

Recent Developments in Acute Pancreatitis

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The incidence of acute pancreatitis (AP) has been increasing worldwide, but the major etiologies remain gallstones and alcohol. Several studies have reported that smoking is an independent risk factor for developing AP. Classification of AP has traditionally used the categories of mild and severe disease. However, a new intermediate category of moderately severe AP has been described with intermediate characteristics including a high incidence of local complications but a low mortality. Assessment criteria that can serve as early predictors of AP severity are often complex and not sufficiently accurate. However, several recently described criteria that rely on criteria such as the body mass index, physical findings, and simple laboratory measurements could prove useful if validated in large prospective studies. Many issues related to the therapy of AP are still unresolved. Although preliminary studies support the importance of early volume expansion for the treatment of acute pancreatitis, optimization of the amount and type of fluids will require further studies. Similarly, preliminary studies suggest that enteral nutrition might benefit patients with AP and could even be useful early in the course of disease. However, the timing and type of fluids as well as the intestinal infusion site require further study. Finally, issues related to the prophylactic use of antibiotics in patients with severe AP have not been resolved. While the process of clinical investigation moves slowly, progress has been made in clinical studies of AP.

Acute pancreatitis (AP) continues to be a clinical challenge. Approximately 220,000 patients are still hospitalized yearly with AP in the United States, making it the third most common gastrointestinal discharge diagnosis. Current estimates rank AP as the 14th most common gastrointestinal cause of death, with an overall mortality of 5%, which can be as high as 47% in those with multi-organ failure.¹ As per the 2003 Health Care cost and utilization project, the direct annual medical costs of AP hospitalizations in the United States were \$2.2 billion, and cost incurred by black patients was higher, owing to a higher rate of hospitalization among them.² Although no definitive treatment is available for AP yet, many recent developments have led us to better understand and manage this problem. Significant recent developments in the areas of epidemiology, etiology, severity assessment, and management controversies will be discussed in this review.

Epidemiology and Etiology

Data from the National Center for Health Statistics have demonstrated a 100% increase in the overall hospitalization for AP in the United States during the last 2 decades.² Similarly, there has been a 75% increase in admissions for AP in The Netherlands between 1992 and 2004, and this is predicted

to increase by another 9.9% in 2010.³ Recent studies from the United Kingdom have shown a 3.1% annual increase in the overall incidence of AP, with the highest increase among women younger than 35 years. The age standardized incidence was higher among elderly people (odds ratio [OR], 1.06 per year) and in economically deprived areas (OR, 2.4 between least and most deprived).⁴ Additional evidence of an increase in the incidence of AP came from a recent meta-analysis of 18 European studies, which also showed a linear increase in the incidence of gallstone pancreatitis and an increase in mortality with age. The meta-analysis also showed that although the case fatality rate has decreased over the years, the overall mortality rate per 100,000 has been the same.⁵

Alcohol and gallstones are the most common causes of AP. With respect to hypertriglyceridemia as a cause of AP, even though the triglyceride threshold required to cause pancreatitis has been established to be 1000 mg/dL, no correlation between the level of triglycerides and severity of AP has been found.⁶

Drug-induced pancreatitis is difficult to diagnose. The precise role of a drug in causing AP, the duration between the exposure and development of AP, the pathogenic mechanisms, and synergy with cofactors are usually not clear. On the basis of an extensive review of 1214 reports describing drug-induced AP during 50-year duration, Badalov et al⁷ classified 120 drugs that were found to be associated with AP into 4 major classes (Class I, positive re-challenge; Class II, consistent latency; Class III, at least 2 cases in the literature without re-challenge and latency; and Class IV, single case report without re-challenge).

Smoking is considered a modifier in the development of alcoholic pancreatitis. However, 2 recent large population-based studies have established smoking as an important independent risk factor for AP. The first prospective cohort study⁸ encompassing more than 30,000 Swedish subjects found a relative risk (RR) of 2.14 (95% confidence interval [CI], 1.48–3.09) of developing AP among current smokers. Smokers who did not consume alcohol also had a high RR of 3.57 (95% CI, 0.98–13.0) for

Abbreviations used in this paper: ANN, artificial neural network; AP, acute pancreatitis; APACHE, Acute Physiology, Age, and Chronic Health Evaluation; AUC, area under curve; BMI, body mass index; CI, confidence interval; EN, enteral nutrition; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; IOC, intraoperative cholangiogram; IRAP, idiopathic recurrent acute pancreatitis; MSAP, moderately severe acute pancreatitis; NG, nasogastric; NJ, nasojejunal; OF, organ failure; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; ROC, receiver operating characteristic; RR, relative risk; SAP, severe acute pancreatitis; SIRS, Structured Interview of Reported Systems; TAP, trypsinogen activation peptide; WOPN, walled off pancreatic necrosis.

