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Acute Pancreatitis
A Review

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IMPORTANCE In the United States, acute pancreatitis is one of the leading causes of hospital admission from gastrointestinal diseases, with approximately 300 000 emergency department visits each year. Outcomes from acute pancreatitis are influenced by risk stratification, fluid and nutritional management, and follow-up care and risk-reduction strategies, which are the subject of this review.

OBSERVATIONS MEDLINE was searched via PubMed as was the Cochrane databases for English-language studies published between January 2009 and August 2020 for current recommendations for predictive scoring tools, fluid management and nutrition, and follow-up and risk-reduction strategies for acute pancreatitis. Several scoring systems, such as the Bedside Index of Severity in Acute Pancreatitis (BISAP) and the Acute Physiology and Chronic Health Evaluation (APACHE) II tools, have good predictive capabilities for disease severity (mild, moderately severe, and severe per the revised Atlanta classification) and mortality, but no one tool works well for all forms of acute pancreatitis. Early and aggressive fluid resuscitation and early enteral nutrition are associated with lower rates of mortality and infectious complications, yet the optimal type and rate of fluid resuscitation have yet to be determined. The underlying etiology of acute pancreatitis should be sought in all patients, and risk-reduction strategies, such as cholecystectomy and alcohol cessation counseling, should be used during and after hospitalization for acute pancreatitis.

CONCLUSIONS AND RELEVANCE Acute pancreatitis is a complex disease that varies in severity and course. Prompt diagnosis and stratification of severity influence proper management. Scoring systems are useful adjuncts but should not supersede clinical judgment. Fluid management and nutrition are very important aspects of care for acute pancreatitis.

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Acute pancreatitis is one of the most common gastrointestinal conditions that results in hospital admission in the United States. The incidence of acute pancreatitis is estimated at 110 to 140 per 100 000 population, with an estimated more than 300 000 US emergency department visits per year.[1,2] Admissions due to acute pancreatitis have increased from 9.48 cases per 1000 hospitalizations in 2002 to 12.19 in 2013, with a median hospital cost of nearly $7000 per hospitalization.[3,4]

Acute pancreatitis is a complex disease with a variable course that is often difficult to predict early in its development (eBox in the Supplement). Approximately 80% of patients develop mild to moderately severe disease (absence of organ failure >48 hours).[5,6] However, one-fifth of patients develop severe disease, with a mortality rate of approximately 20%.[5,7] The purpose of this review is to summarize evidence regarding the recognition of disease severity, fluid and nutrition management, and risk-reduction methods for the prevention of recurrent disease.

Methods

PubMed and the Cochrane databases were searched for English-language studies published from January 2009 through August 2020 for randomized clinical trials (RCTs), meta-analyses, systematic reviews, and observational studies. Manual searches were performed of the references of selected articles, reviews, meta-analyses, and practice guidelines. Select studies prior to 2009 were included for historical context. Emphasis was given to RCTs and meta-analyses. All publications and citations included were mutually agreed on by the authors and selected for clinical importance and relevance with consideration to the general medical readership of *JAMA*. Sixty-six articles were included, which contained 8 RCTs, 12 meta-analyses, and 5 clinical guidelines.

Pathogenesis and Etiology

Acute pancreatitis is characterized by damage to the acinar cells, the functional units of the exocrine pancreas, precipitating inappropriate release and activation of trypsinogen to trypsin within the acini. This triggers the activation of other digestive enzymes, the kinin system, and the complement cascade resulting in autodigestion of the pancreatic parenchyma.[8,9] Pancreatic duct obstruction (eg, gallstone pancreatitis) is one of the more common causes of acinar damage, causing an increase in ductal pressure, interstitial edema, and accumulation of enzyme-rich fluid within the pancreatic tissue.[10] Alternatively, primary acinar injury may be caused by a variety of other factors, such as calcium, which regulates trypsin activation. Inappropriate release of

Box 1. Etiologies of Acute Pancreatitis

A. Etiologies of Acute Pancreatitis

Gallstones (21%-33%)[15a]
Alcohol (16%-27%)[15a]
Triglyceridemia (2%-5%)[4,16a]
Iatrogenic (ERCP/EUS)
Hypercalcemia
Infection
Hereditary
Autoimmune
Medications
Structural
- Pancreas divisum
- Tumors or cystic lesions

B. Select Medications Implicated in Acute Pancreatitis[17,18]

Acetaminophen
Acetaminophen/codeine
5-Aminosalicylate (mesalamine, sulfasalazine)
Amiodarone
Androgenic anabolic steroids
Azathioprine
Cannabis
Carbamazepine
Carbimazole
Cimetidine
Cisplatin
Clomiphene
Didanosine
Enalapril
Estrogen and related products
Furosemide
Isoniazid
Lamivudine
Losartan
Methyldopa
Metronidazole
Nadolol
Pravastatin
Perindopril
Procainamide
Pyritinol
Ranitidine
Rosuvastatin
Saxagliptin
Simvastatin
Sulindac
Tamoxifen
Telaprevir
Tetracycline
Trimethoprim/sulfamethoxazole
Valproic acid

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

[a] Percentages for the 3 most common etiologies in the United States are shown only.

intracellular calcium, enhanced entry of extracellular calcium, or defective calcium extrusion/reuptake mechanisms causes a sustained increase in cytosolic calcium in the acini. This elevation leads to premature activation of trypsinogen to trypsin, resulting in acinar injury and death.[11,12] Ethanol is a common cause of acute pancreatitis, but its pathogenesis remains unknown; there is evidence that it may disrupt multiple biochemical pathways within acinar cells.

