Dropping the “MIC”: Mono- versus Combination Therapy for Carbapenem-Resistant Enterobacteriaceae Bacteremia

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Learning Objectives:
1. Describe the emergence of carbapenemases in Enterobacteriaceae
2. Understand the current epidemiology of carbapenem-resistant Enterobacteriaceae
3. Explain the rational of combination therapy
4. Describe the therapeutic options available for treating carbapenem-resistant Enterobacteriaceae bacteremia
I. Enterobacteriaceae Microbiology
   a. Normal human gut flora and environmental organisms
   b. More than 70 species
   c. Involved in a range of infections
   d. Important cause of healthcare and community-associated infections

II. Gram-negative Rod (GNR) Bacteremia
   a. Significant problem in both hospitalized and community patients
   b. 25% of all blood stream infections (BSI) are caused by GNR
   c. Major cause of morbidity and mortality
      i. 15-40% mortality
   d. Rise in multi-drug resistant (MDR) infections poses increased difficulties

III. The Rise of Antibiotics Resistance
   a. The treatment of gram-negative bacteremia is increasingly complicated by the rising prevalence of multidrug-resistant strains of GNR
   b. The CDC illness and mortality estimates caused by antibiotic resistance
      i. 2,049,422 illnesses
      ii. 23,000 deaths

IV. Mortality Associated with Antibiotic Resistance
   a. Numerous studies have shown that inappropriate initial antimicrobial therapy has an independent adverse effect on mortality
   b. High mortality rates remain when controlling for confounders, such as infection type, pathogen, and APACHE II score

Figure 1: Impact of inappropriate initial antimicrobial therapy on mortality

A. Thompson
V. Mechanisms of Resistance\textsuperscript{14}
\begin{itemize}
  \item a. Porin channels
  \item b. Efflux pumps
  \item c. Target modification
  \item d. Enzymatic
\end{itemize}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{mechanisms.png}
\caption{Examples of mechanisms of antibiotic resistance\textsuperscript{15}}
\end{figure}

VI. Beta-Lactamases\textsuperscript{16}
\begin{itemize}
  \item a. Categorized into 1 of 4 classes
    \begin{itemize}
      \item i. Ambler class A through D
      \item ii. Class A or class C most commonly encountered
    \end{itemize}
  \item b. Class A
    \begin{itemize}
      \item i. Inhibited by β-lactamase inhibitors
      \item ii. Widely seen in Enterobacteriaceae
    \end{itemize}
  \item c. Class B
    \begin{itemize}
      \item i. Hydrolyze all β-lactams except aztreonam
      \item ii. Not inhibited by ANY available β-lactamase inhibitors
    \end{itemize}
  \item d. Class C
    \begin{itemize}
      \item i. Encoded on chromosome and inducible
      \item ii. Not inhibited by OLDER β-lactamase inhibitors
    \end{itemize}
\end{itemize}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Classification} & \textbf{Enzyme} & \textbf{Common Organisms} \\
\hline
Class A & TEM & \textit{E. Coli} \textit{K. pneumoniae} \\
 & SHV & \textit{KPC} \\
 & CTX-M & \\
 & KPC & \\
\hline
Class B & IMP & \textit{P. aeruginosa} \\
 & VIM & \textit{A. baumannii} \\
 & NDM & \\
\hline
Class C & AmpC & SPACE bugs \\
\hline
Class D & OXA & \textit{P. aeruginosa} \\
\hline
\end{tabular}
\caption{Ambler classification of beta-lactamases\textsuperscript{16}}
\end{table}

(SPACE = \textit{Serratio}, \textit{Pseudomonas}, \textit{Acinetobacter}, \textit{Citrobacter}, \textit{Enterobacter})
VII. Beta-Lactamases Through the Years

![Figure 3: Evolution of beta-lactamases](image)