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developing AP, and there was also a dose-dependent increase in the incidence of AP. This study, however, did not make any adjustments for gallstone disease. A Danish study⁹ of more than 17,000 individuals also found smoking to be an independent risk factor for development of AP, with a dose-dependent and time-dependent increase in the hazard ratio after adjustments for alcohol consumption, gallstones, and body mass index (BMI). Thus, there is evidence to counsel patients with AP to stop smoking.

Biliary microlithiasis is considered an important cause of idiopathic recurrent acute pancreatitis (IRAP). In a recent study that followed 75 patients of IRAP during a mean period of 17 months (range, 1–156 months), 35 (47%) patients developed overt chronic pancreatitis on imaging during the follow-up period, and 10 of them were initially found to have biliary microlithiasis on bile microscopy. Eight of these individuals continued to have recurrent AP despite sphincterotomy/cholecystectomy, thereby suggesting that it was probably early chronic pancreatitis, rather than biliary microlithiasis, that was responsible for their recurrent AP.¹⁰

Other controversial etiologies of AP such as sphincter of Oddi dysfunction and pancreas divisum will not be discussed because of limits on the length of this review.

Severity Assessment

Since their inception in 1992, the Atlanta criteria have been considered the standard of severity assessment of AP.¹¹ However, over the years the original Atlanta criteria were subjected to criticism with regard to threshold of serum amylase and lipase for the diagnosis of AP; definitions of local complications such as fluid collections, necrosis, and pseudocysts; and finally, unclear definitions of organ failure (OF) and lack of differentiation of persistent from transient OF. These limitations have been highlighted in a recent American College of Gastroenterology guidelines article.¹ Weaknesses of the Atlanta criteria were also shown in a recent review of 447 articles including 12 guidelines from 1993 to 2006, in which it was found that there were large variations in the interpretation of Atlanta definitions, and alternative definitions were frequently applied.¹² The Atlanta classification is currently under revision by the Acute Pancreatitis Classification Working Group, of which the corresponding author of this review is a member. To arrive at a consensus, the working group is soliciting broad feedback from other pancreatologists.

Even though persistent OF, presence of local complications, and/or death define severe acute pancreatitis (SAP) according to the Atlanta classification, it has been a common observation over the years that death from AP predominantly occurs in patients with persistent OF. Presence of necrosis per se does not necessarily predict death. On the basis of these observations, we

recently characterized a new subgroup of AP, moderately severe acute pancreatitis (MSAP) (Table 1) and also validated the categorization in a prospective cohort. This is a discrete group of patients with local complications such as necrosis and fluid collections. Although the group has a high morbidity that is similar to those with OF, mortality is low.¹³

There are several clinical, laboratory, and radiologic risk factors and scoring systems that are used to predict severity of AP, but none is ideal. The Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II and Structured Interview of Reported Symptoms (SIRS) criteria, which have been found to be useful, are limited by their complexity (APACHE II) or lack of applicability early in the course of disease (SIRS). A new severity score called the BISAP has been found to predict mortality in AP within the first 24 hours of admission.¹⁴ This 5-point scoring system was derived from a multicenter cohort of nearly 18,000 patients and later validated in another 18,000 patients. It was found to have a similar receiver operating characteristic (ROC) area under curve (AUC) as that of APACHE II scoring (0.82; 95% CI, 0.79–0.84, and 0.83; 95% CI, 0.80–0.85, respectively). The individual components of BISAP include blood urea nitrogen of >25 mg/dL, impaired mental status (Glasgow coma scale score, <15), SIRS score of ≥ 2 , age >60 years, and pleural effusion. Even though it has been claimed to be a simple scoring system with only 5 variables, the actual calculation of different components requires measurement of at least 10 components. However, inclusion of a large population over multiple centers tends to make it free of selection bias and thus applicable at the community level.

The Panc 3 score (hematocrit, >44; BMI, >30 kg/m²; and pleural effusion on x-ray) is another recently developed severity assessment tool, in which presence of all 3 components was found to predict severity with a post-test likelihood of 99%.¹⁵ However, the retrospective nature of the study and inclusion of a relatively small number of patients from a single tertiary care center might preclude its general use in the community setting.

