Prophylactic Use of Antibiotics in Acute Pancreatitis: A Way to Prevent Sepsis

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“The Truth would be literally nothing but the shadows of the image”¹

- History offers numerous accounts of the disease
  - Alexander the Great died at the age of 33 in 323 BC after consumption of a heavy meal and substantial alcohol. There is a description of abdominal pain radiating to the chest, vomiting, and fever. In his final days, he developed AMS and symptoms consistent with respiratory failure.²
Reginald Heber Fritz 1843-1913

- Pathologist at MGH
- Published a landmark paper in acute pancreatitis in the *Boston Medical and Surgical Journal* in 1889

> “Pancreatitis has been repeatedly confounded with acute intestinal obstruction, and thus has led...to an ineffective laparotomy; an operation which, in the early stages of the disease, is extremely hazardous.”
Original Articles.

ACUTE PANCREATITIS.

A CONSIDERATION OF PANCREATIC HEMORRHAGE, HEMORRHAGIC, SUPPURATIVE, AND GANGRENOUS PANCREATITIS, AND OF DISSEMINATED FAT-NECROSIS.¹

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Shattuck Professor of Pathological Anatomy in Harvard University and Physician to the Massachusetts General Hospital.

UNTIL the time of Clässen² the evidence of an
Eugene Lindsay Opie 1873-1971

- Formulated a hypothesis that dominated the 20th century thinking about the pathogenesis of pancreatitis

- Proposed that a gallstone might lodge in the ampulla would allow reflux of bile into the pancreatic duct with activation of pancreatic enzymes and pancreatitis
“Never in medical history have so many owed so much to a single stone”\textsuperscript{6}

- Fitzgerald demonstrated that obstruction of the pancreatic duct alone causes necrotizing pancreatitis indistinguishable from that seen when the bile duct is simultaneously occluded.
Irrespective of the initial factor that triggers the disease, severity of pancreatic damage is related to injury of acinar cells and to activation of inflammatory and endothelial cells and arises when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed.
Trigger mechanisms → Acinar cell injury → Cell activation → Release of mediators → Consequences

- Alcohol
- Gallstones
- others

Intra-acinar trypsinogen activation ?

Neutrophil
Monocyte
Lymphocyte
Endothelium

Pancreatic enzymes release
- trypsin
- elastase
- phospholipase A2
- others

Release of mediators
- IL-1
- IL-6
- IL-8
- IL-10
- IL-11
- TNF
- NO
- PAF

Local
- abscess
- necrosis

Systemic
- ARDS
- shock
- vascular leakage
Lord Moynihan in 1925

“Acute pancreatitis is the most terrible of all the calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, all render it the most formidable of catastrophes.”
What To Expect

• About 80,000 cases occur in the United States each year; some 20 percent of them are severe
  – First 2 weeks after the onset of symptoms the disease is characterized by the systemic inflammatory response syndrome (SIRS)
  – SIRS in the early phase of severe pancreatitis may be found in the absence of significant pancreatic necrosis
# Pathophysiology and Clinical Phases of Acute Pancreatitis

<table>
<thead>
<tr>
<th>PHASE</th>
<th>INITIAL</th>
<th>EARLY</th>
<th>MIDDLE</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMING</td>
<td>Hours</td>
<td>1st week</td>
<td>2nd week</td>
<td>3rd-4th week</td>
</tr>
<tr>
<td>MAJOR EVENTS</td>
<td>Altered intra-acinar protein traffic</td>
<td>Inappropriate activation of proteases</td>
<td>Microcirculatory disorders</td>
<td>Gut and biliary bacteria</td>
</tr>
<tr>
<td></td>
<td>Accumulation of trypsinogen in the interstitial space</td>
<td>Necrosis</td>
<td>Progression of necrosis</td>
<td>Infection of necrosis</td>
</tr>
<tr>
<td>DEATHS</td>
<td>?</td>
<td>32%</td>
<td>12%</td>
<td>19% 37%</td>
</tr>
<tr>
<td>Causes</td>
<td>M.O.F.</td>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>26%</td>
<td>0%</td>
<td>0 0</td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>0%</td>
<td>5%</td>
<td>12% 28%</td>
</tr>
</tbody>
</table>

Acute Pancreatitis: Clinical outcome

- **Mild**: No Organ Failure (80-85%)
- **Severe (necrotizing)**: Organ Failure (15-20%)

- **Sterile Necrosis**
  - 60% Mortality 5%
  - 40% Infected Necrosis

- **Mortality 1%**

- **Mortality 25 - 70%**
• Approximately 40% of patients with pancreatic necrosis develop infected necrosis\textsuperscript{10}

