Management of severe acute pancreatitis: it’s all about timing

Marc G.H. Besselinka, Hjalmar C. van Santvoorta, Ben J. Wittemanb and Hein G. Gooszena, for the Dutch Acute Pancreatitis Study Group

Purpose of review
This study provides an update on the treatment of severe acute pancreatitis (SAP) with emphasis on nutrition, infection-prophylaxis, biliary pancreatitis, surgical intervention and new randomized controlled trials.

Recent findings
The most relevant new insights are: (i) early enteral nutrition in SAP is not only capable of reducing infectious complications but may also reduce mortality; (ii) there is increasing evidence that antibiotic-prophylaxis is not capable of preventing infectious complications in SAP; (iii) probiotic-prophylaxis is being considered as an alternative with promising experimental results; (iv) in biliary pancreatitis, early endoscopic retrograde cholangiography with sphincterotomy (within 48 h) is beneficial in case of ampullary obstruction, although it may be withheld in the event of negative endoscopic ultrasound; (v) surgical intervention for infected (peri-)pancreatic necrosis is increasingly being postponed; (vi) minimally invasive strategies are being considered as a full alternative for necrosectomy by laparotomy in infected (peri-)pancreatic necrosis; (vii) the Atlanta classification should no longer be used to describe computed tomography findings in acute pancreatitis; and (viii) only five randomized controlled trials of patients with acute pancreatitis are currently registered in the international trial registries.

Summary
Timing of intervention is becoming increasingly important in SAP management.

Keywords
nutrition, pancreatitis, prophylaxis, review, timing

Introduction
The incidence of acute pancreatitis is increasing in the Netherlands [1] by an astonishing 5% annually in the previous decade [2]. The present review aims at providing an update on the treatment of severe acute pancreatitis (SAP), focusing on studies published in the previous year.

Data retrieval
We performed a Pubmed search using the terms ‘pancreatitis’[MeSH] OR ‘acute pancreatitis’[MeSH] OR ‘pancreatitis’[Title/Abstract] OR ‘acute pancreatitis’[Title/Abstract]). The search, restricted to studies of human adults published in English between August 1, 2005 and August 1, 2006, returned 372 hits. In addition, abstracts from major conferences in the previous year were reviewed.

To review those trials on acute pancreatitis that were in the process of enrolling patients, the two international registries of randomized controlled trials (RCTs), www.controlled-trials.com and www.clinicaltrials.gov, were searched on September 1, 2006 [3]. After contacting the principal investigators of the registered trials, only RCTs that were still actively enrolling patients were included in this study.

Nutrition
The 2006 European Society of Parenteral and Enteral Nutrition guidelines [4] state that enteral nutrition should be initiated as early as possible. Initial fluid replacement therapy should be decreased gradually over 24 h as the enteral supply is increased via pump-assisted jejunal tube feeding.

In a systematic review, McClave et al. [5] concluded, ‘patients with SAP should begin enteral nutrition early...’
because such therapy modulates the stress response, promotes more rapid resolution of the disease process, and results in better outcome’. This conclusion is supported by a Russian RCT from Petrov et al. [6**], in which 70 patients with predicted SAP (defined as APACHE II score >8, high computed tomography (CT) score and/or C-reactive protein >150 U/l) were randomly allocated to receive either total parenteral nutrition (TPN) or total enteral nutrition (TEN). Antibiotic prophylaxis was used in all patients. Multiorgan failure was reduced in the TEN group (20% vs. 50%, P = 0.02). Furthermore, infection of pancreatic necrosis (20% vs. 74%, P < 0.001) and need for surgical intervention (25% vs. 88%, P < 0.001) was reduced in the TEN group. Most strikingly, in contrast with previously published studies, mortality was decreased in the TEN group (6% vs. 35%, P < 0.001).

The Petrov results are confirmed by a nonrandomized study by Targarona et al. [7], which prospectively included 87 patients during a 6-year period. In the first 3 years, 43 patients received TPN and in the latter 3 years, 44 received ‘TEN. Patients that did not receive ‘adequate antibiotic prophylaxis’ (n = 31) and patients in whom enteral nutrition was not started in the first week (n = 29) were excluded. The incidence of multiorgan failure in the TEN group (57% vs. 85%, P ≤ 0.001), infected pancreatic necrosis (20% vs. 74%, P < 0.001) and the need for surgical intervention (25% vs. 88%, P < 0.001) were all reduced. Finally, mortality in the TEN group was significantly reduced (5% vs. 35%, P < 0.0001). With these two new studies, it seems that enteral nutrition has now truly become the ‘standard of care’ in SAP patients.