Gallstone disease and alcohol are the 2 leading causes of acute pancreatitis. Other causes include hypertriglyceridemia (typically >1000 mg/dL), hypercalcemia, familial (hereditary) pancreatitis, and viral infections. Periampullary tumors, pancreatic head masses, and cystic lesions of the pancreas can cause obstruction of the pancreatic duct, impeding the flow of pancreatic enzymes, which may lead to inappropriate enzyme activation within the pancreas. Pancreas divisum and pancreatic strictures can also obstruct the pancreatic duct and cause pancreatitis. Acute pancreatitis can result from instrumentation of the ampulla and pancreatic duct following endoscopic retrograde cholangiopancreatography (ERCP)[13] and endoscopic ultrasound (EUS),[14] with a risk of 5% to 10% and less than 1%, respectively (**Box 1**). More than 500 medications have been implicated as a cause of acute pancreatitis and at least 30 of them have been shown to have a definite association, meaning that they cause acute pancreatitis on repeated administration of the medications when other possible causes are excluded (Box 1B).[17,18] The etiology of acute pancreatitis is not identified in many cases. Additional risk factors associated with acute pancreatitis include obesity, older age, smoking, and HIV-positive status.[5] The etiology of acute pancreatitis also varies geographically.[16] For example, in a recent meta-analysis, gallstone pancreatitis represented 26% of acute pancreatitis cases in the United States compared with 68% in Latin America.[15]

Acute pancreatitis is classified as 2 subtypes: interstitial edematous pancreatitis and necrotizing pancreatitis (**Box 2A**). Interstitial edematous pancreatitis is characterized by inflammation and edema of the pancreatic parenchyma and peripancreatic tissues. Necrotizing pancreatitis occurs when this process progresses to pancreatic or peripancreatic tissue death. Both forms of acute pancreatitis may be associated with the local complications of pancreatic fluid and solid collections. Acute peripancreatic fluid collections (APFCs) develop within 4 weeks of disease onset and contain mostly fluid; acute necrotic collections (ANCs) develop in necrotizing pancreatitis and contain solid and fluid components. Acute intrapancreatic collections are a result of necrotizing pancreatitis and are referred to as ANCs.[19] APFCs and ANCs that persist after 4 weeks from onset of disease are referred to as pseudocysts and walled-off necrosis, respectively (Box 2A and **Figure**). Peripancreatic and pancreatic collections may be secondarily infected and

Box 2. Revised Atlanta Classification Definitions

A. Morphologic Classification of Acute Pancreatitis and Pancreatic Collections

Interstitial Edematous Pancreatitis

Diffuse or localized enlargement of the pancreas with homogenous enhancement of the pancreatic parenchyma

Inflammatory changes of the peripancreatic fat

±Peripancreatic fluid (see "Collections" below)

Collections

<4 wk

APFC

Adjacent to the pancreas (no intrapancreatic extension)

Single or multiple

Homogenous collection with fluid density

No associated peripancreatic necrosis

Confined to normal fascial planes

>4 wk

Pseudocyst

Mature, encapsulated collection(s) of fluid with a well-defined wall outside the pancreas

Homogenous fluid density

No solid component

Necrotizing Pancreatitis

Necrosis often involving both the pancreatic parenchyma and peripancreatic tissue

Variable contrast enhancement pattern in the first few days

Nonenhancing areas should be considered necrosis after the first week of disease

May become secondarily infected

Collections

<4 wk

ANC

Involves the pancreatic parenchyma or peripancreatic tissues

Heterogenous and nonliquid density of varying degrees in different locations

>4 wk

WON

Mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined wall

Heterogeneous with liquid and nonliquid density with varying degrees of loculations

B. Diagnostic Criteria (2 of 3)

1. Abdominal pain consistent with acute pancreatitis
2. Elevated serum amylase or lipase >3 times the upper limit of normal
3. Characteristic findings of acute pancreatitis on imaging (eg, contrast-enhanced computed tomography, magnetic resonance imaging, and, less frequently, ultrasound)

C. Grades of Severity

Mild

1. No organ failure
2. No local or systemic complications

Moderately Severe

1. Organ failure that resolves within 48 h (transient organ failure) and/or
2. Local or systemic complications without persistent organ failure

