Management of severe acute pancreatitis

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ABSTRACT

The risks, measurements of severity, and management of severe acute pancreatitis and its complications have evolved rapidly over the past decade. Evidence suggests that initial goal directed therapy, nutritional support, and vigilance for pancreatic complications are best practice. Patients can develop pancreatic fluid collections including acute pancreatic fluid collections, pancreatic pseudocysts, acute necrotic collections, and walled-off necrosis. Several randomized controlled trials and cohort studies have recently highlighted the advantage of managing these conditions with a progressive approach, with initial draining for infection followed by less invasive techniques. Surgery is no longer an early intervention and may not be needed. Instead, interventional radiologic and endoscopic methods seem to be safer with at least as good survival outcomes. Newly developed evidence based quality indicators are available to assess and improve performance. Development and clinical testing of drugs to target the mechanisms of disease are necessary for further advancements.

Introduction

Although effective drug treatments are lacking, advances have been made in understanding the role of risk factors and specific management steps in patients with acute pancreatitis. We now have an increased appreciation of the role of smoking alone and in combination with alcohol misuse in increasing the risk of pancreatitis in adults, serum triglyceride concentrations during pancreatitis, and genetic risks in children; this information needs to be conveyed to patients to mitigate the risk for recurrence of acute pancreatitis. Updates of the Atlanta classification for severity of acute pancreatitis delineate three severities of acute pancreatitis—mild, moderate, and severe. Newer methods of dynamic measurements of severity have been developed that can be used for making clinical decisions during the course of the disease. Several randomized controlled trials (RCTs) have evaluated the use of antibiotics, peritoneal lavage, and drugs to manage complications and limit the severity of acute pancreatitis, providing high quality data to inform clinical care. Recently, cohort studies and RCTs have provided moderate evidence to support an escalating approach to invasive techniques tackling local complications of severe acute pancreatitis, including pancreatic fluid collections and pancreatic necrosis. These advances provide a platform for future improvements, including the development of therapeutics aligned with the cause of the pancreatitis episode, its severity, and its dynamic activity.

Sources and selection criteria

We searched PubMed from 1980 to April 2019 for systematic reviews, meta-analyses, RCTs, and international guidelines in the English language, using the search terms “severe acute pancreatitis” and “necrotizing pancreatitis”. This found 10 422 articles and 483 clinical trials. We expanded the search to include observational studies on the topics of severity, management and treatment, interventional techniques, and complications of severe acute pancreatitis. We excluded case reports and case series with fewer than 25 patients. We prioritized studies by design in the order noted above, as well as those with large patient numbers and quality.

Epidemiology

Acute pancreatitis is one of the most common indications for inpatient hospital care in the US, with an annual incidence of 13-45 cases per 100 000 people.[1 2] Historically, epidemiology based on population distributions is reported from the US, Europe, and Japan, and more recently reports are coming from other countries.[1] Gallstones and alcohol misuse are key causative factors in the mechanisms of pancreatitis, and the incidence varies between regions as a function of the prevalence of gallstone disease and alcohol misuse.[1]

Equal proportions of men and women develop acute pancreatitis; however, alcohol misuse is more commonly associated with acute pancreatitis in men, whereas gallstones are more commonly associated with acute pancreatitis in women.[1 3] Of note, the differences in alcohol related pancreatitis between men and women disappear when rates are determined as a function of amounts of alcohol consumption.[1] In addition to gallstones, women are more likely

to have acute pancreatitis due to complications of endoscopic retrograde cholangiopancreatography (ERCP) or an autoimmune cause and are more likely to have idiopathic acute pancreatitis.[1] Recent literature suggests that diabetes is associated with a small increase in risk for development of pancreatitis.[4-6]

The diagnosis of acute pancreatitis is less common in children than in adults, and most pediatric cases are caused by underlying genetic influences involving mutations in key digestive enzymes (such as hereditary pancreatitis) and genes in the cystic fibrosis family of mutations.[7 8] Recent data show associations of smoking or combinations of smoking and alcohol misuse with the incidence of pancreatitis.[1 9 10] These studies show that smoking itself is a risk factor for acute pancreatitis and adds to the risk of alcohol induced pancreatitis. Importantly, moderate drinking is unlikely to cause pancreatitis and may provide protection if not associated with smoking.[3 11] Recent studies using experimental models of pancreatitis show that the protective effects of moderate alcohol consumption can be explained by differential effects of alcohol and smoking on the endoplasmic reticulum's unfolded protein response in the acinar cell of the pancreas.[12 13] Further recent work shows associations between diet and the incidence of pancreatitis.[14] For example, increased intake of saturated fat and cholesterol is positively associated with the incidence of gallstone pancreatitis, whereas increased fiber intake is negatively associated with all forms of pancreatitis. Vitamin D intake is negatively associated with gallstone pancreatitis, and coffee consumption is protective against non-gallstone pancreatitis.

Examples of ethnic differences in pancreatitis also exist. For example, the risk of pancreatitis is twofold to threefold higher among black people than white people, although little is known about the factors (genetic or environmental) that account for this difference.[1]

Although some drugs have been implicated in causing acute pancreatitis, as discussed in a subsequent section, a population based retrospective cohort study including 3 967 859 patients from Southern California Kaiser Permanente showed that patients taking statins had a marked reduction in incidence of acute pancreatitis (incidence rate ratio 0.626, 95% confidence interval 0.588 to 0.668).[15] The mechanisms of this beneficial effect are yet to be determined.

