No Carbs for ESBL?

“The use of non-carbapenems for ESBL infections”

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I. Objectives
   a. Identify risk factors for extended-spectrum beta-lactamases (ESBL) infections
   b. Describe the “inoculum effect”
c. Explain the implications of the overuse of carbapenems

d. Evaluate the primary literature regarding the use of non-carbapenems for ESBL infections

II. Introduction¹
   a. Increasing prevalence of ESBL-producing Enterobacteriaceae
   b. ESBL infections are associated with high mortality
   c. Carbapenems have been the drug of choice for ESBL infections
   d. Increasing selection pressure for carbapenem-resistant organisms
   e. Emerging evidence that non-carbapenems may be an effective alternative antibiotic for ESBL infections

III. What are ESBLs?
   a. A subset of beta-lactamases that hydrolyzes penicillins, cephalosporins, and monobactams while cephamycins and carbapenems remain stable

IV. Epidemiology
   a. Prevalence of drug-resistant organisms

<table>
<thead>
<tr>
<th></th>
<th>VBMC 2015</th>
<th>CDC 2011-2014²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL E. coli</td>
<td>25%</td>
<td>13.4%</td>
</tr>
<tr>
<td>ESBL Klebsiella spp.</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>ESBL Enterobacter spp.*</td>
<td>-</td>
<td>28.5%</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae (CRE)*</td>
<td>-</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

*Data not available

V. Risk Factors³
   a. Severity of illness
      1. Length of hospital stay
      2. Length of ICU stay
      3. Prior administration of any antibiotic
      4. Ventilatory assistance
      5. Hemodialysis
   b. Procedural/instrumentation
      1. Presence of central venous or arterial catheters
      2. Presence of a gastrostomy or jejunostomy tube
      3. Emergency abdominal surgery
      4. Presence of a urinary catheter
   c. Prior residence in a long-term care facility (e.g., nursing home, assisted living facility)

VI. ESBLs – Mechanism of resistance

a. Beta-lactamases are resistant to: penicillins, 1ˢᵗ generation cephalosporins, and 2ⁿᵈ generation cephalosporins
   b. ESBL are resistant to: penicillins, 1ˢᵗ generation cephalosporins, 2ⁿᵈ generation cephalosporins, 3ʳᵈ generation cephalosporins, and monobactam
VII. Types of ESBL

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Number of enzymes</th>
<th>Mechanism</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM</td>
<td>100</td>
<td>Amino acid substitution</td>
<td><em>E. coli, K.pneumoniae, Enterobacteriaceae, P. aeruginosa</em></td>
</tr>
<tr>
<td>SHV</td>
<td>&gt;100</td>
<td>Amino acid substitution</td>
<td><em>Enterobacteriaceae, P. aeruginosa, Acinetobacter spp.</em></td>
</tr>
<tr>
<td>CTX</td>
<td>128</td>
<td>Chromosomal mediated</td>
<td><em>Enterobacteriaceae</em></td>
</tr>
</tbody>
</table>

VIII. The “Inoculum Effect”

a. A significant increase in the MIC of an antibiotic when the number of organisms inoculated is increased

b. Example:

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Standard inoculum (1 - 5 x 10⁵ CFU/ml inoculum)</th>
<th>High inoculum (1 - 5 x 10⁷ CFU/ml inoculum)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC⁰</td>
<td>MIC⁵₀</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 0.015 - 0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Cefminox</td>
<td>0.5 - 4</td>
<td>1</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4 - 32</td>
<td>8</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 - 32</td>
<td>4</td>
</tr>
<tr>
<td>Cefepime</td>
<td>4 - 32</td>
<td>8</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>16 - 256</td>
<td>64</td>
</tr>
</tbody>
</table>

IX. Treatment Options

a. Inpatient
   1. Carbapenems – drug of choice
   2. Possible alternatives:
      1. 4th gen cephalosporin
      2. Piperacillin-tazobactam

b. Outpatient
   1. Carbapenem (ertapenem) – drug of choice
   2. Possible alternatives:
      1. Fosfomycin
      2. Nitrofurantoin
      3. Trimethoprim-sulfamethoxazole

X. Why not just use carbapenems?

a. COLLATERAL DAMAGE!

b. Selective pressure for multidrug resistant organisms (i.e. CRE)