Severe

1. Persistent organ failure (>48 h)
   Single organ failure
   Multiple organ failure

Abbreviations: ANC, acute necrotic collection; APFC, acute peripancreatic fluid collection; WON, walled-off necrosis.

described as infected ANC and infected walled-off necrosis. In addition to pancreatic collections, local complications also include gastric outlet dysfunction, splenic or portal vein thrombosis, and colonic necrosis.[20]

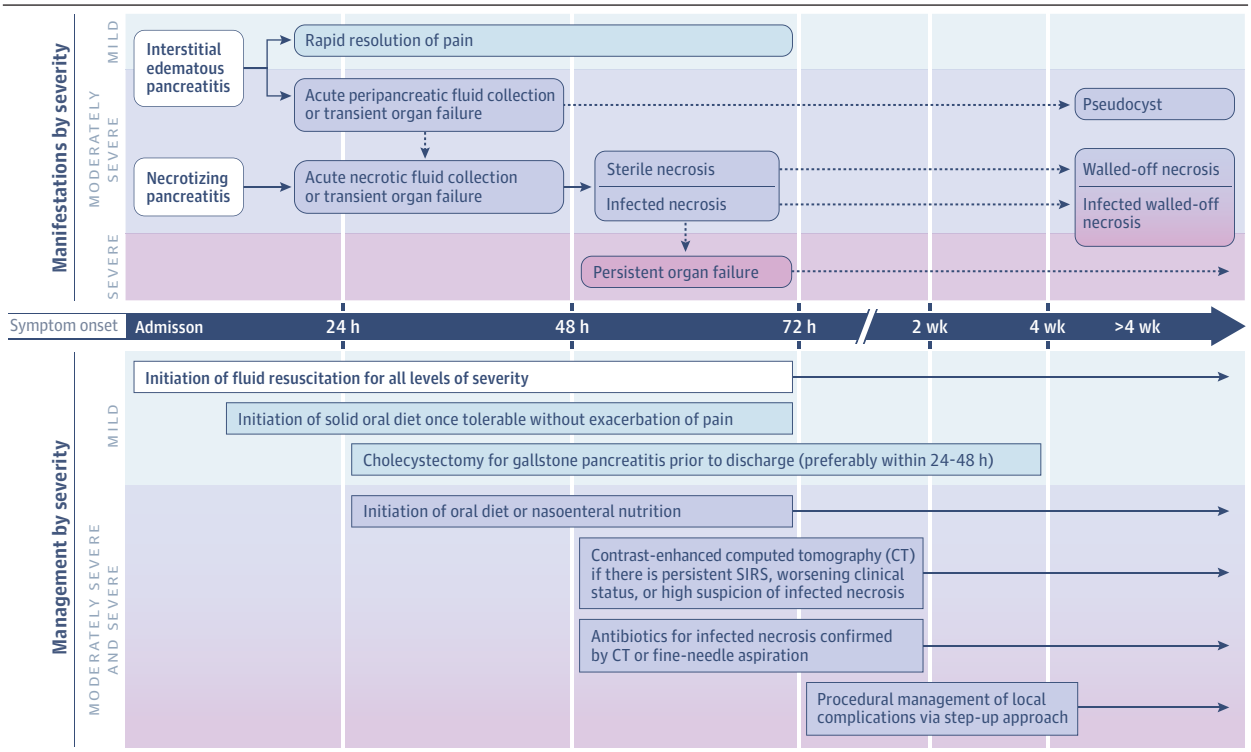
Clinical Presentation and Diagnosis

Abdominal pain is the most common presenting symptom. The pain is usually described as constant and often with radiation to the back that may be exacerbated by eating, drinking, or lying supine. Accompanying symptoms often include nausea, vomiting, and low- to moderate-grade fever. Evaluation of suspected acute pancreatitis begins with a comprehensive history and physical examination. Assessment should focus on a history of episodes of acute pancreatitis and risk factors, including biliary colic/gallstone disease, alcohol use, family history of acute or chronic pancreatitis, recent infections, trauma, insect bites, and new medications. This focused history can assist in identifying the underlying etiology.

Physical examination often reveals abdominal distention and decreased bowel sounds. Rebound tenderness is uncommon. Standard chemistries with amylase, lipase, and liver panel tests can help confirm the diagnosis of acute pancreatitis as well as identify underlying etiology (ie, hypercalcemia). An elevated direct bilirubin and/or alkaline phosphatase level may indicate the presence of a gallstone in the common bile duct (ie, choledocholithiasis) or that a stone recently passed. Additional testing with transabdominal ultrasound to evaluate for gallstones and serum triglyceride levels should also be obtained. IgG4 levels are helpful when autoimmune pancreatitis is suspected. Computed tomography (CT) or magnetic resonance imaging (MRI) may be indicated to evaluate for structural causes of acute pancreatitis, but this is not mandatory during initial management of the disease process. Patients with recurrent acute pancreatitis or family history of acute pancreatitis/chronic pancreatitis without an identifiable etiology with the aforementioned labs or imaging should be referred for genetic testing to evaluate for hereditary pancreatitis.

