

**Prophylactic
Antibiotics in Severe
Acute Pancreatitis:
Antibiotics are good**

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Overview

- Pancreas: The History
- Pancreas: The Organ
- The Disease Pathogenesis
- The Prognosis
- **The Argument over Antibiotics**

History of the Pancreas

- **Herophilus** (335-280 BC) identified the pancreas
- **Ruphos** gave the name "pancreas" meaning "all flesh".
- **Galen** (129-199 AD) taught the pancreas was a cushion to protect the blood vessels behind it



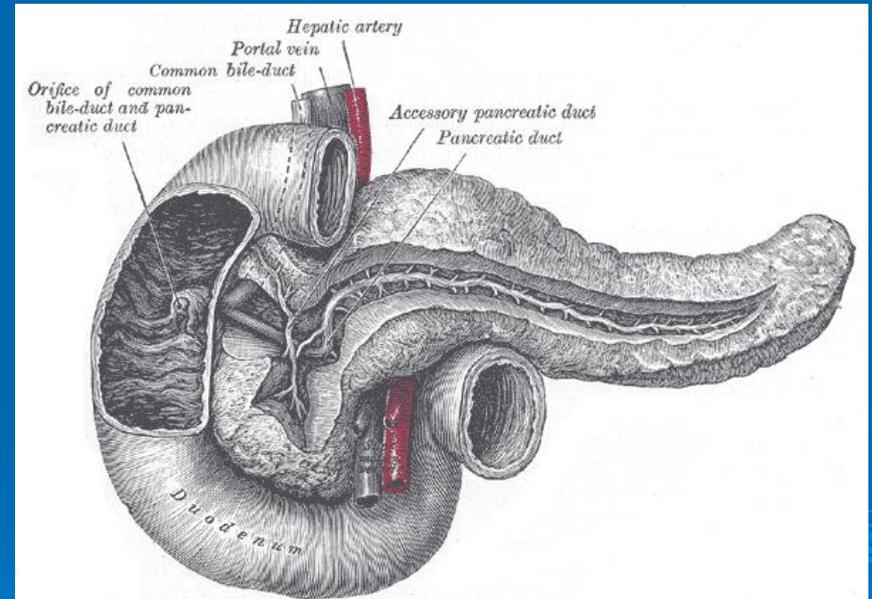
History of Pancreatitis



- 1889 Fritz published paper on acute pancreatitis
- 1901 Opie postulated that a stone impacted at ampulla of Vater could cause pancreatitis

Pancreas: fundamentals

- The pancreas is both
 - Endocrine organ made up of the islets of Langerhans
 - Exocrine organ consisting of acinar and ductal cells.



Pathogenesis of Pancreatitis

- Inflammation of the pancreas
 - Insult usually due to alcohol or gallstones
- Acute pancreatitis begins with injury to **acinar cells**.
- Insult induces activation on digestive enzymes including zymogens, such as trypsinogen, which induces auto digestions