• The risk of pancreatic superinfection is dependent on the amount of necrosis
  – The risk is 20% if the necrosis is less than 50% and increases up to 70% when the pancreatic necrosis exceeds 50%\textsuperscript{11}
<table>
<thead>
<tr>
<th></th>
<th>Ranson’s</th>
<th>APACHE II</th>
<th>CT Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Pancreatitis</td>
<td>≤ 3</td>
<td>&lt; 8</td>
<td>&lt; 7</td>
</tr>
<tr>
<td>Severe Pancreatitis</td>
<td>&gt; 3</td>
<td>≥ 8</td>
<td>≥ 7</td>
</tr>
</tbody>
</table>
## CT Severity Index (CTSI)

### Balthazar
- Normal pancreas: A 0
- Enlargement: B 1
- Inflammation of pancreas and fat: C 2
- Single fluid collection: D 3
- Two or more fluid collections: E 4

### Necrosis
- < 30%: 2
- 30-50%: 4
- > 50%: 6

Max = 10 points
Severe Pancreatic Necrosis, but normal enhancing pancreas Day 1
In a prospective clinical study, necrotic material obtained at surgery was cultured in 114 patients with necrotizing pancreatitis but no abscess formation.

Bacterial contamination was present in 24 percent of patients operated on within the first seven days and rose to 71 percent in patients operated on in the third week.¹²
The Bugs

- The organisms causing infection in necrotizing pancreatitis are predominantly gut-derived
  - *Escherichia coli*, *Pseudomonas*, *Klebsiella*, and *Enterococcus* spp.
  - The majority of infections (about 75 percent) are monomicrobial
  - Fungal infections occur in approximately 9 percent of necrotizing pancreatitis and it is not clear if they are associated with higher mortality
Systemic Antibiotics

• The role of prophylactic systemic antibiotics in acute pancreatitis is unsettled since studies evaluating its benefits and harms have produced disparate results.

• Initial studies done in the mid-1970s failed to show a benefit, possibly because they included patients with mild disease who were at low risk for infection and used antibiotics that had poor penetration into the pancreas (such as ampicillin).
A meta-analysis of eight controlled trials concluded that prophylactic antibiotics reduced mortality, but the advantage was limited to patients with severe acute pancreatitis who received broad-spectrum antibiotics that are capable of achieving therapeutic pancreatic tissue levels\textsuperscript{15}.

- Human and animal studies have demonstrated adequate penetration with imipenem/meropenem, fluoroquinolones, and metronidazole\textsuperscript{16}. 
Some more recent studies have demonstrated improved outcomes associated with the use of prophylactic antibiotics in patients with severe necrotizing pancreatitis.
Two hundred fifteen patients with pancreatitis were randomized to either group A, who started antibiotic therapy (meropenem 500 mg t.i.d.) at admission, or group B, who received antibiotics after the demonstration of necrosis at CT.

CT was performed in both groups after at least 48 hr of hospitalization.
• Antibiotic treatment was started after 4.56 +/- 1.2 days from hospitalization in group B and after 1.07 +/- 0.6 days in A.
• Pancreatic infection occurred in four patients in group A (13.3%) and in nine in B (31%) ($p = 0.1$)
• Extrapancreatic infection occurred in 16.6% of patients in group A and in 44.8% in B ($p < 0.05$)
Conclusion: Early antibiotic treatment is associated with a significant improvement in the prognosis of necrotizing acute pancreatitis because of a reduction in the occurrence of septic complications.
Five evaluable studies randomized 294 patients. Analysis suggested significantly less mortality with therapy (6%) versus controls (15.3%), odds ratio 0.37 (95% CI 0.17, 0.83).

With beta lactam prophylaxis there was significantly less mortality (6.3%) versus controls (16.7%), odds ratio 0.34 (95% CI 0.13, 0.91), and infected pancreatic necrosis (15.6%) versus (29.2%) in controls, odds ratio 0.41 (95% CI 0.20, 0.85).
• “There did not appear to be any significant risk of adverse effects from antibiotic prophylaxis.”

• If prophylaxis is embarked upon, experimental data suggests that it should be commenced as soon as possible and continued for 1 to 2 weeks
Another Meta-Analysis