The new Japanese Severity Score (JSS) is another scoring system that includes 9 components, and a score of 3 or more indicates SAP.¹⁶ The AUC of the new Japanese Severity Score for predicting mortality was found to be 0.822, compared with 0.820, 0.754, and 0.801 of Ranson score, Glasgow score, and APACHE II score, respectively. However, this was based on a retrospective study of just 138 patients, thereby mandating prospective validation studies in larger cohorts before making it usable at the community level.

The Harmless Acute Pancreatitis score (HAPS) is the most recently published severity assessment tool, and it looks into the severity assessment from a different angle.¹⁷ Its components include absence of rebound tenderness and/or guarding, normal hematocrit, and normal serum creatinine. A combination

Table 1. Characteristics of Moderately Severe Acute Pancreatitis (MSAP)

| | Mild AP | MSAP | SAP |
|--------------------------|--------------------|---|---|
| Structural changes | Interstitial edema | Interstitial edema + local complications (necrosis and/or fluid collection) | Interstitial edema + local complications (necrosis and/or fluid collection) |
| Functional abnormalities | No OF | No OF | Persistent OF |
| Morbidity | Low | High | High |
| Mortality | Low | Low | High |

of these 3 components was found to predict a mild course of AP with 98% accuracy within 30 minutes of admission. This scoring system was developed in a prospective study of a cohort of 394 German patients admitted to a municipal clinic and was subsequently validated in another cohort of 452 patients over multiple centers. This merits utility of Harmless Acute Pancreatitis score at the community level and allows even the nonspecialist or the general practitioner to plan management with a high level of confidence.

Some of the recently described individual markers of severity in AP include urinary trypsinogen activation peptide (TAP),¹⁸ procalcitonin (cutoff more than 3.8 ng/mL),¹⁹ coagulation parameters (anti-thrombin III),²⁰ interleukin-6,²¹ intra-abdominal hypertension (>15 mm Hg),¹⁸ and immunoparalysis (reduced HLA-DR expression).¹⁸ TAP and procalcitonin are about to be available in a commercial kit form.

Finally, the utility of artificial neural networks (ANNs) to predict severity of AP has been frequently studied in recent years. ANN is a nonlinear pattern recognition technique that contains a set of processing units that simulate human neurons in that it can learn from the data presented, thereby improvising their predictive capability. In a recent systematic review of 11 studies, ANN was found to predict prolonged hospital stay with 75% sensitivity and was comparable to APACHE II and Ranson score.²²

Treatment

Fluid Therapy

AP is associated with a significant amount of third space fluid sequestration. This can lead to hypovolemia and reduced perfusion pressure, which in concert with microvascular alterations can contribute significantly to the development of major local and systemic complications.²³ There are very few high quality human studies that have assessed the role of fluid management in AP, and a recent review by us has addressed these issues.²³ We have recently shown that aggressive fluid therapy (33% or more of the initial 72-hour fluid volume within the first 24 hours of hospitalization) is associated with a significantly lower OF rate compared with nonaggressive therapy (7.1% vs 22.6%; $P < .03$).²⁴ The other area, besides volume of fluid, that needs further insight is the type of fluid (crystalloid

or colloid) for resuscitation. The most recent American Gastroenterological Association technical review on AP recommends crystalloids in most cases, and that colloids (packed red blood cells and albumin, respectively) be reserved for special situations like a hematocrit drop to less than 25% and a serum albumin drop to less than 2 mg/dL.²⁵ It should also be kept in mind that very aggressive fluid therapy might have its own problems like fluid overload, which might be detrimental to patients with cardiovascular problems and to those with acute respiratory distress syndrome.²⁵

Nutrition

AP is a hypercatabolic state, and early nutrition should be initiated with a therapeutic intent. In patients with mild AP, oral feeding can be considered within 24–72 hours of disease onset. A recent study has shown that initiating re-feeding with low fat soft diet is safe and can reduce hospitalization, when compared with clear liquid diet.²⁶

Early nutrition should also be considered in patients with SAP. Prolonged fasting can potentially lead to bacterial translocation across the gut barrier and subsequent local and systemic complications.²⁷ Contrary to the earlier notion of pancreatic rest and parenteral nutrition (PN), data from recent studies have driven a paradigm shift in nutritional management in SAP toward enteral nutrition (EN). However, adequately powered studies to evaluate the appropriate timing for initiating EN are lacking. Table 2 shows the most recent meta-analysis of randomized controlled trials (RCTs) that have compared EN with PN.^{28–31} In all 4 studies, the most consistent result was a significant reduction in infectious complications with EN. The effect of EN on OF and mortality, however, was not uniform. Some of the studies included in the meta-analysis were flawed in terms of completion and presentation of data. Well-designed RCTs in the future would probably give a better insight into this incongruence. Three of the trials included in these meta-analyses did a cost analysis that demonstrated a significantly lower cost of EN compared with PN. Another recent systematic review showed that EN can maintain good glycemic control,³² which might partially explain the lower infectious complications with EN. However, current data on the type of EN (elemental, semi-elemental, or polymeric) and the effects of additional immunomodulating diets are scant for recommendations to be made.

