Combination Therapy for KPC Producers

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Carbapenem Producing Enterobacteriaceae (CPE). A major Public Health Threat

• Increased mortality (25%-70%)

• Limited treatment options

• High potential for spread
Current Trends in Epidemiology of CPEs

Hospital setting
- Predominant bacterial host
  - *K. pneumoniae*
- Predominant enzymes
  - KPC
  - VIM
  - NDM
  - OXA-48

Community setting
- Predominant bacterial host
  - *E. coli*
- Predominant enzymes
  - NDM
  - OXA-48

- First reported as KPC-1 (later corrected to be KPC-2) in 2001
- Isolated from a patient with nosocomial infection in an ICU in a North-Carolina hospital (1996?) as part of routine surveillance (ICARE project)
- Hydrolyze penicillins, $\beta$-lactamase inhibitors, and all cephalosporins, monobactams, carbapenems and display an extensive drug resistant phenotype
KPC genetic background

• *bla*KPC genes are located onto on Tn3 related Tn4401 transposon which has spread to various Inc groups plasmids (IncFIIAS, IncFIIk/B, IncN, InL/M, IncX, IncR and some non typable)

• *bla*KPC genes have been identified in different bacterial species and in many different clonal lineages

• The predominant bacterial host is Klebsiella and the predominant clone is the ST258
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# KPC Infections from 114 Hospitals

*National Action Plan (2010-2011)*

<table>
<thead>
<tr>
<th>Department</th>
<th>Source of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>51.6%</td>
</tr>
<tr>
<td>Medicine</td>
<td>31.5%</td>
</tr>
<tr>
<td>Surgery</td>
<td>16.9%</td>
</tr>
<tr>
<td></td>
<td>Pneumonia 32.5%</td>
</tr>
<tr>
<td></td>
<td>Bacteremia 31.5%</td>
</tr>
<tr>
<td></td>
<td>UTIs 23%</td>
</tr>
<tr>
<td></td>
<td>SSI 12.9%</td>
</tr>
</tbody>
</table>

Hellenic Center for Disease Control and Prevention (KEELPNO)
Estimated Mortality Rate Among Hospitalized Patients with CRKP infections

✓ Israel 2007: 8/100,000 population
  Schwaber MJ. JAMA 2008; 300:2911

✓ Greece 2011: 10/100,000 population
  Hellenic Center for Disease Control and Prevention
  (National Action Plan)
All-cause Mortality of 338 Patients with Kp Bloodstream Infections

28-day mortality according to carbapenemases
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Slide withheld at request of author
Antimicrobial Agents with \textit{in Vitro} Activity against KPC Kp

- Gentamicin
- Carbapenems
- Colistin
- Tigecycline
- Fosfomycin
Resistance Profile of CPKP

Klebsiella

Colistin: 315 (23%)
Gentamicin: 274 (19%)
Tigecycline: 293 (23%)

Hellenic Center for Disease Control and Prevention
Inferior Clinical Efficacy of Colistin. Why?

- **Suboptimal dosing regimen of the drug.**
  - multivariate analysis of survival data showed that a lower total daily dosage of intravenous colistin was associated with increased mortality (Falagas et al. Int. J. Antimicrob. Agents 2010; 35:194 – 199).

- **Delay in attaining an efficacious drug concentration**

- **Optimal dosing regimen**
  - Once daily, twice daily or three times daily?
Mortality imbalance in the Tigecycline Phase 3 and 4 Clinical Trials

- Logistic regression modelling identified baseline bacteraemia as a predictor of mortality in the TGC treatment group.

- The mortality rate for TGC subjects with VAP and baseline bacteraemia was 50% (9/18 subjects) versus 7.7% (1/13 pts) in the COM group.

