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Practice Guidelines in Acute Pancreatitis

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INTRODUCTION

Guidelines for the diagnosis and treatment of acute pancreatitis were published by the American College of Gastroenterology in 1997 (1). These and subsequent guidelines (2 7) have undergone periodic review (6, 8 13) in accordance with advances that have been made in the diagnosis and treatment of acute pancreatitis. Guidelines for clinical practice are intended to apply to all health-care providers who take care of patients with acute pancreatitis and are intended to be exible, and to suggest preferable (but not the only) approaches. Because there is a wide range of choices in any health-care situation, the physician should select the course best suited to the individual patient and the clinical situation.

These guidelines have been developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee, and approved by the Board of Trustees. The world literature in English was reviewed using a MEDLINE search and also using the Cochrane Library. The ratings of levels of evidence for these guidelines are indicated in Table 1. The nal recommendations are based on the data available at the time of the publication of this document and may be updated with appropriate scienti c development at a later time. The following guidelines are intended for adult and not pediatric patients. The main diagnostic guidelines include an assessment of risk factors of severity at admission and determination of severity. The major treatment guidelines include supportive care, uid resuscitation, transfer to intensive care unit, enteral feeding, use of antibiotics, treatment of infected pancreatic necrosis, treatment of sterile pancreatic necrosis, treatment of associated pancreatic duct disruptions, and role of magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy for detection and treatment of choledocholithiasis in biliary pancreatitis.

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PATHOPHYSIOLOGY

The pathophysiology of acute pancreatitis is generally considered in three phases. In the rst phase, there is premature activation of trypsin within pancreatic acinar cells. A variety of mechanisms have been proposed including disruption of calcium signaling in acinar cells (14 18), cleavage of trypsinogen to trypsin by the lysosomal hydrolase cathepsin-B, and decreased activity of the intracellular pancreatic trypsin inhibitor (17, 18). Once trypsin is activated, it activates a variety of injurious pancreatic digestive enzymes.

In the second phase, there is intrapancreatic in ammation through a variety of mechanisms and pathways (16, 18 28). In the third phase, there is extrapancreatic in ammation including acute respiratory syndrome (ARDS) (16, 19 21, 29). In both phases, there are four important steps mediated by cytokines and other in ammatory mediators: 1) activation of in ammatory cells, 2) chemoattraction of activated in ammatory cells to the microcirculation, 3) activation of adhesion molecules allowing the binding of in ammatory cells to the endothelium, and 4) migration of activated in ammatory cells into areas of in ammation.

In the majority of patients, acute pancreatitis is mild. In 10 20%, the various pathways that contribute to increased intrapancreatic and extrapancreatic in ammation result in what is generally termed systemic in ammatory response syndrome (SIRS) (Table 2). In some instances, SIRS predisposes to multiple organ dysfunction and/or pancreatic necrosis. The factors that determine severity are not clearly understood, but appear to involve a balance between proin ammatory and anti-in ammatory factors. Recent evidence suggests that the balance may be tipped in favor of proin ammatory factors by genetic polymorphisms of in ammatory mediators that increase severity of acute pancreatitis (27, 30, 31).

CLINICAL CONSIDERATIONS

Clinical Diagnosis

It has been estimated that in the United States there are 210,000 admissions for acute pancreatitis each year (13). Most patients with acute pancreatitis experience abdominal

Table 1. Ratings of Evidence Used for This Guideline

I. Strong evidence from at least one published systematic review of multiple well-designed randomized controlled trials
II. Strong evidence from at least one published properly designed randomized controlled trial of appropriate size and in an appropriate clinical setting
III. Evidence from published well-designed trials without randomization, single group prepost, cohort, time series, or matched case-controlled studies
IV. Evidence from well-designed nonexperimental studies from more than one center or research group or opinion of respected authorities, based on clinical evidence, descriptive studies, or reports of expert consensus committees

pain that is located generally in the epigastrium and radiates to the back in approximately half of cases. The onset may be swift with pain reaching maximum intensity within 30 min, is frequently unbearable, and characteristically persists for more than 24 h without relief. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding (32).

There is general acceptance that a diagnosis of acute pancreatitis requires two of the following three features: 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase and/or lipase $\geq$3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan. This definition allows for the possibility that an amylase and/or lipase might be $<$3 times the upper limit of normal in acute pancreatitis. In a patient with abdominal pain characteristic of acute pancreatitis and serum enzyme levels that are lower than 3 times the upper limit of normal, a CT scan must be performed to confirm a diagnosis of acute pancreatitis. In addition, this definition allows for the possibility that presence of abdominal pain cannot be assessed in some patients with severely altered mental status due to acute or chronic illness.