The other debated issue on nutrition in AP is the route for EN. Earlier studies among healthy volunteers demonstrated that pancreatic secretory response to tube feeds delivered into the distal jejunum resulted in lesser pancreatic secretion than feeds delivered into the duodenum.^{33,34} However, subsequent studies have shown that overall exocrine pancreatic secretion in AP is lower than in normal individuals.³⁵ Two recent RCTs comparing nasogastric (NG) and nasojejunal (NJ) tube feeding have shown that both had similar outcome measures like pain score, hospital stay, surgery requirement, and death. Moreover, pancreatitis did not deteriorate in the patients in the NG feed arm.^{36,37} A meta-analysis of these 2 trials showed similar tolerability and safety of the 2 modes of delivery.³⁸ On the other hand, placement and maintenance of an NJ tube might pose logistical challenges.³⁹ However, these 2 trials were not free from notable flaws; one of the most conspicuous was a lack of adequate power to prove any difference or similarity. Another criticism was placement of the NJ tube in one of the studies,

Table 2. Meta-Analysis of Studies Comparing EN With PN in AP

| Year | Author | No. of RCTs | Severity of AP | Outcomes |
|------|----------------|-------------|----------------|---|
| 2006 | McCave et al | 27 | Severe | ↓ Infectious mortality ↓ Hospital stay No effect on organ failure |
| 2006 | Heinrich et al | 6 | Mixed | Similar in OF and mortality ↓ Sepsis and central line infections |
| 2008 | Petrov et al | 15 | Severe | ↓ Infectious complications ↓ Mortality, but not significant |
| 2008 | Petrov et al | 5 | Severe | ↓ Infections ↓ Mortality ↓ OF, but not significant |

Table 3. Meta-Analysis of Studies on Prophylactic Antibiotics in AP With Sterile Necrosis

| Author | Date | No. of trials (patients) | No. of blinded studies | Results |
|-----------------|------|--------------------------|------------------------|--|
| Heinrich et al | 2006 | 5 (288) | 1 | ↓ Overall sepsis/mortality No effect on infection of necrosis |
| Villatoro et al | 2006 | 5 (294) | 1 | Subgroup analysis: ↓ mortality when carbapenems used |
| Mazaki et al | 2006 | 6 (397) | 1 | No effect on infection and mortality ↓ Hospital stay |
| deVries et al | 2007 | 6 (397) | 1 | Inverse relationship between quality of study and effect of antibiotic prophylaxis |
| Jafri et al | 2009 | 8 (502) | 2 | No effect on infection of necrosis and mortality |
| Xu et al | 2008 | 8 (540) | 2 | No effect on mortality/intervention ↓ In peri/extra/pancreatic infections |
| Bai et al | 2008 | 7 (467) | 2 | No effect on infection of necrosis and mortality |
| Hart et al | 2009 | 7 (429) | 2 | No effect on infection of necrosis and mortality ↓ In-hospital stay and extra pancreatic infections |

which was probably duodenal (which would be similar to NG feeding in terms of concept), rather than jejunal, on the basis of the type of the tube and technique described. In the other study, there was a considerable delay of onset of enteral feeding between the NG and NJ groups, respectively.

Therefore, on the basis of current data, EN is the standard of care in SAP. However, adequately powered randomized studies are required to address the issue of the appropriate route for EN for final recommendations to be made. Of note, a National Institutes of Health-sponsored randomized trial comparing NG and distal jejunal feeding is being planned.

