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REVIEW

Management of patients with severe acute pancreatitis in the new millennium: prophylaxis, nutrition, imaging and intervention

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Abstract. *Objective:* **To give an overview of the current management of severe acute pancreatitis focusing on prophylaxis, nutrition, imaging and intervention.** *Search strategy:* **PUBMED, EMBASE and Cochrane database search for clinical studies and guidelines regarding severe acute pancreatitis published in the last five years (from January 1 2002). Ongoing studies of the Dutch Acute Pancreatitis Study Group are summarized.** *Summary of findings:* **The four most important changes in the management of severe acute pancreatitis in recent years are; a) to refrain from giving antibiotic prophylaxis in necrotizing pancreatitis; b) to use enteral nutrition instead of parenteral nutrition whenever possible; c) to use descriptive terms when describing computed tomography findings rather than interpretative definitions such as 'pseudocyst' and 'pancreatic abscess'; d) a strong tendency to postpone intervention, even in cases of suspected or documented infected pancreatic necrosis. In an attempt to improve diagnosis, treatment and outcome of severe acute pancreatitis, the Dutch Acute Pancreatitis Study Group has chosen to perform nationwide randomized trials in patients with infected necrotizing pancreatitis specifically with respect to these issues.** *Conclusion:* **In the third millennium the treatment of severe acute pancreatitis has shifted from routine antibiotic prophylaxis, parenteral nutrition, and early operation to tailored antibiotic treatment, enteral nutrition, and postponing of radiological and surgical intervention.**

Introduction

The incidence of acute pancreatitis is increasing rapidly. Over a 6-year period in Dutch non-university hospitals, a 75% increase in admissions for acute pancreatitis was observed(from 19 to 33 patients per year) compared with a 14% increase in university hospitals (from 33 to 37 patients per year) [1]. One in every five patients with acute pancreatitis develops severe acute pancreatitis. Severe pancreatitis is defined by the presence of organ failure and/or necrotizing pancreatitis. Sterile necrotizing pancreatitis generally needs no intervention. However, in 33% of patients with necrotizing pancreatitis, secondary infection of necrosis occurs: infected necrotizing pancreatitis (INP) [2]. Despite the increasing incidence of acute pancreatitis, the average Dutch hospital will only see 3-4 patients with INP per year. INP is the most severe late complication of acute pancreatitis and carries a mortality rate of close to 100% without intervention. Even after surgical intervention, mortality for INP in the Netherlands (2000-2003) remains as high as 34% [3,4]. It is obvious that this exceedingly high mortality rate for a benign condition represents a major challenge for the health care system. Therefore, we aimed to review the recent literature on necrotizing pancreatitis. We chose to focus on four areas in which due to progress made in recent years patient management has changed, i.e. prophylaxis, nutrition, imaging and intervention. Furthermore, we will summarize the ongoing studies of the nationwide Dutch study group on acute pancreatitis with respect to the above mentioned four issues.

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Methods

A systematic literature search using predefined search terms was carried out in the PUBMED, EMBASE and Cochrane databases for articles published since January 1 2002. Search terms were "*necrotizing pancreatitis*" or "*necrotising pancreatitis*" with limits set at English, Humans and Adults. The search provided 115 hits in PUBMED, 406 hits in EMBASE and 37 hits in the Cochrane databases (up to Sept 28 2007). The title and abstract of all papers identified were screened for studies on clinical acute pancreatitis that focused on any of the four following topics: prophylaxis, nutrition, imaging and intervention. If present, results of randomized controlled trials (RCTs) were included. If RCTs were not present, results of prospective series were included. Furthermore, an overview of the ongoing research of the Dutch Acute Pancreatitis Study Group on these topics is presented.