VIII. Defining CRE

a. 2014 CDC Definition
   i. Nonsusceptible to imipenem, meropenem, or doripenem, and resistant to all 3rd generation cephalosporins

b. 2015 CDC Definition
   i. Resistant to imipenem, meropenem, doripenem, or ertapenem
   ii. Documentation that the isolate possess a Carbapenemase

IX. Mechanisms of Carbapenem Resistance

![Figure 4: Mechanisms of carbapenem resistance](image)

X. Carbapenemase Classification

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Classification</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>Class A</td>
<td>Hydrolyzes all beta-lactams</td>
</tr>
<tr>
<td>NDM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP</td>
<td>Class B</td>
<td>Hydrolyzes all beta-lactams except aztreonam</td>
</tr>
<tr>
<td>VIM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Thompson |
### Table 3: Incidence of CRE infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>2001</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1.6%</td>
<td>11%</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1%</td>
<td>1-2%</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>1.4%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

---

**XI. Epidemiology of Resistance**

a. Carbapenem Resistant Enterobacteriaceae (CRE)\(^{20}\)
   i. Uncommon in the United States before 1992
      1. National Nosocomial Infection Surveillance (NNIS) data from 1986 to 1990, reported only 2.3% of 1825 *Enterobacter* isolates tested nonsusceptible to imipenem
   ii. Rapidly increasing prevalence
      1. The first isolate harboring the KPC beta-lactamase was collected in 1996 and reported in 2001
      2. National Healthcare Safety Network (NHSN) data from 2006–2007, carbapenem resistance was reported in 10.8% of *K. pneumoniae* isolates as compared to <1% in 2000

**XII. Global Spread of CRE**

![Figure 5: Global spread of carbapenemases in Enterobacteriaceae\(^{21}\)](image)

**XIII. Incidence of CRE**

**XIV. KPC Epidemiology**
XV. Increase in Last Resort Antibiotic Use

![Figure 6: Distribution of Klebsiella pneumoniae carbapenemases infections](image)

Figure 6: Distribution of *Klebsiella pneumoniae* carbapenemases infections

XVI. New Antibiotic Approvals

![Figure 7: Utilization of last resort antibiotics, polymyxins and tigecycline, 127 VAMC](image)

Figure 7: Utilization of last resort antibiotics, polymyxins and tigecycline, 127 VAMC

XVII. Combating Antibiotic-Resistant Bacteria

a. Slow the emergence of resistance
b. Prevent the spread
c. Strengthen national One-Health surveillance efforts
d. Advance rapid identification and characterization
e. Accelerate therapeutic development
f. Improve international collaboration

Therapeutic Options

XVIII. Antimicrobials\textsuperscript{25-28}
a. Aminoglycosides
   i. Poor penetration and activity into lungs, abscesses, and the central nervous system
   ii. Inferior outcomes as monotherapy
      1. Higher microbiologic failure
      2. Higher mortality
b. Polymyxins
   i. Associated with emergence of resistance during therapy
   ii. High mortality monotherapy
c. Tigecycline
   i. High volume of distribution with low serum concentrations
   ii. Associated with increased mortality
      1. Boxed warning
d. Carbapenems

Pharmacokinetics

XIX. MICs and Breakpoints
a. Minimum Inhibitory Concentration (MIC)
   i. Lowest concentration that prevents visible growth of a microorganism on agar or in broth
b. Breakpoint
   i. Used in interpretation of results of susceptibility testing to define isolates
      1. Susceptible
      2. Intermediate
      3. Resistant

XX. Carbapenem Breakpoints

Table 4: Carbapenem Breakpoints for 2009 and 2010\textsuperscript{29-30}

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>CLSI 2009 Breakpoints</th>
<th>CLSI 2010 Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Doripenem</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(CLSI = Clinical and Laboratory Standards Institute)

