Continuous Infusion of Beta-Lactams in Critically Ill Patients

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Presentation Outline

- Pharmacology of Beta-Lactams
- Current Problem
- Clinical Question
- Evidence
- Potential Advantages
- Drawbacks
- Applicability and Dosing
- Conclusion
Pharmacology of Beta-Lactams
How beta-lactams work
Mechanism of Action

- Inhibition of cell wall synthesis
- Beta lactam antibiotics target the penicillin-binding proteins or PBPs
  - Four-membered, nitrogen-containing beta-lactam ring at the core of their structure, which is key to the mode of action
- The beta-lactam ring portion of this group of antibiotics binds to these different PBPs, rendering them unable to perform their role in cell wall synthesis
- Classes of beta-lactams: penicillins, cephalosporins, carbapenems
Activity

- Generally bactericidal
- Broad-spectrum: carbapenems, 2nd, 3rd and 4th generation cephalosporins
- Narrow spectrum: penicillin, 1st generation cephalosporins, monobactam
- ALL EXHIBIT TIME DEPENDENT KILLING
  - Duration that drug levels exceed the MIC relative to the dosing interval and the frequency of drug administration are important determinants of outcome for these drugs.
  - A shorter dosing interval will increase the time that concentrations remain greater than the MIC of the infecting microorganism
Mechanisms of Resistance to Beta-Lactams

- Decreased penetration to the target site
  - Outer membrane on gram negative bacilli creates a permeability issue

- Alteration of the target site
  - Alterations of PBP’s may alter binding affinity of the antibiotics
  - Ex: MRSA, pneumococci

- Inactivation by bacterial enzymes
  - Production of beta lactamase
  - Ex: SPICE bugs, ESBL bugs
Current Problem

Increasing resistance to antibiotics globally
Mounting Resistance

- Increasing number of resistant bugs showing up in patients
- Organisms of concern - gram negative (ESBL/SPICE)
  - Escherichia coli
  - Klebsiella spp.
  - Enterobacter spp.
  - Pseudomonas aeruginosa
- No resources being allocated to fight the problem
- Lack of drug development in antibiotics
Antibiotic Drug Approvals

Dramatic Decrease in Antibiotic Drug Approvals
Source: Spellberg, CID 2004, Modified
## Current Pipeline

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Development phase</th>
<th>Company</th>
<th>Drug class</th>
<th>Expected activity against resistant Gram-negative ESKAPE pathogens</th>
<th>Expected activity against a CDC urgent threat pathogen</th>
<th>Potential indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCK 4877</td>
<td>Phase 1</td>
<td>Wockhardt Ltd.</td>
<td>Second-generation ketolide</td>
<td>No</td>
<td>No</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>MGB-BP-3</td>
<td>Phase 1</td>
<td>MGB Biopharma Ltd.</td>
<td>DNA minor groove binder</td>
<td>No</td>
<td>Yes</td>
<td>C. difficile infections</td>
</tr>
<tr>
<td>OPO595 (RG6012)</td>
<td>Phase 1</td>
<td>MeiShi Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc.</td>
<td>Beta-lactamase inhibitor</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>BAL30072</td>
<td>Phase 1</td>
<td>Basilea Pharmaceutica Ltd.</td>
<td>Monosulfamet</td>
<td>Yes</td>
<td>Yes</td>
<td>Multidrug-resistant Gram-negative bacterial infections*</td>
</tr>
<tr>
<td>CRS3123</td>
<td>Phase 1</td>
<td>Crestone Inc.</td>
<td>Methionyl-thiol synthetase (MetRS) inhibitor</td>
<td>No</td>
<td>No</td>
<td>C. difficile infections</td>
</tr>
<tr>
<td>LC801-0371</td>
<td>Phase 1</td>
<td>LegoChem Biosciences Inc.</td>
<td>Onazololone</td>
<td>No</td>
<td>No</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>TD-1607</td>
<td>Phase 1</td>
<td>Theravance Biopharma Inc.</td>
<td>Glycopeptide-cephalosporin heterodimer</td>
<td>No</td>
<td>No</td>
<td>Acute bacterial skin and skin structure infections,* hospital-acquired pneumonia/ ventilator-associated bacterial pneumonia,* bacteremia*</td>
</tr>
<tr>
<td>WCK 2349</td>
<td>Phase 1</td>
<td>Wockhardt Ltd.</td>
<td>Fluoroquinolone (WCK 271 pro-drug)</td>
<td>No</td>
<td>No</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>WCK 777</td>
<td>Phase 1</td>
<td>Wockhardt Ltd.</td>
<td>Fluoroquinolone</td>
<td>No</td>
<td>No</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>Zidebactam + Ceftazidine (WCK 5222)</td>
<td>Phase 1</td>
<td>Wockhardt Ltd.</td>
<td>Novel beta-lactamase inhibitor + beta-lactam</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Complicated urinary tract infections,* hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia*</td>
</tr>
</tbody>
</table>
Clinical Question
Clinical Question

