MANAGEMENT OF THE CRITICALLY ILL PATIENT WITH SEVERE ACUTE PANCREATITIS (Abstract): Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. In about 15-20% of patients with acute pancreatitis, severe damage to the pancreas may lead to a life threatening illness that is often associated with prolong hospitalization, multiple surgical procedures and death in some patients. Incidence is 40 - 250 (millions); 15 - 20% develop necrosis, 30 % develop infected necrosis and 3 - 4 % develop abscess. Infected necrosis causes 80% of all the pancreatitis related mortality. Approximately 2,000 patients per year die from complications related to acute pancreatitis. Mortality varies with etiology, the development of complication or necrosis and the number and severity of co-morbid medical conditions. There are some consensus conferences about the management of the patients with severe acute pancreatitis (SAP). The problems which must solved by these conferences were: When should the patient admitted with acute pancreatitis be monitored in an ICU (Intensive Care Unit) ? Should patients with SAP receive prophylactic antibiotics ? What are the optimal mode and timing of nutritional support for the patient with SAP ? What are the indications for surgery in acute pancreatitis ? Under what circumstances should patients with gallstones pancreatitis undergo intervention for clearance of the bili duct ? Is there a role for therapy targeting the SIRS in the patient with SAP ? My opinions about these problems was: Regular CT scans with FNA sampling; Maximum non-operative support (for avoiding organ dysfunction); Operate for infected necrosis but not too early EN where possible but TNP often required; Beware of abdominal compartment syndrome; Antibiotics only for infected necrosis. KEY WORDS: ACUTE PANCREATITIS, MODS

Acute Pancreatitis

- Mostly self limiting disease
- Etiological factors well understood
- Pathophysiology poorly understood

What is Acute Pancreatitis?

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.

What is Severe Acute Pancreatitis?

In about 15-20% of patients with acute pancreatitis, severe damage to the pancreas may lead to a life threatening illness that is often associated with prolong hospitalization, multiple surgical procedure and death in some patients.

Epidemiology of Acute Pancreatitis

- Incidence 40 - 250 per millions
- 15 -20% develop necrosis
- 30 % develop infected necrosis
- 3- 4 % develop abscess
**Epidemiology of Acute Pancreatitis**

- Infected necrosis causes 80% of mortality
- Approximately 2,000 patients per year die from complication related to acute pancreatitis

**Outcome Infected Necrosis**

<table>
<thead>
<tr>
<th></th>
<th>Oedematous Pancreatitis (n=22)</th>
<th>Sterile necrosis (n=18)</th>
<th>Infected necrosis (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation (%)</td>
<td>81%</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>HD/CVVH (%)</td>
<td>62%</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td>Inotropes (%)</td>
<td>62%</td>
<td>28%</td>
<td>62%</td>
</tr>
<tr>
<td>MODS (%)</td>
<td>62%</td>
<td>33%</td>
<td>81%</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>62%</td>
<td>8%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Rau E et al Intensive Care Med 2000 26:146 - 150

**SAP - Mortality Rate?**

- The patients who require admission to an intensive care unit have mortality rates in the range of 50 - 80% and a mean hospital length of stay > 1 month.


**SAP - Mortality Rate?**

- Mortality varies with etiology, the development of complication or necrosis and the number and severity of co-morbid medical conditions
- The cost of care for these patients is substantial, with estimates of total direct and indirect costs ranging from $3.6 billion to $6 billion annually

**Treatment of Severe Acute Pancreatitis**

- UK guidelines for the management of acute pancreatitis Gut 2005 S41-9
- Conferinta de consens asupra diagnosticului si tratamentului pancreatitelor Chirurgia 2005 103:402 - 406
1. When should the patient admitted with acute pancreatitis be monitored in an ICU or step-down unit?

