Prophylactic Antibiotics in Severe Acute Pancreatitis

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Mortality from Acute Pancreatitis

30% mortality\(^2\)
2–3 weeks after presentation

Infection is most common cause of death in necrotizing pancreatitis (NP)

SAP \(^1\)
- >30% necrosis
- SBP<90, sCr>2.0, PaO2<60
- >500ml GI blood loss
- abscess, or pseudocyst.

Infection in Necrotizing Pancreatitis

Bacterial contamination present, in ANP surgical specimens with no abscess
- 24% at 7d from presentation
- 74% at >14d from presentation

Infection in ANP correlates with degree of necrosis
- E. coli, Klebsiella, Enterococcus, Pseudomonas
- 75% specimens monomicrobial

Approaches to decrease infection in ANP:
- enteral feeding
- CT-guided aspiration
- antibiotics
- necrosectomy

Banks et al, Am J Gastroenterol. 2006;101(10):2379
Berger et al, Gastroenterology. 1986;91(2):433
Role of Antibiotics in SAP


Sainio V, Early antibiotic treatment in acute necrotizing pancreatitis. Lancet 1995


Isenmann R, Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis – a placebo controlled, double-blind trial. Gastroenterology 2004


Cochrane Database Syst Rev 2010
Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.
A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem.


RCT
74 patients with SAP and PN proven on CT.
6 Italian centers.
Imipenem 500mg iv q8 for 14 days

33 patients - intensive medical treatment with no prophylactic antibiotics.
41 patients - intensive medical treatment with prophylactic antibiotics

Pancreatic sepsis detected by (percutaneous CT or ultrasound-guided needle aspiration and intraoperative samples). The incidence of pancreatic sepsis was much less in treated patients (12.2 vs. 30.3%, p < 0.01).

RCT, Randomized, placebo-controlled, double-blind trial

76 patients with severe AP and PN on CT
Ciprofloxacin 400mg iv bd, and Metronidazole 500mg iv bd, 21d treatment

41 patients - supportive treatment and prophylactic antibiotics
-15 patients with clinical deterioration, switch in antibiotics

35 patients – supportive treatment and placebo.
- 20 patients with clinical deterioration, switch in antibiotics

Study medication was given for 3–23 days (med 12 days)

Infected PN → CIP/MET 12% Vs. 9% Placebo ($p \ 0.585$).
Mortality → 5% CIP/MET Vs. 7% Placebo

*Underpowered for oratlity, no reported secondary – outcomes shock, and renal insufficiency, need for resection*

RCT, placebo-controlled, double-blind.

100 patients with severe AP and proven pancreatic necrosis on CT, Multicenter (US and Europe)

Meropenem 1g q8h, recommended 14 (range 7 – 21)

50 patients - supportive treatment and meropenem
50 – received supportive treatment and placebo.

31 patients treatment group, and 32 in placebo, received the study drug for less than 14 days.
Pancreatic or peripancreatic infections → Meropenem 18% Vs. 12% Placebo ($p=0.40$)
Mortality → Meropenem 20% Vs. 18% Placebo ($p=0.799$).
Surgical intervention → Meropenem 26% Vs. 20% ($p=0.476$).

>50% patients on each arm interrupted antibiotics or received non-study antibiotics