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The height of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis. It is usually not necessary to measure both serum amylase and lipase. Serum lipase may be preferable because it remains normal in some nonpancreatic conditions that increase serum amylase including macroamylasemia, parotitis, and some carcinomas. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis. Daily measurement of serum amylase or lipase after the diagnosis of acute pancreatitis has limited value in assessing the clinical progress of the illness or ultimate prognosis (32). If serum amylase and/or lipase remain elevated for several weeks, possibilities include persisting pancreatic/peripancreatic inflammation, blockage of the pancreatic duct, or development of a pseudocyst.

Table 2. Systemic Inflammatory Response Syndrome (SIRS)

Defined by Two or More of the Following Criteria:
Pulse $>$90 beats/min
Respiratory rate $>$20/min or PCO_2 $<$32 mmHg
Rectal temperature $<36^{\circ}C$ or $>38^{\circ}C$
White blood count $<$4,000 or $>$12,000/mm^3

The differential diagnosis of acute pancreatitis is broad and includes mesenteric ischemia or infarction, perforated gastric or duodenal ulcer, biliary colic, dissecting aortic aneurysm, intestinal obstruction, and possibly inferior wall myocardial infarction. In severe pancreatitis, the patients appear toxic and quite ill. In mild pancreatitis, the patients generally appear uncomfortable but not as ill (32).

A detailed discussion of the approach to determining the etiology of acute pancreatitis is beyond the scope of this paper. During the initial hospitalization for acute pancreatitis, reasonable attempts to determine etiology are appropriate, and in particular those causes that may affect acute management. Relevant historical clues include any previous diagnosis of biliary tract disease or gallstones, cholecystectomy, other biliary or pancreatic surgery, acute or chronic pancreatitis or their complications, use of ethanol, medications and the timing of their initiation, recent abdominal trauma, weight loss or other symptoms suggesting a malignancy, or a family history of pancreatitis. Blood tests within the first 24 h should include liver chemistries, calcium, and triglycerides.

Abdominal ultrasound is usually performed at the time of admission to assess for gallstones as the etiology rather than to establish the diagnosis of acute pancreatitis. Detection of common bile duct stones by ultrasound is limited by poor sensitivity, although specificity is quite high if they are identified. Dilation of the common bile duct alone is neither sensitive nor specific for the detection of common bile duct stones. Occasionally, the pancreas is well enough seen by abdominal ultrasound to reveal features that are consistent with the diagnosis of acute pancreatitis including diffuse glandular enlargement, hypoechoic texture of the pancreas reflective of edema, and ascites. Contrast-enhanced CT scan (and in particular a contrast-enhanced thin-section multidetector-row CT scan) is the best imaging technique to exclude conditions that masquerade as acute pancreatitis, to diagnose the severity of acute pancreatitis, and to identify complications of pancreatitis (33–35). Findings on CT scan that confirm the diagnosis of acute pancreatitis include enlargement of the pancreas with diffuse edema, heterogeneity of pancreatic parenchyma, peripancreatic stranding, and peripancreatic fluid collections. With the use of IV contrast, a diagnosis of pancreatic necrosis can be established. In addition, contrast-enhanced CT scan may give clues as to the etiology of acute pancreatitis: for example, a common bile duct stone may occasionally be directly visualized, pancreatic calcifications may indicate underlying chronic pancreatitis due to alcohol or other causes, a pancreatic mass may suggest malignancy, and diffuse dilation of the pancreatic duct or a cystic lesion may suggest intraductal papillary mucinous neoplasia or cystic neoplasm. The

Table 3. Severe Acute Pancreatitis as De ned by Atlanta Symposium

Early Prognostic Signs
Ranson signs ≥3
APACHE-II score ≥8
Organ Failure
and/or
Local Complications
Necrosis
Abscess
Pseudocyst

role of magnetic resonance imaging (MRI) and MRCP in the diagnosis of acute pancreatitis and establishment of severity is undergoing evaluation. These techniques are superior to CT scan in delineating pancreatic ductal anatomy (36 38) and detecting choledocholithiasis (39).