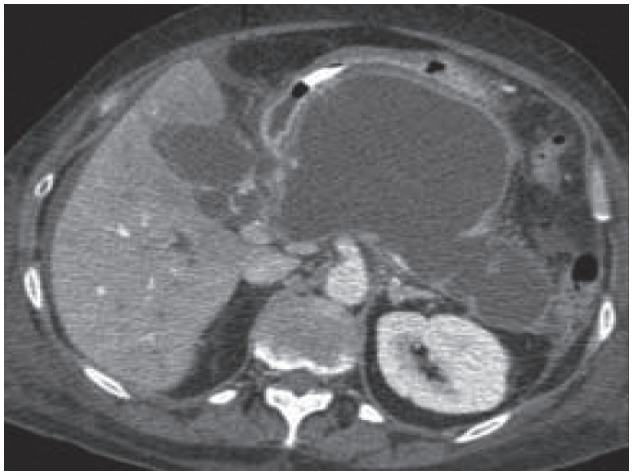
Results

Prophylaxis

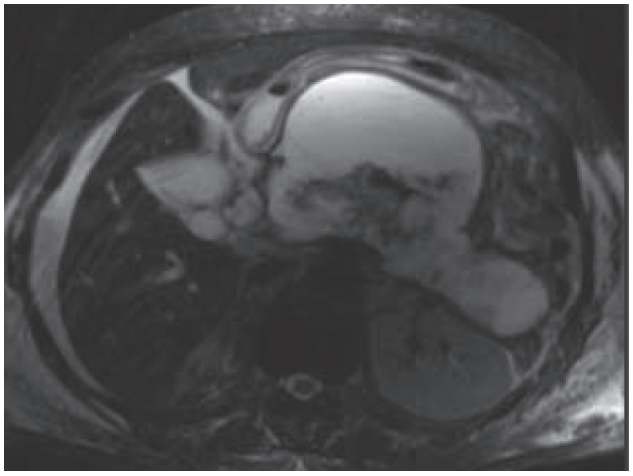
Whereas systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS) are responsible for the majority of early mortality (first 14 days of admission) in acute pancreatitis [5] the main cause of late mortality is INP. Bacterial translocation of gut microflora across the gut barrier is held responsible for the infection of pancreatic or peripancreatic necrosis.

In recent years, systemic antibiotic prophylaxis has been a much

Figure 1. CT and MRI images of a peripancreatic collection, both taken at day 35 in the same patient, illustrating the poor capacity of CT in detecting necrotic tissue in a peripancreatic collection.



a.CT scan shows a large homogenous fluid-like peripancreatic collection that many radiologists and clinicians alike would define as a 'pseudocyst'.



b.MRI, T2-weighted sequence, clearly demonstrates a large amount of necrosis in the peripancreatic collection.

debated strategy to prevent infectious complications in severe acute pancreatitis. Although previous non-blinded trials have shown some beneficial effects, two recent double-blind, placebo-controlled trials were unable to show any significant reduction in the risk of infectious complications and mortality [6,7]. As a result of these trials, the balance has clearly shifted against the use of antibiotic prophylaxis in severe acute pancreatitis. A meta-analysis that included the first placebo-controlled trial, found antibiotic prophylaxis had no beneficial effect [8]. A more recent meta-analysis that included both placebo-controlled trials had the same results and, most interestingly, demonstrated a relationship between the methodological quality of the published RCTs and mortality: the higher the quality of the study, the lower the effect observed [9].

All in all, given the relatively high costs associated with antibiotic prophylaxis and the increased risk of antibiotic resistance and infections with *Candida*, most guidelines advocate not to use any form of systemic antibiotic prophylaxis in predicted or severe acute pancreatitis [10,11].

Nutrition

At present, the only strategy that has been shown to be capable of preventing infectious complications in predicted or severe acute pancreatitis, is enteral nutrition (as opposed to parenteral nutrition) [12,13]. It is believed that enteral nutrition leads to a reduction in small bowel bacterial overgrowth and maintains gastrointestinal mucosal barrier function thus reducing the risk of bacterial translocation and subsequent infection of peripancreatic and pancreatic necrosis. Recently, for the first time, a survival benefit was shown by Petrov *et al.* in a trial randomizing 70 patients with predicted severe acute pancreatitis to enteral nasojejunal nutrition and to total parenteral nutrition [14]. Nutrition was started within 72 hours after onset of symptoms. The incidence of pancreatic infections (infected pancreatic necrosis) was lower in the patients receiving enteral nutrition (20% (7/35) *vs* 47% (16/34), p=0.02). Furthermore, in the enteral nutrition group, seven patients developed multi-organ failure compared with 17 patients in the parenteral group (p=0.02) [14]. Mortality was 6% in the patients receiving enteral nutrition compared with 35% (12/34) in the parenteral group (p<0.01).

