PK-PD and ANTIBIOTIC RESISTANCE
Lessons Learned
24 September 2014
• Does the presence or absence of a resistance determinant(s) predict outcome?

• What is the relationship between drug exposure and resistance emergence?

• Can we alter the shape of drug exposure to increase our chances of attaining positive outcomes?

• How big a challenge is effect site penetration and associated variability?

• Is the answer simply the “not so simple” combination therapy?
MIC DISTRIBUTION PATTERNS
Cefepime versus Klebsiella pneumoniae

Key Question: Does the presence or absence of a resistance determinant predict outcome?

EXPOSURE & RESPONSE IN MICE

Versus Non-ESBL Producing Strains

The Answer: It is not the presence or absence of resistance determinants that predict outcome, but rather the drug exposure indexed to MIC.

CLINICAL DATA

Bacteremic Patients with ESBL-Producing Isolates

Key Question: Are there clinical data to support this non-clinical observation?

The Answer: Yes! Just like in animal infection models, drug exposure indexed to MIC predicts outcome.

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Success/Total (n/N)</th>
<th>Percent Success (n/N • 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>8/11</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>6/8</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>3/9</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>1/7</td>
<td>14</td>
</tr>
</tbody>
</table>

Clinical outcome with cephalosporin mono-therapy in 35 patients with bacteremia due to cephalosporin-susceptible ESBL-producing Klebsiella spp. or E. coli as defined by 2005 CLSI interpretive criteria

EXPOSURE & RESPONSE IN VITRO *Fluoroquinolones and P. aeruginosa*

**Key Question:** What is the relationship between drug exposure and resistance emergence?

EXPOSURE & RESPONSE IN VITRO
Ceftolozane/Tazobactam and E. coli

U-SHAPED EXPOSURE & RESPONSE IN MAN
Daptomycin in Bacteremia-Endocarditis

Key Question: Are there clinical data to support these non-clinical observation?

The Answer: In patients, the shape of the relationship between drug exposure and response can be that of an inverted-U

<table>
<thead>
<tr>
<th>AUC:MIC Ratio</th>
<th>↑ MIC</th>
<th>↔ MIC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1485</td>
<td>0% (0)</td>
<td>100% (21)</td>
<td>21</td>
</tr>
<tr>
<td>≥ 1485 - &lt; 1695</td>
<td>38% (3)</td>
<td>62% (5)</td>
<td>8</td>
</tr>
<tr>
<td>≥ 1695</td>
<td>11% (8)</td>
<td>89% (64)</td>
<td>72</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>90</td>
<td>101</td>
</tr>
</tbody>
</table>

Pearson Chi-square test P = 0.01

Note: Increased MIC was defined as ≥ 4 fold increase in MIC relative to baseline

EXPOSURE-RESPONSE IN MAN

Time to Decreased Susceptibility

U-SHAPED EXPOSURE & RESPONSE IN MAN
Fluoroquinolones in Tuberculosis Meningitis

Key Question: How does the duration of treatment impact the relationship between drug exposure and resistance emergence?

The Answer: In pre-clinical infection models, as the duration of therapy increases, so too does the magnitude of drug exposure needed to suppress resistance.

IMPACT OF EXPOSURE SHAPE

Same Exposure Administered Three Ways

Key Question: Can we alter shape of drug exposure to increase our chances of attaining positive outcomes?

Azithromycin (500 mg load, then 250 mg/day or 500 mg QD X 3 days or 1500 mg X 1 dose) against *H. influenzae* in a Mongolian gerbil acute otitis media infection model

Okusanya OO, Forrest A, Booker BM, Bhavnani SM, Girard D, Ambrose PG. Pharmacokinetics and pharmacodynamics of azithromycin in gerbils with *Haemophilus influenzae* middle ear infection. Presented at 106th American Society for Clinical Pharmacology and Therapeutics, 2005
The identical AUC was administered in two ways with very different effect.

