Clinical practice guideline: management of acute pancreatitis

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There has been an increase in the incidence of acute pancreatitis reported worldwide. Despite improvements in access to care, imaging and interventional techniques, acute pancreatitis continues to be associated with significant morbidity and mortality. Despite the availability of clinical practice guidelines for the management of acute pancreatitis, recent studies auditing the clinical management of the condition have shown important areas of noncompliance with evidence-based recommendations. This underscores the importance of creating understandable and implementable recommendations for the diagnosis and management of acute pancreatitis. The purpose of the present guideline is to provide evidence-based recommendations for the management of both mild and severe acute pancreatitis as well as the management of complications of acute pancreatitis and of gall stone–induced pancreatitis.

Une hausse de l'incidence de pancréatite aiguë a été constatée à l'échelle mondiale. Malgré l'amélioration de l'accès aux soins et aux techniques d'imagerie et d'intervention, la pancréatite aiguë est toujours associée à une morbidité et une mortalité importantes. Bien qu'il existe des guides de pratique clinique pour la prise en charge de la pancréatite aiguë, des études récentes sur la vérification de la prise en charge clinique de cette affection révèlent des lacunes importantes dans la conformité aux recommandations fondées sur des données probantes. Ces résultats mettent en relief l'importance de formuler des recommandations compréhensibles et applicables pour le diagnostic et la prise en charge de la pancréatite aiguë. La présente ligne directrice vise à fournir des recommandations fondées sur des données probantes pour la prise en charge de la pancréatite aiguë, qu'elle soit bénigne ou grave, ainsi que de ses complications et de celles de la pancréatite causée par un calcul biliaire.

Acute pancreatitis can range from a mild, self-limiting disease that requires no more than supportive measures to severe disease with life-threatening complications. The most common causes of acute pancreatitis are gallstones and binge alcohol consumption.[1] There has been an increase in the incidence of acute pancreatitis reported worldwide. Despite improvements in access to care, imaging and interventional techniques, acute pancreatitis continues to be associated with significant morbidity and mortality.

A systematic review of clinical practice guidelines for the management of acute pancreatitis revealed 14 guidelines published between 2004 and 2008 alone.[2] Although these guidelines have significant overlap in their recommendations for diagnosing and managing acute pancreatitis, there is disagreement in some aspects of both the timing and types of interventions that should be used for both mild and severe acute pancreatitis. The availability of new imaging modalities and noninvasive therapies has also changed clinical practice. Finally, despite the availability of guidelines, recent studies auditing clinical management of acute pancreatitis have shown important areas of noncompliance with evidence-based recommendations.[3–9] This underscores the importance of creating understandable and implementable recommendations for the diagnosis and management of acute pancreatitis and emphasizes the need for regular audits of clinical practice within a given hospital to ensure compliance.

The purpose of the present guideline is to provide evidence-based recommendations for the management of both mild and severe acute pancreatitis as well as the management of complications of acute pancreatitis and of gall stone–induced pancreatitis.

Methodology

The guideline was developed under the auspices of the Best Practice in General Surgery group at the University of Toronto. Best Practice in General Surgery is a quality initiative aimed to provide standardized evidence-based care to all general surgery patients treated at the University of Toronto adult teaching hospitals. A working group consisting of general surgeons, critical care intensivists and a gastroenterologist led the development of these recommendations. The working group established the research questions, the analytical framework and clinically relevant outcomes for the guideline. The recommendations pertain to patients with a new presentation of suspected acute pancreatitis. Primary outcomes are complications, both infectious and noninfectious; mortality; length of hospital stay; and readmissions associated with acute pancreatitis. Definitions of key terms were based on the 2012 Atlanta Classification of Acute Pancreatitis[10] (Box 1).

Initially, we performed a scoping review to identify clinical practice guidelines related to the management of acute pancreatitis. We then searched Medline for guidelines published between 2002 and 2014 using the Medical Subject Headings "pancreatitis" and "clinical practice guideline." This search identified 14 guidelines published between 2008 and 2014. A 2010 systematic review of acute pancreatitis clinical practice guidelines that included all of the most recent guidelines was identified.[2]

Another electronic search of Medline was performed using the Medical Subject Headings "pancreatitis," "acute necrotizing pancreatitis," "alcoholic pancreatitis," and "practice guidelines" to update the systematic review. The results were limited to articles published in English between January 2007 and January 2014. The references of relevant guidelines were reviewed. Up-to-date articles on acute pancreatitis diagnosis and management were also reviewed for their references[11] (as of January 2014).

The working group developed the guideline recommendations based on evidence as well as consensus. Then the guideline recommendations were circulated to all general surgeons, gastroenterologists and critical care intensivists at the University of Toronto for feedback.

Box 1. Definitions of key terms (based on the 2012 Atlanta Classification of Acute Pancreatitis[10])

Diagnosis of acute pancreatitis (2 of the following)
- Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging

Mild acute pancreatitis
- No organ failure, local or systemic complications

Moderately severe acute pancreatitis
- Organ failure that resolves within 48 h and/or
- Local or systemic complications without persistent organ failure

Severe acute pancreatitis
- Persistent organ failure > 48 h

Interstitial edematous acute pancreatitis
- Acute inflammation of the pancreatic parenchyma and peri-pancreatic tissues, but without recognizable tissue necrosis

Necrotizing acute pancreatitis
- Inflammation associated with pancreatic parenchymal necrosis and/or peri-pancreatic necrosis

Organ failure and systemic complications of acute pancreatitis
- Respiratory: $Pao_2/FiO_2 \leq 300$
- Cardiovascular: systolic blood pressure < 90 mm Hg (off inotropic support), not fluid responsive, or pH < 7.3
- Renal: serum creatinine ≥ 170 μmol/L

Local complications of acute pancreatitis
- Acute peripancreatic fluid collections
- Pancreatic pseudocysts
- Acute necrotic collections
- Walled-off pancreatic necrosis

Guideline recommendations

Table 1 summarizes the guideline recommendations and grading.

