Multidisciplinary Approach to Acute Pancreatitis
Medical Management of Acute Pancreatitis

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Dartmouth-Hitchcock Medical Center

Objectives

1. Fluid Resuscitation

2. Antibiotic Therapy

3. Nutritional Support

4. Guideline Recommendations
**Case Presentation - Pancreatitis**

**Chief Complaint:**  Epigastric abdominal pain

**History of Present Illness:**

- 52 y/o male
- Chronic alcoholism
- 24 hours of epigastric pain with radiation to back

- WBC count = 21,235
- Lipase = 1,243
- BUN/CR = 52/1.6

HCT = 49

TB = 1.2  AP = 96

AST/ALT = 41/32
Case Presentation - Pancreatitis

Questions to Consider

What is this entity?

What can I do medically to improve this patient’s outcome?

Objectives

1. Fluid Resuscitation
2. Antibiotic Therapy
3. Nutritional Support
Fluid Resuscitation

- Acute pancreatitis leads to approximately 210,000 admissions annually – most common GI admission

- Associated with significant morbidity and mortality of approximately 5%

- There are no pharmacological therapies with a proven clinical benefit for treating acute pancreatitis

Alterations in the Pancreatic Microcirculation

Hypovolemia
Increased Permeability – free radicals
Microthrombi

Acinar Cell Injury
Proinflammatory mediators (TNF, Bradykinin, IL-1, IL-6)

Further Capillary Vasconstriction
Release of second stage proinflammatory mediators
Fluid Resuscitation

Recommendations Based on Expert Opinion Only

Table 1. Fluid Resuscitation Recommendations From Recent Reviews of Acute Pancreatitis

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Journal</th>
<th>Initial resuscitation recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pondol et al</td>
<td>Gastroenterology, 2007</td>
<td>Severe volume depletion: 500–1000 cc/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonpancreatic fluid loss: 300–500 cc/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No volume depletion: 250–300 cc/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vigorous fluid resuscitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine output &gt;0,5 mL/kg body weight/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluid bolus to achieve hemodynamic stability followed by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250–500 mL/h of crystalloid</td>
</tr>
<tr>
<td>Forsmark and Balie</td>
<td>Gastroenterology, 2007</td>
<td>Aggressive IV fluid replacement</td>
</tr>
<tr>
<td>Banks and Freeman</td>
<td>Am J Gastroenterol, 2006</td>
<td>At least 250–300 cc/h for 48 hours</td>
</tr>
<tr>
<td>Veyk et al</td>
<td>JAMA, 2004</td>
<td></td>
</tr>
<tr>
<td>Tenner</td>
<td>Am J Gastroenterol, 2004</td>
<td></td>
</tr>
</tbody>
</table>

Prospective Trials of Fluid Resuscitation in AP

Original article
Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis

Background: Hemodilution may be an important factor that determines the progression of severe acute pancreatitis (AP). In addition, there is increasing interest in the use of intravenous fluid for the prevention of early and late complications of AP. The purpose of this study was to evaluate the relationship between blood hemodilution and patient outcomes. The study also aimed to determine whether early fluid resuscitation is beneficial in patients with severe AP.

Methods: A retrospective review of 100 consecutive patients with severe AP admitted to a university hospital in Spain was conducted. All patients received intravenous fluid therapy within 24 hours of admission, and the initial fluid resuscitation was based on the severity of the disease. The primary outcome was mortality at 90 days. Secondary outcomes included sepsis, renal failure, and need for ventilatory support.

Results: A total of 100 patients were included in the analysis. The median age was 60 years (interquartile range [IQR], 50–70) and 58% were men. The median APACHE II score was 17 (IQR, 12–22). The median fluid resuscitation volume was 3 L (IQR, 2–4). The primary outcome occurred in 32 patients (32%). Severe sepsis occurred in 29 patients (29%). Renal failure occurred in 14 patients (14%). The median duration of mechanical ventilation was 1 day (IQR, 1–3). The median length of stay was 13 days (IQR, 8–21). In univariate analyses, hemodilution was associated with increased risk of mortality (OR, 1.07 per 1% decrease; 95% CI, 1.02–1.13; P = 0.007) and sepsis (OR, 1.03 per 1% decrease; 95% CI, 1.01–1.05; P = 0.01). In multivariate analyses, hemodilution was independently associated with increased risk of mortality (adjusted OR, 1.06 per 1% decrease; 95% CI, 1.02–1.10; P = 0.004) and sepsis (adjusted OR, 1.03 per 1% decrease; 95% CI, 1.01–1.05; P = 0.01).