Trends in causes of pancreatitis

Gallstones migrating out of the gallbladder and causing transient obstruction of the pancreatic duct and exposure of the pancreas to biliary constituents still represent the most common cause of acute pancreatitis.[1 16] The second most common cause of acute pancreatitis is alcohol misuse.[1 16] Intake of a significant amount of alcohol for a prolonged period of time (at least four to five drinks a day over more than five years) is needed to cause pancreatitis.[17] Interestingly, recent studies suggest that moderate drinking of less than 40 g/day is associated with a protective effect against pancreatitis.[9 18]

Cigarette smoking is common with alcohol consumption, and recent studies support an important role for smoking itself and the combination of alcohol consumption with smoking.[3 9 19] These studies show that smoking is an independent risk factor for pancreatitis (acute, recurrent, and chronic) in addition to heavy alcohol use. A prospective analysis of 145 886 participants found that, among smokers, pancreatitis was highest among those who consumed more than four drinks a day (hazard ratio 2.06, 95% confidence interval 1.28 to 3.30).[11] Understanding of the mechanisms of pancreatitis and the roles of alcohol and smoking has increased and is covered in recent reviews.[3 20]

The important role of hypertriglyceridemia in acute pancreatitis is increasingly recognized. Hypertriglyceridemic pancreatitis is the third leading cause of acute pancreatitis.[21] A systematic review of case-control, retrospective, and case seriesstudies including 1979 patients estimated that 15-20% of those with severe hypertriglyceridemia (triglyceride concentrations greater than 1000 mg/dL) will develop acute pancreatitis.[22] A retrospective cohort study including 2519 patients found that the clinical course in patients with elevated triglycerides was more severe, with a greater incidence of persistent multiorgan failure, than in those without elevated triglycerides.[23 24] Of interest are recent studies showing increased severity of pancreatitis in patients with mild (triglyceride concentrations of 150-199 mg/dL) and moderate (200-999 mg/dL) increases in serum triglycerides measured during an episode. These studies suggest that the metabolic effect of pancreatitis associated with increased circulating concentrations of triglyceride promotes the severity of pancreatitis.

Pancreatitis associated with drugs is less common and probably accounts for less than 5% of cases, although multiple drugs have been reported to be associated with development of pancreatitis.[25] Drugs with strong associations with the development of acute pancreatitis include azathioprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin converting enzyme inhibitors, and mesalamine.[25] Although there has been considerable interest in the role of glucagon-like peptide 1 mimetics (incretin mimetics) used for the treatment of diabetes in causing pancreatitis, more thorough investigations show that the increased incidence in these cases is likely due to the underlying diabetes, which increases the risk of acute pancreatitis by two to three times, and not the treatment with these agents.[26-29] One meta-analysis of 113 trials including 33 192 patients found that the incidence of pancreatitis with glucagon-like peptide 1 agonists was not different from comparator arms (odds ratio 0.93, 95% confidence interval 0.65 to 1.34).[27]

As indicated earlier, most cases of acute, recurrent, and chronic pancreatitis in children are associated with mutations in several genes. The general consensus is that only a minority of adult patients

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have pancreatitis resulting from genetic alterations. However, the recent report that a genetic mutation in claudin-2 can augment the effect of alcohol drinking on susceptibility to pancreatitis is important.[30 31]

Sometimes, the cause of pancreatitis is not easily discernible. One should not overlook the possibility of a malignancy, which can occasionally present as acute pancreatitis, especially in patients older than 50.[25] Additionally, the mucinous material of pancreatic cysts such as intraductal pancreatic mucinous neoplasms can obstruct the flow of pancreatic fluid leading to pancreatitis. In cases with an unknown cause, especially with a recurrent episode, a more detailed examination of the pancreas with imaging procedures including endoscopic ultrasonography and testing for genetic abnormalities is warranted.

Identifying the cause of an episode of pancreatitis is of critical importance for providing counseling to patients for prevention of recurrences of acute pancreatitis and the potential for progression to chronic pancreatitis. A review of the effectiveness of prevention methods including cholecystectomy for biliary pancreatitis, alcohol use counseling for patients with alcohol induced pancreatitis, and control of hypertriglyceridemia has recently been published.[32] Similarly, discontinuation of drugs that could have a causative role in acute pancreatitis is necessary to prevent recurrences. Revealing genetic factors underlying the cause of recurrent episodes of acute pancreatitis when other causes are not evident informs the patient about the cause and, more importantly, sets the stage for an important discussion of avoidance of environmental factors (alcohol misuse, smoking, drugs, hypertriglyceridemia) that can provoke the risk of recurrent episodes.

Severity assessment

The diagnosis of acute pancreatitis requires the presence of two out of three characteristic features of the disease.[33-35] These are abdominal pain consistent with acute pancreatitis, serum amylase or lipase concentrations that are at least three times the upper limit of the normal range, and abdominal imaging findings consistent with the diagnosis. Grading systems have been developed for predicting the severity of an episode of acute pancreatitis, for classifying the severity of the episode, and for dynamic measurement of activity during an episode.

Multiple validated methods have been developed to predict the severity of the course of acute pancreatitis on the basis of early observations during the disease. These methods use measures of physiologic responses (cardiopulmonary function and renal function), laboratory studies reflecting extrapancreatic organ injury (liver enzymes), and imaging of the pancreas with and without contrast.[36] Some studies have used single laboratory studies including C-reactive protein, blood urea nitrogen, or procalcitonin. Of these methods, scoring systems are the most reliable. The Ranson score was developed more than three decades ago providing an important impetus in the field, with at least additional eight scoring systems developed since then. One or more of these prediction methods can be used to plan the initial level of care and interventions needed for management of patients during their disease course.

An episode of acute pancreatitis can also be described by classification of severity. The main classification method is the Atlanta classification system that was first developed in 1992 and was revised by international consensus in 2012.[33] The Atlanta classification delineates three severities of acute pancreatitis—mild, moderate, and severe. An episode of mild acute pancreatitis has no organ failure and no local or systemic complications. An episode of moderately severe acute pancreatitis has organ failure that resolves within 48 hours (transient organ failure), local or systemic complications without persistent organ failure, or both. An episode of severe acute pancreatitis has persistent (>48 h) organ failure that can be either single organ failure or multiple organ failure.

A limitation of the prediction and classification methods is that they do not provide the real time measurements of disease activity that are needed for a dynamic disease with fluctuations in disease activity. Although the prediction models are helpful for initial management of the average patient, some patients may initially present with signs of relatively mild disease but rapidly transition to severe and life threatening disease. A real time measurement system for prompt changes in management, as well as monitoring responses to interventions in clinical practice and clinical trials, is a necessary tool for the field.