Antibiotic Prophylaxis in Acute Pancreatitis

Antibiotic prophylaxis to prevent infection of pancreatic necrosis has been another controversial issue. Despite a number of clinical trials and meta-analyses, a clear consensus still does not exist. Earlier meta-analyses showed beneficial results from antibiotic prophylaxis. However, to date there are only 3 double-blind placebo-controlled trials studying role of antibiotic prophylaxis, and none of them showed any benefit in terms of prevention of infection of necrosis, need for surgery, and hospital mortality.⁴⁰⁻⁴³ Table 3 lists the 7 most recent meta-analyses of RCTs since 2006.^{29,43-48} Interestingly, the results of the meta-analysis were not uniform. The major drawback was the heterogeneity of the individual trials in terms of methodologic quality, selection criteria, treatment duration, antibiotic selections, and outcome measures. Mazaki et al⁴³ and de Vries et al⁴⁵ in their meta-analyses also studied the methodologic quality of the individual trials, in which they found that the highest quality studies had the least effect of antibiotics on absolute risk reduction of pancreatic infection. Given these disparate results, antibiotic prophylaxis is not currently recommended in pancreatic necrosis. However, in view of the high rate of delayed mortality (after 2 weeks) in patients with infected necrosis, a 7- to 10-day course of a carbapenem antibiotic might be considered in patients with pancreatic necrosis with OF, which increases the risk of infection significantly. This might also be considered in septic-appearing patients while a source of infection is sought by blood cultures and culture of fine-needle aspiration of necrotic pancreatic tissue. In these patients antibiotics should be discontinued if no source of infection is found.

Fungal infection in necrotizing pancreatitis is not uncommon and might result from antibiotic use. Twenty-five percent

of patients might develop fungal infection even without antibiotic use.⁴⁹ The role of prophylactic antifungal medications in these patients is unclear. A meta-analysis of 4 RCTs has shown no difference in rate of fungal infection between patients who received antibiotics and those who did not (4.9% vs 6.9%; $P = .9$).²⁹ We have recently shown that in patients with SAP, patients with fungal infection, compared with those with bacterial infection, had a significantly longer hospital stay (37 vs 63 days; $P < .01$), longer intensive care unit stay (9 vs 28 days; $P < .01$), and higher rates of OF (47% vs 73%; $P < .04$). However, mortality was similar for both groups.⁵⁰ Early detection of fungal infection and aggressive antifungal treatment might improve mortality rates even without standard prophylaxis.

Treatment of Infected Necrosis

Forty percent to 70% of AP patients with pancreatic/peripancreatic necrosis develop infections, which are largely responsible for late mortality.⁵¹ The treatment of choice for infected necrosis is debridement, which should be done at least 4 weeks after onset of symptoms. A prospective RCT has shown that mortality after early necrosectomy was higher (OR, 3.4) compared with late necrosectomy.⁵² In view of the significantly higher mortality after surgery for sterile necrosis, necrosectomy should be avoided in these patients except for the occasional patient who continues to deteriorate in spite of good conservative management and who feels persistently unwell.

Surgical debridement in the form of either open packing technique⁵³ or single necrosectomy with continuous lavage⁵⁴ has been the traditional standard of care of infected necrosis. Neither of these has been prospectively compared in randomized trials, and both are associated with complications like bleeding, fistula, and abscess formation.⁵²⁻⁵⁷ Other minimally invasive surgical approaches that have been tried include computed tomography/ultrasonography guided transcutaneous drainage, laparoscopic necrosectomy, and retroperitoneal necrosectomy under videoscopic/nephroscopic guidance. The results of the Pancreatitis, Necrosectomy versus Step up Approach (PANTER) trial, a multicentric prospective RCT that has compared surgical debridement with minimally invasive methods, are eagerly awaited.⁵⁸

With technological advances, endoscopic debridement has gained immense popularity in recent years. Initially, this was performed via transgastric or transduodenal routes with wide-bore catheters. More recently, direct endoscopic necrosectomy

has been introduced in which the endoscope is inserted directly into the necrotic area through an opening in the stomach, and debridement is performed under direct vision with various endoscopic accessories. Our center has recently shown successful resolution of walled off pancreatic necrosis (WOPN) with endoscopic necrosectomy in up to 81% of patients.⁵⁹ Similar success rates have also been obtained in other recent studies.^{60,61} We have recently also shown that compared with standard endoscopic drainage, direct endoscopic necrosectomy led to improvement in necrotic cavity in a significantly higher proportion of patients (45% vs 88%; $P < .01$). Moreover, direct endoscopic necrosectomy was associated with fewer requirements for surgical or percutaneous drainage, and there was less recurrence of collection.⁶² Advantages of endoscopic debridement include minimal access, avoidance of risks from open necrosectomy, and fistula formation. Moreover, it offers a therapeutic potential for poor operative risk patients. Disadvantages include bleeding, postprocedure infections, development of recurrent collections requiring repeated drainage, and inadequate debridement of large necrotic areas.^{60,61,63} Currently, minimal access debridement seems to be the procedure of choice, although the exact route of such a procedure depends on the availability of such expertise locally.