Rationale
- Patients with SAP may benefit from an environment with more intensive monitoring given their potential for progressive organ dysfunction and/or life-threatening local complication.
- Avoiding unnecessary ICU admission may limit the risk of nosocomial infection and iatrogenic complications.

Evidence
- Critical Care units may ensure optimal fluid resuscitation in order to prevent, reverse, or attenuate organ dysfunction and facilitate timely use of advanced life support.

2. Should patients with SAP receive prophylactic antibiotics?

3. What are the optimal mode and timing of nutritional support for the patient with SAP?

4. What are the indication for surgery in acute pancreatitis?

5. Under what circumstances should patients with gallstones pancreatitis undergo intervention for clearance of the bile duct?

6. Is there a role for therapy targeting the SIRS in the patient with SAP?

When Should The Patient Admitted with Acute Pancreatitis Be Monitored in an ICU?

Evidence
- The cornerstone of management in early pancreatitis is fluid resuscitation and close monitoring for early manifestation of organ dysfunction.
- Monitoring should be directed toward the repeated evaluation of intravascular volume status by means of physical examination and monitoring of urine output and the early detection of hypoxemia through either pulse oximetry or arterial gas analysis.
Factors that May Predict a Severe Attack, Present within 48 hr of Admission to Hospital

<table>
<thead>
<tr>
<th>Initial assessment</th>
<th>Clinical impression of severity</th>
<th>Body mass index &gt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h after admission</td>
<td>Clinical impression of severity</td>
<td>Glasgow score 3 or more, persisting OF, especially if multiple</td>
</tr>
<tr>
<td>48h after admission</td>
<td>Clinical impression of severity</td>
<td>Persistent organ failure, failure for 48 h, multiple or progressive OF</td>
</tr>
</tbody>
</table>

Clinical impression of severity
Glasgow score 3 or more
Persisting organ failure for 48 h
Multiple or progressive OF

APACHE II Scores in the First 24 hr and Subsequent Survival in 290 patients with Predicted Severe Acute Pancreatitis

<table>
<thead>
<tr>
<th>APACHE II score</th>
<th>Survived</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 - 6</td>
<td>172</td>
<td>38</td>
</tr>
<tr>
<td>7 - 8</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Relationship between the Presence or Absence and Duration of Organ Failure in the First Week of Study, and Subsequent Death in 290 Patients with Predicted SAP

<table>
<thead>
<tr>
<th>No OF</th>
<th>Survived</th>
<th>Died</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OF at entry</td>
<td>60</td>
<td>32</td>
<td>88</td>
</tr>
<tr>
<td>Transient</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Persistent</td>
<td>59</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>New OF 7 days</td>
<td>113</td>
<td>3</td>
<td>116</td>
</tr>
</tbody>
</table>

Significant association of death with persistent OF compared with transient or no OF. X² = 62.54; df = 2; p < 0.001

When Should The Patient Admitted with Acute Pancreatitis Be Monitored in an ICU?

Evidence
Patients with SAP who fulfill conventional criteria for ICU admission should be admitted as well as those patients at high risk of rapid deterioration (elderly, significant obesity - body mass index > 30/kg m², patients requiring ongoing volume resuscitation and patient with evidence of substantial pancreatic necrosis > 30%).

Grading of responses to questions and levels of evidence

Supported by at least two level I investigations (large, randomized trials with clear cut results: low risk of false positive (alpha) error or false negative (beta) error.

Supported by only one level I investigation

Supported by level II investigations only by small, randomized trials with uncertain results moderate to high risk of false-positive (alpha) and/or false-negative (beta) error

Supported by at least one level III investigation (nonrandomized, contemporaneous controls)

Supported by level IV or V evidence (nonrandomized, historical controls and expert opinion; case series, uncontrolled studies, expert opinion.}

When Should The Patient Admitted with Acute Pancreatitis Be Monitored in an ICU?

Evidence
A systematic review of 26 observational studies showed that a heterogeneous group of critically ill patients cared by an intensivist consultant model in ICU had a shorter duration of ICU stay and lower mortality than similar patients cared for in unit without such staffing patterns.