1. Diagnosis of acute pancreatitis

1.1 A serum lipase test should be performed in all patients with a suspected diagnosis of acute pancreatitis. A 3-fold elevation of serum lipase from the upper limit of normal is required to make the diagnosis of acute pancreatitis.

1.2 Ultrasonography should be performed in all patients at baseline to evaluate the biliary tract and in particular to determine if the patient has gallstones and/or a stone in the common bile duct (CBD).

1.3 Magnetic resonance cholangiopancreatography (MRCP) is recommended only in patients in whom there is elevation of liver enzymes and in whom the CBD is either not visualized adequately or is found to be normal on ultrasound.

1.4 Computed tomography (CT) should be performed selectively when 1) a patient presents with substantial abdominal pain and a broad differential diagnosis that includes acute pancreatitis, or 2) in patients with suspected local complications of acute pancreatitis (e.g., peritonitis, signs of shock, suggestive ultrasound findings). Computed tomography for the assessment of local complications is most useful 48–72 hours after the onset of symptoms rather than at the time of admission. Unless contraindicated (e.g., renal dysfunction), intravenous contrast should be given in order to assess for pancreatic necrosis once patients are adequately fluid resuscitated and normovolemia is restored.

Table 1. Summary and grading of recommendations

Guideline recommendation	Strength of evidence	Guideline recommendation
A serum lipase test should be performed in all patients with a suspected diagnosis of acute pancreatitis.	Moderate–high	Strong
Ultrasonography should be performed in all patients at baseline to evaluate the biliary tract to determine if the patient has gallstones and/or a stone in the common bile duct.	High	Strong
Magnetic resonance cholangiopancreatography (MRCP) is recommended only in patients in whom there is elevation of liver enzymes and the common bile duct is either not visualized adequately or is found to be normal on ultrasound.	High	Strong
Computed tomography should be performed selectively when 1) a broad differential diagnosis that includes acute pancreatitis must be narrowed, or 2) in patients with acute pancreatitis and a suspected local complication (e.g., peritonitis, signs of shock, suggestive ultrasound findings).	Low–moderate	Strong
C-reactive protein (CRP) should be assessed at admission and daily for the first 72 h after admission.	Low–moderate	Weak
Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scores should be calculated on admission and daily for the first 72 h after admission.	Moderate	Weak
The diagnosis of severe acute pancreatitis should be made if the patient has a serum CRP ≥ 14 286 nmol/L (150 mg/dL) at baseline or in the first 72 h; APACHE Score ≥ 8 at baseline or in the first 72 h; or exhibits signs of persistent organ failure for > 48 h despite adequate intravenous fluid resuscitation.	Moderate	Strong
Supportive care, including resuscitation with isotonic intravenous fluids like Ringer's Lactate, pain control and mobilization, should be the mainstay of treatment for patients with mild acute pancreatitis.	Low	Strong
Careful consideration of transfer to a monitored unit should be made in patients with • Severe acute pancreatitis based on APACHE II Score > 8, CRP > 14 286 nmol/L (150 mg/dL), or organ dysfunction > 48 h despite adequate resuscitation; • Evidence of present or evolving organ dysfunction; • Need for aggressive, ongoing fluid resuscitation.	Low	Strong
Patients with mild acute pancreatitis should receive a regular diet on admission. If patients initially are unable to tolerate an oral diet owing to abdominal pain, nausea, vomiting, or ileus, they may be allowed to self-advance their diet from withholding oral food and liquid to a regular diet as tolerated.	High	Strong
In patients with severe acute pancreatitis, enteral nutrition should be commenced as soon as possible following admission (within 48 h).	High	Strong
Prophylactic antibiotics are not recommended.	High	Strong
Patients with 1) extensive necrotizing acute pancreatitis, 2) who show no clinical signs of improvement following appropriate initial management, or 3) who experience other complications should be managed in institutions that have on-site or access to therapeutic endoscopy, interventional radiology, surgeons and intensivists with expertise in dealing with severe acute pancreatitis.	Moderate	Weak
Follow-up computed tomography should be based on the clinical status of the patient and not performed routinely at regular intervals.	Low	Strong
Patients with acute peripancreatic fluid collections with no radiological or clinical suspicion of sepsis should be observed, and image-guided fine needle aspiration (FNA) should be avoided owing to the risk of introducing infection into a sterile collection.	Moderate	Weak
When there is radiological or clinical suspicion of infected necrosis in patients with acute necrotic collections (ANCs) or walled-off pancreatic necrosis (WOPN), image-guided FNA with culture should be performed to distinguish infected from sterile necrosis.	Moderate	Strong
Sterile necrosis based on negative FNA and/or stable clinical picture should be managed nonoperatively, and antibiotics are not indicated. For unstable patients in whom sepsis is suspected but no source has been identified, treatment with broad spectrum antibiotics on speculation may be indicated while an appropriate work up (bacterial and fungal cultures, CT scan) is carried out.	Moderate	Weak
In patients with FNA-confirmed infections of ANCs or WOPN, a step-up approach of antibiotics, image-guided drainage, followed by surgical intervention, if necessary, is indicated.	Moderate	Strong
Pancreatic pseudocysts that are asymptomatic should be managed nonoperatively. Intervention is indicated in pseudocysts that are symptomatic, infected, or increasing in size on serial imaging.	Moderate	Strong
Endoscopic retrograde cholangiopancreatography (ERCP) should be performed early (within 24–48 h) in patients with acute gallstone pancreatitis associated with bile duct obstruction or cholangitis. In unstable patients with severe acute gallstone pancreatitis and associated bile duct obstruction or cholangitis, placement of a percutaneous transhepatic gallbladder drainage tube should be considered if ERCP is not safely feasible.	Moderate–high	Strong
Cholecystectomy should be performed during the index admission in patients who have mild acute pancreatitis and delayed until clinical resolution in patients who have severe acute pancreatitis.	Moderate	Strong
If cholecystectomy cannot be performed during the index admission owing to medical comorbidities, patients with acute gallstone pancreatitis should undergo ERCP with sphincterotomy before discharge.	Low	Weak

2. Assessment of severity

2.1 A serum C-reactive protein (CRP) level of 14 286 nmol/L (150 mg/dL) or greater at baseline or in the first 72 hours is suggestive of severe acute pancreatitis and is predictive of a worse clinical course. Thus, CRP should be assessed at admission and daily for the first 72 hours after admission.