- Can giving beta-lactams over a continuous infusion in critically ill patients improve outcomes?
Rationale

- Provide maximal kill
  - Longer time above MIC = more bacteria killed

- Utilize optimal amount of drug
  - Increasing doses in these medications make no difference - time dependent

- Prolong use of drug in clinical practice
  - Reduce resistance by optimizing kill rates

- Overcome elevated MIC’s
  - With longer exposure
Evidence

What the clinical trials are showing
Dulhunty et al. (2016)

- “Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double blind, randomized controlled trial”
- Prospective, double blind, randomized control trial
- P: Intensive care patients with severe sepsis (n=60)
- I: Continuous infusion of a beta-lactam (piperacillin-tazobactam OR meropenem OR ticarcillin-clavulanate)
- C: Intermittent dosing of a beta lactam
- O: Continuous infusion achieved higher plasma antibiotic concentrations than intermittent administration with improvement in clinical cure
Dulhunty et al- Eligibility Criteria

- All of the following criteria needed to be met:
  1. Severe sepsis in the previous 48 hours
     1. Confirmed or suspected infection with new organ dysfunction
  2. Planned commencement or commencement within the previous 24 hours of ticarcillin-clavulanate, piperacillin-tazobactam, or meropenem
  3. Expected or actual ICU stay greater than 48 hours
  4. >18 years of age
  5. No allergies to the medications
**Dulhunty et al Continued- “The Numbers”**

<table>
<thead>
<tr>
<th></th>
<th>Continuous Infusion Group</th>
<th>Intermittent Dosing Group</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma concentrations &gt;MIC</td>
<td>82%</td>
<td>29%</td>
<td>P=.001</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>70%</td>
<td>43%</td>
<td>P=.037</td>
</tr>
<tr>
<td>ICU free days</td>
<td>19.5</td>
<td>17</td>
<td>P=.14</td>
</tr>
<tr>
<td>Survival to hospital discharge</td>
<td>90%</td>
<td>80%</td>
<td>P=.47</td>
</tr>
</tbody>
</table>
Dulhunty et al- Limitations

- Differences in baseline characteristics
  - Intervention group was 6 years younger, 13% more males, 13% higher comorbidity, and 13% higher proportion of pre-ICU in the intervention group

- Small sample size
  - Potential confounding by unmeasured variables

- Only trough levels were taken
  - Time spent above the MIC could only be inferred
  - Could be sample timing errors
Falagas et al. (2013)

- “Clinical outcomes with extended or continuous versus short-term intravenous infusions of carbapenems and piperacillin-tazobactam: a systematic review and meta-analysis”

- Clinical question:
  - “Are the better PK/PD properties of carbapenems and piperacillin-tazobactam associated with lower mortality when the duration of infusion is longer?”