To diagnose acute pancreatitis, the revised Atlanta classification (RAC) requires 2 of the 3 following criteria be present: (1) abdominal pain suggestive of pancreatitis, (2) serum amylase and/or lipase greater than 3 times the upper limit of normal, (3) and cross-sectional imaging (CT or MRI) findings consistent with acute pancreatitis (Box 2B).[20] Acute pancreatitis can be diagnosed in about 80% of patients based on the presence of abdominal pain and elevated pancreatic enzymes only.[21] However, CT is a useful adjunct to confirm acute pancreatitis when the diagnosis is in question and to rule out other intra-abdominal conditions that can mimic acute pancreatitis such as a perforated duodenal ulcer.

Figure. Timeline, Manifestations, and Management of Acute Pancreatitis



SIRS indicates systemic inflammatory response syndrome.

Table 1. Modified Marshall Scoring System for Organ Dysfunction

	Score[a]				
Organ system	0	1	2	3	4
Respiratory (Pao_2/Fio_2)[b]	>400	301-400	201-300	101-200	<101
Kidney (serum creatinine), μmol/L	<134	134-169	170-310	311-439	>439
Kidney (serum creatinine), mg/dL	<1.4	1.4-1.8	1.9-3.6	3.7-4.9	>4.9
Cardiovascular (systolic blood pressure), mm Hg	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2

Abbreviations: Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen.

[a] Score ≥2 for any system defines the presence of organ failure.

[b] For nonventilated patients, Fio_2 can be estimated by the rate of supplemental oxygen (room air, 21%, 2 L/min, 25%; 4 L/min, 30%; 6-8 L/min, 40%; 9-10 L/min, 50%).

Disease Severity and Risk Stratification

The RAC grades acute pancreatitis severity by the presence and duration of organ failure (ie, respiratory, kidney, and cardiovascular as determined by the modified Marshall scoring system; **Table 1**) and the presence of local complications. Patients without local complications or organ failure have *mild acute pancreatitis*. Patients with transient organ failure (recovery within 48 hours) and/or local complications have *moderately severe acute pancreatitis*, and patients with persistent organ failure beyond 48 hours with or without local complications have *severe acute pancreatitis* (Box 2C). Mild pancreatitis is the most common form of acute pancreatitis and is self-limiting; patients are typically discharged within a week. Patients with moderately severe and severe disease often have a protracted course over weeks to months due to local complications and organ dysfunction (Figure).

Given the variable clinical course in acute pancreatitis and the significant mortality rate in severe cases, several risk scores have been developed to predict outcome (**Table 2**). These classification systems may assist in determining the appropriate level of care (intensive care unit [ICU] vs non-ICU) and guide anticipatory management based on the predicted severity of disease.[22] Though they are useful adjuncts for decision-making in acute pancreatitis, scoring tools should not replace clinical judgment. The earliest scoring system was published by Ranson et al[23,24] in 1974 and 1977 and another by Imrie et al[25,26] in 1978 and 1984. However, both of these scoring systems require information acquired in the first 48 hours of hospital presentation and are cumbersome to calculate. In 1985, the APACHE II model[27] was developed as a comprehensive tool designed to predict disease severity and mortality in patients admitted to the ICU. APACHE II requires 12 variables (Table 2) that are not routinely obtained in patients who are not critically ill. Additionally, the Bedside Index for Severity in Acute Pancreatitis (BISAP) score[28] was developed in 2008 and designed as a predictor of mortality based on 5 variables: blood urea nitrogen (BUN) level greater than 25 mg/dL, impaired mental status, systemic inflammatory response syndrome (SIRS), age older than 60 years, or radiographic evidence of pleural effusion within the first 24 hours of admission. The lowest score was associated with a less than 1% mortality rate and the highest with a greater than 20% mortality rate. In addition to mortality, early studies demonstrated a BISAP score of 3 or greater

Table 2. Comparison of APACHE II, BISAP, and Ranson Scores Based on the Revised Atlanta Classification Definitions of Severity