2.2 Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scores should be calculated on admission and daily for the first 72 hours after admission. An APACHE II Score of 8 or higher at baseline or in the first 72 hours is suggestive of severe acute pancreatitis and is predictive of a worse clinical course.

2.3 Severe acute pancreatitis should be diagnosed if a patient exhibits signs of persistent organ failure for more than 48 hours despite adequate intravenous fluid resuscitation.

3. Supportive care

3.1 Supportive care, including resuscitation with isotonic intravenous fluids (e.g., Ringer's Lactate solution), pain control and mobilization should be the mainstay of treatment of patients with mild acute pancreatitis.

3.2 Careful consideration of transfer to a monitored unit should be made in patients with 1) severe acute pancreatitis based on an APACHE II Score greater than 8, CRP greater than 14 286 nmol/L (150 mg/L), or organ dysfunction for more than 48 hours despite adequate resuscitation; 2) evidence of present or evolving organ dysfunction defined as follows

- Respiratory ($PaO_2/FiO_2 \leq 300$ or respiratory rate > 20 breaths per min)
- Cardiovascular (hypotension despite aggressive fluid resuscitation [systolic blood pressure (sBP) < 90 mm Hg off of inotropic support or drop of sBP > 40], need for vasopressors [not fluid responsive], or pH < 7.3)
- Renal (≥ 1.5-fold increase in serum creatinine over 7 d, increase of ≥ 26.5 μmol in serum creatinine over 48 h, urine output < 0.5mL/kg/h for ≥ 6 h);

and/or 3) the need for aggressive, ongoing fluid resuscitation defined as evidence of severe hemoconcentration (hemoglobin [Hb] > 160, hematocrit [HCT] > 0.500). Patients with 1 or more of the above criteria and a body mass index (BMI) above 30 (or BMI > 25 in Asian populations) should be monitored carefully, with a lower threshold for transfer to a monitored unit given the worse course of disease in the obese patient population.

4. Nutrition

4.1 Patients who present with mild acute pancreatitis should receive a regular diet on admission. If patients are unable to tolerate an oral diet owing to abdominal pain, nausea, vomiting, or ileus, they may be allowed to self-advance their diet from withholding oral food and fluids (NPO) to a regular diet as tolerated.

4.2 In patients with severe acute pancreatitis, enteral nutrition should be commenced as soon as possible following admission (within 48 h). A nasojejunal tube is not superior to a nasogastric feeding tube; thus commencement of feeds should not be delayed for the purpose of placing a nasojejunal feeding tube. Enteral feeding is recommended over parenteral nutrition.

5. Prophylactic antibiotics

5.1 Prophylactic antibiotics are not recommended in patients with mild or severe acute pancreatitis.

6. Diagnosis and management of local complications of acute pancreatitis

6.1 Repeat CT should be considered with new (or unresolving) evidence of infection (e.g., leukocytosis, fever) without a known source, new inability to tolerate oral/enteral feeds, change in hemodynamic status, or evidence of bleeding.

6.2 Patients who have extensive necrotizing acute pancreatitis, who show no clinical signs of improvement following appropriate initial management, or in whom other complications develop should be managed in consultation with, or at institutions with therapeutic endoscopy, interventional radiology, surgical and intensive care expertise in dealing with severe acute pancreatitis.

6.3 Patients with acute peripancreatic fluid collections with no radiological or clinical suspicion of sepsis should be observed, and image-guided fine needle aspiration (FNA) should be avoided owing to the risk of introducing infection into a sterile collection.

6.4 When there is radiological or clinical suspicion of infected necrosis in patients with acute necrotic collections (ANCs) or walled-off pancreatic necrosis (WOPN), image-guided FNA with culture should be performed to distinguish infected from sterile necrosis.

6.5 Sterile necrosis based on negative FNA and/or stable clinical picture should be managed nonoperatively, and antibiotics are not indicated. The exception is unstable patients in whom sepsis is suspected but no source has been identified; in these patients, treatment

with broad-spectrum antibiotics on speculation may be indicated while an appropriate workup (bacterial and fungal cultures, CT) is carried out.

6.6 Antibiotics should be prescribed only in patients with infected necrosis confirmed by FNA or if there is gas within a collection visualized on CT scan. Antimicrobial therapy should be tailored to FNA culture speciation and sensitivities; however, empiric treatment with antibiotics active against the most common pathogens in infected pancreatic necrosis (*Escherichia coli*, *Bacteroides species*, *Enterobacter species*, *Klebsiella species* and *Streptococcus faecalis* as well as other gram positive organisms, such as *Staphylococcus epidermidis* and *Staphylococcus aureus*) may be considered until final culture results are available.

6.7 In patients with FNA-confirmed infections of ANCs or WOPN, a step-up approach of antibiotics and image-guided drainage, followed by surgical intervention if necessary, is indicated. Surgical consultation should occur early; however, surgical intervention should be delayed until later in the course of disease whenever possible. Minimally invasive image-guided or endoscopic drainage is recommended as first line therapy, and multiple drains may be necessary. Surgery should be considered for patients in whom less invasive approaches fail, but should be delayed long enough to allow demarcation of necrotic pancreatic tissue.