Pancreatitis

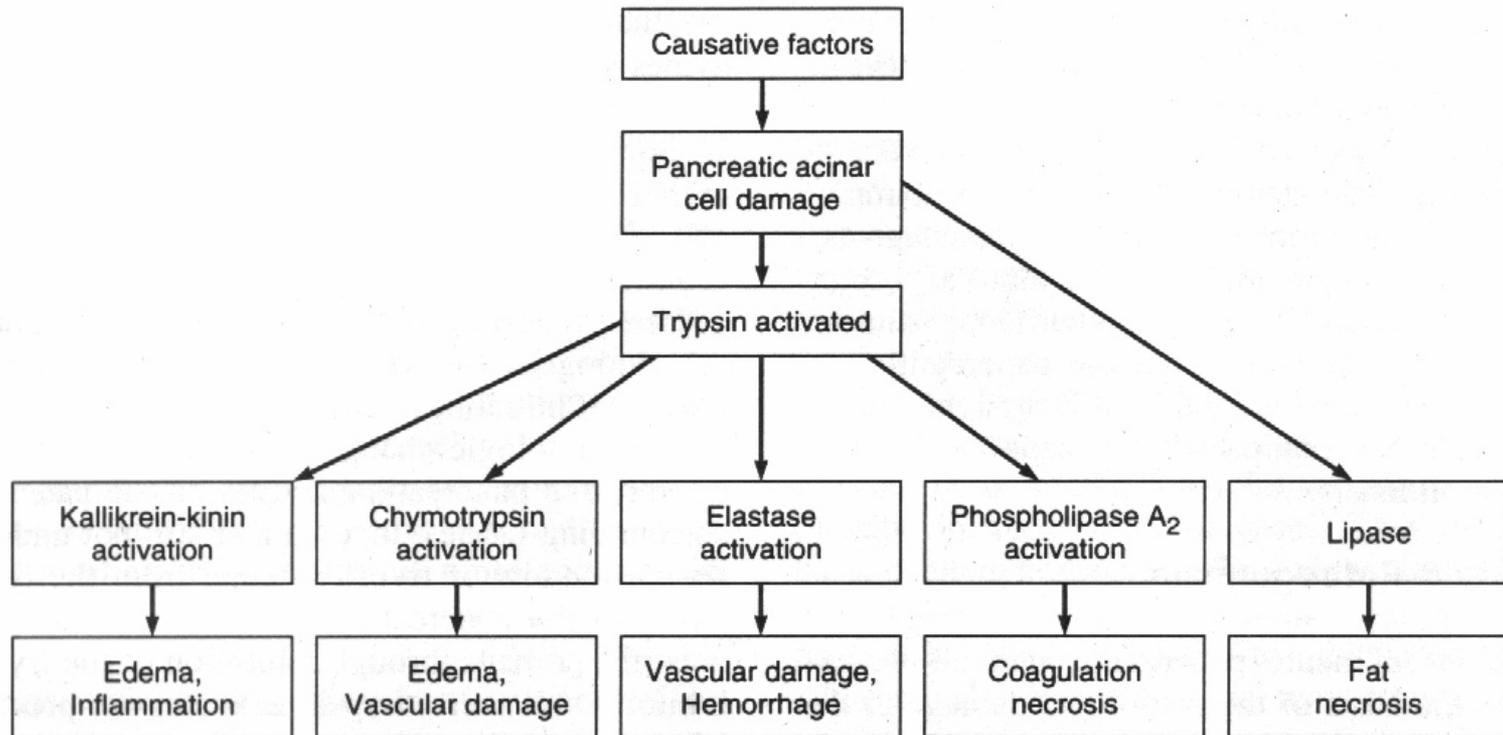


Figure 15–3. Hypothesized pathogenesis of acute pancreatitis. (Reproduced with permission from Marshall JB: Acute pancreatitis: A review with an emphasis on new developments. *Arch Intern Med* 1993;153:1185.)

Ranson's Criteria: Prognosis

On admission

- Glucose over 200
- Age over 55
- LD over 350
- AST over 250
- WBC over 16

After 48 hours

- Hct drop by more 10%
- BUN increase by 5 US
- Ca under 8
- Arterial pO₂ under 60
- Base Deficit greater than 4
- 6 L of fluid sequestration

CT Severity Index: prognosis

Balthazar

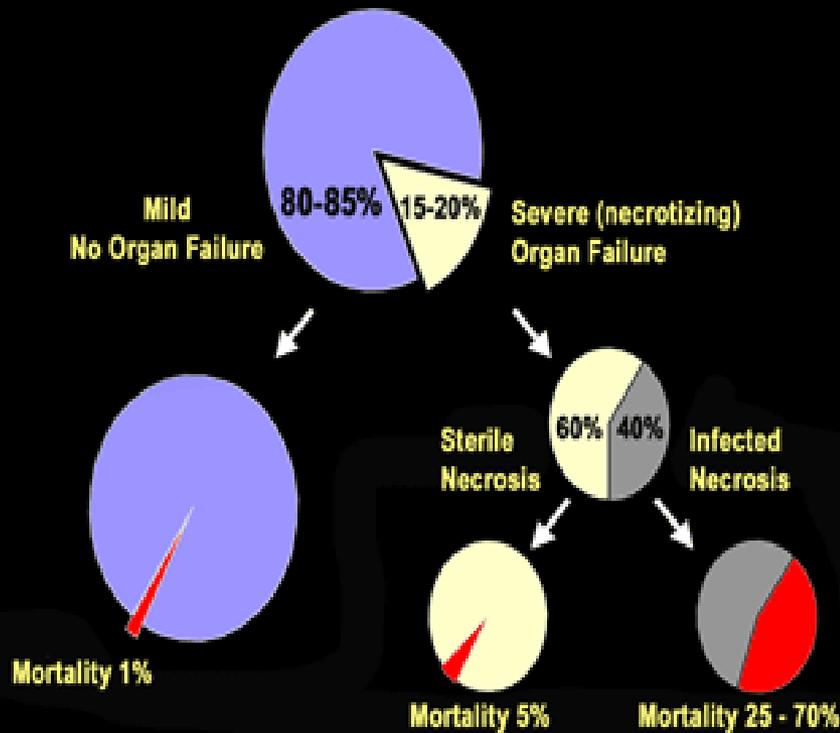
- 0 pt Grade A - Normal pancreas
- 1 pt Grade B - Focal or diffuse gland enlargement
- 2 pt Grade C - Intrinsic gland abnormality recognized by haziness on the scan
- 3 pt Grade D - Single ill-defined collection or phlegmon
- 4 pt Grade E - Two or more ill-defined collections or the presence of gas in or nearby the pancreas