One of the main mechanisms through which enteral nutrition is thought to exert its beneficial effects is normalization of increased intestinal permeability [8]. A multicenter RCT by Kocher et al. (ISRCTN12838218) is currently being conducted to study the effect of TEN on gastrointestinal permeability. It is hypothesized that compared with ‘standard’ fluid replacement, TEN is better capable of normalizing the increased gastrointestinal permeability typically present in SAP.

Apart from the issue of the timing and route of administering nutrition, two new RCTs on the optimal type of nutrition were performed. Tiengou et al. [9] randomized 30 acute pancreatitis patients to receive either semi-elemental or polymeric formula. All feeding was administered through a nasojejunal tube, and tolerance was similar in both groups. In the semi-elemental group, both hospital stay was reduced (23 vs. 27 days, P = 0.006) and weight loss was lower (1 kg vs. 2 kg, P = 0.01). A semi-elemental formula therefore seems superior in feeding SAP patients.

At the 2006 Digestive Disease Week, Jacobsen et al. [10] presented a RCT allocating 121 patients recovering from mild pancreatitis (as defined by the Atlanta criteria) to an initial clear liquid diet or low-fat solid diet meal. Although the latter group had a higher intake of calories and grams of fat (P < 0.0001), the primary endpoint, postrefeeding length of stay, did not differ between groups (1.7 days, P = 0.94).

At the 2005 United European Gastroenterology Week, Levy et al. [11] presented the results of a placebo-controlled, double-blind RCT on the use of lanreotide, a somatostatin analogue, in the prevention of pain relapse following reintroduction of oral diet following necrotizing pancreatitis. Seventy-seven patients were randomly allocated to receive lanreotide or placebo. No beneficial effect could be shown since two patients in the lanreotide group vs. six in the placebo group had pain relapse in the first 4 weeks (P = 0.263).

Antibiotic prophylaxis

Secondary infection of pancreatic and/or peripancreatic necrosis by gut-derived bacteria is responsible for up to 80% of mortality in acute pancreatitis. Whether antibiotic prophylaxis is effective in preventing secondary infections has been much debated during the previous decades [12]. This issue was addressed in two recent meta-analyses. Heinrich et al. [13**] concluded, ‘patients with proven pancreatic necrosis should receive antibiotic prophylaxis using imipenem or meropenem’. In contrast, Mazaki et al. [14**] concluded, ‘prophylactic antibiotics do not prevent infected necrosis or death in acute necrotizing pancreatitis’. The Heinrich meta-analysis was criticized [15] for not taking into account the mortality data of the first placebo-controlled trial by Isenmann et al. [16] and because it excluded two Czech RCTs by Spicak et al. [17,18], both of which showed no effect of antibiotic prophylaxis. The Mazaki study, including the Isenmann mortality data and the Czech trials, clearly demonstrated that the use of antibiotic prophylaxis in SAP is not evidence-based.

Our group analyzed the methodological quality of RCTs on antibiotic prophylaxis in SAP using a previously published scoring system [19]. A correlation was demonstrated between the methodological quality of the RCTs and the relative risk reduction of mortality due to antibiotic prophylaxis (correlation coefficient −0.975, P = 0.005) [20]. Thus, the better the trial the less effect of antibiotics on mortality was observed.

At the 2006 Interscience Conference on Antimicrobial Agents and Chemotherapy meeting, Dellinger et al. [21] presented the results of a placebo-controlled multicenter trial using meropenem prophylaxis in 100 patients with predicted SAP, including the largest number of patients with extensive (>30%) pancreatic necrosis (n = 53) to date. No beneficial effect of antibiotic prophylaxis
was found. When incorporating this RCT into a new meta-analysis, again no beneficial effect of antibiotic prophylaxis could be demonstrated [20].

In June 2006, Manes et al. [22**] published the results of an RCT with an interesting study design. All 215 patients admitted with acute pancreatitis were randomized to receive either meropenem prophylaxis immediately after admission (early group) or to start meropenem treatment as soon as pancreatic necrosis had been detected using contrast enhanced CT (CECT). CECT was performed in both groups at least 48 h after admission. In the early group, meropenem treatment was stopped when no pancreatic necrosis was detected with CECT. The final analysis consisted only of patients in whom pancreatic necrosis had been detected. In the early group there was a reduction in extra-pancreatic infections (5/30 vs. 13/29, \( P < 0.03 \)), need for surgical intervention (4/30 vs. 11/30, \( P < 0.05 \)) and length of hospital stay (18 vs. 30 days, \( P = 0.01 \)). No significant differences were noted in the incidences of infected necrosis (early 4/30 vs. late 9/29, \( P = 0.1 \)), local complications, systemic complications, multiorgan failure and mortality (3/30 vs. 3/29, \( P = 1.0 \)). These interesting findings require validation; until such time there is no indication for antibiotic prophylaxis.

