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

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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 (P_{O_2} < 60 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

Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993; 128: 586-90.

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.

Pooling the Data:

- Cochrane Review 2003:
  - 4 studies examined, looking at prophylactic antibiotics in CT-diagnosed necrotizing pancreatitis. (Pederzoli 1993, Saino 1995, Schwarz 1997, Nordback 2001)
  - 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

Villatoro E, Larvin M, Bassi C. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2003, Issue 4

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

Villatoro E, Larvin M, Bassi C. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2003, Issue 4

Pooling the Data 2.0:

- 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

Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, Maier L, Malfertheiner P, Goebell H, Beger HG. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;**126**:997-1004.

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2006, Issue 4.

Pooling the Data 2.0:

- 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.

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2006, Issue 4.

Pooling the Data 2.0:

- Cochrane Review 2006:
  - Problems:
    - Mortality still influenced widely by Saino 1995
    - Heterogeneity in treatment regimens
    - Subgroup analysis under-powered for Beta-lactams.

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2006, Issue 4.

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."

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2006, Issue 4.

"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

Dellinger EP, Tellado JM, Soto NE, et al. Early Antibiotic Treatment for Severe Acute Necrotizing Pancreatitis. Ann Surg 2007, 245: 674-83.

"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%).

Dellinger EP, Tellado JM, Soto NE, et al. Early Antibiotic Treatment for Severe Acute Necrotizing Pancreatitis. Ann Surg 2007, 245: 674-83.

"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)

Dellinger EP, Tellado JM, Soto NE, et al. Early Antibiotic Treatment for Severe Acute Necrotizing Pancreatitis. Ann Surg 2007, 245: 674-83.

Meta-Analyses of ALL the Data: Cochrane Review 2010:

- Cochrane Review 2010:
  - Utilized all previous studies included for analysis, plus Dellinger 2007, Rokke 2007.

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2010, Issue 5.

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)

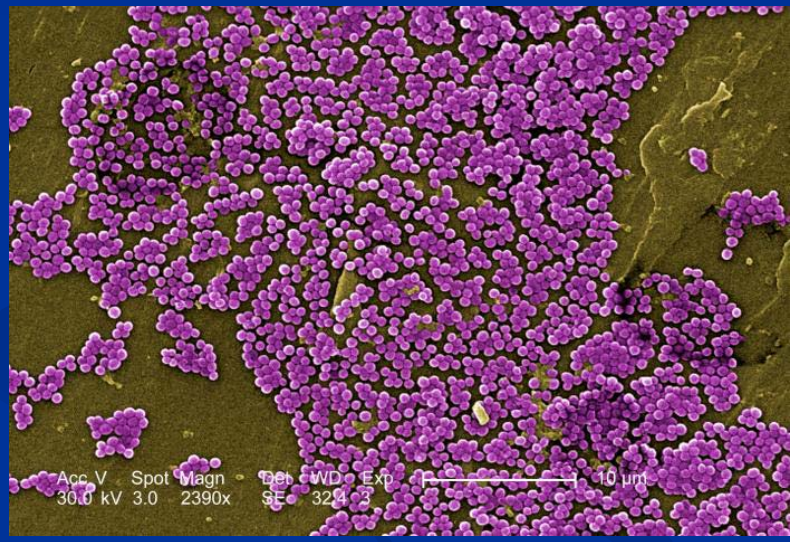
Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews 2010, Issue 5.

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

Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:

- Howard, et al 2002:
  - 95 pts with operatively treated necrotizing pancreatitis retrospectively examined:
    - 34 pts treated prior to routine use of prophylactic Abx (1977-1992) vs 61 pts in era of routine prophylaxis with imipenem (1993-2001).
    - 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)



Howard TJ, Temple MB. Prophylactic Antibiotics Alter the Bacteriology of Infected Necrosis in Severe Acute Pancreatitis. J Am Coll Surg 2002; 195: 759-67.

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

Howard TJ, Temple MB. Prophylactic Antibiotics Alter the Bacteriology of Infected Necrosis in Severe Acute Pancreatitis. J Am Coll Surg 2002; 195: 759-67.

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

De Waele JJ, Vogelaers D, Hoste E, et al. Emergence of Antibiotic Resistance in Infected Pancreatic Necrosis. Arch Surg 2004;139:1371-5

Antibiotic Resistance in Prophylactic Antibiotic Administration in SAP:

Table 4. Comparison of Patients With AB-R and AB-S Infections

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

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.

De Waele JJ, Vogelaers D, Hoste E, et al. Emergence of Antibiotic Resistance in Infected Pancreatic Necrosis. Arch Surg 2004;139:1371-5

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*

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

Abbreviations: AB-R, antibiotic-resistant; AB-S, antibiotic-susceptible; ICU, intensive care unit.

*Data are given as the mean (SD) unless otherwise indicated.

De Waele JJ, Vogelaers D, Hoste E, et al. Emergence of Antibiotic Resistance in Infected Pancreatic Necrosis. Arch Surg 2004;139:1371-5

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 3. Characteristics of 8 Patients With Fungal Infection of Pancreatic Necrosis vs 25 Patients With Bacterial Infection Only*

	Fungal Infection (n = 8)	Bacterial Infection (n = 25)
Male	3 (37)	18 (72)
Female	5 (63)	7 (28)
Biliary pancreatitis	5 (63)	15 (60)
Post-ERCP pancreatitis	0	1 (4)
Alcohol-induced pancreatitis	1 (12)	8 (32)
Other or unknown etiology	2 (25)	1 (4)
Total parenteral nutrition	4 (50)	16 (56)
Antibiotic treatment for <7 d	0	5 (20)
Antibiotic treatment for 7-14 d	3 (37)	8 (32)
Antibiotic treatment for >14 d	5 (63)	12 (48)
Necrosis of >50% of the gland	8 (100)	18 (72)
Mortality	2 (25)	5 (20)
APACHE II score during first week of the disease (range)	12.7 (7-21)	11.8 (6-22)
Mean ± SEM preoperative ICU stay, d	27.6 ± 17.9	16 ± 14.8
Mean ± SEM preoperative mechanical ventilation, d	18.5 ± 17.9	11 ± 9

**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

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