The need for a continuous monitoring system for acute pancreatitis was recently addressed by a group of international experts who developed the acute Pancreatitis Activity Scoring System (PASS) using a modified Delphi process.[37] The PASS uses routinely obtained clinical measures to provide dynamic measures of disease activity over the complete spectrum of severity during the entire duration of the illness. This measurement system is an additive function of five weighted clinically important parameters (organ failure, systemic inflammatory response, pain, pain medication, and intolerance to solid diet) that is calculated continuously during an episode of pancreatitis.

Recently, the PASS was tested for validation in patients treated at the Los Angeles County Hospital.[38] This prospective study enrolled 439 patients and found that, in addition to predicting the severity of a pancreatitis episode from initial scores (odds ratio 3.5, 95% confidence interval 2.0 to 6.3), the dynamic score was associated with local complications such as pseudocysts and necrosis (odds ratio 3.1, 1.7 to 5.7) and the length of hospital admission and readmission to hospital after discharge (odds ratio 5.1, 2.4 to 10.7). These promising results should lead to continued interest in development of dynamic real time scoring systems for both clinical management and intervention trials with agents designed to improve outcome in acute pancreatitis.

The course of an episode of acute pancreatitis can be defined by prediction models, classification of severity, and dynamic activity. Each of these measurements has value during the disease course. The prediction and dynamic activity measurements are used to assign a level of care and interventions during the initial phases of the disease, and the dynamic activity measurement is needed for adjustments in level of care and interventions during the course of the episode. The classification system for severity provides an overall account of an episode that can be used to provide a consolidated characterization of an episode for both clinical care and research purposes.

Early resuscitation

Patients with severe acute pancreatitis develop hypovolemia and may have hypotension secondary to a systemic inflammatory response. Several liters of fluid resuscitation may be needed to preserve organ function. Oliguria, diminished cardiac output, and hypotension are common during severe acute pancreatitis and need intensive monitoring.

Various fluid preparations are available for resuscitation. Two trials suggest that lactated Ringer's solution decreases the systemic inflammatory response in patients with acute pancreatitis.[39 40] Although a randomized trial including 41 patients and investigating hydroxyethyl starch suggested that patients receiving hydroxyethyl starch had lower intra-abdominal pressure and need for mechanical ventilation (15% *v* 48%),[41] in a randomized trial with 804 patients hydroxyethyl starch increased the rate of renal failure (relative risk 1.35, 95% confidence interval 1.01 to 1.80) and mortality (relative risk 1.17, 1.01 to 1.36) compared with lactated Ringer's in the face of severe sepsis.[42] Although the type of fluid does not seem to affect mortality, consensus guidelines from the International Association of Pancreatology and American Pancreatic Association recommend lactated Ringer's for the initial phase of resuscitation.[43]

Fluid resuscitation should be initially assessed with non-invasive monitoring targeting heart rate, mean arterial pressure, and adequate urine output. A larger trial including 200 patients suggested that patients with severe pancreatitis managed with invasive monitoring targeting a central venous pressure of 8-12 mm Hg and mixed venous oxygen saturation of at least 70% needed fewer days of ventilation and in hospital, had less organ failure, and had a lower mortality rate (24% *v* 18%; P<0.05).[44] The American Gastroenterological Association recommends goal directed therapy for fluid management.[45] Fluid requirements may be considerable, and the amount of intravenous fluid administered should be sufficient to normalize clinical and biochemical targets of perfusion including heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit. Goal directed intravenous fluid therapy with 5-10 mL/kg/h should be used initially until resuscitation goals are reached (table 1).

Imaging

Ultrasound examination may show evidence of pancreatic and peripancreatic edema or fluid collections, but it is generally less effective at visualizing the pancreas because of overlying bowel. Ultrasonography can determine whether gallstones are present and provide an initial assessment of the likelihood of common bile duct stones if the bile duct is dilated. A computed tomography (CT) scan is indicated for initial assessment if the diagnosis is uncertain, to confirm severity when severe acute pancreatitis is suspected, or if initial treatment fails or in the case of clinical deterioration (table 1). CT can also be used to evaluate complications of pancreatitis including necrosis, infection, pseudocyst, and hemorrhage. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography are helpful to define pancreatic and biliary ductal anatomy and identify causes of pancreatitis including choledocholithiasis, but they are less useful in the initial and early assessment of this condition.

Preventing infection

Prevention of infection with prophylactic antibiotics during severe acute pancreatitis has been studied extensively. A meta-analysis of six RCTs including 329 patients found no evidence to support the use of prophylactic antibiotics.[47] The use of antibiotics was not associated with less infected necrosis (relative risk 0.77, 95% confidence interval 0.54 to 1.12), mortality (relative risk 0.8, 0.44 to 1.39), non-pancreatic infections (relative risk 0.71, 0.32 to 1.58), or the need for surgical intervention (relative risk 0.78, 0.55 to 1.11). It was, however, associated with a significant reduction in hospital stay (P=0.04). A second meta-analysis of six studies with 397 patients confirmed this, with no significant effect on infection of pancreatic necrosis (relative risk 0.055, 0.084 to 0.194) or mortality (relative risk 0.058, 0.017 to 0.134).[48] However, a meta-analysis including seven randomized trials with 404 participants reported a reduction in pancreatic infection in the case of pancreatic necrosis in patients who were treated prophylactically with imipenem (relative risk 0.34, 0.13 to 0.84).[49] Studies have documented the efficacy of the carbapenem family, including imipenem and meropenem, over cephalosporins or fluoroquinolones when pancreatic infection is documented. Overall, antibiotic prophylaxis is not recommended to prevent infection in patients with severe acute pancreatitis.