Supported by at least one level III investigation (nonrandomized, contemporaneous controls)
**When Should The Patient Admitted with Acute Pancreatitis Be Monitored in an ICU?**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 1</td>
<td>Admission in ICU is recommended for patients with SAP who fulfill conventional criteria for ICU admission as well as those patients at high risk of rapid deterioration (elderly, significant obesity, requiring ongoing volume resuscitation and patient with evidence of substantial pancreatic necrosis &gt;30%).</td>
</tr>
<tr>
<td>Recommendation 2</td>
<td>Critically ill patients with pancreatitis will be cared for by an intensivist-led multidisciplinary team with ready access to physicians skilled in endoscopy, ERCP, surgery, and interventional radiology.</td>
</tr>
<tr>
<td>Recommendation 3</td>
<td>Close clinical observation of patients with pancreatitis is strongly recommended. These patients require early and aggressive fluid resuscitation. They are at the risk for the early development of organ dysfunction as a result of inadequate resuscitation and systemic and local complication of pancreatitis. Clinical monitoring should focus on intravascular volume assessment (physical examination, urine output, acid-base status) and pulmonary function.</td>
</tr>
<tr>
<td>Recommendation 4</td>
<td>Against the routine use of markers such as CRP or procalcitonin to guide clinical decision making, predict the clinical course of pancreatitis or triage patients.</td>
</tr>
<tr>
<td>Recommendation 5</td>
<td>In presence of diagnostic uncertainty at the time of initial presentation, a CT scan of the abdomen (with intravenous contrast in the absence of contraindication) be performed after adequate fluid resuscitation to confirm the diagnostic of pancreatitis and to rule out alternate diagnosis. An admission CT scan may also serve as baseline for future scan.</td>
</tr>
<tr>
<td>Recommendation 6</td>
<td>CT to identify local complications be delayed for 48-72 hrs when possible, as necrosis might not be visualized earlier.</td>
</tr>
</tbody>
</table>
2. Should Patients with Severe Acute Pancreatitis Receive Prophylactic Antibiotics?

Infection of necrotic pancreas develops in 30-50% of patients with necrosis documented by CT or surgery. Infection might occur within the first week, but its incidence tends to peak in the third week of disease. Rates of organ failure and mortality appear to be highest among patients with infected pancreatic necrosis.

**Rationale**
- Infection of necrotic pancreas develops in 30-50% of patients with necrosis documented by CT or surgery.
- Infection might occur within the first week, but its incidence tends to peak in the third week of disease.
- Rates of organ failure and mortality appear to be highest among patients with infected pancreatic necrosis.

**Onset of Infected Necrosis**

<table>
<thead>
<tr>
<th>&lt; 8 days</th>
<th>8-14 days</th>
<th>14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>24%</td>
<td>77%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Bayer H. Gastroenterology 1996; 20:74-78

**Outcome Infected Necrosis**

<table>
<thead>
<tr>
<th>Infected Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation (%)</td>
</tr>
<tr>
<td>HD/CVVH (%)</td>
</tr>
<tr>
<td>Inotropes (%)</td>
</tr>
<tr>
<td>MODS (%)</td>
</tr>
<tr>
<td>Mortality (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infected Necrosis</th>
<th>Sterile necrosis</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation (%)</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>HD/CVVH (%)</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>Inotropes (%)</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>MODS (%)</td>
<td>0</td>
<td>8%</td>
</tr>
</tbody>
</table>