XXI. Pharmacokinetics/Pharmacodynamics (PK/PD)
XXII. Pharmacokinetic of Carbapenems\textsuperscript{32-33}

a. Time
   i. 30\% Time > MIC
      1. Possibly 50\% Time > MIC

b. Concentration
   i. 4-5x MIC

XXIII. Prolonged Meropenem Infusion

XXIV. Prolonged Meropenem Infusion
Figure 11: Target attainment for 50% time above MIC for each meropenem dosage regimen at each MIC\textsuperscript{34}

<table>
<thead>
<tr>
<th>Literature Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXV. Literature Review</td>
</tr>
</tbody>
</table>


TREATMENT OUTCOME OF BACTEREMIA DUE TO KPC-PRODUCING KLEBSIELLA PNEUMONIAE: SUPERIORITY OF COMBINATION ANTIMICROBIAL REGIMENS

<table>
<thead>
<tr>
<th>Objective</th>
<th>To describe the treatment and outcomes of KPC-Producing Klebsiella pneumoniae BSI in a single large tertiary care center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Non-interventional, retrospective chart review of KPC-Producing Klebsiella pneumoniae BSI from Jan 2007 to May 2009 at Cleveland Clinic</td>
</tr>
</tbody>
</table>
| Population| All pts with positive BSI for KPC-Producing Klebsiella pneumoniae (first episode only)  
Only pts who received active in vitro therapy for >24 hours |
| Endpoints | Primary  
28-day mortality  
Secondary  
Risk factors for mortality |
| Results   | 41 patients identified  
Appropriate therapy  
Treatment with at least one agent for at least 48 hours to which the isolate was susceptible \textit{in vitro} based on the interpretative criteria from the CLSI published in 2011  
Empirical therapy  
Treatment given before final culture results became available  
Definitive therapy  
Antimicrobial therapy given after the susceptibility testing results became available, regardless of the \textit{in vitro} susceptibility to the agent  
Combination therapy  
Administration of two antimicrobials with Gram-negative activity for at least 48 hours after the susceptibility results became available, regardless of the \textit{in vitro} susceptibility to each agent  
Baseline Characteristics |
<table>
<thead>
<tr>
<th>Variable</th>
<th>Combination (n=15)</th>
<th>Monotherapy (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>6 (40)</td>
<td>11 (57.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Severity of Illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU at enrollment</td>
<td>10 (66.6)</td>
<td>10 (52.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17.4 ± 6.65</td>
<td>21.3 ± 8.69</td>
<td>0.15</td>
</tr>
<tr>
<td>Underlying Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>11 (73.3)</td>
<td>9 (47.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>3 (20)</td>
<td>3 (15.8)</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3 (20)</td>
<td>3 (15.8)</td>
<td>1</td>
</tr>
<tr>
<td>Transplant</td>
<td>8 (53.3)</td>
<td>0</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

- **Sources of Infection**
  - IV catheter (13; 31.7%)
  - Pneumonia (10; 24.4%)
  - Urinary tract infection (7; 17.1%)
  - Unknown (6; 14.6%)

- **Antibiotic Susceptibility**
  - 40 (75.5%) to colistin
  - 45 (89.9%) to tigecycline
  - 51 (96.2%) to gentamicin
  - 21 (39.6%) to meropenem

- **Treatment Regimens**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>Infection Mortality n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>15 (44)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Colistin-polymixin B with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>5 (33)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>3 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>19 (46)</td>
<td>11 (57.8)</td>
</tr>
<tr>
<td>Colistin-polymyxin B</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>Total</td>
<td>34 (83)</td>
<td>13 (38.2)</td>
</tr>
</tbody>
</table>