	APACHE II	BISAP (2008, Gut)	Ranson
Variables	• Age • Temperature • Mean arterial pressure • pH • Heart rate • Respiratory rate • Sodium • Potassium • Creatinine • Acute kidney failure • Hematocrit • WBC count • Glasgow Coma Scale • FIO_2	• BUN >25 mg/dL (>8.9 mmol/L) • Impaired mental status • >2 SIRS criteria • Age >60 y • Pleural effusion present	Admission: • Age >55 y • WBC count >16 000/μL • Lactate dehydrogenase >350 U/L • AST >250 U/L • Glucose >200 mg/dL Within 48 h: • Fall in hematocrit >10% • Increase in BUN >5 mg/dL • Calcium <8 mg/dL • PaO_2 <60 mm Hg • Base deficit >4 mEq/L • Fluid loss >6 L
Original purpose	Severity of disease and mortality in ICU patients	Prediction of mortality in AP	Prediction of mortality in AP
Prediction of severity, AUC (SE)[22]	• 0.82 (0.03)	Score ≥3 • 0.87 (0.16)	• 0.83 (0.08)
Prediction of severity[22] • Sensitivity (95% CI) • Specificity (95% CI)	Score ≥8 • 0.83 (0.77-0.88) • 0.59 (0.56-0.63)	Score ≥3 • 0.51 (0.43-0.60) • 0.91 (0.89-0.92)	Score ≥3 • 0.66 (0.59-0.72) • 0.78 (0.76-0.81)
Prediction of mortality, AUC (SE)[22]	• 0.83 (0.16)	Score ≥3 • 0.87 (0.03)	• 0.92 (0.05)
Prediction of mortality[22] • Sensitivity (95% CI) • Specificity (95% CI)	Score ≥8 • 0.95 (0.77-1.00) • 0.68 (0.63-0.73)	Score ≥3 • 0.56 (4.23-7.55) • 0.91 (0.90-0.91)	Score ≥3 • 0.93 (0.78-0.99) • 0.69 (0.65-0.79)
Advantages	• Can be calculated within 24 h	• 5 Variables • Easy to calculate (1 point per variable) • Can be calculated within 24 h • Specific to AP	• Comprehensive • Specific to AP
Limitations	• Designed for patients admitted to ICUs • Large set of mandatory variables • Not specific to AP	• Lower sensitivity and specificity for predicting disease severity than APACHE II	• At least 48 h to calculate score • All data points not collected routinely in non-ICU patients

Abbreviations: AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; AUC, area under curve; BISAP, Bedside Index of Severe Acute Pancreatitis; BUN, blood urea nitrogen; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, partial pressure of arterial oxygen; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

was associated with developing organ failure (odds ratio [OR], 7.4 [95% CI, 2.8-19.5]), persistent organ failure (OR, 12.7 [95% CI, 4.7-33.9]), and pancreatic necrosis (OR, 3.8 [95% CI, 1.8-8.5]).[29] BISAP is widely used because of its simplicity and ease of calculation (Table 2).[28]

In addition to scoring systems, individual biomarkers may also have predictive value in acute pancreatitis. C-reactive protein (CRP) is commonly obtained in hospitalized patients. CRP levels of 190 mg/L or greater within the first 48 hours of admission or an absolute increase of greater than 90 mg/L have positive predictive values of 31.7% and 27.4% for predicting severe disease, respectively.[30]

Radiologic scoring systems, such as the CT Severity Index, may also be useful to accurately diagnose the extent and severity of pancreatitis.[31,32] However, imaging scores are not reliable when scans are obtained at the time of admission because contrast-enhanced CT may underestimate or incorrectly classify disease severity if it is obtained less than 72 hours after symptom onset.[20,33,34] Therefore, CT is recommended later in the disease course to fully recognize the extent of disease process in patients with moderately severe or severe acute pancreatitis.

Management

Overview of Management

There are 2 cornerstones in acute pancreatitis management, regardless of the etiology: (1) fluid resuscitation to maintain or restore tissue perfusion and (2) nutritional support to counter the catabolic state and decrease the rate of infectious complications.

Fluid Resuscitation

Intravascular volume depletion from fluid sequestration associated with pancreatic, peripancreatic, and systemic edema is characteristic of patients with acute pancreatitis. Vomiting, reduced oral intake, and peripancreatic inflammation contribute to fluid deficits. The diminished circulating volume leads to decreased tissue perfusion and may result in multiorgan failure. Intravascular volume status can be estimated by observing vital signs and measuring urine output, BUN, and hematocrit. A low intravascular volume increases complications and mortality rate. For example, in a study of 5819 patients with acute pancreatitis, every 5-mg/dL increase in BUN level within the first 24 hours of admission was associated with an increased OR for mortality by 2.2 (95% CI, 1.9-2.9).[35] Another study of 1043 patients with acute pancreatitis found an association of hospital mortality in patients with an admission BUN level greater than 20 mg/dL (OR, 4.6 [95% CI, 2.5-8.3]), and any rise in BUN level 24 hours after admission was associated with an OR of 4.3 (95% CI, 2.3-7.9) for death.[36] Thus, most scoring systems used in acute pancreatitis incorporate a marker of volume status (Table 2).

