Prophylactic Antibiotics in Severe Acute Pancreatitis: An Unnecessary And Potentially Dangerous Therapy

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October 11, 2010
Necrotizing Pancreatitis

- Occurs in approximately 20% of all cases of acute pancreatitis
- If necrosis is present, organ failure will occur around 50% of the time
- Percent of gland destruction not directly tied to greater mortality
  - Early death - 1-3 days: overwhelming SIRS response, not necessarily sequelae of infection
  - Later death – 1-2 weeks: often the result of infection, but more often pneumonia, bacteremia, not necessarily infected necrotizing pancreatitis
Severe Acute Pancreatitis (SAP):

- Atlanta Criteria for SAP:
  - Diagnosis of acute pancreatitis, also
  - Any one of the four:
    - 1) organ failure manifested by shock, pulm insufficiency, renal failure, GI bleed
    - 2) Pancreatic necrosis, pseudocyst, abscess
    - 3) 3 of Ranson’s Criteria
    - 4) APACHE II score of >7

Ranson’s Criteria on Admission:
- age greater than 55 years
- a white blood cell count of > 16,000/μL
- blood glucose > 11 mmol/L (>200 mg/dL)
- serum LDH > 350 IU/L
- serum AST >250 IU/L

Ranson’s Criteria after 48 hours of admission:
- fall in hematocrit by more than 10 percent
- fluid sequestration of > 6 L
- hypocalcemia (serum calcium < 2.0 mmol/L (<8.0 mg/dL))
- hypoxemia (F_{O2} < 50 mmHg)
- increase in BUN to >1.98 mmol/L (>5 mg/dL) after IV fluid hydration
- base deficit of >4 mmol/L

The prognostic implications of Ranson’s criteria are as follows:
- Score 0 to 2: 2% mortality
- Score 3 to 4: 15% mortality
- Score 5 to 6: 40% mortality
- Score 7 to 8: 100% mortality

Severe Acute Pancreatitis (SAP):

- Mortality in sterile necrotic pancreatitis: 10-20%
- Mortality in infected necrotic pancreatitis: 20-40%
- Thought to develop in 40-70% of necrotic pancreatitis
- Postulated migration of gut-derived organisms through pancreatic duct from duodenum, or via lymphatics, or directly as gut mucosal defenses against translocation are dysfunctional
History of a Therapy: Prophylactic Antibiotics in SAP

- Early studies in 1970’s looked at all acute pancreatitis (mild to severe), also used antibiotics now known to have poor pancreatic penetrance, showed no benefit for antibiotic prophylaxis.

- Newer studies have looked at only severe pancreatitis, with drugs now known to have good bioavailability in viable pancreatic tissue.
Cochrane Review 2003:


Conclusions:

- Mortality advantage with Abx: (6/109 pts vs 18/109 pts, p=0.02)
- Infected pancreatitis advantage with Abx: (23/109 pts vs 35/109 pts, p=0.04)
- No significant difference for extra-pancreatic infections, operative interventions
Pooling the Data:

Cochrane Review 2003:

- Problems:
  - Underpowered: Even pooling pts, only 109 in each arm
  - Mixed antibiotic regimens
  - No blinded, placebo controlled RCTs
  - Weight of survival advantage came from 1 study (Saino 1995, where 1/30 pts died in tx group, 7/30 died in control.
    - 2 controlled pts died within 2 and 4 days of study implementation, most likely not from direct sequelae of infected pancreatitis
Cochrane Review 2006:

- Added double-blind RCT comparing ciprofloxacin/flagyll to placebo (Isenmann 2004)
  - This study originally powered for 200 pts, but stopped enrollment at 114 pts
  - Interim analysis showed no advantage to prophylactic antibiotics

**Mortality, infected pancreatitis no different**

- Mortality 3/40 (7.5%) for Abx vs 4/40 (10%) for control
- Infected necrosis 7/40 (12%) for Abx vs 5/40 (9%) for control

Cochrane Review 2006:

- Conclusions:
  - Significant mortality advantage:
    - Abx 6% vs Control 15.3%, OR 0.37 (0.17, 0.83)
  - No significant difference for infected necrotizing pancreatitis, extra-pancreatic infections, operative interventions