Table 1. Characteristics of RCTs Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Setting</th>
<th>Total No.</th>
<th>Blinding</th>
<th>Risk of Bias</th>
<th>Dosage and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli (9)</td>
<td>1993</td>
<td>Multicenter</td>
<td>74</td>
<td>Single</td>
<td>High</td>
<td>Imipenem 0.5 g IV 8 hourly</td>
</tr>
<tr>
<td>Sainio (22)</td>
<td>1995</td>
<td>Single center</td>
<td>60</td>
<td>Single</td>
<td>High</td>
<td>Cefuroxime 1.5 g IV 8 hourly</td>
</tr>
<tr>
<td>Schwarz (23)</td>
<td>1997</td>
<td>Single center</td>
<td>26</td>
<td>Single</td>
<td>High</td>
<td>Ofloxacin 0.2 g b.i.d. IV &amp; metronidazole 0.5 g b.i.d. IV</td>
</tr>
<tr>
<td>Nordback (10)</td>
<td>2001</td>
<td>Single center</td>
<td>39</td>
<td>Single</td>
<td>High</td>
<td>Imipenem 1 g IV 8 hourly</td>
</tr>
<tr>
<td>Isenmann (11)</td>
<td>2004</td>
<td>Multicenter</td>
<td>76</td>
<td>Double</td>
<td>Low</td>
<td>Ciprofloxacin 0.4 g b.i.d. IV &amp; metronidazole 0.5 g b.i.d. IV</td>
</tr>
<tr>
<td>Dellinger (24)</td>
<td>2007</td>
<td>Multicenter</td>
<td>100</td>
<td>Double</td>
<td>Low</td>
<td>Meropenem 0.5 g IV 8 hourly</td>
</tr>
<tr>
<td>Rokke (25)</td>
<td>2007</td>
<td>Multicenter</td>
<td>73</td>
<td>No</td>
<td>High</td>
<td>Imipenem 0.5 g IV 8 hourly</td>
</tr>
</tbody>
</table>

IV = intravenous.
Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

**Mortality** $p=0.07$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H Fixed 95% CI</td>
<td></td>
<td>M-H Fixed 95% CI</td>
</tr>
<tr>
<td>Pederzoli 1993</td>
<td>3/41</td>
<td>4/33</td>
<td></td>
<td>15.1%</td>
<td>0.60 [0.15, 2.51]</td>
</tr>
<tr>
<td>Sainio 1995</td>
<td>1/30</td>
<td>7/30</td>
<td></td>
<td>23.9%</td>
<td>0.14 [0.02, 1.09]</td>
</tr>
<tr>
<td>Schwarz 1997</td>
<td>0/13</td>
<td>2/13</td>
<td></td>
<td>8.5%</td>
<td>0.20 [0.01, 3.80]</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>2/25</td>
<td>5/33</td>
<td></td>
<td>14.7%</td>
<td>0.53 [0.11, 2.50]</td>
</tr>
<tr>
<td>Isenmann 2004</td>
<td>3/41</td>
<td>4/35</td>
<td></td>
<td>14.7%</td>
<td>0.64 [0.15, 2.67]</td>
</tr>
<tr>
<td>Dellinger 2007</td>
<td>6/41</td>
<td>5/41</td>
<td></td>
<td>17.1%</td>
<td>1.20 [0.40, 3.62]</td>
</tr>
<tr>
<td>Rikke 2007</td>
<td>2/12</td>
<td>2/16</td>
<td></td>
<td>5.9%</td>
<td>1.33 [0.22, 8.16]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>203</strong></td>
<td><strong>201</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.60 [0.34, 1.05]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 17 (Antibiotics), 29 (Control)

Heterogeneity: $\chi^2 = 4.75, df = 6 (P = 0.58); I^2 = 0.0%$
Test for overall effect: $Z = 1.80 (P = 0.072)$
Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