The clinical guidelines for fluid resuscitation from a number of expert groups agree that intravenous volume resuscitation should be initiated as soon as the diagnosis of acute pancreatitis is made,

Table 3. Comparison of Guidelines for Fluid Resuscitation, Nutrition, and Timing of Cholecystectomy

Recommendation	IAP and APA (2013)[37]	AGA (2018)[38]	ACG/Acute Pancreatitis Task Force on Quality (2019)[39]	Quality Improvement Expert Panel (2019)[40]
Rate and/or targets of intravenous fluid resuscitation	Moderate-quality evidence Goal-directed intravenous fluid therapy with 5-10 mL/kg/h Heart rate <120/min; mean arterial pressure, 65-85 mm Hg; urinary output >0.5-1 mL/kg/h; hematocrit, 35%-44%	Very low quality of evidence Goal-directed therapy for fluid management No recommendation on rate, volume, or duration	Moderate-quality evidence Bolus and maintenance fluid resuscitation with titration according to interval assessment of vital signs, urine output, BUN, and hematocrit during the first 48 h No recommendation on rate or volume	Quality of evidence: B[a] ≥3 mL/kg/h, should be initiated unless prohibitive comorbidities exist (eg, heart or kidney failure) Trend BUN, hematocrit, creatinine every 8-12 h for the first 24-48 h
Type of fluid for initial resuscitation	Moderate quality of evidence Lactated Ringer solution	Low quality of evidence No recommendation	Moderate-quality evidence Lactated Ringer solution unless contraindicated	Quality of evidence: B[a] Lactated Ringer solution
Timing of enteral nutrition	Moderate quality of evidence In mild AP, oral feedings can be restarted once abdominal pain is decreasing and inflammatory markers are improving	Moderate quality of evidence Early nutrition within 24 h	High quality of evidence Within 48-72 h unless it is not tolerated or is contraindicated (ie, bowel obstruction or paralytic ileus)	Quality of evidence: B[a] In mild AP, oral feedings should be started within 24 h of symptom control
Route of nasoenteral nutrition (nasogastric vs nasojejunal)	High-quality evidence Nasogastric or nasojejunal	Low-quality evidence Nasogastric or nasojejunal for predicted severe or necrotizing AP	Nasogastric or nasojejunal[b]	Quality of evidence: B[a] Nasojejunal nutrition for severe AP if oral nutrition not tolerated within 3-5 d
Type of nutrition	Moderate-quality of evidence Elemental or polymeric enteral nutrition formulations	No recommendation	High-quality evidence Low-fat solid diet	No recommendation
Timing of cholecystectomy for biliary AP	Low-quality evidence Initial admission for mild AP Low-quality evidence Cholecystectomy in biliary AP complicated by collections should be deferred until collections resolve or if they persist beyond 6 weeks	Moderate-quality evidence Initial admission	High-quality evidence Surgery consultation to consider cholecystectomy prior to discharge Moderate-quality evidence Cholecystectomy in biliary AP complicated by necrosis or collections should be deferred until inflammation subsides or collections resolve/stabilize	Quality of evidence: B[a] Within 2 wk for mild AP

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; AP, acute pancreatitis; APA, American Pancreatic Association; BUN, blood urea nitrogen; IAP, International Association of Pancreatology.

[a] Limited or conflicting evidence from single randomized trial or nonrandomized studies.

[b] Quality of evidence for recommendation not provided.

while the patient is still in the emergency department, and that isotonic crystalloid formulations are preferred (**Table 3**). Specifically, lactated Ringer solution is recommended by most guidelines because of an association between an apparent anti-inflammatory effect and decreased odds of developing SIRS at 24 hours compared with normal saline. The evidence favoring one crystalloid formulation over another is low to moderate quality. The American College of Gastroenterology's (ACG) Acute Pancreatitis Task Force on Quality guideline cited a meta-analysis reporting decreased odds of developing SIRS with lactated Ringer solution compared with normal saline when used for the initial resuscitation in acute pancreatitis (OR, 0.38 [95% CI, 0.15-0.98]).[39,41] This meta-analysis was based on 3 RCTs of which only 1 demonstrated a significant effect favoring lactated Ringer solution.[42]

Most authorities recommend titrating intravenous fluid administration to specific measurable targets of perfusion.[38] For example, the International Association of Pancreatology/American Pancreatic Association (IAP/APA) recommends a crystalloid infusion of 5 to 10 mL/kg/h until 1 or more resuscitation goals are met (eg, heart rate <120 beats per minute; mean arterial pressure, 65-85 mm Hg; urine output >0.5 to 1 mL; hematocrit, 35%-44%). The risks of fluid overload due to aggressive resuscitation in patients with preexisting kidney disease or heart failure must always be considered. These risks can manifest as pulmonary edema, excessive hemodilution leading to hypoxia, and intra-abdominal hypertension.[43]

Nutrition

The provision of nutrition is an important feature of the care of patients with acute pancreatitis. (1) Moderately severe and severe acute pancreatitis elicit an intense systemic inflammatory response resulting in a catabolic state, increasing caloric and nutritional requirements. (2) Reduced intestinal vascular perfusion in acute pancreatitis may result in gut mucosal damage. Subsequently, intestinal permeability increases, which may enable the translocation of bacteria from the bowel lumen to the portal circulation and mesenteric lymphatics. This could result in organ failure, sepsis, and secondary infection of pancreatic and peripancreatic necrosis.[44] Early nutrition, particularly *enteral* nutrition, mitigates these effects by several mechanisms: replenishing caloric losses, increasing splanchnic blood flow to preserve the integrity of the bowel mucosa, and stimulating intestinal motility.