- Searched PubMed and Scopus for studies
  - Excluded if: 1) case reports/series including <10 patients, 2) reported on comparative outcomes of extended vs. short term duration but for different carbapenems in the 2 arms

- Fourteen studies were included in the meta-analysis- n=1229
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Extended or continuous Deaths</th>
<th>Total</th>
<th>Short-term Deaths</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Extended vs short-term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dow 2011</td>
<td>8</td>
<td>67</td>
<td>11</td>
<td>54</td>
<td>17.1%</td>
<td>0.59 [0.25, 1.35]</td>
<td></td>
</tr>
<tr>
<td>Esterly 2010</td>
<td>12</td>
<td>42</td>
<td>7</td>
<td>29</td>
<td>11.7%</td>
<td>1.18 [0.53, 2.64]</td>
<td></td>
</tr>
<tr>
<td>Itabashi 2007</td>
<td>1</td>
<td>18</td>
<td>9</td>
<td>24</td>
<td>10.9%</td>
<td>0.15 [0.02, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Lodise 2007</td>
<td>9</td>
<td>102</td>
<td>14</td>
<td>92</td>
<td>20.7%</td>
<td>0.58 [0.26, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Patel 2009</td>
<td>4</td>
<td>70</td>
<td>5</td>
<td>59</td>
<td>7.6%</td>
<td>0.67 [0.19, 2.40]</td>
<td></td>
</tr>
<tr>
<td>Wang 2009</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>34</td>
<td>314</td>
<td>273</td>
<td>68.0%</td>
<td>0.63 [0.41, 0.95]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>34</td>
<td>46</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.54, df = 4 (P = 0.34); I² = 12%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.18 (P = 0.03)</td>
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<tr>
<td><strong>1.1.2 Continuous vs short-term</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grant 2002</td>
<td>0</td>
<td>47</td>
<td>5</td>
<td>51</td>
<td>7.4%</td>
<td>0.10 [0.01, 1.73]</td>
<td></td>
</tr>
<tr>
<td>Lau 2006</td>
<td>1</td>
<td>130</td>
<td>3</td>
<td>132</td>
<td>4.2%</td>
<td>0.34 [0.04, 3.21]</td>
<td></td>
</tr>
<tr>
<td>Lorente 2009</td>
<td>8</td>
<td>37</td>
<td>14</td>
<td>46</td>
<td>17.6%</td>
<td>0.71 [0.33, 1.51]</td>
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<tr>
<td>Okimoto 2009</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts 2010</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sakka 2007</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>2.8%</td>
<td>0.50 [0.05, 4.87]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>10</td>
<td>257</td>
<td>272</td>
<td>32.0%</td>
<td>0.50 [0.26, 0.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>10</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.18, df = 3 (P = 0.54); I² = 0%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.07 (P = 0.04)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>571</td>
<td>545</td>
<td>100.0%</td>
<td></td>
<td>0.59 [0.41, 0.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>44</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 6.84, df = 8 (P = 0.55); I² = 0%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.97 (P = 0.003)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subarou differences: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Falagas et al.- Findings

- Mortality was lower in the continuous infusion groups compared to the short term
  - Risk ratio: 0.59, 95% confidence interval, 0.41-0.83
- Pneumonia patients who got continuous infusions had lower mortality than those with short term
  - Risk ratio: 0.50, 95% confidence interval, 0.26-0.96
- Data for other specific infections were not available
- Evidence is mainly from non-randomized studies
  - Can only really say at this point there is a trend to benefit
  - RCT’s are warranted to confirm what is being shown
Paper #3
Roberts et al. (2016)

- “Continuous versus intermittent beta-lactam infusion in severe sepsis: a meta analysis of individual patient data from randomized trials”

- P: Critically ill patients with severe sepsis (n=632; 3 trials included)

- I: Continuous infusions of beta-lactam antibiotics (meropenem or piperacillin-tazobactam)

- C: Intermittent dosing of beta-lactam antibiotics

- O: Continuous infusions in this population is associated with decreased hospital mortality and increased clinical cure
Roberts et al. – Inclusion Criteria

- All of the following needed to be met to be included in the meta-analysis:
  1. Were prospective
  2. Enrolled patients with severe sepsis or septic shock
  3. Randomized patients to receive either continuous infusions or intermittent dosing of a beta lactam at equivalent dosing in each treatment arm
  4. Reported assessment of outcomes by a clinician blinded to treatment allocation
Roberts et al. – “The Numbers”