Rau E et al Intensive Care Med 2000; 26:146 - 150

**Summary of Randomized Trials Examining Routine Prophylactic Antibiotics for SAP**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Unit</th>
<th>Number</th>
<th>Control</th>
<th>Experimental</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>mg</td>
<td>118</td>
<td>54, 152</td>
<td>34, 452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>mg</td>
<td>118</td>
<td>53, 152</td>
<td>34, 429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flomoxim</td>
<td>mg</td>
<td>118</td>
<td>54, 152</td>
<td>34, 462</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flomoxim</td>
<td>mg</td>
<td>118</td>
<td>54, 152</td>
<td>34, 452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglucoside</td>
<td>mg</td>
<td>118</td>
<td>53, 152</td>
<td>34, 462</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglucoside</td>
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<td>Aminoglucoside</td>
<td>mg</td>
<td>118</td>
<td>54, 152</td>
<td>34, 452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>236</td>
<td>108</td>
<td>68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**A Randomized Multicenter Clinical Trial of Antibiotic Prophylaxis of Septic Complication in Acute Necrotizing Pancreatitis with Imipenem**

74 patients with severe necrotizing pancreatitis were prospectively randomized to receive imipenem-cilastatin or no antibiotics.

- No significant difference in organ dysfunction (antibiotics 29% versus non-antibiotic, 39%; p = not significant) or mortality (antibiotics 7% versus no antibiotic 12%; p = not significant).

**Early Antibiotic Treatment in Acute Necrotizing Pancreatitis**


Randomized study of 60 patients with acute necrotizing pancreatitis; 30 patients were treated with cefuroxime 4.5g/day intravenously, versus 30 patients no antibiotic treatment.

- More infectious complications in the non-antibiotic than in the antibiotic group (mean per patient 1.8 versus 1.0 p = 0.01).
- Mortality was higher in non-antibiotic group (7 versus 1; p = 0.03).

**Prophylaxis with Meropenem of Septic Complication in Acute Pancreatitis, a Randomized, Controlled Trial versus Imipenem**

One hundred seventy-six patients with necrotizing pancreatitis were prospectively randomized to prophylactic treatment with:
- 0.5 g meropenem t.i.d. intravenously
- or 0.5 g imipenem q.i.d. intravenously.

No difference was observed between patients treated with meropenem and those treated with imipenem, in terms of incidence of pancreatic infection (11.4% versus 13.6%) and extrapancreatic infections (21.6% versus 23.9%) and clinical outcome.

Early Antibiotic Treatment of Septic Complications in SAP: a Prospective, Randomized, Multicenter Study Comparing Two Regimens with Imipenem – Cilastatin

- 92 patients with SAP randomized to receive:
  - antibiotic prophylaxis 14 days
  - antibiotic prophylaxis at least 14 days and as long as major systemic complications of the disease persisted (19.7 ± 10.9 days)

Early Antibiotic Treatment of Septic Complications in SAP: a Prospective, Randomized, Multicenter Study Comparing Two Regimens with Imipenem – Cilastatin

- The incidence of:
  - infected necrosis, pancreatic abscess, and extrapancreatic infections was 11%, 17% and 27% in group 1 and 17.4%, 13 and 35% in group 2

Early Antibiotic Treatment of Septic Complications in SAP: a Prospective, Randomized, Multicenter Study Comparing Two Regimens with Imipenem – Cilastatin

- The incidence of pancreatic and extrapancreatic infections with candida occurred in 7% and 22%
- Global mortality was 18.5%, without difference between groups
- In patients with persisting systemic complications at 14 days mortality decreased from 25% (group 1) to 8.8% (group 2) by maintaining antibiotic prophylaxis

Acute Necrotizing Pancreatitis: Treatment Strategy According to the Status of infection.