A NEW ORITAVANCIN DOSE REGIMEN

PK-PD Assessment of 200 & 1200 mg Regimens

Box plots represent the median and interquartile range for daily average total-drug AUC:MIC ratios based on simulations of 2,000 patients. The associated whiskers represent the 5th and 95th percentile for the daily average total-drug AUC:MIC ratios. The horizontal solid and dashed lines represent the average total-drug AUC:MIC targets of 1078 and 1204 associated with net bacterial stasis and a 1 log_{10} CFU decline, respectively, based on data from a murine thigh-infection model for S. aureus after 48 hrs of study [Okusanya OO, et. al., ICAAC 2009. Abstract A1-1287]. Data on File, The Medicines Company.
ORITAVANCIN NOVEL DOSE REGIMENS
A Phase 2 Study

<table>
<thead>
<tr>
<th>Population (N)</th>
<th>Percent Success at Test-Of-Cure Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg daily for 3-7 days</td>
</tr>
<tr>
<td>ITT (300)</td>
<td>72.4</td>
</tr>
<tr>
<td>Clinical evaluable (228)</td>
<td>72.4</td>
</tr>
<tr>
<td>Microbiologically evaluable (161)</td>
<td>69.1</td>
</tr>
</tbody>
</table>

As early exposure intensity increases, so too does efficacy

### Key Question: How big a challenge is effect site penetration and associated variability?

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC(<em>{ELF}/AUC</em>{SERUM})</th>
<th>Median</th>
<th>5(^{th}) – 95(^{th}) Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin(^1)</td>
<td>1.43</td>
<td>1.43</td>
<td>0.14 – 19</td>
</tr>
<tr>
<td>Tigecycline(^2)</td>
<td>1.15</td>
<td>1.15</td>
<td>0.56 – 5.2</td>
</tr>
<tr>
<td>Ceftobiprole(^3)</td>
<td>0.153</td>
<td>0.153</td>
<td>0.035 – 7.87</td>
</tr>
</tbody>
</table>

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The Answer: Effect site penetration and associated variability is likely a huge challenge

- Given the **effect site penetration lower margins** and the **high exposures** needed to **prevent resistance**, it may be mission impossible to prevent resistance using mono-therapy with safe dosing regimens.

- Combination therapy a must to push us “over the hump” of the inverted U

COMBINATION THERAPY

Is The Answer as Simple as it Sounds?

Key Question: Should we be simply administering drug combinations that are synergistic or at least additive?

The Answer: What makes or breaks a regimen is not the presence or absence of synergy but is regimen activity

- Traditionally, we think of antimicrobial interactions as synergistic, additive or antagonistic
  - While interesting, these categories miss the point
    - Synergistic agents can have horrible activity and visa versa
- Vancomycin and rifampin are often antagonistic
  - Rifampin wildly active but resistance emerges rapidly;
  - Vancomycin prevents rifampin resistance emergence; and
  - Together are a more active regimen than either alone
### COMBINATION THERAPY

**Colistin Combinations Against A. baumannii**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Log Kill (range)</th>
<th>Log Kill due to Synergy (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem (N =12)</td>
<td>8.8 (8-9)</td>
<td>5.8 (0-8)</td>
</tr>
<tr>
<td>Cefepime (N = 11)</td>
<td>8.3 (7-9)</td>
<td>7 (4.5-7)</td>
</tr>
<tr>
<td>Amikacin (N = 11)</td>
<td>7.8 (3-9)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Teicoplanin (N = 11)</td>
<td>7.5 (7-9)</td>
<td>5.5 (0-7)</td>
</tr>
<tr>
<td>Rifampin (N = 11)</td>
<td>6.9 (3-9)</td>
<td>0.1 (0-1)</td>
</tr>
</tbody>
</table>

TAKE HOME MESSAGES *It’s About the Magnitude, Shape and Duration of Drug Exposure!*

- Drug exposure indexed to MIC, rather than the presence or absence of resistance determinants, predicts response
  - *Think about magnitude of drug exposure* when designing regimens for drug-resistant pathogens
  - The trade-off may be, but not necessarily, more toxicity
- **Think about manipulating drug exposure shape** to take advantage of each drug’s PK-PD profile to provide:
  - Best chance to maximize bacterial kill,
  - Best chance to maximize positive clinical outcomes,
  - Best chance to reduce spontaneous mutation, and
  - Best chance to eliminate a pre-existing resistant subpopulations
TAKE HOME MESSAGES  It’s About the Magnitude, Shape and Duration of Drug Exposure!

• Relationships between drug exposure and resistance emergence are **U-shaped and time-dependent**
  o Just don’t think about magnitude and shape, *but also therapy duration*
  o Consider front-loading exposure and *shortening therapy* for antibiotics with high resistance potential

• Effect site penetration variability is high and often will necessitate the need for combination therapy

• Consider regimens, not simply drugs
  o Consider multiple, combination administration routes
  o Consider combining multiple new active drugs rather than one new active drug with less active old ones
THANK YOU FOR YOUR ATTENTION

Questions, Comments or Wise Remarks?