Prophylactic Antibiotics for Severe Acute Pancreatitis - Overrated

Robert Larke, M.D.
PGY-2
Pancreatitis

- Pancreatic insult
- Intracellular trypsin activation
- Auto-digestion of pancreas
Pancreatitis
220,000/year in US

Mild (<7 day recovery)
80%

Sever Acute Pancreatitis
20%

Acute Necrotizing Pancreatitis
25%

Sterile Necrosis
30-60%

Infected Necrosis
40-70%

No Necrosis
75%

Mortality 10%

Mortality 25%

Mortality 4%

Mortality 25%

Predicting Outcomes

- Many Scoring Systems Used
  - Ranson’s Criteria
  - POP – Pancreatitis outcome prediction
  - BISAP – Bedside Index for Severity in Acute Pancreatitis
  - Imrie scoring system
  - MODS – Multiple Organ Dysfunction Score
  - SOMA – Sequential Organ Failure Assessment
  - APACHE – Acute Physiology and Chronic Health Evaluation
Goals of Treatment

- Supportive care
- Prevent complications
  - Most common systemic complications
    - Acute renal failure
    - Respiratory Failure
    - Hemodynamic/Cardiac instability
    - Infectious
Infected Pancreatic Necrosis

- Necrosis diagnosed by contrast CT
- Infected necrosis difficult to diagnose
  - Non-contrast CT with retroperitoneal gas
  - CT guided FNA
  - Direct examination and culture
- Mortality 25%
- Treatment – broad spectrum antibiotics
Prophylactic Antibiotics

- First studies published in 1970’s
  - Small randomized trials
  - Outcome was mortality -> no difference
- First meta-analysis by Golub et al. in 1998
  - First 8 trials – 514 patients
  - Mortality benefit with broad spectrum antibiotics
  - Only 1 of the 8 trials showed a mortality benefit
First Double-blinded randomized control trial
- 200 patients, Multicenter
- Inclusion – Acute pancreatitis + 3-fold elevation amy/lip, CRP > 150mg/L and/or necrosis on CT
- Ciprofloxacin + Metronidazole vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Cipro/Met</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Infected Pancreatic Necrosis</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Mortality</td>
<td>7%</td>
<td>11%</td>
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<tr>
<td>Study</td>
<td>Infected Necrosis</td>
<td>Mortality</td>
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<td>-----------------------</td>
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</tr>
<tr>
<td>Sharma et al. 2001</td>
<td>No</td>
<td>Yes</td>
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<td>Xiong et al. 2006</td>
<td>No</td>
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<tr>
<td>Dambrauskas et al. 2007</td>
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Dambrauskas et al. 2007

- 10 trials with total of 1279 patients
- Included trials that had been rejected by other studies
  - Takeda et al. – Continuous infusion antibiotics + protease inhibitor
  - Bassi et al. and Manes et al. – compared 2 antibiotic arms without controls
  - Maravi-Poma et al. – no control group

Dellinger et al. 2007

- Double Blinded, Randomized Control Trial
- 100 patients (50 Meropenem, 50 Placebo)
- Multi-center (N. America and Europe)
- Contrast CT or non-contrast CT + CRP > 120 or MOD > 2
- Meropenem vs placebo

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<thead>
<tr>
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<th>Meropenem</th>
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<th>P value</th>
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<tbody>
<tr>
<td>Infected Pancreatic Necrosis</td>
<td>18%</td>
<td>12%</td>
<td>P=0.401</td>
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<tr>
<td>Mortality</td>
<td>20%</td>
<td>18%</td>
<td>P=0.799</td>
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<tr>
<td>Surgical Intervention</td>
<td>26%</td>
<td>20%</td>
<td>P=0.476</td>
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de Vries et al. 2007

- Meta-analysis

<table>
<thead>
<tr>
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<th>Absolute Risk Reduction</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Infected Pancreatic Necrosis</td>
<td>0.055</td>
<td>-0.084-0.194</td>
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<tr>
<td>Mortality</td>
<td>0.058</td>
<td>-0.017-0.134</td>
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</table>

- Inverse-linear relationship between the methodologic quality score of included trials and the mortality benefit.
- Correlation coefficient -0.841, p = 0.036

de Vries AC et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology. 2007
**Double-Blinded RTCs**

- Garcia-Barrasa et al. 2009
  - 41 patients
  - Single center
  - Acute pancreatitis, contrast CT with necrosis
  - Ciprofloaxcin vs placebo

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<tbody>
<tr>
<td>Infected Pancreatic Necrosis</td>
<td>36%</td>
<td>42%</td>
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<td>Mortality</td>
<td>18%</td>
<td>11%</td>
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<tr>
<td>Surgical Intervention</td>
<td>50%</td>
<td>42%</td>
<td>P=0.613</td>
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### More Meta Analyses

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<td>de Vries - 2007</td>
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<td>Hart - 2008</td>
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<td>Xu – 2008</td>
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<td>Bai - 2008</td>
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<td>Jafri - 2009</td>
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Cochrane Review

- Cochrane follows suit as literature changes
  - 2003 – Mortality and Infected Necrosis Benefit
  - 2006 – Mortality Benefit Only
  - 2010 – No Mortality or Infected Necrosis Benefit

de Vries AC et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology. 2007
Consequences

• Ciprofloxacin resistance in 78% of isolates (Cipro/Flagyl) vs. 21% (placebo) Isenmann et al. 2004

• Imipenem resistance in 42-46% of isolates Maravi-Poma et al. 2003

• Resistance in 52% infected pancreatic necrosis treated with antibiotics, antibiotic resistant infections associated with longer ICU stay 53 days vs. 31 days (p = 0.02) De Waele et al. 2004
Conclusions

- No benefit to prophylactic antibiotics in preventing or decreasing the mortality associated with pancreatic necrosis
- Overuse of antibiotics leads to resistant strains of organisms
- Use antibiotics judiciously on an as needed basis in patients with severe acute pancreatitis
Questions?