6.8 Pancreatic pseudocysts that are asymptomatic should be managed nonoperatively. Intervention is indicated in pseudocysts that are symptomatic, infected, or increasing in size on serial imaging, and should be performed in a high-volume centre.

7. Management of patients with acute gallstone pancreatitis

7.1 Endoscopic retrograde cholangiopancreatography (ERCP) should be performed early (within 24–48 h) in patients with acute gallstone pancreatitis associated with bile duct obstruction or cholangitis. In unstable patients with severe acute gallstone pancreatitis and associated bile duct obstruction or cholangitis, placement of a percutaneous transhepatic gallbladder drainage tube should be considered if ERCP is not safely feasible.

7.2 Cholecystectomy should be performed during the index admission in patients who have mild acute pancreatitis and should be delayed until clinical resolution in patients who have severe acute pancreatitis.

7.3 If cholecystectomy is contraindicated in patients because of medical comorbidities, ERCP and sphincterotomy should be considered prior to discharge in patients with acute gall stone pancreatitis.

SUMMARY OF THE EVIDENCE

Diagnosis of acute pancreatitis

Serum lipase has a slightly higher sensitivity for detection of acute pancreatitis, and elevations occur earlier and last longer than with elevations in serum amylase.[12,13] One study demonstrated that at day 0–1 from onset of symptoms, serum lipase had a sensitivity approaching 100% compared with 95% for serum amylase.[13] For days 2–3 at a sensitivity set to 85%, the specificity of lipase was 82% compared with 68% for amylase. Serum lipase is therefore especially useful in patients who present late to hospital. Serum lipase is also more sensitive than serum amylase in patients with acute pancreatitis secondary to alcohol overuse.[12] Furthermore, simultaneous determination of serum lipase and amylase only marginally improve the diagnosis of acute pancreatitis in patients with acute abdominal pain.[13]

Biliary stones and alcohol overuse are the causes of acute pancreatitis in 70%–80% of cases.[14] It is important to distinguish between these etiologies owing to differences in management. Right upper quadrant ultrasonography is the primary imaging modality for suspected acute biliary pancreatitis owing to its low cost, availability and lack of associated radiation exposure.[15] Ultrasonography has a sensitivity and specificity greater than 95% in the detection of gallstones, although the sensitivity may be slightly lower in the context of ileus with bowel distension, commonly associated with acute pancreatitis.[16–19] Ultrasonography can also identify gallbladder wall thickening and edema, gallbladder sludge, pericholecystic fluid and a sonographic Murphy sign, consistent with acute cholecystitis. When these signs are present, the positive predictive value of ultrasonography in the diagnosis of acute cholecystitis is greater than 90%, and additional studies are rarely needed.[20]

Magnetic resonance cholangiopancreatography is useful in identifying CBD stones and delineating pancreatic and biliary tract anatomy. A systematic review that included a total of 67 studies found that the overall sensitivity and specificity of MRCP to diagnose biliary obstruction were 95% and 97%, respectively. Sensitivity was slightly lower, at 92%, for detection of biliary stones.[21] However, the cost of MRCP should limit its use in the diagnosis of gallstones or acute cholecystitis especially with the availability and utility of ultrasonography for the same purpose.[22]

In severe disease, CT is useful to distinguish between interstitial acute pancreatitis and necrotizing acute pancreatitis and to rule out local complications.[23] However, in acute pancreatitis these distinctions typically occur more than 3–4 days from onset of symptoms, which makes CT of limited use on admission unless there is a broad differential diagnosis that must be narrowed.[23,24]

Assessment of severity

Levels of serum CRP above 14 286 nmol/L (150 mg/dL) at 48 hours from admission help discriminate severe from mild disease. At 48 hours, serum CRP levels above 14 286 nmol/L (150 mg/dL) have a sensitivity, specificity, positive predictive value and negative predictive value of 80%, 76%, 67%, and 86%, respectively, for severe acute pancreatitis.[25] Levels greater than 17 143 nmol/L (180 mg/dL) within the first 72 hours of disease onset have been correlated with the presence of necrosis with the sensitivity and specificity both greater than 80%. Serum CRP generally peaks 36–72 hours after disease onset, so the test is not helpful in assessing severity on admission.[26,27] C-reactive protein rises steadily in relation to the severity of acute pancreatitis and is inexpensive to measure, and testing is readily available.[28–30]

A variety of reports have correlated a higher APACHE II Score at admission and during the first 72 hours with a higher mortality (< 4% with an APACHE II Score < 8 and 11%–18% with an APACHE II Score ≥ 8).[31–37] The advantage of using the APACHE II Score is the availability of this information within the first 24 hours and daily thereafter. In general, an APACHE II Score that increases during the first 48 hours is strongly predictive of the development of severe acute pancreatitis, whereas an APACHE II Score that decreases within the first 48 hours strongly predicts mild acute pancreatitis. There are some limitations in the ability of the APACHE II Score to stratify patients for disease severity. For example, studies have shown that it has limited ability to distinguish between interstitial and necrotizing acute pancreatitis, which confer different prognoses.[36,38,39] At 24 hours, the Score also has limited utility. In a recent report, APACHE II Scores generated within the first 24 hours had a positive predictive value of only 43% and negative predictive value of 86% for severe acute pancreatitis.[40] Even with its limitations, a study of 49 patients found that generic measures of disease severity like the APACHE II Score were superior to disease-specific scoring systems in predicting mortality.[41] For instance, the Ranson score was found to be a poor predictor of severity in a meta-analysis of 110 studies.[42]