A recent meta-analysis, incorporating the Petrov trial, demonstrated that in all patients with pancreatitis (both mild and severe), enteral nutrition as opposed to parenteral nutrition, significantly reduced the risk of infectious complications (relative risk (RR) 0.47, 95% confidence interval (CI) 0.26-0.85), but not the risk of death (RR 0.60, 95% CI 0.19-1.88) [15]. In patients with predicted or severe acute pancreatitis, a significant reduction in both infectious complications (RR 0.49, 95% CI 0.25-0.93), and mortality (RR 0.32, 95% CI 0.11-0.98) was found. Furthermore, on comparison with parenteral nutrition, enteral nutrition reduced the risk of hyperglycaemia (relative risk (RR) 0.53, 95% CI 0.29-0.98) and insulin requirement (RR 0.41, 95% CI 0.24-0.70) [15]. Based on these data, a paradigm shift has occurred from total parenteral nutrition towards a preference for early enteral nutrition in acute pancreatitis [13]. In this new paradigm, parenteral nutrition is only used as a means of supplying complementary nitrogen and calories to patients, where full caloric and nitrogenous requirements cannot be met by the enteral route alone.

Whilst the concept of resting the bowel has definitely been abandoned, it has been suggested recently that immediate oral feeding in patients with mild pancreatitis is just as safe as enteral tube-feeding.[16]. Furthermore, two small RCTs have shown that in patients with severe pancreatitis the intragastric route may also be feasible and safe [17,18]. Eatock et al. randomized 50 consecutive patients with predicted severe pancreatitis to either nasogastric or nasojejunal feeding by means of a fine bore feeding tube [17]. If randomization was successful, no differences were found in tolerance to feeding, pain and analgesic requirements during hospital admission. The second trial by Kumar et al. randomized 31 patients and also found no differences in recurrence of pain, diarrhoea, hospital stay, need for surgery and death between patients randomized to nasogastric or nasojejunal feeding [18]. Neither trial detected an increase in feeding-related complications in patients receiving nasogastric feeding. Nevertheless, one should bear in mind that these were relatively small studies. Larger studies should first confirm the benefits of nasogastric feeding before it can be implemented in clinical practice.

Probiotics are viable micro-organisms, mostly lactobacilli and bifidobacteria, capable of inhibiting the growth of gastrointestinal

pathogens [19]. Prophylactic enteral use of probiotics aims at preventing bacterial translocation from the intestine. Several placebo-controlled RCTs have demonstrated that perioperative enteral administration of probiotics (in addition to perioperative enteral nutrition) prevents infectious complications after pancreatic cancer, liver resection and transplantation surgery [20-24]. Two small RCTs, both from the same group, have been carried out using probiotic prophylaxis in predicted severe acute pancreatitis. The first RCT [25] demonstrated a significant reduction in the number of pancreatic infections but in the second, slightly larger, RCT these results could not be reproduced and consequently it is still unclear whether probiotics are of added value in the management of acute pancreatitis [26]. Furthermore, both trials were of arguable methodological quality: no sample size calculations were provided and neither performed an intention-to-treat-analysis [27,28].