**Probiotic prophylaxis**

Probiotics are living micro-organisms which exert a range of health promoting properties upon oral delivery. In recent years, Olah et al. [23,24] have published two RCTs on probiotic prophylaxis in patients with acute pancreatitis. In both studies, enterally administered probiotics reduced the incidence of infectious complications. It is hypothesized that probiotics act on three different levels [25*]: (i) intestinal motility and small bowel bacterial overgrowth; (ii) the structural mucosal barrier function; and (iii) the immune system. In an experimental study, Van Minnen et al. [26] randomly allocated 48 rats to receive multispecies probiotics (Ecologic 641) or placebo until 7 days after induction of acute pancreatitis. At day 7, the rats receiving probiotics had reduced bacterial overgrowth of potential pathogens in the duodenum and reduced bacterial counts in the spleen, liver and pancreas. Furthermore, reduced bacterial loads in mesenteric lymph nodes and reduced late mortality were detected. A nationwide placebo-controlled RCT using Ecologic 641 multispecies probiotic prophylaxis (PRO-PATRIA; probiotics in pancreatitis trial) in 15 Dutch centers is currently underway [27].

**Biliary pancreatitis**

Venneman et al. [28*] retrospectively analyzed 528 patients with gallstone disease, including 115 biliary pancreatitis patients. They demonstrated that especially small gallstones (<5 mm) are associated with pancreatitis. Acosta et al. [29] randomized 61 patients with acute biliary pancreatitis and ampullary obstruction to either conservative management and endoscopic retrograde cholangiography (ERC) ± endoscopic sphincterotomy after 48 h (control group) or systematic ERC ± endoscopic sphincterotomy within 48 h if obstruction persisted 24 h or longer (study group). Patients in the study group had a lower rate of immediate complications (\( P = 0.026 \)) as compared with controls; mortality was zero, indicating that systematic early ERC ± endoscopic sphincterotomy is superior.

Liu et al. [30*] randomized 140 patients with biliary pancreatitis to receive either endoscopic ultrasonography (EUS) with ERC during the same session when choledocholithiasis was detected (EUS group) or diagnostic ERC (ERC group). Both interventions were performed within 24 h of admission. EUS successfully visualized the biliary tree in all patients, whereas cannulation of the common bile duct failed in 14% (10/70) of patients in the ERC group. There were no differences in hospital stay, morbidity or mortality. This study is interesting as it shows that EUS can be readily used, thus preventing the potential additional risk of ERC in biliary pancreatitis patients.

**Surgical intervention: timing**

Walser et al. [31] once more pointed out why sterile pancreatic fluid collections should not be drained. In 13/22 patients in whom culture-negative collections were aspirated and consequently drained, aspirates turned culture-positive (59%) versus 3/15 (20%, \( P = 0.04 \)) in case of single aspiration.

In case of infected (peri-)pancreatic necrosis, the guidelines of the International Association of Pancreatology [32] recommend that surgical intervention be performed in the third or fourth week after onset of symptoms. A recent paper suggests that when intervention can be postponed until after this time period (>30 days after onset of symptoms) outcome is improved [33]. Furthermore, in a systematic review of 879 patients from nine studies (single center studies with >25 patients) an association was observed between (postponed) timing and (decreased) mortality \( (\hat{r} = -0.741, P = 0.022) \) [33]. The median timing of surgical intervention for infected (peri-)pancreatic necrosis was 27 days (3–31 days), indicating that in expert centers, up to 50% of patients are already operated upon after the initial 4 weeks. The median mortality for infected (peri-)pancreatic necrosis was 25% (range 6–56%).

There is, however, ongoing debate regarding the timing of intervention once infected pancreatic necrosis is diagnosed [34]. Some authors intervene within 24 h after the diagnosis of infected pancreatic necrosis, irrespective of the patients’ clinical condition, arguing that escalation
in organ failure is imminent. Others postpone intervention, allowing areas of necrosis to organize and demarcate, even in the presence of organ failure, as organ failure can frequently be stabilized by conservative, intensive care therapy [34].