The organ failure–based criteria for the prediction of severity in acute pancreatitis are taken, in part, from the modified Multiple Organ Dysfunction Score[43] presented by Banks and colleagues[44] in their revision of the Atlanta Classification. A diagnosis of severe acute pancreatitis should also be made if a patient exhibits signs of persistent organ failure for more than 48 hours despite adequate intravenous fluid resuscitation. In a study of 174 patients who experienced early (within the first week) organ failure due to acute pancreatitis, Johnson and Abu-Hilal[45] examined the mortality and morbidity associated with transient organ failure (resolving in < 48 h) and persistent organ failure (lasting > 48 h). In the transient organ failure group (n = 71) mortality was 1%, and 29% of these patients went on to experience local complications of acute pancreatitis; in the persistent organ failure group (n = 103) mortality was 35%, and 77% of patients experienced a local complication.[45] In a study of 759 patients with acute pancreatitis, patients with systemic inflammatory response syndrome (SIRS) lasting for more than 48 hours were demonstrated to have a significantly higher rate of multiorgan dysfunction (as determined by the mean Marshall Score) and death than those with transient SIRS lasting less than 48 hours (4 [25.4%] v. 3 [8%], $p < 0.001$).[46]

In a recent meta-analysis of 12 clinical studies examining the impact of obesity on severity of acute pancreatitis, Chen and colleagues[47] demonstrated a significantly increased risk of severe acute pancreatitis (relative risk [RR] 2.20, 95% confidence interval [CI] 1.82–2.66), local complications (RR 2.68, 95% CI 2.09–3.43), systemic complications (RR 2.14, 95% CI 1.42–3.21) and in-hospital mortality (RR 2.59, 95% CI 1.66–4.03) in obese compared with nonobese patients. Owing to these increased risks, special consideration should be given to patients with suspected severe acute pancreatitis who have a BMI greater than 30 (or a BMI > 25 in Asian populations).

Supportive care

Animal studies have shown that aggressive fluid replacement supports pancreatic microcirculation and prevents necrosis.[48] There have been no high-quality trials to test the effectiveness of aggressive fluid resuscitation in patients with acute pancreatitis, and the approach to fluid resuscitation in these patients remains an under-investigated topic.[49] However, poor outcomes, including more deaths and necrosis, have been reported in patients in whom there was hemoconcentration. In an observational study, necrotizing acute pancreatitis developed in all patients who received inadequate fluid replacement as measured by a rise in hematocrit at 24 hours.[50] Further, a recent randomized controlled trial (RCT)[51] compared the use of normal saline versus Ringer's Lactate in goal-directed and standard fluid resuscitation in patients with acute pancreatitis. In this RCT (n = 40), Wu and colleagues[51] found that after 24 hours of resuscitation there was an 84% reduction in the incidence of SIRS in patients resuscitated with Ringer's Lactate (p = 0.035) as well as a significant reduction in CRP from 9905 nmol/L (104 mg/dL) to 5143 nmol/L (54 mg/dL) when Ringer's Lactate was selected over normal saline (p = 0.02).

Pain control is an important part of the supportive management of patients with acute pancreatitis. Therefore, in the absence of any patient-specific contraindications, a multimodal analgesic regimen is recommended, including narcotics, nonsteroidal anti-inflammatories and acetaminophen.[52,53]

There are no studies assessing the impact of different models of critical care delivery and outcomes in patients with severe acute pancreatitis. However, a systematic review of 26 observational studies showed that critically ill patients cared for by an intensivist or using an intensivist

consultant model in a closed intensive care unit (ICU) had a shorter stay in the ICU and lower mortality than similar patients cared for in units without such staffing patterns.[54]

Nutrition

The underlying pathogenesis of acute pancreatitis is the premature activation of proteolytic enzymes resulting in the autodigestion of the pancreas. In the past, it was accepted practice that bowel rest would limit the inflammation associated with this process.[55] Recently, however, a series of RCTs have convincingly shown that early oral/enteral feeding in patients with acute pancreatitis is not associated with adverse effects and may be associated with substantial decreases in pain, opioid usage and food intolerance.[56–58] Furthermore, Eckerwall and colleagues[59] demonstrated that oral feeding on admission for mild acute pancreatitis was associated with a significant decrease in length of stay from 6 to 4 days ($p = 0.047$) compared with withholding oral food and fluids.[59] The major benefits from early feeding appear to be effective only if feeding is commenced within the first 48 hours following admission,[60] and the current recommendation based on a 2010 meta-analysis of 32 RCTs is to commence oral feeding at the time of admission if tolerated or within the first 24 hours.[60,61] Finally, a low-fat diet was shown to be preferable to clear fluids on admission for mild acute pancreatitis owing to a higher caloric intake with no associated adverse effects.[57,58] There is no evidence to suggest that a low-fat diet is preferable to a regular diet.

A 2010 Cochrane meta-analysis of 8 RCTs involving 348 patients comparing enteral nutrition to total parenteral nutrition for acute pancreatitis showed reduced mortality (RR 0.50, 95% CI 0.28–0.91), multiorgan failure (RR 0.55, 95% CI 0.37–0.81), systemic infection (RR 0.39, 95% CI 0.23–0.65), operative interventions (RR 0.44, 95% CI 0.29–0.67), local septic complications (RR 0.74, 95% CI 0.40–1.35), and other local complications (RR 0.70, 95% CI 0.43–1.13).[62] Mean length of hospital stay was reduced by 2.37 days in the enteral nutrition compared with the total parenteral nutrition group (95% CI –7.18 to 2.44). Furthermore, a subgroup analysis of enteral versus total parenteral nutrition in patients with severe acute pancreatitis showed an RR for death of 0.18 (95% CI 0.06–0.58) and an RR for multiorgan failure of 0.46 (95% CI 0.16–1.29). Several meta-analyses have shown similar results, with significant reductions in infectious complications, mortality and multiorgan dysfunction when enteral nutrition is commenced within the first 48 hours following admission.[61,63,64]