**Endpoints**

- Overall 28-day mortality
  - 39% (16/41)
- Definitive therapy 28-day mortality
  - 38.3% (13/34)
- Combination therapy
  - 13.3% (2/15)
- Monotherapy
  - 57.8% (11/19)
- Univariate and Multivariate Analysis
<table>
<thead>
<tr>
<th>Variable</th>
<th>Survived (n=25)</th>
<th>Died (n=16)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (12)</td>
<td>7 (43.7)</td>
<td>5.7 (0.98–3.68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>5 (31.2)</td>
<td>∞ (1.59–∞)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>0</td>
<td>3 (18.7)</td>
<td>∞ (0.72–∞)</td>
<td>0.05</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>13 (60)</td>
<td>2 (12.5)</td>
<td>0.13 (0.01–0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Multivariate Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>13 (60)</td>
<td>2 (12.5)</td>
<td>0.07 (0.009–0.71)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Author’s Conclusions**
- The use of combination therapy for definitive therapy appears to be associated with improved survival in bacteremia due to KPC-producing *K. pneumoniae*

**Critique**
- Small sample size
- Retrospective, observational study
- Choice of regimen closely associated with clinical status
- Treatment was based on old CLSI breakpoints
- Trend towards high severity of illness in monotherapy arm
- More transplant patients in combination therapy arm

**Take Home Points**
- Most common successful combo was colistin or tigecycline with a carbapenem
- Colistin and tigecycline monotherapy were associated with >50% mortality

**Table 6: Zarkotou et al. Clin Microbiol Infect. 2011;17(12):1798-803.**

Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment

**Objective**
- To investigate outcomes, risk factors for mortality and impact of appropriate antimicrobial treatment in patients with BSIs caused by molecularly confirmed KPC-producing *K. pneumoniae*

**Design**
- Observational, case-control study
- 2008 to 2010

**Population**
- 53 patients

**Endpoints**
- All-cause mortality
- Risk factors for mortality

**Results**
- Appropriate empirical treatment
  - Administration of in vitro active antimicrobials against the study isolates, within ≤24 hours from infection onset
- Appropriate definitive treatment
  - Administration of in vitro active antibiotics for at least 48 hours
- Microbiological
  - 2009 CLSI breakpoints for carbapenems
  - FDA breakpoint for tigecycline
  - EUCAST breakpoint for colistin
- Source of infection
  - Central venous catheters – 12 (22.6%)
  - Respiratory – 7 (13.2%)
  - Urinary tract – 6 (11.3%)
• Skin or soft tissue – 4 (7.6%)
• Central nervous system – 1 (1.9%)
• Unknown – 23 (43.4%)

• Susceptibilities
  o 40 (75.5%) to colistin
  o 45 (89.9%) to tigecycline
  o 51 (96.2%) to gentamicin
  o 21 (39.6%) to meropenem

• Treatment Regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>Infection Mortality, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>20 (57.1)</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>9 (26.5)</td>
<td>0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3 (8.8)</td>
<td>0</td>
</tr>
<tr>
<td>Colistin + carbapenem</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Colistin + gentamicin</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Colistin + gentamicin</td>
<td>2 (5.8)</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenem + gentamicin</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>15 (42.9)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Colistin</td>
<td>7 (20)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>5 (14.7)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>1 (2.9)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>7 (20)</td>
</tr>
</tbody>
</table>

Endpoints

• Overall mortality
  o 52.8% (28/53)
• Infection mortality
  o 34% (18/53)
• Appropriate therapy infection mortality
  o 20% (7/35)
• Combination
  o 0% (0/20)
• Monotherapy
  o 46.7% (7/15)

• Univariate Factors of Infection Mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-catheter-related bacteremia</td>
<td>0.13 (0.01–1.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Appropriate antimicrobial treatment</td>
<td>0.16 (0.04–0.56)</td>
<td>0.003</td>
</tr>
<tr>
<td>Combination schemes</td>
<td>--</td>
<td>0.001</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe sepsis or septic shock</td>
<td>14 (3.50–55.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• Multivariate Factors of Infection Mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score at infection onset</td>
<td>1.26 (1.04–1.53)</td>
<td>0.021</td>
</tr>
<tr>
<td>Age</td>
<td>1.21 (1.02–1.44)</td>
<td>0.029</td>
</tr>
<tr>
<td>Appropriate antimicrobial treatment</td>
<td>0.05 (0.003–0.74)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