- 204 patients with SAP. 86 (42%) had necrotizing disease, from whom 57 (66%) had sterile and 29 (34%) infected.
- Patients with infected necrosis had more organ failure and a greater extent of necrosis

Intra-abdominal Candida Infection during Acute Necrotizing Pancreatitis Has a High Prevalence and Is Associated with Increased Mortality

- 37 patients with infected pancreatic necrosis
- 13 patients (35%) with Candida infection
- Mortality with Candida 53.9 and without Candida 12.5%
- Candida infection independent risk factor for mortality
- Mortality odds ratio for Candida infection without anti-fungal therapy 29.2
Characteristics of Infection with Candida Species in Patients with SAP
- 92 patients with infected pancreatic necrosis
- 22 patients (24%) with Candida infection
- Candida patients suffered a higher mortality (64% vs 19%, p = 0.0001) and experienced more systemic complications (3.2 - 1.6 vs 2.1 - 1.4, p=0.004)
- Preoperative antibiotics were given significantly longer prior to Candida infection (19.0-13. vs 6.4-10.3 days; p = 0.001)

Should Patients with Severe Acute Pancreatitis Receive Prophylactic Antibiotics?
- The lack of any consistent benefit across studies (totaling 192 patients), their variable inclusion criteria, variable methodological quality, different antimicrobial regimens, and the significant potential harm preclude recommendation for routine intravenous prophylactic antimicrobial therapy in patients with SAP.
- While there is inconclusive data supporting the use of prophylactic antibiotics in the setting of SAP, there is some evidence suggesting that misuse of antibiotics leads to devastating super-infections.

Selective decontamination of digestive tract
Controlled Clinical Trial of Selective Decontamination for the Treatment of Severe Acute Pancreatitis
- 102 patient were to gut decontamination or to standard treatment
- The prophylaxis treatment was associated with a significant reduction in pancreatic infections
- The number of patient requiring surgical intervention was no different
- Overall mortality and length of stay were not affected by the prophylaxis treatment

Table 2. Clinical Trial on Selective Decontamination of the Digestive Tract in Acute Pancreatitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Mortality%</th>
<th>Infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luiten et al</td>
<td>1995</td>
<td>SDD</td>
<td>51</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>52</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>Mc Collard et al</td>
<td>1992</td>
<td>SDD</td>
<td>4</td>
<td>60 patients</td>
<td>19 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>6</td>
<td>41 patients</td>
<td>51 patients</td>
</tr>
</tbody>
</table>

Selective decontamination of digestive tract
- Other large trial utilizing gastrointestinal decontamination in groups of critically ill patients have failed to demonstrate a decrease in mortality or intensive care days
- This extensive protocol requires significant resource utilization, and carries a potential risk of the development of bacterial resistance

Should Patients with Severe Acute Pancreatitis Receive Prophylactic Antibiotics?
- Against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis in light of inconclusive and divided expert opinion. Subsets of patients who benefit from prophylactic antibiotic may be identified by further investigation

Recommendation 7
- Recommendation Grad B, level 2b evidence
Should Patients with Severe Acute Pancreatitis Receive Prophylactic Antibiotics?

**Recommendation B**
- Against the routine use of selective decontamination of the digestive tract in the management of necrotizing pancreatitis.
- Further investigation of this promising strategy in SAP is warranted.

Recommendation Grad B, level 2b evidence.

UK Guidelines for Management of Acute Pancreatites

**Recommendation**
- The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Some trials show benefit others do not. At the present there is no consensus on this issue. If antibiotic prophylaxis is used, it should be given for a maximum of 14 days (recommendation grade B).

Gut 2005 54: 1111 - 1119

3. What is the Optimal Mode and Timing of Nutritional Support for the Patient with Severe Acute Pancreatitis

**Rationale**
- Patients with SAP are hypercatabolic; timely institution of feeding is important if malnutrition is to be avoided or treated.
- A large body of evidence, suggests that there are several potential benefit to enteral nutrition compared with parenteral nutrition including a reduction in microbial translocation, improved in gut blood flow and preservation of gut, mucosal surface immunity.
What is The Optimal Mode and Timing of Nutritional Support for Patients with SAP?