**Surgical intervention: minimally invasive strategies**

Several authors have recently reported on the results of minimally invasive strategies in the treatment of infected (peri-)pancreatic necrosis. Although different terminology is used, there are major similarities [35–37]. In all techniques, a percutaneous drain is placed through the left retroperitoneum. After drain placement, a ‘wait-and-see’ policy is usually followed [36,37] although some authors move straight to surgery once a drain has been positioned [35]. Mortality rates varied from 0% to 16%. Interestingly, Farkas et al. [38] showed that in recent years, necrosectomy by laparotomy is also associated with favorable outcome (8% mortality, 17/220). This finding once more stresses the need for randomized studies comparing minimally invasive strategies with laparotomy in the treatment of infected (peri-)pancreatic necrosis.

In the meta-analysis of Heinrich et al. [13]** it was concluded that single necrosectomy and continuous postoperative lavage (CPL) with large-bore surgical drains without planned relaparotomies is the preferred strategy for surgical treatment of infected (peri-)pancreatic necrosis. This is in line with a recent national Dutch survey [2**] in which it was demonstrated that single necrosectomy and CPL is the preferred strategy in the Netherlands with 25% mortality (13/53 patients). Furthermore, minimally invasive strategies with preoperative placement of percutaneous drains seemed beneficial with 11% mortality (2/18 patients). In the USA, Horvath et al. are conducting a single-arm prospective study with videoscopic assisted retroperitoneal debridement (VARD, NCT00061269). The first RCT on this subject has been initiated in the Netherlands; it is designed to compare a minimally invasive ‘step-up approach’ (including percutaneous or endoscopic drainage and VARD) with laparotomy followed by CPL [39]. Patients are currently being enrolled from 20 Dutch centers.

**Describing computed tomography findings in severe acute pancreatitis**

The 1992 Atlanta classification aimed to define the disease of acute pancreatitis. Recently, a first interobserver study [40**] demonstrated a very poor interobserver agreement when judging CT scans using the Atlanta classification. One of the most common mistakes made is the use of the term ‘pseudocyst’ (definition: collection with a surrounding wall filled with fluid, without necrosis) in patients that actually have collections containing both necrosis and fluid. Only ultrasound and/or magnetic resonance imaging can readily diagnose a pseudocyst. As a consequence of the poor interobserver agreement, radiologists should not be asked to define collections according to the Atlanta classification. Radiologists should rather report findings objectified from the scan, like presence or absence of pancreatic parenchyma necrosis, extrapancreatic necrosis, air collections etc.

**New randomized controlled trials**

Table 1 demonstrates the RCTs presented from August 1, 2005 to August 1, 2006. Most of these have already been

<table>
<thead>
<tr>
<th>Subject</th>
<th>Randomized controlled trial</th>
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<tbody>
<tr>
<td>Nutrition</td>
<td>Petrov et al. [6**]: enteral vs. parenteral feeding in predicted severe acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>→ enteral feeding reduces the incidence of infected necrosis, multiorgan failure, surgical intervention and mortality</td>
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<tr>
<td></td>
<td>Levy et al. [11]: lanreotide vs. placebo in the prevention of pain relapse following reintroduction of diet</td>
</tr>
<tr>
<td></td>
<td>→ no reduction in the occurrence of pain relapse</td>
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<tr>
<td></td>
<td>Jacobsen et al. [10]: clear liquid vs. low fat solid diet as the initial meal after mild pancreatitis</td>
</tr>
<tr>
<td></td>
<td>→ no reduction in postrefeeding length of stay</td>
</tr>
<tr>
<td>Infection prophylaxis</td>
<td>Dellinger et al. [21]: meropenem vs. placebo in predicted severe acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>→ no reduction of infectious complications and mortality</td>
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<tr>
<td></td>
<td>Manes et al. [22**]: meropenem started at admission and stopped in case of no necrosis on CECT (early group) or meropenem started once necrosis detected on CECT (late group)</td>
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<tr>
<td></td>
<td>→ early meropenem administration reduced extra-pancreatic infections, need for surgical intervention and length of hospital stay. No reduction of infected necrosis, organ failure and mortality</td>
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<tr>
<td>Antioxidant therapy</td>
<td>Srinwardena et al. [41]: antioxidant therapy vs. placebo in severe acute pancreatitis</td>
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<tr>
<td></td>
<td>→ no reduction in organ dysfunction</td>
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<tr>
<td>Biliary pancreatitis</td>
<td>Acosta et al. [29]: early ERC with sphincterotomy within 48 h vs. observation with possible ERC with sphincterotomy after 48 h</td>
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<tr>
<td></td>
<td>→ early ERC reduced morbidity</td>
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<tr>
<td></td>
<td>Liu et al. [30*]: EUS and ERC when choledocholithiasis detected vs. ERC in all patients, both within 24 h after admission</td>
</tr>
<tr>
<td></td>
<td>→ no differences in morbidity and mortality although cannulation of the common bile duct failed in 14% of cases in the ERC group</td>
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CECT, contrast enhanced computed tomography; ERC, endoscopic retrograde cholangiography; EUS, endoscopic ultrasonography.
Ongoing randomized controlled trials
Table 2 shows all registered RCTs on acute pancreatitis enrolling patients at September 1, 2006. The Edwards et al. RCT (ISCRTN42476855) set out in 2001 to randomize 100 patients with acute pancreatitis to early or delayed cholecystectomy, hypothesizing that early cholecystectomy may be beneficial in terms of morbidity.