**Author’s Conclusions**
- Mortality associated with severity of illness, older age, and inappropriate treatment

**Critique**
- Small sample size
- Retrospective design
- Older CLSI breakpoint
- Baseline characteristics were not stratified between mono vs combination therapy

**Take Home Points**
- Active in vitro antimicrobials associated with better outcomes
- Combination therapy associated with improved survival

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*Predictors of Mortality in Bloodstream Infections Caused by Klebsiella pneumoniae Carbapenemase–Producing K. pneumoniae: Importance of Combination Therapy*

**Objective**
- To pinpoint risk factors for mortality in bloodstream infections caused by KPC-producing *K. pneumoniae*

**Design**
- Multicenter retrospective cohort study
- 2010 to 2011

**Population**
- 125 patients with BSIs caused by KPC-*K. pneumoniae*

**Endpoints**
- Risk factors for mortality
- Impact of antimicrobial regimens used in the nonempirical phase of treatment

**Results**
- **Adequate therapy**
  - Therapy including at least 1 drug displaying in vitro activity against the KPC-*K. pneumoniae* isolate
- **Combination therapy**
  - >1 in vitro-active drugs

- **Microbiological**
  - Revised CLSI breakpoints for carbapenems
  - FDA breakpoint for tigecycline
  - EUCAST breakpoint for colistin

- **Source of infection**
  - Central venous catheters – 13 (10.4%)
  - Respiratory – 28 (22.4%)
  - Urinary tract – 17 (13.6%)
  - Other – 5 (4%)
  - Unknown – 75 (60%)

- **Susceptibilities**
  - **Meropenem**
    - ≥16mg/L – 78 (62.4%)
    - 8 mg/L – 17 (13.6%)
    - 4 mg/L – 16 (12.8%)
    - 2 mg/L – 13 (10.4%)
  - 1 mg/L – 1 (0.8%)
  - Colistin – 110 (88%)
  - Tigecycline – 114 (91.2%)
Gentamicin – 118 (94.4%)

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monotherapy (n=46)</th>
<th>Combination (n=79)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65 ± 15</td>
<td>61 ± 16</td>
<td>0.08</td>
</tr>
<tr>
<td>Severity of Illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>14 (30.4)</td>
<td>39 (49.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>APACHE III</td>
<td>30 ± 20</td>
<td>34 ± 21</td>
<td>0.27</td>
</tr>
<tr>
<td>Underlying Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>7 (15.2)</td>
<td>9 (11.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>5 (10.9)</td>
<td>7 (8.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (19.6)</td>
<td>20 (25.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Shock</td>
<td>8 (17.4)</td>
<td>9 (11.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Isolates with suboptimal</td>
<td>4 (8.6)</td>
<td>22 (27.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>colistin/tigecycline MICs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment Regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Died (n = 52)</th>
<th>Survivors (n = 73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>25 (48.1)</td>
<td>21 (28.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>10 (19.2)</td>
<td>9 (12.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Colistin</td>
<td>11 (21.5)</td>
<td>11 (15.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4 (7.6)</td>
<td>1 (1.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>27 (51.9)</td>
<td>52 (71.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>2-drug combinations</td>
<td>23 (44.2)</td>
<td>33 (45.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Tigecycline + colistin</td>
<td>7 (13.4)</td>
<td>16 (21.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Tigecycline + gentamicin</td>
<td>6 (11.5)</td>
<td>6 (8.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>3-drug combinations</td>
<td>4 (7.7)</td>
<td>19 (26.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Tigecycline + colistin + meropenem</td>
<td>2 (3.8)</td>
<td>14 (19.2)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Endpoints

- 30-day mortality
  - 41.6% (52/125)
- Monotherapy
  - 54.3% (25/46)
- Combination therapy
  - 34.1% (27/79) - P = .02