A meta-analysis[65] of 4 prospective studies of patients with predicted severe acute pancreatitis ($n = 92$) demonstrated no change in intolerance of feeding (RR 1.09, 95% CI 0.46–2.59, $p = 0.84$) or in mortality (RR 0.77, 95% CI 0.37– 1.62, $p = 0.5$) when given enteral feeds by nasogastric feeding tube versus nasojejunal feeding tube. In a more recent meta-analysis of 3 RCTs ($n = 157$), Chang and colleagues[66] found no significant differences in mortality (RR 0.69, 95% CI 0.37–1.29, $p = 0.25$), tracheal aspiration (RR 0.46, 95% CI 0.14–1.53, $p = 0.20$), diarrhea (RR 1.43, 95% CI 0.59–3.45, $p = 0.43$), exacerbation of pain (RR 0.94, 95% CI 0.32–2.70, $p = 0.90$) and meeting energy balance (RR 1.00, 95% CI 0.92–1.09, $p = 0.97$) between patients fed through nasogastric and nasojejunal feeding tubes. While no high-quality RCTs exist on this topic, to date there has been no evidence to suggest that enteral feeds should be delayed for the purposes of acquiring a nasojejunal feeding tube, especially in light of morbidity and mortality benefits of commencing enteral feeds within the first 48 hours.

Although semi-elemental, immune-enhanced and probiotic enteral feeds showed initial promise in the management of severe acute pancreatitis, meta-analyses still indicate that there is insufficient evidence to recommend the use of any of these nutritional formulations at this time.[61,67,68] Given its promise in the context of other critically ill and septic patients,[69–71] the use of probiotics in the management of acute pancreatitis may yet prove effective as research continues.

Prophylactic antibiotics

A 2010 meta-analysis of 7 RCTs involving 404 patients comparing prophylactic antibiotics versus placebo in CT-proven necrotizing acute pancreatitis concluded that there was no statistically significant reduction of mortality with therapy (8.4% in the antibiotic group v. 14.4% in controls, $p = 0.07$), nor a significant reduction in infection rates of pancreatic necrosis (19.7% in the antibiotic group v. 24.4% in controls, $p = 0.47$). Nonpancreatic infection rates (23.7% in the antibiotic group v. 36% in controls, $p = 0.08$) and overall infections (37.5% in the antibiotic group v. 51.9% in controls, $p = 0.12$) were not significantly reduced with prophylactic antibiotics. The need for operative treatment and fungal infections were not significantly different.[72]

Similar results were found in a 2008 meta-analysis of 7 RCTs involving 467 patients with CT-proven necrotizing acute pancreatitis comparing prophylactic antibiotics with placebo or no treatment. The rate of infected pancreatic necrosis was not significantly different (17.8% in the antibiotic group v. 22.9% in controls, RR 0.81, 95% CI 0.54–1.22). There was a nonsignificant decrease in mortality in the antibiotic group compared with the control group (9.3% v. 15.2%, RR 0.70, 95% CI 0.42–1.17). Subsequent subgroup analysis confirmed that antibiotics were not significantly superior to placebo or no treatment in reducing the rate of infected necrosis or mortality.[73]

A 2012 meta-analysis of 11 RCTs looking at the efficacy of prophylactic antibiotics in acute pancreatitis calculated the number needed to treat to be 1429,[74] and yet another meta-analysis of 14 RCTs ($n = 841$) showed no statistically significant reduction in mortality (RR 0.74, 95% CI 0.50–1.07), incidence of infected pancreatic necrosis (RR 0.78, 95% CI 0.60–1.02), incidence of nonpancreatic infections

(RR 0.70, 95% CI 0.46–1.06), or in surgical interventions (RR 0.93, 95% CI 0.72–1.20).[75]

In light of the lack of demonstrated benefit of prophylactic antibiotics in the treatment of acute pancreatitis, the adverse effects of this practice must be carefully considered. In a prospective, randomized controlled trial (n = 92), Maraví-Poma and colleages[76] demonstrated a 3-fold increase in the incidence of local and systemic fungal infection with *Candida albicans* (from 7% to 22%) in patients with prolonged treatment with prophylactic antibiotics, a finding consistent with those of other similar studies.[77–79] In addition, overuse of antibiotics is associated with the increased risk of antibiotic-associated diarrhea and *Clostridium difficile* colitis[80] and with the selection of resistant organisms,[81] all of which suggest that the adverse effects of prophylactic antibiotic coverage outweighs any benefit offered by the practice.

Diagnosis and management of local complications of acute pancreatitis

Two recent review articles on acute pancreatitis have summarized the importance of managing patients with complications of acute pancreatitis at high-volume centres in which all services are well versed in the multidisciplinary step up approach to severe and/or complicated disease.[82,83]

Computed tomography evidence of necrosis has been shown to correlate with the risk of other local and systemic complications.[38,84,85] Local complications that can be recognized on abdominal CT scans include peripancreatic fluid collections, gastrointestinal and biliary complications (e.g., obstructions), solid organ involvement (e.g., splenic infarct), vascular complications (e.g., pseudoaneurysms, splenic vein thrombosis) and pancreatic ascites.[86–88]

Fine needle aspiration has been established as an accurate, safe and reliable technique for identification of infected acute peripancreatic fluid collections (APFCs), pancreatic pseudocysts, ANCs and WOPN.[84,89–91] However, FNA of pancreatic pseudocysts, APFCs, ANCs and WOPN should not be performed in the absence of a clinically or radiologically suspected infection owing to the small but documented risk of introducing an FNA-associated infection into a previously sterile collection.[92,93]

Elevations in white blood cell count and temperature may occur in the context of sterile necrosis and be similar to those seen in patients with infected necrosis;[36] therefore, it is difficult to distinguish between these conditions clinically. Fine needle aspiration has been established as an accurate, safe and reliable technique for identification of infected necrosis.[84,89–91] A 1995 retrospective observational study[90] assessed the value of CT-guided FNA in 104 patients with acute pancreatitis suspected of having pancreatic infection on the basis of systemic toxicity and CT evidence of severe acute pancreatitis. Cultures were positive in 58 out of 58 aspirates from the 51 patients with CT scans suspicious for infection, all but 2 of which were confirmed surgically (2 patients died without confirmation). Of the 53 patients with CT imaging suggestive of sterile acute pancreatitis, all but 2 aspirates judged to be sterile by FNA were validated on the basis of negative cultures obtained surgically or by clinical resolution of acute pancreatitis without the need for surgery (2 patients died without confirmation). There were no complications. These findings are consistent with those of other studies.[84,89,91]