### Pancreatic Necrosis $p=0.42$

#### Analysis 1.2. Comparison 1 Antibiotics versus control, Outcome 2 Infected Pancreatic Necrosis.

**Review:** Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

**Comparison:** 1 Antibiotics versus control

**Outcome:** 2 Infected Pancreatic Necrosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli 1993</td>
<td>5/41</td>
<td>10/33</td>
<td></td>
<td>14.2%</td>
<td>0.40 [0.15, 1.06]</td>
</tr>
<tr>
<td>Sainio 1995</td>
<td>9/30</td>
<td>12/30</td>
<td></td>
<td>24.3%</td>
<td>0.75 [0.37, 1.51]</td>
</tr>
<tr>
<td>Schwarz 1997</td>
<td>8/13</td>
<td>7/13</td>
<td></td>
<td>26.5%</td>
<td>1.14 [0.59, 2.22]</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>1/25</td>
<td>6/33</td>
<td></td>
<td>3.6%</td>
<td>0.22 [0.03, 1.71]</td>
</tr>
<tr>
<td>Isenmann 2004</td>
<td>7/41</td>
<td>5/35</td>
<td></td>
<td>12.3%</td>
<td>1.20 [0.42, 3.43]</td>
</tr>
<tr>
<td>Dellinger 2007</td>
<td>8/41</td>
<td>5/41</td>
<td></td>
<td>12.8%</td>
<td>1.60 [0.57, 4.48]</td>
</tr>
<tr>
<td>Riske 2007</td>
<td>2/12</td>
<td>4/16</td>
<td></td>
<td>6.3%</td>
<td>0.67 [0.15, 3.06]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>203</strong></td>
<td><strong>201</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.85 [0.57, 1.26]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 40 (Antibiotics), 49 (Control)

Heterogeneity: $\tau^2 = 0.04; \ Chi^2 = 6.94, df = 6 (P = 0.33); I^2 = 13%$

Test for overall effect: $Z = 0.80 (P = 0.42)$
Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Non-pancreatic Infections $\rho=0.08$
Cochrane Database Syst Rev 2010
Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Fungal Infection $p=0.9$

Analysis 1.5. Comparison 1 Antibiotics versus control, Outcome 5 Fungal Infection.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

Comparison: 1 Antibiotics versus control

Outcome: 5 Fungal Infection

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics n/N</th>
<th>Control n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Pederzoli 1993</td>
<td>0/41</td>
<td>4/33</td>
<td></td>
<td>10.6 %</td>
<td>0.09 [0.01, 1.61]</td>
</tr>
<tr>
<td>Sainio 1995</td>
<td>1/30</td>
<td>0/30</td>
<td></td>
<td>8.8 %</td>
<td>3.00 [0.13, 70.83]</td>
</tr>
<tr>
<td>Schwarz 1997</td>
<td>3/13</td>
<td>2/13</td>
<td></td>
<td>33.9 %</td>
<td>1.50 [0.30, 7.55]</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>1/25</td>
<td>0/33</td>
<td></td>
<td>8.9 %</td>
<td>3.92 [0.17, 92.43]</td>
</tr>
<tr>
<td>Isenmann 2004</td>
<td>1/41</td>
<td>1/35</td>
<td></td>
<td>11.8 %</td>
<td>0.85 [0.06, 13.15]</td>
</tr>
<tr>
<td>Dellinger 2007</td>
<td>2/41</td>
<td>1/41</td>
<td></td>
<td>15.9 %</td>
<td>2.00 [0.19, 21.21]</td>
</tr>
<tr>
<td>Rijke 2007</td>
<td>0/12</td>
<td>2/16</td>
<td></td>
<td>10.2 %</td>
<td>0.26 [0.01, 4.99]</td>
</tr>
</tbody>
</table>

Total (95% CI) 203 201 100.0 % 1.06 [0.41, 2.70]

Total events: 8 (Antibiotics), 10 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 5.47, df = 6 (P = 0.49); $I^2 =0.0$
Test for overall effect: Z = 0.11 (P = 0.91)
Conclusions on Antibiotics for Severe Acute Pancreatitis

A mortality benefit, p=0.07, reported as a trend, cannot disregard potential clinical benefit.

Benefit in non-pancreatic infection can lead to long term mortality benefit and has not been followed.

Heterogeneity of the methods and patients in the previous studies make it difficult to combine their results.

Beta-lactams have yielded the best result vs. FQ/MET.

Most antibiotic courses studied have included 14-23 days.

No increase in incidence of fungal infection.

Reports of increased incidence of bacterial resistance have not been associated with antibiotic use.