Outcomes stratified by carbapenem MIC

<table>
<thead>
<tr>
<th>Meropenem MIC (mcg/mL)</th>
<th>Total</th>
<th>Nonsurvivors</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1 (100)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4 (100)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>2 (20)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>≥16</td>
<td>17</td>
<td>6 (35.2)</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>9 (25)</td>
<td>27 (75)</td>
</tr>
</tbody>
</table>

Multivariate Predictors of Mortality
<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>7.17 (1.65–31.03)</td>
<td>0.008</td>
</tr>
<tr>
<td>Inadequate initial antimicrobial treatment</td>
<td>4.17 (1.61–10.76)</td>
<td>0.03</td>
</tr>
<tr>
<td>High APACHE III scores</td>
<td>1.04 (1.02–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Definitive therapy with tigecycline + colistin + meropenem</td>
<td>0.11 (.02–.69)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Author’s Conclusions**

- KPC-*K. pneumoniae* BSIs are associated with high mortality
- Combination therapy is more effective than active monotherapy

**Critique**

- Small sample size
- Retrospective design
- Clinical decisions based on old CLSI breakpoints for a portion of the study period
- High-dose extended infusions

**Take Home Points**

- Combination of tigecycline, colistin, and meropenem was associated with lower mortality
- Meropenem high-dose extended infusions utilized
- Benefits of carbapenem seen up to MIC of 8


**Objective**

- To evaluate the clinical outcome of patients with carbapenemase producing-*K. pneumoniae* (CP-Kp) bloodstream infections, identify predictors of mortality, and evaluate the various antibiotic schemes employed

**Design**

- Retrospective, Observational Study of 2 tertiary hospitals
- 2009 to 2010

**Population**

- 205 patients identified
  - 163 (79.5%) were infected with KPC or KPC and VIM, and 42 were infected with VIM producers

**Endpoints**

- Primary
  - Mortality
- Secondary
  - Predictors of mortality
  - Evaluate the various antibiotic schemes employed

**Results**

- Appropriate therapy
  - Treatment with at least one agent for at least 48 hours to which the isolate was susceptible *in vitro* based on the interpretative criteria from the CLSI published in 2011
- Definitive therapy
  - Antimicrobial therapy given after the susceptibility testing results became available, regardless of the *in vitro* susceptibility to the agent
- Combination therapy
  - Administration of two antimicrobials with Gram-negative activity for at least 48 hours after the susceptibility results became available, regardless of the *in vitro* susceptibility to each agent
- Source of infection
  - Lung – 43 (21%)
  - Abdomen – 29 (14.1%)
  - Intravascular catheter – 22 (10.7%)
  - Genitourinary tract – 19 (9.3%)
  - Skin or soft tissue – 6 (2.9%)
  - CNS – 3 (1.5%)
  - Unknown – 83 (40.5%)
- Susceptibilities
- Ciprofloxacin (2.4%)
- Meropenem (46.3%)
- Tigecycline (84.9%)
- Colistin (74.6%)
- Gentamicin (68.8%)
- Amikacin (31.7%)

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monotherapy (n=72)</th>
<th>Combination therapy (n=103)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.5 (14.4)</td>
<td>58.4 (19.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>ICU</td>
<td>39 (54.2)</td>
<td>62 (60.2)</td>
<td>0.427</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2 (0-3)</td>
<td>2 (0-3)</td>
<td>0.474</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (9.7)</td>
<td>7 (6.8)</td>
<td>0.483</td>
</tr>
<tr>
<td>Urinary source</td>
<td>7 (9.7)</td>
<td>6 (5.8)</td>
<td>0.333</td>
</tr>
<tr>
<td>Septic shock</td>
<td>15 (20.8)</td>
<td>16 (15.5)</td>
<td>0.629</td>
</tr>
</tbody>
</table>