Definitions

The International Symposium, held in Atlanta, GA, in 1992, established a clinically based classi cation system for acute pancreatitis (40, 41). The goal was to establish international standards of de nitions of acute pancreatitis and its complications to make possible valid comparisons of severity of illness and results of therapy and also to establish criteria for patient selection in randomized prospective trials. According to the Atlanta Symposium, acute pancreatitis was de ned as an acute in ammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. Criteria for severity included organ failure (particularly shock, pulmonary insuf ciency, and renal failure) and/or local complications (especially pancreatic necrosis but also including abscess and pseudocyst). Early predictors of severity within 48 h of initial hospitalization included Ranson signs and APACHE-II points (Table 3).

Interstitial pancreatitis was de ned as focal or diffuse enlargement of the pancreas with enhancement of the parenchyma that is either homogeneous or slightly heterogeneous in response to IV contrast. There may be in ammatory changes in peripancreatic fatty tissue characterized by a hazy appearance.

Pancreatic necrosis was de ned as diffuse or focal areas of nonviable pancreatic parenchyma that was typically associated with peripancreatic fat necrosis. The criteria for the CT diagnosis of necrosis included focal or diffuse well-marginated zones of nonenhanced pancreatic parenchyma greater than 3 cm in size or greater than 30% of the pancreas. It was recognized that pancreatic necrosis could be either sterile or infected and that infected necrosis was characterized by the presence of bacteria (and/or fungi) within the necrotic tissue.

An extrapancreatic uid collection was de ned as pancreatic uid that extravasates out of the pancreas during acute pancreatitis into the anterior pararenal spaces and other areas as well. Fluid collections may occur both with interstitial and necrotizing pancreatitis. Most uid collections remain sterile and disappear during the recovery period.

Table 4. Organ Failure as De ned by Atlanta Symposium

Shock systolic pressure <90 mmHg
PaO_2 ≤60 mmHg
Creatinine >2.0 mg/L after rehydration
Gastrointestinal bleeding >500 cc/24 h

A pancreatic pseudocyst was de ned as a collection of pancreatic juice enclosed by a nonepithelialized wall that occurs as a result of acute pancreatitis, pancreatic trauma, or chronic pancreatitis. It is generally believed that a period of at least 4 wk is required from the onset of acute pancreatitis to form a well-de ned wall composed of granulation and brous tissue. Pancreatic pseudocysts contain considerable pancreatic enzymes and are usually sterile. According to the Atlanta Symposium, an infected pancreatic pseudocyst should be termed a pancreatic abscess. A pancreatic abscess may also occur when an area of pancreatic necrosis undergoes secondary liquefaction and then becomes infected.

Mild acute pancreatitis was de ned as pancreatitis associated with minimal organ dysfunction and an uneventful recovery. Severe pancreatitis was de ned as pancreatitis associated with organ failure and/or local complications (necrosis, abscess, or pseudocyst).

Organ failure was de ned as shock, pulmonary insuf ciency, renal failure, or gastrointestinal bleeding (Table 4). There were a number of additional systemic complications that were identi ed as characteristic of severe acute pancreatitis including disseminated intravascular coagulation (platelets ≤100,000/mm^3, brinogen ≤100 mg/dL, brin split products >80 μg/mL), or a severe metabolic disturbance (serum calcium ≤7.5 mg/dL).

The Atlanta Symposium was an important initiative in establishing a clinically based classi cation system. However, it is now clear some of the information included in the classi cation was subject to different interpretations, and that criteria of severity as de ned by the Atlanta Symposium have not been used in a uniform fashion in recent publications (3, 10, 13, 25, 27, 31, 42 165). In addition, there is new scienti c information that should be included in a revised classi cation. Areas of major concern are as follows:

1. In the Atlanta Symposium, a uniform threshold was not established for serum amylase and/or lipase for the diagnosis of acute pancreatitis. In recently published articles, the threshold varied from ≥2 times to ≥4 times the upper limit of normal.
2. In the Atlanta Symposium, criteria for severe pancreatitis included organ failure and/or local complications (Table 3). This broad de nition describes a heterogeneous group of patients with varying levels of severity. For example, the prognosis of pancreatic necrosis is more serious than a pseudocyst or pancreatic abscess. Also, almost all patients with necrotizing pancreatitis without organ failure survive, whereas those with multisystem organ failure

Table 5. Mortality in Acute Pancreatitis

	Median (%)	Range (%)	References
All cases	5	2 9	2, 25, 44, 46, 50, 56, 59, 61, 73, 75, 76, 86, 109, 140, 168
Interstitial pancreatitis	3	1 7	46, 50, 82, 133, 145, 153, 168
Necrotizing pancreatitis	17	8 39	46, 50, 54, 55, 59, 60, 66, 67, 75, 83, 86, 91, 92, 109, 111, 113, 114, 120, 121, 128, 133, 145, 147, 148, 153, 168, 169
Infected necrosis	30	14 62	45, 62 64, 68, 69, 83, 109 111, 113, 118, 120, 121, 126, 128, 134, 138, 148, 161, 164, 170
Sterile necrosis	12	2 44	68, 83, 109 111, 113, 118, 120, 121, 128, 134, 138, 148, 161, 170

have a median mortality of 47% (48, 66, 68, 83, 120, 163, 164).