Necrosis:

- 1/3 2 pt
- 1/3- 1/2 4 pt
- Over 1/2 6 pt

Acute Pancreatitis: epidemiology

Acute Pancreatitis: Clinical outcome



- About 210,000 people in the US are hospitalized for Acute Pancreatitis (AP)
- 25% of people presenting with AP have **Severe Acute Pancreatitis (SAP)**
- **SAP** has 10-20% mortality

Severe Acute Pancreatitis

➤ Definition:

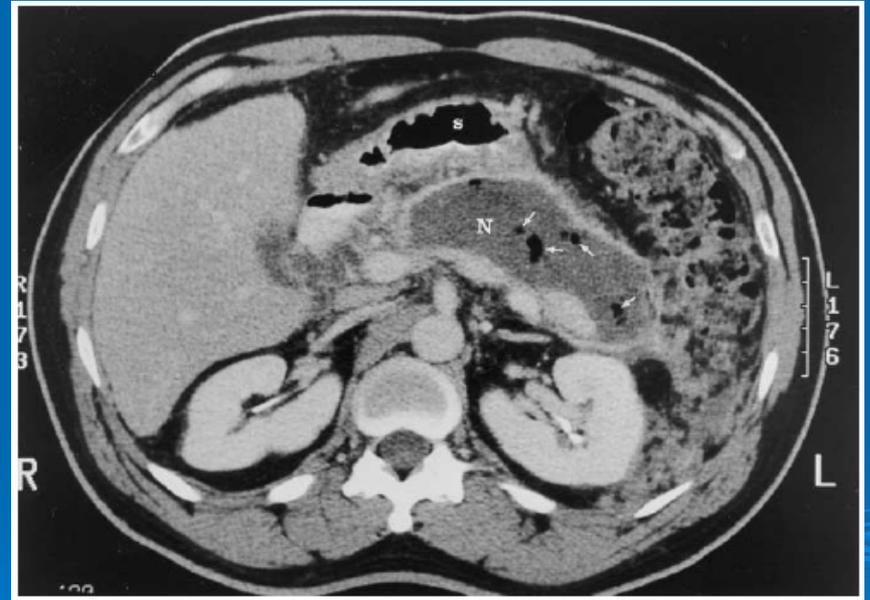
- Presence of organ failure and /or local pancreatic necrosis, pseudocyst and abscess
- Ranson's greater 3, APACHE II* greater than 8
- CRP greater 210 on days 2-4



Severe Acute Pancreatitis

➤ Course:

- Day 1-14: Systemic inflammatory response syndrome progressing to multiple organ dysfunction syndrome
- Day 14-21: **infection** of pancreatic necrosis



Risk of peripancreatic infection directly related to degree of pancreatic necrosis

- Approximately 40% of patients with pancreatic necrosis develop infected necrosis
- Infection rates:
 - Pancreatic necrosis greater 30% 15-30%
 - Pancreatic necrosis greater 50% 40-70%

Pancreatic infections

- Infection of pancreatic necrosis though to be caused by translocation of gut flora.
- Infection rate proportional to extent of necrosis.
- Complications due to infections are responsible for up to **80% of Deaths**