Conclusion: Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Early fluid resuscitation may be beneficial in patients with severe AP.
**Fluid Resuscitation**

Prospective Trials of Fluid Resuscitation in AP

**Table 4. Effect of extreme hemodilution on prognosis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rapid hemodilution (HCT &lt;35%)</th>
<th>Slow hemodilution (HCT ≥35%)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balthazar CT Scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>6.1±1.7</td>
<td>5.7±2.1</td>
<td>0.26</td>
</tr>
<tr>
<td>1 week</td>
<td>7.1±2.2</td>
<td>6.8±1.4</td>
<td>0.39</td>
</tr>
<tr>
<td>2 weeks</td>
<td>7.3±2.5</td>
<td>7.2±2.2</td>
<td>0.997</td>
</tr>
<tr>
<td>Time interval for sepsis presented (d)</td>
<td>7.4±1.9</td>
<td>10.2±2.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Incidence of sepsis (%)</td>
<td>78.6 (44/56)</td>
<td>57.6 (34/59)</td>
<td>0.016</td>
</tr>
<tr>
<td>In-hospital Survival rate (%)</td>
<td>66.1 (37/56)</td>
<td>84.7 (50/59)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis

Fluid Resuscitation

Prospective Trials of Fluid Resuscitation in AP

- Praised for large number of patients and only those with SAP included
- Criticized for a somewhat unusual treatment approach

Fluid Resuscitation

Study Design

Goal-Directed Therapy

Standard of Care Therapy

Group 1

Group 2

Group 3

Group 4

Targeting BUN

BUN

20 mL/kg bolus + 3 mL/kg/hr

Fluid refractory

No bolus + 1.5 mL/kg/hr

Fluid responsive

Checkpoints 1 and 2

BUN

0 8 hrs 16 hrs 24 hrs

20 mL/kg bolus + 3 mL/kg/hr

Fluid refractory

No bolus + 1.5 mL/kg/hr

Fluid responsive

**Fluid Resuscitation**


**Figure 1:**
- Comparison of SIRS (Systemic Inflammatory Response Syndrome) in patients receiving different fluids: GD, STD, LR, NS.
- Significant difference in SIRS scores between admission and 24 hours for LR: $P=0.035$.

**Figure 2:**
- Comparison of CRP (C-reactive protein) levels: GDR, STD, LR, NS.
- Significant differences in CRP levels for LR: $P=0.018$.

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Fluid Resuscitation

Prospective Trials of Fluid Resuscitation in AP

- Praised for employing standard clinical resuscitation parameters
- Criticized for small number of patients and surrogate clinical outcomes


Guideline Recommendations
Guideline Recommendations

INITIAL MANAGEMENT

**Recommendations**

1. Aggressive hydration, defined as 250–500 ml per hour of isotonic crystalloid solution should be provided to all patients, unless cardiovascular, renal, or other related comorbid factors exist. Early aggressive intravenous hydration is most beneficial during the first 12–24 h, and may have little benefit beyond this time period (strong recommendation, moderate quality of evidence).

2. In a patient with severe volume depletion, manifest as hypotension and tachycardia, more rapid repletion (bolus) may be needed (conditional recommendation, moderate quality of evidence).

3. Lactated Ringer’s solution may be the preferred isotonic crystalloid replacement fluid (conditional recommendation, moderate quality of evidence).

4. Fluid requirements should be reassessed at frequent intervals within 6 h of admission and for the next 24–48 h. The goal of aggressive hydration should be to decrease the BUN (strong recommendation, moderate quality of evidence).
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2. Antibiotic Therapy

3. Nutritional Support

Antibiotic Therapy

Admission Antibiotics

“Do they prevent a bad clinical outcome?”

Infected Pancreatic Necrosis

“Can we get away with medical therapy only?”
**Antibiotic Therapy**

**Admission Antibiotics**
“Do they prevent a bad clinical outcome?”

**IMIPENEM FOR INFECTED NECROSIS**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio 95% CI</th>
<th>Weight</th>
<th>Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedoret (199?)</td>
<td>3/41</td>
<td>1/23</td>
<td>0.10 (0.01, 1.05)</td>
<td>0.032</td>
<td>0.34 (0.13, 0.84)</td>
</tr>
<tr>
<td>Nordmark (2001)</td>
<td>3/25</td>
<td>2/23</td>
<td>1.4 (0.3, 6.8)</td>
<td>0.194</td>
<td>0.5 (0.14, 2.0)</td>
</tr>
<tr>
<td>Nike (2007)</td>
<td>2/21</td>
<td>4/16</td>
<td>2.0 (0.8, 5.0)</td>
<td>0.60</td>
<td>0.13 (0.03, 0.51)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>78/82</td>
<td></td>
<td>1.00 (0.7, 1.3)</td>
<td>0.347</td>
<td>0.61 (0.13, 0.84)</td>
</tr>
</tbody>
</table>

Villatoro et al. Cochrane Database Sys Rev 2010

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Antibiotic Therapy

Admission Antibiotics

“Do they prevent a bad clinical outcome?”

ALL ANTIBIOTICS - MORTALITY

Antibiotics Do Not Improve Mortality
Antibiotic Therapy

Infected Pancreatic Necrosis

“Can we get away with medical therapy only?”