**Evidence**
- Eight trials have directly compared enteral nutrition and parenteral nutrition.
- Two studies demonstrated an attenuated inflammatory response as measured by resolution of SIRS, reduction level of circulating CRP, TNFα, or IL-6.
- In remaining studies, which compare parenteral nutrition with jejunal feed, outcome related to infections, organ failure, and mortality were either similar or lower.

**Random Effects Model of Relative Risk (95% Confidence Interval) of Infections Associated with Enteral Compared with TPN**

**Recommendation 9**
- Enteral nutrition should be used in preference to parenteral nutrition in patients with SAP.
- Enteral nutrition should be initiated after initial resuscitation.
- The jejunal route should be used if possible.

**Recommendation Grad A, level 1a evidence**

**What is The Optimal Mode and Timing of Nutritional Support for Patients with SAP?**

**Recommendation 10**
- Parenteral nutrition only be used in when attempts at enteral nutrition have failed after 5 to 7 day trial.

**Recommendation Grad D, level 5 evidence**

**What is The Optimal Mode and Timing of Nutritional Support for Patients with SAP?**

**Recommendation 11**
- When used, parenteral nutrition should be enriched with glutamine.

**Recommendation Grad D, level 5 evidence**
**What is The Optimal Mode and Timing of Nutritional Support for Patients with SAP?**

**Recommendation 12**

- Patients both enterally and parenterally fed, be managed with protocol ensuring strict glycemic control

**Recommendation Grad A, level 1b evidence**

**Recommendation 13**

- Against the routine use of immune-enhancing enteral feed formula or probiotics

**Recommendation Grad D, level 5 evidence**

---

**What Are The Indication for Surgery in SAP and What is The Optimal Timing for Intervention? What are The Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?**

**Rationale**

- There are several incontrovertible indication for operative intervention in patients with SAP
  - intestinal infarct or perforation
  - exsanguinating hemorrhage
  - abdominal compartment syndrome
- Routine operative of the peripancreatic fluid collection and pancreatic necrosis is not necessary and may infect otherwise sterile tissue

**Rationale (cont)**

- The presence of tissue necrosis further exacerbate or impairs the resolution of local and systemic inflammatory response
- Nonviable tissue might be seeded by enteric organisms, resulted infected necrosis
- Necrosis in context of severe clinical disease mandates repeated assessment of need for intervention, which involves operative debridment of pancreas and peripancreatic tissue
- Later in the disease, necrotic pancreas demarcates from viable tissue leading to an easier and safer debridement
What Are The Indication for Surgery in SAP and What is The Optimal Timing for Intervention? What are the Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?

Rationale (cont)

- Over time the area of necrosis undergoes liquefaction resulting in an abscess that might be more amenable to percutaneous drainage
- The optimal intervention depends on clinical course of the patient and the precise timing of intervention

Evidence

- Discrimination between sterile and infected pancreatic necrosis
  - SAP—archetypical examples of sterile inflammatory process leading to organ dysfunction
  - The clinical picture is often one of SIRS and can be indistinguishable from severe sepsis.

What Are The Indication for Surgery in SAP and What is The Optimal Timing for Intervention? What are the Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?

Evidence (cont)

- CT is helpful because the finding of retroperitoneal air is generally indicative of the presence of gas-forming organisms and thus infected necrosis
- In absence of retroperitoneal gas ultrasound or CT-guided fine needle aspiration (FNA) of the necrotic tissue with Gram-negative stain and culture can discriminate between sterile and infected necrosis

Evidence

- CT is helpful because the finding of retroperitoneal air is generally indicative of the presence of gas-forming organisms and thus infected necrosis

Diagnostic utility of the needle aspiration in patients with pancreatic necrosis and clinically suspected infection

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of infection</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Positive predictive value %</th>
<th>Negative predictive value %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rau et al 1998</td>
<td>94</td>
<td>37</td>
<td>83</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>Gersof et al Gastroenter 1997</td>
<td>60</td>
<td>46</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Evidence (cont)

- From more studies results that patients with SAP and without evidence of pancreatic infection can be managed without operation with low rates of mortality and morbidity even in face of organ dysfunction.