Some evidence supports the concept of selective oral decontamination to prevent infection. A multicenter randomized trial enrolled 102 patients with severe acute pancreatitis.[50] Mortality and incidence of Gram negative infection were significantly reduced in the selective decontamination group (35% *v* 22% mortality, P=0.05; 33% *v* 8% infection, P=0.003), which consisted of treatment with an oral paste containing colistin, amphotericin, and norfloxacin. Additional studies are needed to confirm these results.

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Table 1 | Recommendations adapted from the International Association of Pancreatology/American Pancreatic Association (IAP/APA)[43]; the American Gastroenterological Association (AGA)[34]; and the American Society of Gastrointestinal Endoscopy (ASGE)[46]

Recommendation	Strength of recommendation
The definition of acute pancreatitis is based on the fulfillment of two of the following three criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3×upper limit of normal), and/or imaging (CT, MRI, ultrasonography) criteria (IAP/APA)	High
The indication for initial CT assessment in acute pancreatitis can be: diagnostic uncertainty, confirmation of severity based on clinical predictors of severe acute pancreatitis, or failure to respond to conservative treatment or in the setting of clinical deterioration (IAP/APA)	High
Ringer's lactate is recommended for initial fluid resuscitation in acute pancreatitis (IAP/APA, AGA)	Moderate
Goal directed intravenous fluid therapy with 5-10 mL/kg/h should be used initially until resuscitation goals are reached (IAP/APA, AGA)	Low
Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention (IAP/APA)	High
Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis (IAP/APA)	High
Probiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis (IAP/APA)	High
In patients with acute biliary pancreatitis and no cholangitis, the recommendation is against the routine use of urgent ERCP (AGA)	Moderate
Urgent ERCP (<24 h) is required in patients with acute cholangitis (IAP/APA)	High
In patients with acute pancreatitis, early (within 24 h) oral feeding is recommended as tolerated, rather than keeping the patient nil by mouth (AGA)	High
In patients with acute pancreatitis and inability to feed orally, enteral rather than parenteral nutrition is recommended (AGA)	High
In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, a nasogastric or nasojejunal route is acceptable (AGA)	Moderate
For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (ie, percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until ≥4 weeks after initial presentation to allow the collection to become "walled-off" (IAP/APA, ASGE)	High
All infected pancreatic fluid collections should be drained in patients who fail to improve with conservative management alone (ASGE)	High
Symptomatic sterile necrosis lasting >8 weeks after the onset of acute pancreatitis should be drained (ASGE)	High
The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy (IAP/APA, ASGE)	Moderate
Endoscopic drainage of pancreatic fluid collections should be performed only with the availability of surgical and interventional radiology support (ASGE)	High

CT=computed tomography; ERCP=endoscopic retrograde cholangiopancreatography; MRI=magnetic resonance imaging.

Another potential approach to prevent infectious complications is the use of probiotics for reduction of gastrointestinal bacterial overgrowth, restoration of the gastrointestinal barrier, and immune modulation. PROPATRIA (Probiotics in Pancreatitis Trial) was a multicenter RCT that included 298 patients with severe acute pancreatitis who received a probiotic or placebo within 72 hours of symptoms.[51] Infectious complications occurred equally between groups, but the risk of death was 2.53 (95% confidence interval 1.22 to 5.25) times higher in the probiotic group compared with placebo. The authors suspected that probiotic administration led to intestinal ischemia and hence a higher mortality rate. Probiotics are not recommended in the case of severe acute pancreatitis.

Nutritional support

Enteral nutritional support has been found to improve outcomes and limit complications in patients with severe acute pancreatitis, and this has been confirmed by a meta-analysis including five RCTs with 202 patients showing a reduced risk of infectious complications (relative risk 0.47, 95% confidence interval 0.28 to 0.77), pancreatic infections (relative risk 0.48, 0.26 to 0.91), and mortality (relative risk 0.32, 0.11 to 0.98).[52] A meta-analysis including eight trials with 348 participants found that enteral feeding was superior to parenteral nutrition in terms of complications and mortality (relative risk 0.50, 95% confidence interval 0.28 to 0.91).[53] A meta-analysis of 20 RCTs including 1070 patients found that no particular type of enteral nutrition improved outcome.[54] The Dutch Pancreatitis Study Group conducted a randomized trial (PYTHON trial) of 208 patients to evaluate early enteral feeding within 24 hours. Enteral feeding did not seem to reduce the rate of infection or death (relative risk 1.07, 0.79 to 1.44).[55] An RCT including 31 patients found that enteral feeding could be safely delivered via either nasogastric or nasojejunal routes.[56] Enteral nutrition may support the gut-mucosal barrier and reduce bacterial translocation, and through this reduce the risk of infected peripancreatic necrosis and other serious acute pancreatitis outcomes. Daily caloric requirements can be calculated on the basis of the patient's weight and severity of illness, with the goal of improving serum nutritional parameters including prealbumin and albumin.

Therapeutic agents

Octreotide is a peptide that inhibits exocrine secretion of the pancreas, and, as trypsinogen and other enzymes are known to initiate and propagate pancreatitis, octreotide has been theorized to improve the course of severe acute pancreatitis. To date, 13 trials have been reported with variable results. Generally, some agreement exists, albeit supported by weak evidence, that octreotide or the analog somatostatin lowers the incidence of organ failure but not infected necrosis or mortality.[57]

Several recent and ongoing trials have advocated the benefit of antioxidants and vitamin C for patients in the intensive care unit. One double blind trial randomized 43 patients with severe acute pancreatitis to treatment with the intravenous antioxidants N-acetylcysteine, selenium, and vitamin C or placebo.[58] The primary endpoint of organ dysfunction was no different between the antioxidant and placebo groups (32% *v* 19%; P=0.33), and a trend was seen toward more organ dysfunction in the antioxidant group. Given these findings, the authors cautioned against considering antioxidant treatment in patients with severe acute pancreatitis.