On the other hand, conservative management of infected necrosis is also being increasingly reported, indicating that all such patients might not need debridement. Runzi et al⁶⁴ evaluated 28 patients with SAP with confirmed infected necrosis, of whom 16 were followed with tailored antibiotic treatment without surgical intervention. Fourteen (87.5%) of these patients recovered completely, and the 2 who died had preexisting severe cardiac comorbidities and very high APACHE II scores.

Endoscopic Sphincterotomy and Cholecystectomy in Biliary Pancreatitis

Even though biliary pancreatitis is a mild disease, persistent biliary obstruction might increase the severity of AP, worsen outcomes, and predispose the patient to cholangitis and sepsis. Most studies suggest that in mild disease, patients should be treated with cholecystectomy with intraoperative cholangiogram (IOC). Endoscopic sphincterotomy (ES) should be performed if the IOC shows common bile duct stones and if laparoscopic bile duct clearance fails.²⁹

Until recently, urgent endoscopic retrograde cholangiopancreatography (ERCP) was recommended for patients with acute biliary pancreatitis, irrespective of the presence of cholangitis. An earlier meta-analysis of 4 RCTs suggested a reduction in

mortality and overall complications with urgent ERCP.⁶⁵ However, the results of this meta-analysis should be interpreted with caution because of variability among the individual trials; for example, one of the trials included patients even with non-biliary causes of AP, whereas another excluded patients with cholangitis.^{66,67} Table 4 shows 3 more recent meta-analyses, but again with variable results.^{29,68,69} The most recent meta-analysis by Petrov et al⁶⁹ showed no reduction in complication and mortality from biliary AP with early ES (24–72 hours) in the absence of cholangitis. Even though this makes it appear that urgent ERCP in acute biliary pancreatitis is indicated only in the presence of cholangitis, further well-designed RCTs are needed before a recommendation could be made.

Another controversial issue in the treatment of biliary AP is the timing for cholecystectomy. If ES has already been performed, then elective cholecystectomy should be performed after 6 weeks if not otherwise contraindicated.⁷⁰ A recent study has demonstrated that early cholecystectomy (within 2 weeks) did not have significant effects on conversion to open surgery, local or systemic complications, and postoperative hospital stay. However, delaying cholecystectomy was associated with an increase in biliary complications in patients with non-necrotizing biliary AP.⁷¹ Until further guidelines based on stronger powered RCTs are available, it is probably reasonable to follow the current American Gastroenterological Association guidelines that suggest cholecystectomy as early as possible in surgically fit candidates, preferably within 2–4 weeks after discharge. If cholecystectomy is not performed, one third to two thirds of these patients can have recurrent AP within 3 months.^{1,25}

Conclusion

The incidence of AP has been increasing globally, and mortality from SAP with OF is still very high. Recent studies have established smoking as an independent risk factor. The Atlanta classification is currently under modification, and many new severity assessment systems have been developed. However, none of them is ideal. Aggressive fluid resuscitation in patients with AP needs to be initiated with a therapeutic intent. Studies are needed to evaluate the best type of fluid and the volume to be administered according to different grades of severity. In patients with mild disease, EN can be considered, preferably within 24–72 hours of disease onset unless contraindicated. However, the appropriate timing for enteral feeding in patients with severe disease, the type of enteral feeds, and its effects on fluid collections and ductal disruption need to be evaluated further. Endoscopic debridement is rapidly gaining momentum toward universal acceptance. However, prospective RCTs are needed to establish the best method of debridement. ES should be reserved for patients with biliary AP with cholangitis. Currently, there is no evidence that supports the use of probiotics, immunomodulatory diets, and agents like gabaxate, aprotinin, lexpafant, and octreotide.

References

1. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006;101:2379–2400.
2. Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. *Curr Gastroenterol Rep* 2009;11:97–103.
3. Spanier BW, Dijkgraaf MG, Bruno MJ. Trends and forecasts of

Table 4. Meta-Analysis of Early ES in Acute Biliary Pancreatitis

| Year | Author | No. of RCTs (patients) | Outcomes |
|------|----------------|------------------------|--|
| 2006 | Heinrich et al | 3 (445) | ↓ Overall complications and mortality |
| 2008 | Moretti et al | 5 (702) | ↓ Pancreatitis-related complications Mortality not affected |
| 2008 | Petrov et al | 3 (450) | Overall complications and mortality not affected in the absence of cholangitis |