CID 2012:54 (15 June) • Prasad et al
Fosfomycin for the Treatment of 11 Critically-ill Patients infected with CR *K. pneumoniae*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>67.5</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.4</td>
</tr>
<tr>
<td>No. of organ dysfunction, median</td>
<td>3</td>
</tr>
<tr>
<td>VAP</td>
<td>5</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
<tr>
<td>All-cause in hospital mortality</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

All patients received combination Rx Fosfomycin with CMS or GM or Pip/tazo

*Michalopoulos A et. al Clin Microbiol Infect 2010; 16: 184-6*
Can we use carbapenems against carbapenemase-producing organisms?

- Experimental data
- PK/PD studies
- Human data
Distribution of Meropenem MICs for 372 Consecutive *K. pneumoniae* Blood Isolates

<table>
<thead>
<tr>
<th>MICs (μg/ml)</th>
<th>≤0.032</th>
<th>0.06</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>≥32</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIM</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPC, KPC+VIM</td>
<td></td>
<td>60</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO CARBAPENEMASE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. of Isolates

MICs (μg/ml)
Comparison of the efficacies of two different doses of doripenem against carbapenemase-producing K. pneumoniae isolates in immunocompromised and immunocompetent animals.

MIC: 354=4, 356=8, 359=16
A critical interpretation of the animal infection model data suggests that optimized regimens of carbapenems are able to achieve at least a static effect in severely compromised hosts and a modest bactericidal effect in immunocompetent animals infected with KPC-positive isolates with MICs up to 4 or even up to 8 μg/ml.

Pharmacokinetics of three different dosing regimens of meropenem
Simulated Target Attainment Probabilities for 50% T>MIC of three Different Dosing Regimens of Meropenem
### Carbapenem Monotherapy in 50 Patients with Serious CPE Infections

(Results compiled from 15 studies)

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>No. of patients</th>
<th>No. of successes</th>
<th>No. of failures</th>
<th>% failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>17</td>
<td>12</td>
<td>5</td>
<td>29.4</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>75</td>
</tr>
</tbody>
</table>

Tzouvelekis et al CMR 2012; 25: 682-707
Synergy Studies
**In vitro** activity of drug combinations against KPC-Kp

**Carbapenem combinations**

- CB+AG: N=16
- CB+Tig: N=9
- CB+PM: N=58

**Other combinations**

- CS+Gen: N=12
- Fos+other: N=268
- CS+Tig: N=4

Mean bacterial densities over 48 h for KPC-producing Klebsiella pneumoniae isolates with a tigecycline MIC of 1 μg/ml and a meropenem MIC of 8 μg/ml.

A

B

Bacterial densities of KPC 354 over 24 h in the in vitro chemostat model (doripenem MIC, 4 μg/ml).

Characterization of porin expression in *KPC producing Kp* identifies isolates most susceptible to the combination of colistin and carbapenems

- Colistin-doripenem combination was more effective than any of the agents alone against KPC-Kp
- The addition of ertapenem to colistin-doripenem further enhanced bactericidal activity and synergy
- The enhanced activity of colistin-doripenem-ertapenem was observed exclusively against KPC-Kp isolates with high levels of *ompK35* or *ompK36* expression.

Bactericidal Activity and Degree of killing of single, 2-, 3- drug combinations against 12 KPC-Kp isolates

Hong JH Antimicrob. Agents Chemother 2013
Survival of Animals Infected with KPC-Kp Clinical Isolates (pneumonia in neutropenic mice)

- KP6153
  - MICs: AM=32, DOR=32mg/L
- KPVM9
  - MICs: AM=64, DOR=16mg/L

Clinical studies
Outcomes of infections caused by carbapenemase-producing Klebsiella pneumoniae, according to treatment regimen.

