on KPC-producers

• Optimal combination yet to be elucidated

• Ceftazidime-avibactam promising alternative to dated therapies
Treatment Algorithm For CRE Bacteremia

1\textsuperscript{st} line

- **KPC**: Ceftazidime-avibactam

2\textsuperscript{nd} line

- Ceftazidime-avibactam resistant
- B-lactam allergy
- Metallo-B-lactamase

- Colistin + Tigecycline
  - If carbapenem MIC ≤ 4
    - Consider addition of carbapenem

- Consider aminoglycoside if urinary source
Treatment Options for Bacteremia Secondary to Carbapenem-Resistant Enterbacteriaceae

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The speaker has no actual or potential conflict of interest in relation to this presentation