Imaging

Contrast-enhanced computed tomography (CECT) is the cornerstone of imaging in severe acute pancreatitis. When performed after the initial 72-96 hours of disease, CECT can reliably detect pancreatic parenchymal non-enhancement (pancreatic necrosis) [29]. Radiologists tend to describe CECT findings in patients with acute pancreatitis according to the definitions of the 1992 Atlanta classification (acute fluid collection, pancreatic abscess, pancreatic pseudocyst and pancreatic necrosis) [30]. However, these definitions are frequently used inconsistently. This is an important point since it may have management consequences. A recent Dutch study found that five experienced abdominal radiologists agreed on the Atlanta definitions in only three of 70 CECTs [31]. From this study and from the literature it has become apparent that a peripancreatic collection in necrotizing pancreatitis is often mischaracterized as a 'pancreatic pseudocyst' (defined by the Atlanta classification as a collection that solely contains pancreatic juice without any pancreatic necrosis being present) [32]. This is explained by the inability of CT to reliably detect necrotic tissue in collections containing fluid (Fig. 1) [33]. Consequently, the 2005 UK guidelines on acute pancreatitis advocate that ultrasound or MRI should be performed before any collection can be defined as a pseudocyst [29]. Practically, however, it is rather cumbersome to perform an MRI on an intensive care patient. It is, therefore, stated that a patient with peripancreatic collections should be considered to have necrotizing pancreatitis until proven otherwise [29]. In order to overcome the shortcomings of CT in the characterization of collections in acute pancreatitis, Bradley (the founder of the 1992 Atlanta classification), suggested the use of descriptive terms instead of subjective Atlanta definitions when reporting manifestations of acute pancreatitis on CT[34].

Intervention

Timing of intervention: first 14 days

In the first 10-14 days after onset of acute pancreatitis (multi-)organ failure is generally driven by SIRS and not by infection of pancreatic or peripancreatic collections. In the vast majority of cases, infection of pancreatic necrosis occurs in the third or fourth week after onset of disease. For this reason, several guidelines specifically recommend that surgical intervention in necrotizing pancreatitis should not be performed within the first 14 days after onset of symptoms [35,36]. The only RCT on timing of surgical intervention in patients with necrotizing pancreatitis was performed by Mier et al. [37]. Thirty-six patients with necrotizing pancreatitis were randomized to undergo surgical intervention within 72 hours after admission as compared with intervention after 12 days [37]. Although the difference in mortality (58% *vs* 27%) was not significant, the odds ratio of 3.4 led to the early termination of the study. More recently, several series have confirmed the poor outcome for surgical intervention in the first 14 days of hospital admission [38-41] and data from a recent retrospective nationwide survey in the Netherlands points in the same direction [4]. A recent study found an 88% mortality in 17 patients with mono- or multi-organ failure operated on during the first 14 days after onset of symptoms [38]. Therefore, nowadays intervention in the first 14 days is only considered indicated in severe bleeding or abdominal compartment syndrome, the latter being quite rare and difficult to diagnose. In cases of haemodynamic instability due to bleeding, radiological intervention (angiographic coiling) is the intervention of first choice [42]. The treatment of abdominal compartment syndrome is controversial. Recent guidelines suggest that percutaneous drainage of intra-abdominal fluid may be considered as an initial step in treating abdominal compartment syndrome [43]. However, even though surgery may be needed for an abdominal compartment syndrome in the early phase of disease, bursal necrosectomy must be delayed.

During the first 14 days of multi-organ failure, the question of draining the peripancreatic collection percutaneously instead of performing an operation straight away, is often raised. It is reasoned by some that the minimal invasive character of percutaneous drainage will provide less of a 'hit' to the patient. However, it has been shown that drainage of sterile collections may lead to secondary bacterial infection [44]. Therefore, withholding both radiological and surgical intervention in the first 14 days of acute pancreatitis is advised.

Timing of intervention: after the first 14 days

If the patient's condition does not improve after the first 14 days, the question arises whether secondary infection of peripancreatic and pancreatic collections is present. Because infection of pancreatic necrosis is an indication for intervention, several guidelines advocate weekly fine needle aspiration of peripancreatic collections to determine the presence of infection [45,46]. However, false negative rates for fine needle aspiration of up to 50% have been reported and infection may be introduced by the aspiration procedure [38]. Furthermore, in a recent study, 18 out of 23 operated patients (73%) with necrotizing pancreatitis were found to have positive cultures (i.e. infected necrosis), without having undergone preoperative fine needle aspiration [38]. Apparently, clinical judgement can be as reliable as fine needle aspiration. Nevertheless, there is worldwide consensus that radiological or surgical intervention is only indicated in cases of infected necrotizing pancreatitis (and in the rare event of bowel perforation, bleeding, ischaemia or abdominal compartment syndrome). If not documented by positive fine needle aspiration or clinical judgment, the presence of air bubbles in the peripancreatic collections on imaging is considered highly indicative of infection.