Elevations in white blood cell count and temperature may occur in sterile necrosis and be similar to those seen in patients with infected necrosis.[36] Therefore, it is difficult to distinguish between these conditions clinically, and if infected necrosis is suspected, an FNA is indicated to rule out infection. Most patients with sterile necrosis respond to conservative medical management.[84,94] For these patients, there have been several retrospective reports suggesting that a delay in surgical necrosectomy and at times a total avoidance of surgery results in less morbidity and mortality than early surgical débridement.[95–101] Second, when sterile necrosis is debrided surgically, a common sequela is the development of infected necrosis and the need for additional surgery.[96,101–103] In at least 1 report, patients so treated had a very high mortality.[101] Finally, in a randomized controlled trial[95] that compared early to late surgery in a small number of patients with sterile necrosis, there was a trend toward greater mortality among those operated within the first 3 days after admission.

Antibiotics should be prescribed only in patients with infected necrosis confirmed by FNA or if there is gas within a collection visualized on CT scan. Antimicrobial therapy should be tailored to FNA culture speciation and sensitivities; however, empiric treatment with antibiotics active against the most common pathogens in infected pancreatic necrosis (*E. coli*, *Bacteroides species*, *Enterobacter species*, *Klebsiella species* and *S. faecalis* as well as other gram-positive organisms such as *S. epidermidis* and *S. aureus*[103,104]) may be considered until final culture results are available.

Although insufficient evidence exists to make definitive recommendations regarding empiric antimicrobial therapy choices in infected pancreatic necrosis, a number of studies have looked at the pancreatic penetration of various antibiotics. Imipenem and ertapenem have both been shown to penetrate pancreatic tissue and pancreatic fluid at levels exceeding the minimum inhibitory concentration (MIC_{90}) for the most commonly seen bacteria after as little as a single intravenous dose.[105,106] Similar findings were documented for moxifloxacin, with concentrations greater than the MIC_{90} after a dose of 400 mg, either oral or intravenous.[107] An in vitro study of the most commonly isolated bacteria from pancreatic necrosis — *E. coli*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Bacteroides fragilis* — compared the effectiveness of imipenem, ertapenem and moxifloxacin against these pathogens. While all 3 antibiotics demonstrated good coverage in this in vitro acute pancreatitis

model, moxifloxacin demonstrated superior activity against *Enterococci* and slightly better anaerobic coverage.[108]

The mortality of patients with infected pancreatic necrosis is higher than 30%, and up to 80% of fatal outcomes in patients with acute pancreatitis are due to septic complications resulting from pancreatic infection.[24,109,110] The nonoperative management of infected pancreatic necrosis associated with multiple organ failure has a mortality of up to 100%.[111] Surgical treatment of patients with infected pancreatic necrosis is associated with mortality as low as 10%–30% in some specialized centres.[84,94,112] However, the benefit of a step-up approach to surgery was shown in a 2010 RCT that included 88 patients. Patients with confirmed or suspected infected necrosis were randomized to open necrosectomy or a step-up approach of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. New-onset multiorgan failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% v. 40%, $p = 0.002$). Mortality did not differ significantly between groups (19% v. 16%, $p = 0.70$). Patients assigned to the step-up approach had a significantly lower rate of incisional hernias (7% v. 24%, $p = 0.03$) and new-onset diabetes (16% v. 38%, $p = 0.02$).[113]

A small RCT by Mier and colleagues[95] compared mortality among 41 patients with fulminant acute pancreatitis undergoing either early (48–72 h after admission) or late necrosectomy (≥ 12 d after admission).[95] The mortality odds ratio for the early surgery cohort compared with the late necrosectomy cohort was 3.94, and the study was stopped owing to this finding despite the fact that the small sample size resulted in a lack of statistical significance. Wittau and colleagues[114] reported a similar and statistically significant reduction in mortality from 41% to 18% ($p = 0.026$) when necrosectomy was performed early in the course of illness (< 2–3 wk) compared with a delayed approach to surgical intervention (≥ 29 d).[114] Accepted indications for necrosectomy still include persistent evidence of organ dysfunction and sepsis, or patients requiring ongoing treatment in the ICU for more than 1 month after admission for severe acute pancreatitis.

Walled-off pancreatic necrosis is the result of the organization of ANCs or APFCs over time by a wall of granulation or fibrotic tissue without epithelial lining.[44,115] In the context of an FNA-proven infected WOPN, surgical intervention, if indicated, should be delayed until after the third or fourth week to allow demarcation of the viable pancreatic tissue and peripancreatic necrosis.[116] If intervention is required before the fourth week, percutaneous drainage serves as a bridge to a more definitive procedure.[115] Multiple treatment modalities have been described, including percutaneous retroperitoneal or endoscopic drainage as well as open or laparoscopic surgical approaches. Minimally invasive approaches (laparoscopic, percutaneous retroperitoneal, endoscopic) are equally effective as open surgical approach.[117–119]