- hospital admissions for acute and chronic pancreatitis in The Netherlands. *Eur J Gastroenterol Hepatol* 2008;20:353–358.
4. Roberts SE, Williams JG, Meddings D, et al. Incidence and case fatality for acute pancreatitis in England: geographical variation, social deprivation, alcohol consumption and aetiology: a record linkage study. *Aliment Pharmacol Ther* 2008;28:931–941.
 5. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;33:323–330.
 6. Balachandra S, Virlos IT, King NK, et al. Hyperlipidaemia and outcome in acute pancreatitis. *Int J Clin Pract* 2006;60:156–159.
 7. Badalov N, Baradaran R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007;5:648–661; quiz 644.
 8. Lindkvist B, Appelros S, Manjer J, et al. A prospective cohort study of smoking in acute pancreatitis. *Pancreatol* 2008;8:63–70.
 9. Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. *Arch Intern Med* 2009;169:603–609.
 10. Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. *Clin Gastroenterol Hepatol* 2007;5:75–79.
 11. Bradley EL 3rd. A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11–13, 1992. *Arch Surg* 1993;128:586–590.
 12. Bollen TL, van Santvoort HC, Besselink MG, et al. The Atlanta Classification of acute pancreatitis revisited. *Br J Surg* 2008;95:6–21.
 13. Vege SS, Gardner TB, Chari ST, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include “moderately severe acute pancreatitis.” *Am J Gastroenterol* 2009;104:710–715.
 14. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut* 2008;57:1698–1703.
 15. Brown A, James-Stevenson T, Dyson T, et al. The Panc 3 score: a rapid and accurate test for predicting severity on presentation in acute pancreatitis. *J Clin Gastroenterol* 2007;41:855–858.
 16. Ueda T, Takeyama Y, Yasuda T, et al. Utility of the new Japanese severity score and indications for special therapies in acute pancreatitis. *J Gastroenterol* 2009;44:453–459.
 17. Lankisch PG, Weber-Dany B, Hebel K, et al. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. *Clin Gastroenterol Hepatol* 2009;7:702–705; quiz 607.
 18. Rau BM. Predicting severity of acute pancreatitis. *Curr Gastroenterol Rep* 2007;9:107–115.
 19. Rau BM, Kempainen EA, Gumbs AA, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenter study. *Ann Surg* 2007;245:745–754.
 20. Maeda K, Hirota M, Ichihara A, et al. Applicability of disseminated intravascular coagulation parameters in the assessment of the severity of acute pancreatitis. *Pancreas* 2006;32:87–92.
 21. Sathyanarayan G, Garg PK, Prasad H, et al. Elevated level of interleukin-6 predicts organ failure and severe disease in patients with acute pancreatitis. *J Gastroenterol Hepatol* 2007;22:550–554.
 22. Bartosch-Harlid A, Andersson B, Aho U, et al. Artificial neural networks in pancreatic disease. *Br J Surg* 2008;95:817–826.
 23. Gardner TB, Vege SS, Pearson RK, et al. Fluid resuscitation in acute pancreatitis. *Clin Gastroenterol Hepatol* 2008;6:1070–1076.
 24. Gardner TB, Vege SS, Chari ST, et al. Lack of aggressive fluid resuscitation is associated with organ failure in acute pancreatitis (abstract). *Gastroenterology* 2008;134(Suppl 1):A-373.
 25. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007;132:2022–2044.
 26. Sathiaraj E, Murthy S, Mansard MJ, et al. Clinical trial: oral feeding with a soft diet compared with clear liquid diet as initial meal in mild acute pancreatitis. *Aliment Pharmacol Ther* 2008;28:777–781.
 27. Olah A, Romics L Jr. Early enteral nutrition in acute pancreatitis: benefits and limitations. *Langenbecks Arch Surg* 2008;393:261–269.
 28. McClave SA, Chang WK, Dhaliwal R, et al. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN J Parenter Enteral Nutr* 2006;30:143–156.
 29. Heinrich S, Schafer M, Rousson V, et al. Evidence-based treatment of acute pancreatitis: a look at established paradigms. *Ann Surg* 2006;243:154–168.
 30. Petrov MS, Pylypchuk RD, Emelyanov NV. Systematic review: nutritional support in acute pancreatitis. *Aliment Pharmacol Ther* 2008;28:704–712.
 31. Petrov MS, van Santvoort HC, Besselink MG, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. *Arch Surg* 2008;143:1111–1117.
 32. Petrov MS, Zagainov VE. Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review. *Clin Nutr* 2007;26:514–523.
 33. O’Keefe SJ, Lee RB, Anderson FP, et al. Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G27–G36.
 34. Kaushik N, Pietraszewski M, Holst JJ, et al. Enteral feeding without pancreatic stimulation. *Pancreas* 2005;31:353–359.
 35. O’Keefe SJ, Lee RB, Li J, et al. Trypsin secretion and turnover in patients with acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G181–G187.
 36. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol* 2005;100:432–439.
 37. Kumar A, Singh N, Prakash S, et al. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol* 2006;40:431–434.
 38. Petrov MS, Correia MI, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis: a systematic review of the literature to determine safety and tolerance. *JOP* 2008;9:440–448.
 39. Ioannidis O, Lavrentieva A, Botsios D. Nutrition support in acute pancreatitis. *JOP* 2008;9:375–390.
 40. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology* 2004;126:997–1004.
 41. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann Surg* 2007;245:674–683.
 42. Garcia-Barrasa A, Borobia FG, Pallares R, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. *J Gastrointest Surg* 2009;13:768–774.
 43. Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. *Br J Surg* 2006;93:674–684.
 44. Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2006:CD002941.