Historically, there was reluctance to feed patients with acute pancreatitis enterally because of concern that the inflamed pancreas would be stimulated to secrete, exacerbating the disease. Parenteral nutrition was widely used. However, this concern about enteral nutrition has not been validated, and evidence overwhelmingly

supports enteral nutrition over parenteral nutrition. A Cochrane meta-analysis of 8 studies involving 348 patients compared enteral nutrition vs total parenteral nutrition for the treatment of acute pancreatitis, finding that enteral nutrition was associated with decreases in mortality (relative risk [RR], 0.5 [95% CI, 0.28-0.91]), multiple organ failure (RR, 0.55 [95% CI, 0.37-0.81]), and systemic infection (RR, 0.39 [95% CI, 0.23-0.65]). On subgroup analysis for severe acute pancreatitis, the decreased risk for death in patients receiving enteral nutrition was even more profound (RR, 0.18 [95% CI, 0.06-0.58]).[45]

It is unnecessary to wait until the pain has resolved before resuming a diet in patients who have acute pancreatitis. The most recent guidelines from the American Gastroenterological Association (AGA),[38] Acute Pancreatitis Task Force on Quality,[39] and a quality indicator expert panel[40] recommend initiating enteral feeding within 24 to 72 hours (Table 3). One meta-analysis of 7 RCTs with 691 patients demonstrated that initiating enteral feeding within 24 hours of admission compared with delayed enteral feeding (>24 hours) or parenteral nutrition was associated with a decrease in multiple organ failure (OR, 0.4 [95% CI, 0.2-0.79]; $P = .008$).[46] In general, patients tolerating oral nutrition should be placed on a low-fat soft or solid diet.[47] If patients are unable to tolerate an oral diet within 72 hours, they should be started on nasoenteral nutrition (ie, nasogastric or nasojejunal).[48,49] Patients who cannot tolerate enteral feeding due to paralytic ileus, obstruction, or other causes should be started on parenteral nutrition within 72 hours.

Many patients are malnourished prior to the episode of acute pancreatitis. The consensus guidelines from the European Society for Clinical Nutrition and Metabolism recommend performing a nutrition screen for all patients with mild to moderately severe acute pancreatitis using tools such as the Malnutrition Screening Tool and Nutrition Risk Screening instrument (NRS-2002) (https://espen.info/documents/Screening.pdf). All patients with severe acute pancreatitis are considered at risk for nutritional deficiencies.[50] Patients with evidence of malabsorption (steatorrhea) require evaluation for exocrine pancreatic insufficiency (eg, fecal elastase-1 and fecal fat assays or direct pancreatic function tests). Semielemental formulations (ie, contain predigested proteins, carbohydrates, and fat) and/or pancreatic enzyme supplementation should be considered for these patients.[50] There is a lack of compelling evidence to support the routine use of semielemental nutrition or enteral formulas enriched with probiotics or immunonutrition.[51]

Risk Reduction and Follow-up Care

Cholecystectomy

Gallstones are a leading cause of acute pancreatitis. When cholecystectomy is not performed at the index admission for gallstone acute pancreatitis, 8% of patients are at risk for recurrence of acute pancreatitis within a median of 40 days after discharge. The risk increases to 22% at 5 years if cholecystectomy is not performed.[52,53] Early cholecystectomy (within 24 to 48 hours of hospital admission) is safe and shortens hospital duration in patients with a predicted mild course of acute pancreatitis.[54-57] Same-admission cholecystectomy may not be feasible for various reasons: patient preference, patients not medically optimized for surgery, and a lack of hospital resources. Optimally, these patients should undergo cholecystectomy within 2 to 4 weeks after discharge, if deemed medically fit, to minimize the risk of recurrent acute pancreatitis related to gallstones. Patients with moderately severe or severe acute pancreatitis should be evaluated for peripancreatic fluid collections prior to cholecystectomy by performing a contrast-enhanced CT or MRI examination. For patients who have peripancreatic collections or severe acute pancreatitis, early cholecystectomy should not be performed because of the risk of superinfection of the peripancreatic fluid collections and limitation of visualization from a bulging retroperitoneum. The operation should be delayed until the fluid collections resolve or after waiting for 6 weeks after the episode of acute pancreatitis so that cholecystectomy can be combined with an internal drainage procedure (eg, cystgastrostomy) if necessary.[58] ERCP with sphincterotomy should be considered during the index admission to minimize recurrent pancreatic duct obstruction from another migrating gallstone in patients who require a delayed cholecystectomy or in patients who are high surgical risk but this intervention may not reduce the rate of subsequent biliary colic or cholecystitis.[37,39]

Alcohol Cessation Strategies

Alcohol-related acute pancreatitis is an independent predictor of developing recurrent acute pancreatitis (hazard ratio, 2.72 [95% CI, 1.91-3.88]; 8.5-month median time to recurrence) and chronic pancreatitis (hazard ratio, 9.16 [95% CI, 2.71-30.90]; 4-month median time to chronic pancreatitis).[59] The AGA recommends performing a brief alcohol intervention during the index admission for alcohol-related acute pancreatitis, and additional educational sessions in 6-month intervals for 2 years after discharge.[60] Patients are counseled regarding 3 aspects of the alcohol-pancreas relationship: the toxic effects of alcohol on the pancreas, behavioral changes/altering drinking habits, and a focus on socioeconomic issues.