Evidence (cont)

- The significant risk of iatrogenic bowel injuries, hemorrhage, an open abdomen, and infecting sterile pancreatic necrosis should be considered before proceeding with operative debriement of sterile necrosis.
What Are The Indication for Surgery in SAP and What is The Optimal Timing for Intervention? What are The Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?

Evidence (cont)
- Management of infected pancreatic necrosis
  - several studies suggest a reduction in the relative risk of death 37–69% in patients in whom necrosectomy is performed at least 2-3 weeks after presentation.

Severe Acute Pancreatitis - Timing of Surgical Intervention

- several large cases series suggest that the diagnosis of infected pancreatic necrosis warrants consideration of a single or a series of intervention designed to achieve the goal of a pancreatic debridement and/or drainage.
- there are no report suggesting that antimicrobial therapy alone is adequate.

Intra-abdominal Hypertension in Patients with Severe Acute Pancreatitis

Evolution of intra-abdominal pressure (IAP) in the first Week after admission

De Waele et al. Critical Care 2005 9:R452
Intra-abdominal Hypertension in Patients with Severe Acute Pancreatitis

Correlation between maximal intra-abdominal pressure and APACHE II score in patients with severe acute pancreatitis

De Waele et al. Critical Care 2005 9:R452

APACHE II score and Ranson scores were higher in patients who developed IAH.

The incidence of organ dysfunction was high in patients with IAH:
- respiratory failure 95%
- cardiovascular failure 91%
- renal failure 86%

Mortality in the patients with IAH was not significantly higher compared to patient without IAH (38% versus 16%, p=0.63)

De Waele et al. Critical Care 2006 9:R452

What Are The Indication for Surgery in SAP and what is The Optimal Timing for Intervention? What are The Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?

Recommendation 14

Use of sonographic or CT guided FNA with Gram stain and culture of pancreatic or peri-pancreatic tissue to discriminate between sterile and infected necrosis in patients with radiological evidence of pancreatic necrosis and clinical feature consistent with infection.

Recommendation Grad C, level 4 evidence

Recommendation 15

Against debridement and/or drainage in patients with sterile necrosis.

Recommendation Grad C, level 4 evidence

Recommendation 16

Debridement and/or drainage in patients with infected necrosis and/or abscess confirmed by radiological evidence of gas or results of FNA.

The gold standard for achieving this goal is open operative debridement.

Minimally invasive techniques including laparoscopic and/or percutaneous interventions might be effective in selected patients.

Recommendation Grad C, level 4 evidence
What Are The Indication for Surgery in SAP and What is The Optimal Timing for Intervention? What are The Roles for Less Invasive Approach Including Percutaneous Drainage and Laparoscopy?

Recommendation 17
- When possible, operative necrosectomy drainage be delayed at least 2-3 weeks to allow for demarcation of the necrotic pancreas.
- However, the clinical picture (severity and evolution) should be primary determinant of the timing of intervention

Recommendation Grad C, level 4 evidence

5. Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct?

Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct?

Rationale
- Gallstones represent one of the most common etiologies of acute pancreatitis accounting for 40-60%. All patients with pancreatitis should be evaluated for the presence of gallstones since this etiology has specific therapeutic implications.

Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct? (cont)

Rationale
- The mechanism by which gallstones initiate the process of pancreatitis is by temporary or persistent obstruction of the sphincter of Oddi.
- Given this purported mechanisms, it has postulated that prompt removal of stone would attenuate the inflammatory response.

Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct?

Evidence
- Ultrasound should be performed to assess for gallblad stones as a potential cause of pancreatitis and the abdominal CT scan should be reviewed with this in mind.
- The sensitivity of ultrasound for identification of cholelithiasis in presence of acute pancreatitis is approximately 85%, whereas the sensitivity for coledocholithiasis is < 50%.

Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct? (cont)

Evidence
- Identification for the patients with biliary pancreatitis
- Endoscopic ultrasound offers significantly more sensitivity and specificity.
- A three-fold or greater increase in alanine aminotransferase had a positive predictive value in identifying pancreatitis with biliary etiology.
Under What Circumstances Should Patients with Gallstones Pancreatitis Undergo Interventions for Clearance of The Bile Duct?

Evidence

Timing of biliary clearance

- For patients with severe acute gallstones pancreatitis urgent biliary drainage and clearance of the bile duct must be considered.
- There is a general consensus that patients with obstructive jaundice should undergo urgent ERCP and if gallstones are identified, endoscopic sphincterotomy should be performed.

Summary of Randomized Controlled Trial Comparing Early ERCP within 72 hrs of Presentation or 24 hrs of Symptom Onset of SAP

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</table>

Recommendation 18

- Gallstone pancreatitis be suspected in all patients with SAP and therefore all patients should have evaluation with sonography and biochemical tests.

Recommendation Grad C, level 4 evidence

Recommendation 19

- In the setting of obstructive jaundice (or other evidence of acute obstruction of the of the biliary and/or pancreatic tract) and acute pancreatitis due to suspected or confirmed gallstones, urgent ERCP should be performed within 72 hours of onset of symptom.

Recommendation Grad D, level 5 evidence

Recommendation 20

- In the absence of obstructive jaundice, but with SAP due to suspected or confirmed gallstones ERCP be strongly considered within 72 hours of onset of symptoms.

Recommendation Grad B, level 1c evidence

6. Is There a Role for Therapy Targeting The Inflammatory Response In The Patients with Severe Acute Pancreatitis?
Is There a Role for Therapy Targeting The Inflammatory Response in The Patients with Severe Acute Pancreatitis?

Rationale
- The physiologic response and many of the complications of SAP occur as result of an uncontrolled inflammatory response.
- Recent therapeutic strategies have been directed toward interrupting the SIRS to mitigate the development of organ dysfunction.

Evidence
- TNFα is considered to be a key mediator in shock and is found in high circulating concentrations in acute pancreatitis. There are no data available on its effectiveness in SAP.
- PAF blockage – lexipafant – PAF antagonist have been shown to attenuate the inflammatory response and to lower the incidence of organ dysfunction in two small trials.
- Modulation of the coagulation cascade – rh-APC has proven effectiveness in reducing mortality in patients with severe sepsis.

Recommendation 21
- General supportive measure used in the critically ill should be employed in patients with SAP as these interventions might play an important role in attenuating the inflammatory response.
  - Recommendation Grad A, level 1b evidence
  - Recommendation Grad A, level 1 evidence

Recommendation 22
- Once the presence of infection is documented or highly suspected and patients with SAP meets the definition of severe sepsis, management according to current sepsis guidelines be initiated. These therapy include the use of rh-ACP (grade A level 1b) and low dose corticosteroid (grade B level 1b evidence).
  - The careful consideration be used before administration of rh - ACP based on the theoretical but unproven concern of retroperitoneal hemorrhage.
  - Recommendation Grad D, level 5 evidence
Is There a Role for Therapy Targeting The Inflammatory Response in The Patients with Severe Acute Pancreatitis?

**Recommendation 23**
- Against the use of other immune-modulating therapies targeting inflammatory mediators in SAP such as anti-TNF-α therapy and lexipafant
  - Recommendation Grad A, level 1 evidence for lexipafant
  - Recommendation Grad D level 5 evidence for all other therapy

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**My Opinions**

- Regular CT scans with FNA sampling
- Maximum non-operative support (for avoiding organ dysfunction)
- Operate for infected necrosis but not too early
- EN where possible but TNP often required
- Beware of abdominal compartment syndrome
- Antibiotics only for infected necrosis

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THANK YOU Ladies and Gentlemen