45. de Vries AC, Besselink MG, Buskens E, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. *Pancreatology* 2007;7:531–538.
46. Jafri NS, Mahid SS, Idstein SR, et al. Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis. *Am J Surg* 2009;197:806–813.
47. Bai Y, Gao J, Zou DW, et al. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2008;103:104–110.
48. Xu T, Cai Q. Prophylactic antibiotic treatment in acute necrotizing pancreatitis: results from a meta-analysis. *Scand J Gastroenterol* 2008;43:1249–1258.
49. De Waele JJ, Vogelaers D, Blot S, et al. Fungal infections in patients with severe acute pancreatitis and the use of prophylactic therapy. *Clin Infect Dis* 2003;37:208–213.
50. Vege SS, Gardner TB, Chari ST, et al. Outcomes of intra-abdominal fungal vs bacterial infections in severe acute pancreatitis. *Am J Gastroenterol* 2009;104:2065–2070.
51. Larvin M. Management of infected pancreatic necrosis. *Curr Gastroenterol Rep* 2008;10:107–114.
52. Mier J, Leon EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997;173:71–75.
53. Bradley EL 3rd, Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 1991;161:19–25.
54. Begeer HG. Operative management of necrotizing pancreatitis: necrosectomy and continuous closed postoperative lavage of the lesser sac. *Hepatogastroenterology* 1991;38:129–133.
55. Kalfarentzos FE, Kehagias J, Kakkos SK, et al. Treatment of patients with severe acute necrotizing pancreatitis based on prospective evaluation. *Hepatogastroenterology* 1999;46:3249–3256.
56. Tsiotos GG, Luque-de Leon E, Soreide JA, et al. Management of necrotizing pancreatitis by repeated operative necrosectomy using a zipper technique. *Am J Surg* 1998;175:91–98.
57. Nordback I, Paajanen H, Sand J. Prospective evaluation of a treatment protocol in patients with severe acute necrotizing pancreatitis. *Eur J Surg* 1997;163:357–364.
58. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al. Minimally invasive “step-up approach” versus maximal necrosectomy in patients with acute necrotizing pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. *BMC Surg* 2006;6:6.
59. Papachristou GI, Topazian MD, Gleeson FC, et al. EUS features of annular pancreas (with video). *Gastrointest Endosc* 2007;65:340–344.
60. Voermans RP, Veldkamp MC, Rauws EA, et al. Endoscopic transmural debridement of symptomatic organized pancreatic necrosis (with videos). *Gastrointest Endosc* 2007;66:909–916.
61. Escourrou J, Shehab H, Buscail L, et al. Peroral transgastric/transduodenal necrosectomy: success in the treatment of infected pancreatic necrosis. *Ann Surg* 2008;248:1074–1080.
62. Gardner TB, Chahal P, Papachristou GI, et al. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. *Gastrointest Endosc* 2009;69:1085–1094.
63. Charnley RM, Lochan R, Gray H, et al. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. *Endoscopy* 2006;38:925–928.
64. Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas* 2005;30:195–199.
65. Sharma VK, Howden CW. Metaanalysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. *Am J Gastroenterol* 1999;94:3211–3214.
66. Folsch UR, Nitsche R, Ludtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis: the German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 1997;336:237–242.
67. Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993;328:228–232.
68. Moretti A, Papi C, Aratari A, et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Dig Liver Dis* 2008;40:379–385.
69. Petrov MS, van Santvoort HC, Besselink MG, et al. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. *Ann Surg* 2008;247:250–257.
70. Boerma D, Rauws EA, Keulemans YC, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. *Lancet* 2002;360:761–765.
71. Nebiker CA, Frey DM, Hamel CT, et al. Early versus delayed cholecystectomy in patients with biliary acute pancreatitis. *Surgery* 2009;145:260–264.

Reprint requests

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Conflicts of interest

The authors disclose no conflicts.