In a small clinical trial, 28 patients with severe acute pancreatitis were randomized to receive pentoxifylline (400 mg three times a day) or placebo within 72 hours of diagnosis.[59] Pentoxifylline is a phosphodiesterase inhibitor that lowers tumor necrosis factor and leukotrienes, dampening inflammation. It also improves red blood cell deformability, diminishes blood viscosity, and decreases platelet aggregation and the formation of thrombus. The pentoxifylline group had fewer days in the intensive care unit and in hospital (P<0.05). Although not significant, none of the treatment group developed new necrosis or organ failure, whereas two patients in the placebo group had progressive necrosis and three manifested organ failure.

The effect of lexipafant, a potent platelet activating factor antagonist, was compared with placebo in a multicenter RCT of 286 patients with predicted severe acute pancreatitis.[60] The investigators found a small decrease in the organ failure score in the treatment group (P=0.023), but lexipafant had no effect on markers of systemic inflammatory response, new organ failure, or mortality.

On the basis of promising preclinical data, a multicenter study was conducted to investigate the use of a protease inhibitor, gabexate mesilate, in patients with moderate to severe acute pancreatitis. Two hundred and twenty three patients were randomized to receive placebo or the study drug (4 mg daily for seven days). No differences were seen in mortality or complications between the two groups.[61]

To date, no drug has been identified that consistently modulates the outcome of severe acute pancreatitis. A systematic review of 78 RCTs with 7366 patients, investigating drug interventions including antioxidants, aprotinin, atropine, calcitonin, cimetidine, ethylenediaminetetraacetic acid, gabexate, glucagon, iniprol, lexipafant, non-steroidal anti-inflammatory drugs, octreotide, oxyphenonium, activated protein C, somatostatin, somatostatin plus omeprazole, somatostatin plus ulinastatin, thymosin, and ulinastatin, found no effect on short term mortality.[62] Fewer adverse events were found for lexipafant (rate ratio 0.67, 95% confidence interval 0.46 to 0.96; n=290, one study), octreotide (rate ratio 0.74, 0.60 to 0.89; n=770, five studies), somatostatin plus omeprazole (rate ratio 0.36, 0.19 to 0.70; n=140, one study), and somatostatin plus ulinastatin (rate ratio 0.30, 0.15 to 0.60; n=122, one study). Overall, the authors rated the studies as of very low quality and found no consistent clinical benefits with treatment.

Early intervention

Peritoneal lavage has been used in patients with severe acute pancreatitis and intraperitoneal fluid, with the theory that this removes toxins and various metabolites from the peritoneal cavity, minimizing systemic absorption and effect on the systemic inflammatory response and organ failure. Although controlled trials failed to show that this decreased mortality rates, some evidence from individual studies suggests fewer cardiopulmonary complications.[63-66] However, a systematic review of 10 RCTs including 469 patients found that peritoneal lavage did not lead to a significant difference in the risk of mortality (relative risk 0.82, 95% confidence interval 0.32 to 1.79) or complications (relative risk 1.33, 0.99 to 2.12).[67]

Patients with severe acute biliary pancreatitis may be helped by early endoscopic sphincterotomy and stone extraction. Four randomized studies have evaluated the utility of urgent sphincterotomy and stone extraction.[68-71] Overall, these studies seem to show benefit in patients who have severe disease and are not responding to resuscitative therapy. The Dutch Acute Pancreatitis Study Group reported a prospective multicenter study of 153 patients and found that patients with cholestasis who underwent endoscopic retrograde ERCP had fewer complications than those who did not (25% *v* 54%, P=0.02; odds ratio 0.35, 95% confidence interval 0.13 to 0.99).[72] Severe acute pancreatitis patients with biliary obstruction or cholangitis may benefit from sphincterotomy after a period of early resuscitation. The American Gastroenterological Association recommends against urgent ERCP (<24 h) in patients with acute biliary pancreatitis and no cholangitis.[45] The International Association of Pancreatology and American Pancreatic Association recommend urgent ERCP in acute pancreatitis patients with acute cholangitis (table 1).[43]

In patients with mild biliary pancreatitis that resolves within two or three days, cholecystectomy should be performed during the same hospital admission, as the incidence of recurrent pancreatitis may be as high as 60-80% in the ensuing months. On the other hand, patients with a severe episode of biliary pancreatitis should undergo cholecystectomy

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after the pancreatitis and the subsequent local complications have resolved. By this time, abdominal inflammation has subsided and the operation can be done without increased risk. Bile duct stones will not usually need operative intervention, as endoscopic approaches are so effective, but a laparoscopic or open common bile duct exploration can be used.

Local complications of pancreatitis

In 2012 the Atlanta classification for pancreatitis was revised, and the local collections resulting from pancreatitis have a defined nomenclature (table 2).[33] Each type of collection has a particular natural history and, therefore, treatment approach.

Acute pancreatic fluid collection

An acute pancreatic fluid collection is a homogeneous fluid collection adjacent to the pancreas associated with pancreatitis without evidence of pancreatic necrosis. This term applies to a collection within the first four weeks after the inception of pancreatitis. This is distinct from a pseudocyst, as there is no wall encapsulating the fluid. Acute pancreatic fluid collections rarely become infected, and most resolve without intervention.

Pseudocysts

Pseudocysts are encapsulated fluid collections with an inflammatory wall. These usually occur more than four weeks into the course of severe acute pancreatitis. Many pseudocysts resolve spontaneously. The size of the pseudocyst no longer drives the decision for intervention, although some evidence suggests that cysts greater than 5 cm are less likely to resolve. As long as the pseudocyst is asymptomatic, observation and follow-up imaging with contrast enhanced CT or MRI is sufficient to confirm ultimate resolution. When a pseudocyst is symptomatic, patients can experience pain, varying degrees of gastric or duodenal obstruction, weight loss, or biliary obstruction. Rarely, an acute complication can occur, including rupture leading to pancreatic ascites, bleeding or infection of the cyst, or erosion into surrounding vessels such as the splenic or gastroduodenal arteries.