- Subgroup analysis of Beta-lactam antibiotic studies:
  - Significant difference in mortality, infected necrosis.
Cochrane Review 2006:

Problems:

- Mortality still influenced widely by Saino 1995
- Heterogeneity in treatment regimens
- Subgroup analysis under-powered for Beta-lactams.
Prophylactic Antibiotics in Severe Acute Pancreatitis:

- Cochrane Review 2006:
  - “Further doubly blinded RCTs are undoubtedly required to confirm the benefits of antibiotic prophylaxis, … The full results of the international meropenem study are awaited with great interest, and will trigger a further update of this review.”
“The full results of the international meropenem study…”

Dellinger et al, 2007:

- Prospective, Double-Blinded RCT
- 100 pts, 50 in control (placebo), vs 50 in treatment group (meropenem)
  - Administration of study drug < 120 hrs after onset of sx
  - CT-proven pancreatic necrosis >30%, OR Balthazar Grade E on CT with CRP >120 or MOD >2
“The full results of the international meropenem study…”

- Dellinger et al, 2007:
  - Pancreatic/peripancreatic infection:
    - Meropenem: n = 9/50 (18%), vs Placebo: n = 6/50 (12%). (p=0.401)
  - Time to Onset of Infection:
    - Meropenem: 21 days, vs Placebo: 21 days
  - Operative/Percutaneous Intervention:
    - Meropenem: 13/50 (26%), vs Placebo: 10/50 (20%). (p=0.476)
  - Non-Pancreatic Infections:
    - Meropenem: 16/50 (32%), vs Placebo: 24/50 (48%). (p<0.20)
  - Mortality:
    - Meropenem: 10/50 (20%), vs Placebo: 9/50 (18%).

“The full results of the international meropenem study…”

- Dellinger et al, 2007:
  - No difference in pancreatic infection, operative intervention, mortality when given prophylactic meropenem

- Problems:
  - Study underpowered
  - Pts randomized at outer limit of 120 hours from onset
    - Meropenem time to administration: 3 days (range 1-6)
    - Placebo time to administration: 3 days (range 1-8)
Meta-Analyses of ALL the Data:
Cochrane Review 2010:

- Utilized all previous studies included for analysis, plus Dellinger 2007, Rokke 2007.
Meta-Analyses of ALL the Data: Cochrane Review 2010:

- Cochrane Review 2010:
  - Conclusions:
    - Antibiotic vs control:
      - No significant differences in mortality, infected pancreatic necrosis, non-pancreatic infections, operative interventions
    - Beta-Lactam vs control:
      - No significant difference in mortality, infected pancreatic necrosis, non-pancreatic infections, operative interventions
    - Imipenem vs control:
      - No significant difference in mortality, infected pancreatic necrosis, operative intervention
      - Significant difference in infections overall (25.6% vs 52.4%, p=0.01)

Use of Antibiotics in Necrotizing Pancreatitis: A Summary:

- Double blinded RCT using carbipenem showed no benefit in early prophylactic antibiotic use vs treatment on demand.

- Meta-analysis of all available data in CT-diagnosed necrotizing pancreatitis shows no benefit in all types of prophylaxis, and in subset analysis.
Howard, et al 2002:

- 95 pts with operatively treated necrotizing pancreatitis retrospectively examined:
  - Incidence of infection was not significant (59% historically vs 66% contemporary)
- Initial surgical cultures taken:
  - Gram negatives: 56% of control vs 26% of prophylaxis (p=0.005)
  - Gram positives: 23% in control vs 52% in prophylaxis (p=0.009)
  - MRSA: Non-significant trend toward increasing numbers in prophylaxis group (n=15) vs control (n=6)
Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:

- Howard et al, 2002:
  - No change in rate of infected pancreatitis, however the use of routine prophylactic carbipenems is associated with a shift from gram negative coliforms to Gram positive organisms
  - As MRSA and other resistant Gram positives increase, more resistant infections will follow

Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:

De Waele, et al 2004:

- Case series of 46 pts with infected pancreatic necrosis:
  - 80% had previous Abx prophylaxis (variable regimens)
  - 24 total pts (52%) had infection with resistant organism: 7 infected primarily, 21 after intervention (FNA vs operative Cx)
    - Of these, 20 pts (83%) had been on antibiotic prophylaxis
    - Duration of antibiotic therapy prior to development of a resistant organism was 24.5 days, compared to 15.4 days for non-resistant organisms

Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AB-R Infection (n = 24)</th>
<th>AB-S Infection (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y*</td>
<td>52.5 (13.35)</td>
<td>55.0 (13.45)</td>
<td>.53</td>
</tr>
<tr>
<td>Gender distribution, M/F</td>
<td>17/7</td>
<td>12/10</td>
<td>.25</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)*</td>
<td>19.9 (10.86)</td>
<td>20.4 (8.73)</td>
<td>.86</td>
</tr>
<tr>
<td>Ranson score, mean (SD)*</td>
<td>6.4 (1.72)</td>
<td>5.8 (2.0)</td>
<td>.38</td>
</tr>
<tr>
<td>Organ failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>18 (75)</td>
<td>17 (77)</td>
<td>.86</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>12 (50)</td>
<td>13 (59)</td>
<td>.54</td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>16 (67)</td>
<td>15 (68)</td>
<td>.91</td>
</tr>
<tr>
<td>Use of antibiotic prophylaxis</td>
<td>20 (83)</td>
<td>17 (77)</td>
<td>.61</td>
</tr>
<tr>
<td>Duration of antibiotic treatment prior to infection, mean (SD), d*</td>
<td>24.5 (15.05)</td>
<td>15.4 (9.35)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: AB-R, antibiotic-resistant; AB-S, antibiotic-susceptible; APACHE II, Acute Physiology and Chronic Health Evaluation II.

*Data are given as number (percentage) of patients unless otherwise indicated.
Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:

Table 5. Outcome and Length of Stay in Patients With and Without Antibiotic-Resistant (AB-R) Infections*

<table>
<thead>
<tr>
<th>Variable</th>
<th>AB-R Infection (n = 24)</th>
<th>AB-S Infection (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of operations</td>
<td>2.25 (1.51)</td>
<td>2.29 (1.48)</td>
<td>.94</td>
</tr>
<tr>
<td>Duration postoperative lavage, d</td>
<td>27 (27.1)</td>
<td>23 (16.3)</td>
<td>.56</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>53 (36.8)</td>
<td>31 (20.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>78 (44.5)</td>
<td>65 (43.2)</td>
<td>.35</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>9 (37)</td>
<td>5 (23)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: AB-R, antibiotic-resistant; AB-S, antibiotic-susceptible; ICU, intensive care unit.
*Data are given as the mean (SD) unless otherwise indicated.
Fungal Infection in Prophylactic Antibiotics:

- Gloor et al, 2001:
  - All pts treated with prophylactic imipenem
  - Increased risk of candidal infection of pancreatic necrosis with increasing antibiotic usage.
  - Trend in increased mortality among those with fungal infections in necrotic pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Fungal Infection (n = 8)</th>
<th>Bacterial Infection (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3 (37)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (63)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Biliary pancreatitis</td>
<td>5 (63)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Post-ERCP pancreatitis</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Alcohol-induced pancreatitis</td>
<td>1 (12)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Other or unknown etiology</td>
<td>2 (25)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>4 (50)</td>
<td>16 (56)</td>
</tr>
<tr>
<td>Antibiotic treatment for &lt;7 d</td>
<td>0</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Antibiotic treatment for 7-14 d</td>
<td>3 (37)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Antibiotic treatment for &gt;14 d</td>
<td>5 (63)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Necrosis of ≥50% of the gland</td>
<td>8 (100)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (25)</td>
<td>5 (20)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. ERCP indicates endoscopic retrograde cholangiopancreatography; APACHE II, Acute Physiology and Chronic Health Evaluation II; and ICU, intensive care unit. None of the characteristics or parameters was statistically different between the 2 groups.
Summary:

- No reduced risk of mortality, infection of necrotic pancreas, operative interventions
  - Studies are underpowered, heterogeneous in inclusion criteria/treatment type/duration.
  - Trends do exist but are non-statistically significant

- Potential for production of antibiotic resistant organisms, fungal infection
  - While no definite increase in mortality, studies are small
  - Known increased mortality in resistant infection in VAP, bacteremia
References