Pancreatitis Bugs

- Infections in Necrotizing pancreatitis are gut derived:
 - E Coli 25-35%
 - Enterococcus 25%
 - Klebsiella 15%
 - Pseudomonas 7-11%
- 75% are monomicrobial



Severe Acute Pancreatitis and antibiotics, your friend



Historically

- In 1970s clinical trials showed no benefit of prophylactic antibiotics. **WHY?**
 - **Ampicillin** was the most commonly used drug in these studies
 - Failed to reach minimal inhibitory concentration in Pancreatic tissue

Pederzoli 1993

- Randomized Multi center study
- N=74 with pancreatic necrosis on CT scan
- Randomized:
 - Inipenem for 14 days or no antibiotics

RESULTS:

- **Less Pancreatic Sepsis in Antibiotic arm**
 - 12% vs 30% ($p < 0.01$)

Sainio 1995

- N=60 pt with pancreatitis.
- Randomized to:
 - 30 patients were assigned cefuroxime (4.5 g/day IV) from admission.
 - 30 patients no antibiotic treatment
 - until clinical or microbiologically verified infection or
 - after a rise in C-reactive protein.

Sainio 1995

- **Less** infectious complications in the antibiotic group
 - (mean per patient 1.0 vs 1.8, $p = 0.01$).
- Mortality was **lower** in antibiotic group
 - (1 vs 7 in the antibiotic group; $p = 0.03$).
- Conclusion:
 - **Antibiotics given early in necrotizing pancreatitis is beneficial and may reduce mortality, probably by decreasing the frequency of sepsis.**

Cochrane 2003

- “ strong evidence that intravenous antibiotic prophylactic therapy for 10 to 14 days decreased the risk of superinfection of necrotic tissue and mortality in patients with severe acute pancreatitis with proven pancreatic necrosis at CT.”

Cochrane 2006

➤ Objective:

- To determine the effectiveness and safety of prophylactic antibiotics in CT proven acute pancreatitis complicated by pancreatic necrosis.

➤ Methods:

- 5 RC Studies with 294 patients

Cochrane 2006

Beta lactam prophylaxis had:

- Significantly **less mortality**
 - **6.3% vs 16.7%**
- Significantly **less infected pancreatic necrosis**
 - **15.6% vs 29.2%**

Arguments against Prophylaxis antibiotics

- Resistant organisms
- Fungal infection
- Cost

Cochrane 2010

- 7 Randomized controlled studies 404 patients
- Objective:
 - Pancreatic necrosis may complicate severe acute pancreatitis, and is detectable by computed tomography (CT). If it becomes infected mortality increases, but the use of prophylactic antibiotics raises concerns about **antibiotic resistance and fungal infection.**

Cochrane 2010

➤ Results:

- Fungal infections were not significantly different.
- Insufficient data were provided concerning antibiotic resistance.

Arguments against Prophylaxis antibiotics

- Resistant organisms
- Fungal infection
- Cost

Arguments against Prophylaxis antibiotics and why they are just wrong

- Resistant organisms- **Nope**
- Fungal infection- **Nope**
- Cost- **unable to determine**

Xu's 2008 meta analysis 8 RCT:

- Prophylactic antibiotic treatment is associated with a significant reduction of pancreatic or peripancreatic infection, non-pancreatic infection, and **length of hospital stay**

Cochrane 2010

- Mortality lower in antibiotic group
 - 8.4% vs. 14.4%
- Non-pancreatic infection lower in antibiotic groups
 - 23.7% vs. 36%

Cochrane 2010

Furthermore:

Imipenem (beta lactam) use had significant decrease in pancreatic infections were found.

Final recommendation:

further research is needed

About the antibiotic haters...



Isenmann study 2004

- RCT that concluded that no benefit in prophylaxis antibiotics.

HOWEVER:

- Underpowered
- Had people in the control arm on antibiotics
- Used ciprofloxacin and metronidazole

Dellinger study 2007

- International, multi-institutional double blind placebo-controlled study
- 100 patients CT confirmed necrotizing pancreatitis

However

- Patients in study arm were included up to **120 hours** after onset of symptoms
- 46% patients in control arm on antibiotics
- The calculated number of patients (n = 240) was not reached.

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

- Lord Moynihan, 1925

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