<table>
<thead>
<tr>
<th>Year</th>
<th>Medical</th>
<th>Surgical</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-2002</td>
<td>N = 12</td>
<td>N = 18</td>
<td>N = 30</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 (8)</td>
<td>12 (66.6)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>2003-2006</td>
<td>N = 40</td>
<td>N = 10</td>
<td>N = 50</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>11 (27.5)</td>
<td>3 (33.3)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>2007-2008</td>
<td>N = 19</td>
<td>N = 8</td>
<td>N = 27</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>6 (31.5)</td>
<td>2 (25)</td>
<td>8 (29.6)</td>
</tr>
</tbody>
</table>

Antibiotics and supportive care should be used as first-line therapy against infected necrosis.

Antibiotic Therapy

Infected Pancreatic Necrosis
“Can we get away with medical therapy only?”


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Antibiotic Therapy

Infected Pancreatic Necrosis
“Can we get away with medical therapy only?”

<table>
<thead>
<tr>
<th>Study</th>
<th>Success of primary conservative management (95% CI)</th>
<th>Success (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runzi et al11</td>
<td>0.50 (0.31, 0.69)</td>
<td>11.80</td>
<td></td>
</tr>
<tr>
<td>Song et al14</td>
<td>0.79 (0.61, 0.97)</td>
<td>11.05</td>
<td></td>
</tr>
<tr>
<td>Lee et al15</td>
<td>0.71 (0.55, 0.87)</td>
<td>12.49</td>
<td></td>
</tr>
<tr>
<td>Gerg et al17</td>
<td>0.85 (0.63, 0.66)</td>
<td>13.70</td>
<td></td>
</tr>
<tr>
<td>Van Santvoort et al18</td>
<td>0.95 (0.21, 0.49)</td>
<td>12.95</td>
<td></td>
</tr>
<tr>
<td>Zerem et al19</td>
<td>0.95 (0.77, 0.92)</td>
<td>14.40</td>
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</tr>
<tr>
<td>Gluck et al20</td>
<td>0.76 (0.65, 0.94)</td>
<td>11.87</td>
<td></td>
</tr>
<tr>
<td>Ahlbacker et al21</td>
<td>0.95 (0.44, 0.86)</td>
<td>11.14</td>
<td></td>
</tr>
<tr>
<td>Overall (5-lobe)</td>
<td>0.64 (0.51, 0.78)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Antibiotic Therapy

Infected Pancreatic Necrosis
“Can we get away with medical therapy only?”

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<td>0.65 (0.44, 0.86)</td>
<td>11.14</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.04 (0.51, 0.70)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

64% successfully treated with medical therapy

Guideline Recommendations
Guideline Recommendations

THE ROLE OF ANTIBIOTICS IN AP

Recommendations

1. Antibiotics should be given for an extrapancreatic infection, such as cholangitis, culture-acquired infections, bacteremia, urinary tract infections, pneumonia (strong recommendation, moderate quality of evidence).

2. Routine use of prophylactic antibiotics in patients with severe AP is not recommended (strong recommendation, moderate quality of evidence).

3. The use of antibiotics in patients with sterile access to prevent the development of infected necrosis is not recommended (strong recommendation, moderate quality of evidence).

4. Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalization. In these patients, either (a) initial CT-guided fine-needle aspiration (FNA) for Gram stain and culture to guide use of appropriate antibiotics or (b) empiric use of antibiotics after obtaining necessary cultures for infectious agents, without CT FNA, should be given (strong recommendation, moderate evidence).

5. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis, such as carbapenems, quinolones, and metronidazole, may be useful in delaying or sometimes totally avoiding intervention, thus decreasing morbidity and mortality (conditional recommendation, moderate quality of evidence).

6. Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not recommended (conditional recommendation, low quality of evidence).
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Objectives

1. Fluid Resuscitation

2. Antibiotic Therapy

3. Nutritional Support

Nutritional Support

Mild Disease

• Most patients able to eat within 7 days

• Initial diet can be low-fat (no need to start with clear liquids)

• Do not use probiotics
**Nutritional Support**

**Severe Disease**

- Start low fat enteral nutrition as soon as possible (Peptamen)

- Nasogastric tube feedings probably comparable to nasojejunal feedings

- Avoid TPN unless cannot deliver full nutritional support enterally

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**Nutritional Support**

Enteral vs Parenteral Nutrition for Acute Pancreatitis: Mortality

| Study or subgroup | Enteral n (%) | Parenteral n (%) | Risk Ratio | 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>165</td>
<td>183</td>
<td>0.50</td>
<td>[0.28, 0.91]</td>
</tr>
</tbody>
</table>

Guideline Recommendations

American College of Gastroenterology Guideline: Management of Acute Pancreatitis

Guideline Recommendations

NUTRITION IN AP

Recommendations
1. In mild AP, oral feedings can be started immediately if there is no nausea and vomiting, and the abdominal pain has resolved (conditional recommendation, moderate quality of evidence).
2. In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet (conditional recommendations, moderate quality of evidence).
3. In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided, unless the enteral route is not available, not tolerated, or not meeting caloric requirements (strong recommendation, high quality of evidence).
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