Patients with symptomatic pseudocysts require intervention to establish drainage. Pseudocysts can be drained percutaneously, surgically, or endoscopically. Endoscopic techniques have largely replaced surgical and percutaneous approaches, as these offer both efficacy and low morbidity.[46] The evolution favoring endoscopic techniques began with a large study including 27 533 patients from the National Inpatient Sample comparing percutaneous and surgical drainage, which suggested that percutaneous drainage was not sufficient.[73] The study found significant differences in length of stay (15 *v* 21 days; P<0.001) and inpatient mortality (5.9% *v* 2.8%; P<0.001) favoring surgical drainage. Surgical drainage may have a slight advantage over other techniques in terms of successful drainage. However, a randomized trial including 40 patients undergoing either endoscopic or surgical techniques for pancreatic pseudocysts showed reduced hospital stay (2 *v* 6 days in the surgery group; P<0.001) and expense ($7011 (£5460; €6360) *v* $15 052; P=0.003), along with better quality of life (P=0.025), for patients undergoing endoscopic drainage.[74] No differences were seen in successful treatment, complications, or need for additional procedures. Therefore, endoscopic techniques using transmural (stomach or duodenum) or transpapillary drainage and stenting are now preferred.

Pancreatic necrosis

Pancreatic necrosis is classified into two conditions—acute necrotic collection and walled-off necrosis. Acute necrotic collections occur in the setting of

Table 2 | Definitions of inflammatory pancreatic fluid collections

Term	Definition	CT findings
Acute pancreatic fluid collection	Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial edematous pancreatitis and without the features of a pseudocyst	Homogeneous collection with fluid density
		Confined by normal peripancreatic fascial planes
		No definable wall encapsulating the collection
		Adjacent to the pancreas (no intrapancreatic extension)
Pancreatic pseudocyst	An encapsulated collection of fluid with a well defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually requires >4 weeks after onset of interstitial edematous pancreatitis to mature	Well circumscribed, usually round or oval, homogeneous fluid density
		No non-liquid component
		Well defined wall (completely encapsulated)
		Maturation usually requires >4 weeks after onset of acute pancreatitis
Acute necrotic collection	A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma, the peripancreatic tissues, or both	Occurs in the setting of acute necrotizing pancreatitis
		Heterogeneous and non-liquid density of varying degrees in different locations
		No definable wall encapsulating the collection
		Can be intrapancreatic and/or extrapancreatic
Walled-off necrosis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well defined inflammatory wall. This usually occurs >4 weeks after the onset of necrotizing pancreatitis	Heterogeneous with liquid and non-liquid density with varying degrees of loculations
		Well defined wall
		Intrapancreatic and/or extrapancreatic location
		Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

Adapted from Banks et al.[33]

necrotizing pancreatitis and contain both fluid and necrosis involving the pancreas, the surrounding peripancreatic tissue, or both. These collections are distinct from wall-off necrosis, which is surrounded by a well defined inflammatory wall (fig 1). Usually, wall-off collections are so denoted four weeks or more from presentation, as this amount of time is needed for a wall to develop.

Over the past decade, a major evolution in the management of pancreatic necrosis has occurred, with a shift from aggressive surgical debridement by open necrosectomy to a "step-up" approach. This begins with percutaneous drainage followed by minimally invasive approaches if needed. Case series have indicated that sterile necrosis may resolve without intervention.[75] Endoscopic techniques have taken the lead for symptomatic or infected pancreatic necrosis, and a systematic review including 14 studies and 455 patients found that endoscopic necrosectomy was successful 81% of the time as a single treatment.[76]

Minimally invasive approaches to managing necrotic and infected material include percutaneous drainage, video assisted retroperitoneal debridement, laparoscopic surgical debridement, transgastric endoscopic drainage, and any combination of these modalities. These techniques offer efficacy along with reduced complication and mortality rates compared with open surgery. Percutaneous drainage should be the first early intervention in patients with severe systemic compromise and organ failure and will often stabilize the patient until a more definitive intervention can be safely made. Remarkably, however, a systematic review including 10 retrospective reports and one RCT with 384 patients found that percutaneous drainage was sufficient as a definitive treatment in 56% of patients with necrotizing pancreatitis.[77] In these cases, some of the necrosum is evacuated by the drain and the remainder is resorbed.

In 2010 the Dutch Pancreatitis Research Group reported the PANTER (PAncreatitis, Necrosectomy versus sTEp up approach) trial.[78] This RCT included 88 patients with infected pancreatic necrosis who were treated with either a step-up approach consisting of percutaneous drainage followed by video assisted retroperitoneal debridement if necessary or open surgical debridement of the necrotic material. The rate of mortality was similar between the groups (19% *v* 16%; P=0.70), but the step-up group had significantly fewer complications such as incisional hernias and new onset diabetes, as well as less new onset multiorgan failure (12% *v* 40%; P=0.002). Percutaneous drainage was the definitive treatment for 35% of the patients in the step-up group.

Following this publication, the same group reported the PENGUIN (Pancreatitis Endoscopic Transgastric vs Primary Necrosectomy in Patients with Infected Pancreatic Necrosis) trial.[79] Patients who had endoscopic necrosectomy had a less inflammatory state after the procedure (20% *v* 80% occurrence of composite clinical endpoint; risk difference 0.60, 95% confidence interval 0.16 to 0.80), resulting in less organ failure (0% *v* 50%; risk difference 0.50, 0.12 to 0.76) and fewer pancreatic fistulas (10% *v* 70%; risk difference 0.60, 0.17 to 0.81). Recently, this group has reported a follow-up study (TENSION trial: transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected pancreatic necrosis).[80] This trial included 418 patients randomized to either an endoscopic arm consisting of endoscopic ultrasound guided transluminal drainage followed by endoscopic necrosectomy if needed or a surgical arm consisting of percutaneous catheter drainage followed by video assisted retroperitoneal debridement. No difference was found between the groups in terms of complications or death. However, the rate of pancreatic fistula (5% *v* 38%; risk ratio 0.15, 95% confidence interval 0.04 to 0.62) and length of hospital stays (53 *v* 69 days; P=0.01) were lower in the endoscopic group.