### Treatment Regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survived</th>
<th>Died</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>75</td>
<td>28</td>
<td>27.2</td>
</tr>
<tr>
<td>Carbapenem-containing regimen:</td>
<td>25</td>
<td>6</td>
<td>19.3</td>
</tr>
<tr>
<td>Tigecycline + aminoglycoside or colistin</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Carbapenem-sparing regimen:</td>
<td>50</td>
<td>22</td>
<td>30.6</td>
</tr>
<tr>
<td>Tigecycline + aminoglycoside + colistin</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tigecycline + aminoglycoside</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Tigecycline + colistin</td>
<td>16</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside + colistin</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>40</td>
<td>32</td>
<td>44.4</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

### Endpoints
- 28-day all-cause mortality
  - 40% (82/205)
- Appropriate therapy mortality
  - 38.3% (13/175)
    - Combination therapy: 27.2% (28/103)
    - Monotherapy: 44.4% (32/72)
- Factors associated with mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock/sepsis</td>
<td>2.15 (1.16–3.96)</td>
<td>0.015</td>
</tr>
<tr>
<td>Ultimately fatal/nonfatal</td>
<td>3.25 (1.51–7.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>Rapidly fatal/nonfatal</td>
<td>4.20 (2.19–8.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monotherapy/combination therapy</td>
<td>2.08 (1.23–3.51)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

### Therapy by severity of illness
Outcomes of stratified by carbapenem MIC

<table>
<thead>
<tr>
<th>Carbapenem MIC (mcg/mL)</th>
<th>Carbapenem combination with:</th>
<th>In vitro active agent(s)</th>
<th>In vitro inactive agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survived/Died</td>
<td>Mortality, %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Survived/Died</td>
<td>Mortality, %</td>
</tr>
<tr>
<td>≤8</td>
<td></td>
<td>25/6</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/7</td>
<td>58.3</td>
</tr>
<tr>
<td>&gt;8</td>
<td></td>
<td>20/11</td>
<td>35.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/2</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Author’s Conclusions
• Combination therapy was strongly associated with survival, mostly due to the effectiveness of the carbapenem containing regimens

Critique
• Small sample size
• Retrospective in nature
• Breakpoints used for carbapenems
• Meropenem MIC analysis

Take Home Points
• Combinations with carbapenem containing regimens were most effective
• Combination therapy more beneficial in severely ill patients
• Beneficial carbapenem effect up to MIC of 8

Conclusions

XXVI. Future Direction
a. Beta-lactams
   i. Ceftazidime-Avibactam
   ii. Ceftazidime-Avibactam
   iii. Aztreonam-Avibactam
   iv. Ceftaroline-Avibactam
   v. Imipenem/cilastatin+relebactam
   vi. Carbavance
b. Aminoglycosides
   i. Plazomicin
c. Fluoroquinolone
   i. Finafloxacin
d. Tetracyclines
   i. Eravacycline
   ii. Omadacycline
XXVII. Therapeutic Recommendations
   a. Infectious diseases consult
   b. MIC ≤8 μg/mL
      i. High dose extended infusion meropenem/doripenem backbone
         1. Consider additional in vitro active antimicrobial(s) for critically ill patients
            a. Colistin and/or high-dose tigecycline and/or aminoglycoside
   c. MIC >8 μg/mL
      i. Combination of 2 or 3 in vitro active antimicrobials
         1. Colistin and/or high-dose tigecycline and/or aminoglycoside

Appendix

Breakpoints - Carbapenems

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>CLSI Breakpoints</th>
<th>EUCAST Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤0.5</td>
<td>1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td>Doripenem</td>
<td>≤1</td>
<td>2</td>
</tr>
</tbody>
</table>

Breakpoints – Aminoglycosides

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>CLSI Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤4</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤4</td>
</tr>
<tr>
<td>Amikacin</td>
<td>≤16</td>
</tr>
</tbody>
</table>

Breakpoints - Tigecycline

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>US FDA Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤2</td>
</tr>
</tbody>
</table>

Breakpoint – Colistin

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>EUCAST Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Colistin</td>
<td>≤2</td>
</tr>
</tbody>
</table>

References


20th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.