A pancreatic pseudocyst is a collection of pancreatic fluid (either direct leakage from the inflamed gland or disruption of the pancreatic duct) enclosed by a nonepithelialized wall of granulation or fibrous tissue. They usually evolve more than 4 weeks after the onset of acute pancreatitis and contain pancreatic enzyme-rich fluid. They are most often sterile but can become infected.[44,120] Half of all pseudocysts resolve spontaneously.[121,122] Neither size nor duration of the pseudocyst are predictive of the natural course.[123,124] Clinical signs of sepsis or the presence of air bubbles in a pseudocyst indicate potential infection. At this point, aspiration of the fluid with gram stain, culture and sensitivities is indicated. The most common bacteria cultured in an infected pseudocyst are enteric microorganisms, such as *E. coli*, *Bacteroides species*, *Enterobacter species*, *Klebsiella species* and *S. faecalis* as well as other gram-positive organisms, such as *S. epidermidis* and *S. aureus*.[103,104] General indications for intervention are symptomatic pseudocysts, complications or infection of a pseudocyst, or increasing size on serial imaging.[125–128] Many options are available for the management of pancreatic pseudocysts, including percutaneous, endoscopic or surgical drainage (open and laparoscopic) and creation of a cystogastrostomy (endoscopically or surgicallly). These procedures should be performed at high-volume centres with integrated multidisciplinary teams.

Management of acute gallstone pancreatitis

A 2012 Cochrane meta-analysis[129] included RCTs comparing early routine ERCP versus early conservative management with or without selective use of ERCP in patients with suspected acute gallstone pancreatitis. There were 5 RCTs with a total of 644 patients. Overall, there were no statistically significant differences between the 2 treatment strategies in mortality (RR 0.74, 95% CI 0.18–3.03), local (RR 0.86, 95% CI 0.52–1.43) or systemic complications (RR 0.59, 95% CI 0.31–1.11) as defined by the Atlanta Classification. Among trials that included patients with cholangitis, the early routine ERCP strategy significantly reduced mortality (RR 0.20, 95% CI 0.06–0.68), local (RR 0.45, 95% CI 0.20–0.99) and systemic complications (RR 0.37, 95% CI 0.18–0.78) as defined by the Atlanta Classification. Among trials that included patients with biliary obstruction, the early routine ERCP strategy was associated with a significant reduction in local complications as defined by authors of the primary study (RR 0.54, 95% CI 0.32–0.91), and a nonsignificant trend toward reduction of local (RR 0.53, 95% CI 0.26–1.07) and systemic complications (RR 0.56, 95% CI 0.30–1.02) as defined by the Atlanta Classification. Complications of ERCP were infrequent.

In an RCT from China ($n = 101$),[130] patients with severe acute gallstone pancreatitis were randomized to early treatment (within 72 h of onset) with ERCP or image-guided

percutaneous transhepatic gallbladder drainage (PTGD). Success rates were comparable between the ERCP and PTGD (92% v. 96%, respectively), and 4-month mortality ($p = 0.80$), local complications ($p = 0.59$) and systemic complications ($p = 0.51$) did not differ significantly. The author concluded that PTGD is a safe, effective and minimally invasive option that should be considered for all patients with severe acute gallstone pancreatitis who are poor candidates for or who are unable to tolerate ERCP.[130]

A systematic review[131] of 8 cohort studies ($n = 948$) and 1 RCT ($n = 50$) revealed that while the readmission rate for gallstone disease in patients admitted for acute gallstone pancreatitis and discharged without cholecystectomy was 18% within the first 58 days after discharge, it was 0% in the cohort that underwent index admission cholecystectomy ($p < 0.001$). These results are supported by several retrospective studies that also cited significantly higher recurrence rates of gallstone disease (15%–32%) in patients who did not undergo index admission cholecystectomy.[132–134] The majority of these recurrent attacks occurred before the time of interval cholecystectomy.[133,134]

In an RCT that included 50 patients with mild acute gallstone pancreatitis, laparoscopic cholecystectomy performed within 48 hours of admission resulted in a shorter hospital stay (mean 3.5 [95% CI 2.7–4.3] d, median 3 [IQR 2–4] d) than one performed after resolution of pain and laboratory abnormalities (mean 5.8 [95% CI 3.8–7.9] d, median 4 [IQR 4–6] d, $p = 0.002$).[135] A second study demonstrated similar findings, with a significant reduction in the mean total length of stay from 7 to 5 days ($p < 0.001$).[134]

While studies have demonstrated no increase in complication rates or mortality in patients with acute gallstone pancreatitis who underwent early versus late cholecystectomy,[131,136] special consideration should be given to patients admitted for severe necrotizing acute pancreatitis and/or requiring ICU admission. In this patient population, delaying cholecystectomy for at least 3 weeks may be reasonable because of an increased risk of infection.[137]

High recurrence rates of gallstone disease in patients admitted for acute gallstone pancreatitis and discharged without cholecystectomy has prompted several studies addressing the effectiveness of ERCP and sphincterotomy to reduce this risk. In a prospective study of 233 patients with acute gallstone pancreatitis, a subgroup analysis of patients discharged without undergoing cholecystectomy revealed that 37% of patients discharged with no intervention had recurrent gallstone disease within 30 days compared with 0% of patients who underwent ERCP and sphincterotomy alone ($p = 0.019$).[132] In a retrospective analysis of 1119 patients admitted for acute gallstone pancreatitis, Hwang and colleagues[133] reported a reduction of recurrent gallstone disease from 17% to 8% ($p < 0.001$) with ERCP and sphincterotomy alone, as opposed to no intervention in individuals discharged home without cholecystectomy.[133] A systematic review of 8 cohort studies and 1 RCT demonstrated a similar reduction in biliary events from 24% to 10% ($p < 0.001$) when patients not undergoing index admission cholecystectomy underwent ERCP and sphincterotomy before discharge.[131] These data strongly support the consideration of ERCP with sphincterotomy for patients unable to tolerate surgery on the index admission owing to comorbidities or deconditioning.

All data regarding the use of ERCP with sphincterotomy to prevent recurrent complications of gallstone disease have been generated in patients with mild to moderate acute gallstone pancreatitis, and currently, there is a lack of evidence on which to base definitive recommendations for the management of patients with severe and complicated acute gallstone pancreatitis.

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