Hemorrhage

Hemorrhage and vascular emergencies are uncommon but life threatening in the face of severe acute

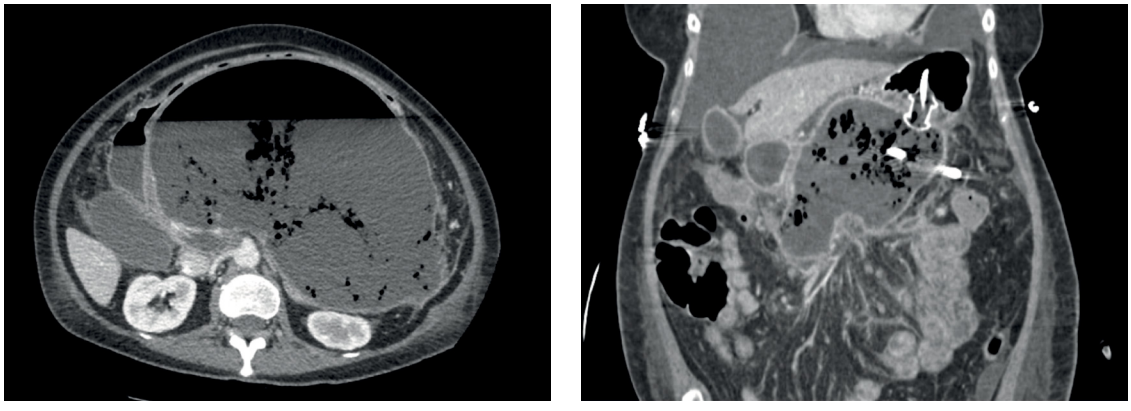

Fig 1 | Left: Contrast enhanced computed tomography scan showing a large area of walled-off necrosis with a mature wall, an air-fluid level, and gas in solid necrotic material implying infection. Right: A luminal opposing stent has been placed between the stomach and the walled-off necrosis, and a pigtail drain runs through the center of the stent. The patient has also had a percutaneous drain placed

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pancreatitis. Bleeding is often caused by erosion of the splenic or gastroduodenal artery or other vessels near the pancreas and is suspected with clinical signs of hypovolemia and a falling hematocrit. CT angiography will confirm the diagnosis and may identify a contrast blush suggesting the vessel involved. Large database analyses and randomized trials are not available for this condition owing to its low incidence and emergent nature, and most of the publications are case reports or small series. One review collated 200 cases from the literature and found that angiography with embolization or stenting achieved hemostasis in 75% of cases.[81] Mortality was higher in patients who underwent surgery as a first intervention compared with angiography. Patients with severe acute pancreatitis should have an angiographic attempt to control bleeding (fig 2); if this is not successful, emergency surgery with ligation of the vessel is needed.

Guidelines

Table 1 summarizes guidelines from the American Gastroenterology Association,[34] the joint International Association of Pancreatology and American Pancreatic Association,[43] and the American Society of Gastrointestinal Endoscopy.[46] Each organization has focused on various aspects of the medical management of acute pancreatitis, and, in particular, the American Society of Gastrointestinal Endoscopy highlights the treatment of pancreatic necrosis and pseudocysts. The International Association of Pancreatology and American Pancreatic Association joint guidelines were published in 2013 and are in need of an update incorporating new data. Generally, the American Gastroenterology Association and International Association of Pancreatology/American Pancreatic Association guidelines are aligned as highlighted in table 1.

The diagnostic criteria and initial imaging assessment are well established and acknowledged across the fields. Initial resuscitation with intravenous fluid is a mainstay, but the type of fluid and endpoints remain uncertain and should be the subject of additional investigation. Recommendations on the use of prophylactic antibiotics to prevent infection of pancreatic necrosis and acute fluid collections are supported by several investigations, but advice on whether to administer antibiotics without evidence of infection either by Gram stain or culture shifts every few years. For now, prophylactic antibiotics are not recommended. Research studies and guidelines recommend early enteral feeding by any means to improve outcomes and decrease infectious complications.

American Society of Gastrointestinal Endoscopy guidelines have incorporated the findings of the "step-up" approach advocated by the Dutch Pancreatitis Study Group and others. This includes delaying intervention for pancreatic necrosis or acute fluid collections for at least four weeks. If the patient shows signs of worsening condition or an infected pancreatic collection in the early phase, a percutaneous drainage catheter is recommended until definitive treatment is started. Definitive treatment can reliably be anticipated with endoscopic techniques. For now, patients with asymptomatic sterile collections should be managed expectantly, and the question of whether intervention is warranted for these is unanswered and will need additional studies.

Quality indicators

Recently, a multidisciplinary expert panel supported by the American College of Gastroenterology