- Only showed significance in decreased mortality
  - 19.6% Continuous Infusion vs. 26.3% Intermittent (RR: 0.74) P=0.045
Paper #4

Last paper!
Lodise, T., Lomaestro, B., and Drusano, G. (2007)

- “Piperacillin-Tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended infusion dosing strategy”
- Cohort study performed from January 2000-June 2004 in Albany, New York
- P: Patients with Pseudomonas aeruginosa infection susceptible to piperacillin-tazobacam (Pip/Taz) (n= 194)
- I: Continuous infusion of Pip/Taz 3.375g IV q8H over 4 hours
- C: Intermittent dosing of Pip/Taz 3.375g IV q4-6H over 30 minutes
- O: 14 day mortality rate (12.2% vs. 31.6%; P= .04) and duration of hospital stay (21d vs. 38d; P=.02) was significantly lower in intervention group
<table>
<thead>
<tr>
<th>Demographic or clinical characteristic</th>
<th>Extended Infusion (n = 102)</th>
<th>Intermittent Infusion (n = 92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>62.8 ± 18.3</td>
<td>63.9 ± 16.1</td>
<td>.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>65 (63.7)</td>
<td>54 (58.7)</td>
<td>.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 (27.5)</td>
<td>28 (30.4)</td>
<td>.6</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1 (1.0)</td>
<td>2 (2.2)</td>
<td>.5</td>
</tr>
<tr>
<td>History of health care exposure</td>
<td>35 (34.3)</td>
<td>37 (40.2)</td>
<td>.4</td>
</tr>
<tr>
<td>Duration of stay prior to culture sample collection, median days (range)</td>
<td>7 (0–89)</td>
<td>6 (0–52)</td>
<td>.5</td>
</tr>
<tr>
<td>In ICU at onset of infection</td>
<td>63 (61.8)</td>
<td>63 (68.5)</td>
<td>.3</td>
</tr>
<tr>
<td>Consecutive days in ICU prior to onset of infection, median days (range)</td>
<td>3.5 (0–30)</td>
<td>2 (0–52)</td>
<td>.9</td>
</tr>
<tr>
<td>Receiving mechanical ventilation at culture sample collection</td>
<td>56 (54.9)</td>
<td>52 (56.5)</td>
<td>.8</td>
</tr>
<tr>
<td>Consecutive days receiving mechanical ventilation prior to culture sample collection, median days (range)</td>
<td>1 (0–59)</td>
<td>1 (0–48)</td>
<td>.8</td>
</tr>
<tr>
<td>APACHE II score at onset of infection, mean ± SD</td>
<td>15.3 (6.7)</td>
<td>16.2 (7.6)</td>
<td>.3</td>
</tr>
<tr>
<td>Duration of therapy, mean days ± SD</td>
<td>8.4 (4.4)</td>
<td>8.4 (4.5)</td>
<td>.9</td>
</tr>
<tr>
<td>Concomitant treatment with an aminoglycoside</td>
<td>21 (22.8)</td>
<td>26 (25.5)</td>
<td>.6</td>
</tr>
<tr>
<td>Concomitant treatment with a fluoroquinolone</td>
<td>5 (5.9)</td>
<td>10 (10.9)</td>
<td>.2</td>
</tr>
<tr>
<td>Primary source of culture sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>55 (53.9)</td>
<td>48 (52.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>21 (20.6)</td>
<td>12 (13.0)</td>
<td>.2</td>
</tr>
<tr>
<td><strong>Skin or soft tissue</strong></td>
<td>11 (10.8)</td>
<td>23 (25.0)</td>
<td>.009</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>3 (2.9)</td>
<td>0 (0)</td>
<td>.1</td>
</tr>
<tr>
<td>Abdomen</td>
<td>4 (3.9)</td>
<td>1 (1.1)</td>
<td>.2</td>
</tr>
<tr>
<td>Other</td>
<td>8 (7.8)</td>
<td>8 (8.7)</td>
<td>.8</td>
</tr>
</tbody>
</table>
Potential Advantages