Conclusion
The most important new insights in the management of SAP from the previous year are: (i) early enteral nutrition in SAP is not only capable of reducing infectious complications but may also reduce mortality; (ii) there is increasing evidence that antibiotic-prophylaxis is not capable of preventing infectious complications in SAP; (iii) probiotic-prophylaxis is being considered as an alternative to promising experimental results; (iv) in biliary pancreatitis early ERC with sphincterotomy (within 48 h) is beneficial in case of ampullary obstruction, although in case of negative endoscopic ultrasound, one may withhold ERC; (v) surgical intervention for infected (peri-)pancreatic necrosis is being increasingly postponed; (vi) minimally invasive strategies are being considered as a full alternative for necrosectomy by laparotomy in infected (peri-)pancreatic necrosis; (vii) the Atlanta classification should no longer be used to describe CT findings in acute pancreatitis; and (viii) only five randomized controlled trials of patients with acute pancreatitis are currently registered in the international trial registries. In order to truly improve care for patients with SAP, RCTs of high methodological quality are urgently needed. The issues of infection-prophylaxis, timing of surgical intervention and minimally invasive surgical and endoscopic strategies in SAP in particular are heavily debated and need further study. The present review did not aim at providing a complete overview of the recent literature of SAP. New topics not addressed in this review include new imaging modalities [42–46] and autoimmune pancreatitis [47–55].

Besides high-quality studies, so-called ‘implementation and surveillance studies’ remain of utmost importance. Several studies have pointed out that the best available evidence is often not used in daily practice [56,57]. We feel that the combination of high-quality RCTs and optimal implementation is what would best serve the interests of the increasing number of patients with SAP.

Acknowledgements
Authors’ contributions: MGHB drafted the manuscript. All authors edited the manuscript. All authors read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

MGH Besselink is a MD-medical research trainee for the Netherlands Organisation for Health Research and Development (ZonMw, grant number 920-03-368).

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 244–245).

5 International guidelines on enteral nutrition in pancreatic disease.
7 High-quality RCT that demonstrates a reduction in mortality by the use of enteral nutrition in SAP.

Table 2 Ongoing randomized controlled trials on patients with acute pancreatitis registered on the controlled-trials.com and clinicaltrials.gov websites, Sep 1, 2006

<table>
<thead>
<tr>
<th>Subject</th>
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<tr>
<td>Nutrition</td>
<td>Kocher et al.: early enteral nutrition vs. standard fluid replacement studying gastrointestinal permeability, ISCRTN12838128</td>
</tr>
<tr>
<td>Infection prophylaxis</td>
<td>Gooszen et al. [27]: the Netherlands: probiotics vs. placebo PROPATRIA trial, ISCRTN38327949</td>
</tr>
<tr>
<td>Management of infected (peri-)pancreatic necrosis</td>
<td>Horvath et al.: prospective single-arm series of VARD, NCT00061269</td>
</tr>
<tr>
<td>Timing of cholecystectomy</td>
<td>Edwards et al.: early vs. delayed cholecystectomy, ISCRTN42476855</td>
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</table>

VARD, videoscopic-assisted retroperitoneal debridement.

addressed; the antioxidant trial of Siriwardena et al. [41] was stopped early because predefined stopping criteria had been fulfilled. A total of 44 patients were randomized with 7/22 (31%) organ failure in the treatment group as compared with 4/21 (19%) in the placebo group (P = 0.49).
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28 Venneman NG, Buskens E, Bessellink MG, et al. Small gallstones are associated with increased risk of acute pancreatitis: potential benefit of prophylactic cholecystectomy? Am J Gastroenterol 2005; 100:2540–2550. Study nicely demonstrating that small gallstones are associated with increased risk of acute pancreatitis.


RCT demonstrating the relevance of endoscopic ultrasonography in acute biliary pancreatitis.


First interobserver study on the Atlanta classification demonstrating very poor interobserver agreement.