- Eight RCTs including 540 patients
  - The outcomes included infected necrosis, death, non-pancreatic infection, surgical intervention, and length of hospital stay
- Prophylactic antibiotic treatment is associated with a significant reduction of pancreatic or peripancreatic infection, non-pancreatic infection, and length of hospital stay
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. (treatment/control)</th>
<th>Mean age (years)</th>
<th>Mean Ranson score</th>
<th>Dosage of antibiotics</th>
<th>Duration of antibiotic use (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli 1993</td>
<td>41/33</td>
<td>54.0/50.0</td>
<td>3.7</td>
<td>Imipenem 0.5 g Q8 h</td>
<td>14</td>
</tr>
<tr>
<td>Sainio 1995</td>
<td>30/30</td>
<td>43.0/38.7</td>
<td>5.5</td>
<td>Cefuroxime 1.5 g Q8 h</td>
<td>&gt;14</td>
</tr>
<tr>
<td>Schwarz 1997</td>
<td>13/13</td>
<td>43.0/46.0</td>
<td>4.8</td>
<td>Ofloxacin 0.2 g b.i.d. with metronidazole 0.5 g b.i.d.</td>
<td>10</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>25/33</td>
<td>47.0/46.0</td>
<td>NR</td>
<td>Imipenem 1.0 g Q8 h</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Isenmann 2004</td>
<td>58/56</td>
<td>49.4/46.5</td>
<td>2.3</td>
<td>Ciprofloxacin 0.4 g b.i.d. with metronidazole 0.5 g b.i.d.</td>
<td>21</td>
</tr>
<tr>
<td>Spicák 2004</td>
<td>17/18</td>
<td>59.0/55.7</td>
<td>NR</td>
<td>Ciprofloxacin 0.2 g, b.i.d. with metronidazole 0.5 g Q8 h or meropenem 0.5 g Q8 h</td>
<td>10</td>
</tr>
<tr>
<td>Dellinger 2007</td>
<td>50/50</td>
<td>54.4/49.6</td>
<td>4.5</td>
<td>Meropenem 1.0 g Q8 h</td>
<td>10.6*</td>
</tr>
<tr>
<td>Røkke 2007</td>
<td>36/37</td>
<td>60.0/57.0</td>
<td>NR</td>
<td>Imipenem 0.5 g t.i.d.</td>
<td>5–7</td>
</tr>
</tbody>
</table>

Abbreviations: NR = not reported; Q8 h = every 8 hours; b.i.d. = twice a day; t.i.d. = three times a day. *Mean days.
One Prospective Trial

- 60 consecutive patients with severe acute alcoholic pancreatitis with necrosis of at least one-third of the pancreas by contrast-enhanced CT, were randomly assigned to cefuroxime (1.5 g three times daily) or placebo.

- A marked decline in mortality was observed in the cefuroxime group (3 versus 23 percent).
  - In addition, cefuroxime was associated with a reduction in total infectious complications (30 versus 54).
• A second study of 23 patients used a regimen consisting of ceftazidime, amikacin, and metronidazole given intravenously for 10 days
• The incidence of sepsis was reduced from 58 percent in the placebo group to 0 percent with the antibiotics"^^\14
First experiment: all animals were evaluated at 24 hours after induction of acute necrotizing pancreatitis with a histological assessment of edema, inflammation and necrosis.

Animals receiving prophylactic antibiotic treatment every eight hours as a single dose started six hours after induction of acute pancreatitis were compared with a control group that did not receive antibiotic treatment.

Septic complications were evaluated by bacteriological assessments of blood, ascites, pancreas and mesenteric lymph nodes of both the colon and small bowel, as well as by 24-hour mortality rates.
Second experiment: treatment effects of meropenem were evaluated 72 hours after induction of necrotizing pancreatitis.

In order to imitate the clinical setting of severe necrotizing pancreatitis, animals were treated with meropenem either prophylactically before infection of pancreatic necrosis was observed, or therapeutically after superinfection of pancreatic necrosis was present.
• Conclusion: Both prophylactic and delayed antibiotic treatment on-demand reduced septic complications in a standardized setting of experimental necrotizing pancreatitis
  – However, pancreatic superinfection, bacteraemia and mortality rates were reduced significantly by early treatment

• Thus, in the absence of statistically relevant and well-designed clinical trials, the study demonstrates that prophylactic antibiotic treatment is superior to antibiotic treatment on-demand
What’s Wrong With the “Other” Data?

- Dellinger et al\textsuperscript{21} was a result of a multi-institutional double-blind, placebo-controlled clinical trial of 100 patients with clinically severe, confirmed necrotizing pancreatitis randomized to treatment with either prophylactic antibiotics (meropenem 1 g every 8 hours) or placebo, started within 5 days from the onset of symptoms, and continued for 7 to 21 days
- The hope was that this trial would finally provide definitive answers
• The study suffered from a high percentage of patients in the placebo group who were treated with IV antibiotics: 46%
• The trial was stopped prior to the original recruitment goal of 240 patients due to slow patient accrual and resource restriction despite having the trial open at 32 sites in North America and Europe
• The study was powered based on an infection rate of 40% in placebo patients assuming a reduction to 20% with the use of prophylactic antibiotics

• Accurate powering of a definitive study of prophylactic antibiotics patterned after Dellinger’s trial would now require the screening of approximately 8383 patients and randomization of 1006
So, Where Does that Leave Us?

“...It is certain that recovery from this disease, apart from operation, is so rare that no case should be left untreated.”
2. Sbarounis CN. *Did Alexander the Great die of acute pancreatitis?* J clin gastroenterol 1997; 24:294-6
20. http://ccforum.com/content/12/6/R141