Even when infection is documented there may be arguments in favour of postponing surgical intervention. A recent systematic review of 879 patients operated on for necrotizing pancreatitis, reported an association between the timing of the first surgical intervention and a decrease in mortality ($r = -0.741$, $p=0.022$) [38]. Centres that postponed surgical intervention the most, had the lowest mortality. In this review, the median timing of surgical intervention for INP was 27 days (range 3-31 days) and mortality 25% (range 6-56%).

Some authors, however, always operate within 24 hours after the

diagnosis of infected pancreatic necrosis has been made [38,47]. They argue that the risk of deterioration of the clinical condition is too high. Others postpone intervention until the necrosis has demarcated, a process that usually takes about four weeks, and the risk of peroperative bleeding is reduced, thus optimizing the conditions for safe necrosectomy [47]. We favour the latter approach. In daily practice, if a patient has stable organ failure for several weeks, then detection of infection does not require an emergency intervention. If a patient who has been on the ward for three weeks suddenly deteriorates and CT-scan shows infected necrosis, surgical intervention will take place shortly after the conditions for surgical intervention have been optimized by resuscitation.

Technique of intervention

A recent Dutch nationwide survey demonstrated that the most frequently used technique for the operative management of intervention in IPN is laparotomy, necrosectomy, closure of the abdomen and a continuous postoperative lavage system [4]. The mortality accompanying this procedure, both in the Netherlands and other countries is 25% [4,48]. In the past, the open abdomen approach was used in several hospitals as a primary strategy in INP. As the mortality was shown to be as high as 70%, this technique is nowadays only used as a rescue strategy [4]. The recent Dutch survey also demonstrated that centres that use minimally invasive surgical strategies in the treatment of INP tend to intervene later (median 25 *vs* 7 days, p=0.001) and have a lower mortality (28 *vs* 58%, p=0.052) than centres that carry out laparotomy only [4].

Minimally invasive strategies in the management of INP are gaining popularity, but randomized studies are lacking to show any evidence of their superiority [49,50]. The feasibility of placing a percutaneous (or transgastric) drain in the infected collection is a prerequisite for all minimally invasive techniques. If possible, left retroperitoneal access will prevent the peritoneal cavity from being contaminated [51]. The drain is not only intended to drain infected fluid but it also serves as a route indicator for the surgeon if subsequent minimally invasive surgery is needed (drain-guided surgery). Therefore, the position of a percutaneous drain in severe pancreatitis is of vital importance and the timing and indication of drain-placement should be discussed in a multidisciplinary setting. Both in the United States and in the Netherlands, the most frequently performed minimally invasive approach is videoscopic assisted retroperitoneal debridement (VARD): through a mini-incision in the flank, a videoscope (a conventional laparoscope) is inserted in order to provide an overview during necrosectomy [52-54]. In a recent case-matched study, comparing laparotomy with VARD, the latter technique was associated with a reduction in postoperative new-onset postoperative multi-organ failure and a trend toward lower mortality [55].

If minimally invasive surgical techniques are technically impossible, because the necrotic cavity is inaccessible, transgastric endoscopic drainage with debridement is also feasible [56]. This technique is a form of natural orifice transluminal endoscopic surgery (NOTES) and uses endoscopic ultrasound and a flexible endoscope with graspers and retrieving baskets to enter the collection. This technique is, however, still experimental and is only performed in a handful of pancreatitis-referral centres in the Netherlands.