Why you should consider advocating for continuous infusions
Advantages

- Less susceptible pathogens
  - Bugs with higher MIC’s but are still susceptible benefit from prolonged strategies
  - Obtain killing activity for longer periods of time
- Patients with altered pharmacokinetics
  - Critical illness, young, obese patients can result in altered drug clearance, changes in protein binding, differing volumes of distribution, etc.
  - Getting adequate serum levels can be challenging; higher doses for longer periods may be best
Advantages Continued

▪ Safety
  ▪ No more toxicity risk than intermittent dosing

▪ Reduced selection for drug resistance
  ▪ Prolonged infusions provide shorter periods of time where the levels go below the MIC
  ▪ Less opportunity to acquire resistance or turn on resistance genes

▪ Cost benefit
  ▪ Studies have shown in decreased drug costs, reduced length of stay, reduced complication costs, and labour costs

▪ Ease of administration- outpatient
Drawbacks

The caveats to continuous infusions
Drawbacks

- Logistical barriers
  - Continuous infusions require use of an IV pump for longer periods of time
    - Problematic if patients have limited IV access or lower levels of nursing care
  - Staffing is an issue and flushing has to occur at the end of the infusion for complete administration of drug
  - Prolonged infusions may also require higher IV catheter use with poses its own risks
Drawbacks Continued

- **Compatibility**
  - Administering other medications in the same IV line can cause compatibility issues
  - Shifting medication administration times may not be able to alleviate

- **Stability**
  - Drugs must be stable over the time they are administered
  - Ex: carbapenems are not stable at room temperature for long durations

- **Clinical efficacy**
  - At this point very little is known about applicability or correct dosing.
  - More work needs to be done in this area
Applicability and Dosing

Where can this be used?
Potential Indications

- Patients with structural lung disease
- Frequent healthcare exposure
- Prior repeated antibiotic exposures
- Intensive care patients/critically ill
  - Especially those with gram-negative rod infections with elevated but susceptible MICs
- Infections due to pathogens with high intrinsic resistance and predilection for developing acquired resistance during therapy
## Dosing

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
<th>Dosing Interval</th>
<th>Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3.375-4.5g for all</td>
<td>Q8H Q12H Q8H</td>
<td>4 hours for all</td>
</tr>
<tr>
<td>&gt;20 CRRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>0.5-1g</td>
<td>Q24H Q12H Q12H</td>
<td>3 hours for all</td>
</tr>
<tr>
<td>10-24</td>
<td>0.5-1g</td>
<td>Q12H</td>
<td></td>
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<td>Q12H</td>
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<tr>
<td>&gt;50 CRRT</td>
<td>1-2g</td>
<td>Q8H</td>
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<tr>
<td></td>
<td>1-2g</td>
<td>Q12H</td>
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</table>

Dosing recommendations from clinical trials and expert opinion- may not be appropriate for all practice settings.
Case Study: GR- HSN experience

- Patient developed ESBL intra-abdominal infection post bowel resection
- ESBL also grew in urine, respiratory secretions, and sacral area
- Given meropenem continuous infusion
  - Meropenem 500mg IV Q4H over 4 hours (max. stability time)
- Duration of meropenem continuous infusion was 7 days
- Patient’s infection resolved and was able to return home a week later
Conclusion

Wrap up of what we’ve covered
Summary

▪ We have a growing bacterial problem with not much coming down the pipeline
  ▪ We have to start getting creative

▪ Evidence shows that continuous infusions are at least equally effective and in some cases have mortality benefit over traditional intermittent measures

▪ Additional benefits of reducing resistance, cost savings, and administration benefits for outpatients

▪ Drawbacks include logistical barriers, compatibility, and poor stability

▪ No established indications as of yet but potential areas include critically ill patients
  ▪ Need more robust studies in specific patient populations

▪ Optimal dosing hasn’t been established- more studies needed
References


References


Pssst! Hey kid! Wanna be a Superbug...?
Stick some of this into your genome...
Even penicillin won't be able to harm you...!

QUESTIONS?

Thank you for your time!