Outcome of Infections Caused by KPC-Kp According to Treatment Regimen

41 patients with KPC-Kp BSIs
15 pts received combination Rx
  Polymyxines based=7
  Tigecycline based=5
  Other=3
19 pts received monotherapy
  Polymyxines=7
  Tigecycline=5
  Carbapenem=4
  Other=3
7 pts received Rx for < 48 h
# Treatment Outcome of Bacteremia Due to KPC-Producing Klebsiella pneumoniae: Superiority of Combination Antimicrobial Regimens

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Survived N (%)</th>
<th>Died N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>8 (42)*</td>
<td>11 (58)*</td>
</tr>
<tr>
<td>Combination</td>
<td>13 (86.7)**</td>
<td>2 (13.3%)</td>
</tr>
</tbody>
</table>

* In 3 pts the infecting organism was resistant to administered agent (CLSI 2009)
** In 5 pts the infecting organism was resistant to carbapenems (CLSI 2009)

## Mortality of Patients with KPC BSIs According to Treatment

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Died/Survived</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>25/21</td>
<td>54.3%</td>
</tr>
<tr>
<td>2 drug combination</td>
<td>23/33</td>
<td>41.1%</td>
</tr>
<tr>
<td>3 drug combination</td>
<td>4/19</td>
<td>17.4%</td>
</tr>
<tr>
<td>TIG + COL + MER</td>
<td>2/14</td>
<td>12.5%</td>
</tr>
<tr>
<td>TIG + GENT + MER</td>
<td>1/5</td>
<td>16.7%</td>
</tr>
<tr>
<td>COL + GENT + MER</td>
<td>1/0</td>
<td>100%</td>
</tr>
</tbody>
</table>

Kaplan Meier Curves of Survival Probability of Patients with KPC BSIs According to Treatment

\[ P = 0.002 \]
## Multivariate Analysis of Factors Associated with all-cause 30-day Mortality of Patients with KPC BSIs

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>0.008</td>
<td>7.17 (1.65-31.03)</td>
</tr>
<tr>
<td>APACHE</td>
<td>&lt;0.001</td>
<td>1.04 (1.02-1.07)</td>
</tr>
<tr>
<td>Inadequate empirical Rx</td>
<td>0.003</td>
<td>4.17 (1.61-10.76)</td>
</tr>
<tr>
<td>Definitive Rx Col+tigecl+merrop</td>
<td>0.01</td>
<td>0.11 (0.02-0.69)</td>
</tr>
</tbody>
</table>

*Tumbarello M et al. CID 2012; 55: 943*
Carbapenem-sparing antibiotic regimens for infections caused by KPC-producing Klebsiella pneumoniae in ICU

- 26 episodes in 22 patients
- 11 episodes were VAP, 5 VAP+bacteremia, 7 BSIs, and 3 other infections
- Treatment regimens
  - TIG + GENT + FOSFO = 8
  - TIG + COL + FOSFO = 5
  - TIG + COL + GENT = 5
  - TIG + GENT = 5
  - TIG + COL = 1
  - COL + GENT = 1
  - TIG = 1
- Overall favorable response 24/26 (92%)

Sbrana F Clinical Infectious Diseases 2013
Prospective Observational Study of *K. pneumoniae* BSIs

- Consecutive patients with *K. pneumoniae* BSIs
- A total of 338 patients were included in the analysis
  - 133 carbapenemase-negative
  - 205 carbapenemase-positive
  - 42 VIM-positive
  - 163 KPC/KPC+VIM
Treatment of Patients Infected with CPKP

- 12 pts received no active therapy
- 72 pts received one active drug
- 103 pts > 1 active drug
- 18 pts received Rx for <48 h and were excluded from the analysis

The pts who received 1 active drug were comparable with those who received > 1 active drug in terms of severity of underlying diseases, severity of sepsis, ICU or no ICU stay
Online Lecture Library

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## Novel Agents in Clinical Development with Activity Against KPC-Kp

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avibactam</td>
<td>Phase III</td>
<td>BLI, not effective against metallo-β-lactamases (MBLs)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Phase III (entering)</td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK7655</td>
<td>Phase II</td>
<td>BLI, not effective against MBLs</td>
</tr>
<tr>
<td>Imipenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biapenem</td>
<td>Phase I</td>
<td>Boronate inhibitor</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Phase II (completed)</td>
<td>Compromised by rRNA methylases which are present in NDMs</td>
</tr>
</tbody>
</table>
Conclusions

• The in vitro and in vivo data along with the current clinical experience indicate that combination therapy is more effective than monotherapy in the treatment of infections caused by KPC-producers.