Dutch Acute Pancreatitis Study Group

Due to the worldwide low case-volume of severe acute pancreatitis, very few RCTs have been performed and current evidence is largely derived from high volume expert-centres [57]. With the high population-density and the excellent track record of nationwide gastro-intestinal research in the Netherlands, it was a logical step that in 2002 the Dutch Acute Pancreatitis Study Group should be founded. This multidisciplinary study group made up of surgeons, gastroenterologists, radiologists and intensivists, aims at improving the care of patients with severe acute pancreatitis through a combination of collaborative research, consultation and referral [3,58,59].

To clarify the issue of probiotic prophylaxis in acute pancreatitis, the probiotics in pancreatitis trial (PROPATRIA) study randomized 296 patients with predicted severe acute pancreatitis to multispecies probiotics or placebo in 15 Dutch centres between 2004 and 2007 [60]. The results will be available in 2008.

To investigate the suggested superiority of VARD over laparotomy, the PANTER trial will randomize 88 patients with INP or suspected INP from 20 Dutch centres, including all eight university medical centres, to undergo either laparotomy (and continuous postoperative lavage; the gold standard) or a 'step-up' approach [61]. The latter approach consists of two steps; first, placement of a percutaneous drain, preferably via the left retroperitoneal route and second, if drainage fails, VARD. The primary endpoint is a composite endpoint of mortality and major morbidity. Patients with sterile pancreatic or peripancreatic collections will not be randomized but will be registered prospectively as this will provide valuable information on the natural history of necrotizing pancreatitis [61]. Accrual is on schedule and results are expected by 2009.

In 2008, the Dutch nationwide PYTHON study is to start that will randomize 204 patients with predicted severe acute pancreatitis within 24 hours after admission to early nasogastric feeding as compared to delayed onset of feeding as advised in the current guidelines.

Because the indication for intervention in necrotizing pancreatitis may be difficult and the case-load per hospital is low, the Dutch Acute Pancreatitis Study Group has instituted a multidisciplinary panel of experts. This panel consists of members from all specialties involved with representatives from seven university medical centres and can be consulted by any physician treating patients with necrotizing pancreatitis. The study group co-ordinator (www.pancreatitis.nl), is available 24 hours a day, 7 days a week, and ensures that a standardized case-form with all relevant clinical and radiological (CT-scan) information, is filled out by the panel members. Within 24 hours, the local clinician receives advice from the panel of experts. So far, the panel has advised on the treatment of over 75 patients and this initiative has been valued greatly by all involved.

Conclusion

Severe acute pancreatitis remains a challenging disease with a high mortality. In recent years many studies have greatly improved our understanding and treatment of severe acute pancreatitis. Both recent RCTs and meta-analyses have made it clear that antibiotic prophylaxis is no longer indicated in acute necrotising pancreatitis.

Enteral feeding has been shown superior to parenteral nutrition in acute pancreatitis. Nasogastric feeding, if safe, would greatly benefit the clinician because it is much easier than placing a nasojejunal tube, but there remains uncertainty whether this approach will also benefit the patient. With regard to imaging in acute pancreatitis, serious concerns have been raised regarding the use of the Atlanta definitions in clinical practice. In the near future, the use of MRI will most likely increase and provide us with better insight into the content of peripancreatic collections in severe acute pancreatitis. This will open the way for further tailored interventions in patients with INP. The timing of intervention especially, was shown to be of the essence. Postponing intervention in patients with INP may reduce mortality. Although promising, the use of minimally invasive intervention in INP will have to be studied in larger series before routine use can be recommended.

In conclusion, this review has identified several measures that are clearly ready for implementation in clinical practice: a) to refrain from giving antibiotic prophylaxis in case of necrotizing pancreatitis; b) to use enteral nutrition instead of parenteral nutrition whenever possible; c) to use descriptive terms when describing computed tomography findings in severe acute pancreatitis, and d) a strong tendency to postpone intervention to at least the third or fourth week of disease, even in suspected or documented infected pancreatic necrosis.

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.

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Key words: pancreatitis, necrotizing pancreatitis, intervention, surgery, drainage, review, timing, nutrition, prophylaxis

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