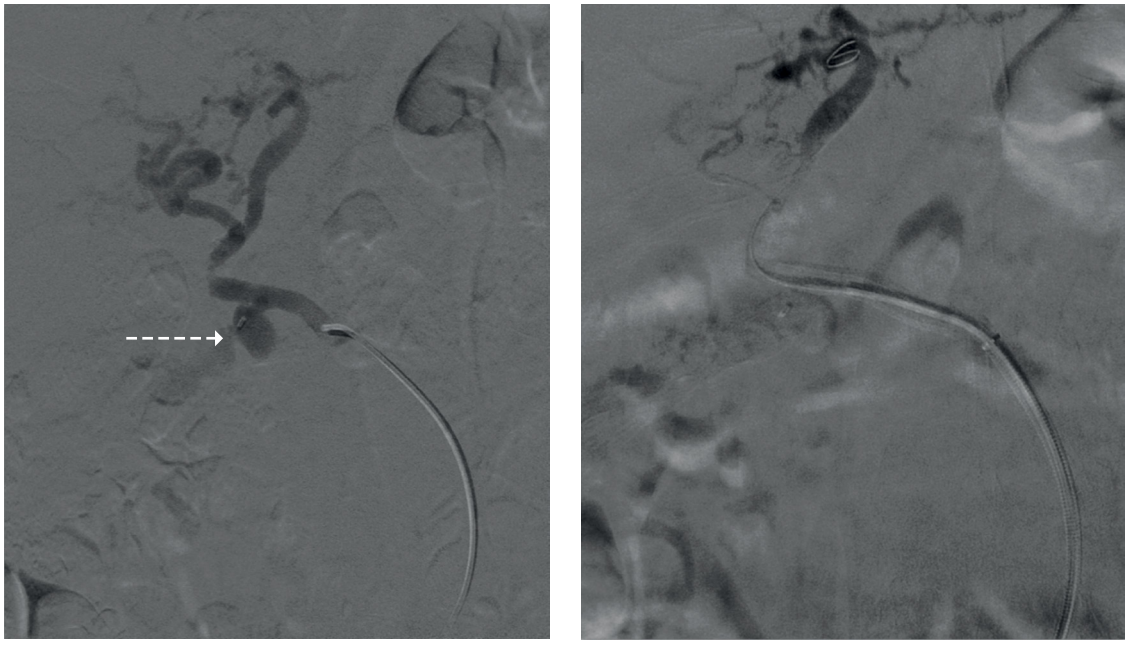

Fig 2 | Left: Selective celiac angiography with a gastroduodenal artery pseudoaneurysm (arrow). Right: The artery was successfully embolized with gelfoam and coils

formally developed and published a comprehensive set of 40 quality indicators for acute pancreatitis in several domains including diagnosis, causes, initial assessment, risk stratification, initial management, ERCP use, nutrition, drug treatment, management of early complications, surgery, and structure of care.[82] These quality indicators are meant to enable hospitals and providers to identify opportunities for improving medical care and outcome for patients with pancreatitis.

Emerging treatments

Several studies are now recruiting participants for investigation of the management of patients with acute pancreatitis, treatments to limit the severity of this condition, and methods to tackle pancreatic necrosis. Some of these trials are described here.

Clinicaltrials.gov NCT03642769—This study will revisit the mainstay of treatment for acute pancreatitis, fluid resuscitation. More than 100 patients will be enrolled and randomized to normal saline or lactated Ringer's solution at a large metropolitan hospital in Los Angeles. The primary outcome will be the change in prevalence of early systemic inflammatory response syndrome, using the PASS score to determine the severity of pancreatitis. This large study aims to finalize recommendations for the fluid management for pancreatitis, and enrolment is expected to be completed by 25 February 2020.

Clinicaltrials.gov NCT03807856—Patients with acute pancreatitis will be treated with dabigatran 150 mg twice a day for three days. Dabigatran is an anticoagulant used to treat blood clots and to prevent stroke in patients with atrial fibrillation. This is a novel study based on an additional effect of dabigatran as a highly effective inhibitor of trypsin, which is activated during pancreatitis and contributes to the pathophysiology of this condition. Inhibiting a central pancreatic enzyme in the early phases of pancreatitis may ameliorate the severity and duration of the episode. The study is scheduled to complete recruitment in February 2020.

Clinicaltrials.gov NCT03684278—The Randomised Treatment of Acute Pancreatitis with Infliximab: Double-blind Multi-centre Trial (RAPID-1) is still recruiting patients. This may be the first biologic studied for treatment of pancreatitis. Infliximab is a monoclonal antibody drug that blocks tumor necrosis factor alpha (TNF-α) and has been used to treat autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. TNF-α has a major role in the pathogenesis and severity of acute pancreatitis.

Clinicaltrials.gov NCT03185806—The Trial of Early Percutaneous Catheter Drainage of Sterile Pancreatic Fluid Collections in Severe Acute Pancreatitis (EPCDSAP) will study how this approach affects mortality, secondary infection of peripancreatic collections, organ failure, length of stay in hospital or intensive care, and inflammatory biomarkers by randomizing 100 patients to early percutaneous drainage of sterile acute fluid collections or standard management. Currently, sterile collections are managed expectantly with the understanding that instrumenting these may lead to an increased chance of infection. This trial is scheduled to be completed by October 2020.

Conclusions

Substantial evidence supports vigilance and best practice in critical care to treat patients with severe acute pancreatitis. This includes early imaging to secure the diagnosis and assess the extent of pancreatitis, goal directed resuscitation, and nutritional support (enteral rather than parenteral). Despite many randomized trials and cohort studies, no drug has been identified that consistently alters the course and outcome of this condition. For patients with biliary pancreatitis, early ERCP may be considered if the patient is not responding to resuscitation and has evidence of biliary obstruction or cholangitis. Patients can develop local pancreatic complications including pancreatic fluid collections, necrosis, and bleeding. Infection should be suspected in patients who manifest signs 10-14 days after presentation. In this circumstance, re-imaging may confirm the cause including infected necrosis or fluid collections. A minimalist step-up approach with percutaneous drainage will allow the patient to recover, especially if organ systems have failed. Endoscopic approaches with transgastric and transduodenal stenting and debridement or minimally invasive surgical techniques are the best approaches to minimize the systemic inflammatory response that can worsen organ dysfunction after intervention. Nearly all patients can be managed without surgical debridement, but on occasion surgery is important to manage other intra-abdominal conditions that can arise with severe illness. Patients with complex severe acute pancreatitis need combined expertise from many disciplines, particularly critical care medicine, surgery, gastroenterology, and interventional radiology.

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QUESTIONS FOR FUTURE RESEARCH

- What type of fluid replacement strategies would allow for correction of hypovolemia from pancreatitis without compromising pulmonary and abdominal organ function?
- What drugs can mitigate the conditions of inflammation, necrosis, and organ failure in severe acute pancreatitis?
- What are the long term nutritional and metabolic consequences of acute pancreatitis, and how should these be managed?
- How does the gut microbiome influence the course of severe acute pancreatitis, and what measures can support normal microbiome function during pancreatitis?

intervention; and serves as the guarantor. Both authors reviewed all sections of the manuscript, providing suggestions for included content and references.

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