Other Interventions

Obese patients and those with hypertriglyceridemia should be counseled regarding weight reduction, dietary modifications, and alcohol avoidance. Pharmacologic therapies include fibrates, statins, niacin, and omega 3 fatty acids. Fibrates (eg, fenofibrate) have the greatest efficacy in lowering triglyceride levels and may be used in combination with the other listed medications for refractory cases.

Patients found to have hypercalcemia during an episode of acute pancreatitis should be evaluated for primary hyperparathyroidism or, less commonly, malignancy and thyrotoxicosis.

Sequelae

The long-term effects of acute pancreatitis are considerable, even in those with mild and first-time episodes. Patients are at risk to develop recurrent episodes of acute pancreatitis, progress to chronic pancreatitis, and develop endocrine and exocrine insufficiency. The greatest risk factors for developing recurrent acute pancreatitis are alcoholic acute pancreatitis, biliary acute pancreatitis without interval cholecystectomy, and tobacco smoking. Risk factors for progressing to chronic pancreatitis include recurrent acute pancreatitis, tobacco smoking, pancreatic necrosis, and alcoholic acute pancreatitis.[59,61]

Pancreatic exocrine insufficiency will develop in up to 35% of all patients. The most important risks factors include necrotizing acute pancreatitis and alcohol etiology.[50,62,63] Patients with diarrhea, steatorrhea, and/or positive pancreatic exocrine insufficiency assays, such as fecal elastase-1, fecal fat, or direct pancreatic

function tests, may benefit from pancreatic enzyme supplementation. Pancreatogenic diabetes mellitus (type 3c diabetes) is the impairment in pancreatic endocrine function related to *structural* pancreatic damage due to pancreatitis. Type 3c diabetes is closely related to chronic pancreatitis, but it may also develop in patients who experienced an episode of severe necrotizing acute pancreatitis.[64]

Patients with peripancreatic fluid collections should be followed regularly and assessed for stable, improved, or worsening symptoms such as pain, feeding intolerance, and fevers.

In summary, acute pancreatitis is a complex and dynamic disease process with a variable clinical course. Prompt recognition, diagnosis, and initiation of treatment with early fluid resuscitation and early nutrition are important for good outcomes. Scoring tools are useful adjuncts for predicting severity and mortality. In particular, the BISAP score is easy to calculate and can be performed within 24 hours. However, these tools should not substitute clinical judgment. Patients need to be evaluated frequently, and management adjusted based on clinical findings and trends. There is consensus for early and aggressive volume resuscitation, but the rate, duration, and volume are not well-defined. The trend in markers (laboratory studies, vitals) are important to follow. *Enteral* feeding is a critical aspect of managing all severities of acute pancreatitis. If possible, cholecystectomy should be performed in patients with mild gallstone acute pancreatitis during the index admission or, if considered unsafe during the admission, within 2 to 4 weeks after discharge to reduce risk of recurrence of acute pancreatitis. Inpatient and outpatient alcohol modification/cessation strategies are likely helpful if used both in the hospital and outpatient settings.

Limitations

This review has some limitations. First, a formal systematic review was not performed. Second, a comprehensive evaluation of acute pancreatitis management (ie, for necrotizing acute pancreatitis, local complications, or other sequelae of acute pancreatitis) was not reviewed. Third, although the importance of fluid resuscitation and nutrition in the initial management of acute pancreatitis is widely accepted, the evidence for specific interventions is limited, of moderate to low quality, and reported inconsistent findings. Fourth, methodological diversity and statistical heterogeneity were frequently encountered. For example, the meta-analyses on the fluid and nutritional management of acute pancreatitis incorporated a combination of studies that used either the RAC severity classification, an alternative or outdated severity scoring system. This has implications when comparing methods of management and the effect on disease severity.[65] Fifth, there are several acute pancreatitis management guidelines of varying quality. Features of guidelines with the highest quality include those endorsed by professional organizations (eg, IAP, AGA, ACG), include a summary of recommendations, and provide evidence grading for the various recommendations.[66]

Conclusions

Acute pancreatitis is a complex disease that varies in severity and course. Prompt diagnosis and stratification of severity influences proper management. Scoring systems are useful adjuncts but should not supersede clinical judgment. Fluid management, nutrition, and risk-reduction strategies are very important aspects of care for acute pancreatitis.

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