3. There was no distinction between transient and persistent organ failure. Patients with persistent organ failure have a more serious prognosis than those with transient organ failure (71, 72, 151).
4. Criteria for organ failure that were established have not been used in a uniform fashion. Some reports have restricted organ failure to shock, hypotension, renal failure, and gastrointestinal bleeding (10, 13, 44, 46, 50 52, 57, 73, 74, 83, 84, 89, 140, 145, 148). Other reports have altered thresholds for organ failure, or have included additional criteria, or have used alternative or nonspeci ed scoring systems (3, 25, 31, 43, 45, 47, 48, 53, 54, 56, 58 61, 64, 66 69, 77 80, 82, 86 88, 90 95, 97 100, 102, 103, 105 112, 114, 119 123, 125 129, 134 136, 138, 139, 142, 143, 146, 147, 149 153, 155, 156, 159 161, 165). A revision of the Atlanta criteria will undoubtedly delete gastrointestinal bleeding (which is rarely encountered in acute pancreatitis) and will retain shock, hypotension, and renal failure as the important components of organ failure. In addition, a revision will likely include one of the formal scoring systems for organ failure that are currently available.
5. In the Atlanta Symposium, pancreatic necrosis was considered as either greater than 30% of the pancreas or greater than 3 cm in size. These are, in effect, two different de nitions. Because of the variability in the minimum criteria used for the presence of necrosis, it is dif cult to compare studies from different institutions (10, 13, 25, 27, 31, 44 60, 62 64, 66 74, 77 92, 98, 100 102, 104 107, 113, 115, 116, 119 121, 126 129, 131, 133 135, 137, 138, 140, 142 148, 150, 153, 154, 156, 157, 159, 161). A revision of the Atlanta criteria will undoubtedly provide a uniform threshold for the diagnosis of pancreatic necrosis.
6. Regarding the term pancreatic pseudocyst, a distinction was not made between two relatively distinctive entities. The rst is a collection of pancreatic juice enclosed by a nonepithelialized wall that occurs mostly near the pancreas. While the contents may also include peripancreatic necrotic material, the contents are usually mostly uid. The second type of pancreatic pseudocyst is that which takes place within the con nes of the pancreas and involves pancreatic necrotic tissue with variable amounts of pancreatic uid. This entity, frequently termed organized necrosis (166), is a distinct clinical entity that poses substantially greater management challenges (167). Additional terminology will be needed to separate these two conditions.

Overview of Acute Pancreatitis

Overall, 85% of patients have interstitial pancreatitis; 15% (range 4 47%) have necrotizing pancreatitis (25, 44, 46, 50, 68, 83, 86, 128, 140, 169). Among patients with necrotizing pancreatitis, 33% (range 16 47%) have infected necrosis (62, 66, 68, 83, 91, 111, 113, 117, 118, 120, 121, 147, 159, 169, 170).

Approximately 10% of patients with interstitial pancreatitis experience organ failure, but in the majority it is transient with a very low mortality. Median prevalence of organ failure in necrotizing pancreatitis is 54% (range 29 78%) (31, 50, 54, 82, 83, 120, 147, 148). Prevalence of organ failure is the same or somewhat higher in infected necrosis (34 89%) than in sterile necrosis (45 73%) (66, 83, 138, 161).

The overall mortality in acute pancreatitis is approximately 5%: 3% in interstitial pancreatitis, 17% in necrotizing pancreatitis (30% in infected necrosis, 12% in sterile necrosis) (Table 5).

The mortality in the absence of organ failure is 0 (50, 66, 68, 83), with single organ failure is 3% (range 0 8%) (66, 83, 163), with multisystem organ failure 47% (range 28 69%) (48, 66, 68, 83, 120, 163, 164).

Although older literature suggested that 80% of deaths occur after several weeks of illness as a result of infected necrosis, more recent surveys have shown considerable variation with several reports showing a reasonably even distribution of early deaths (within 1 2 wk) *versus* later deaths (46, 72, 76, 150, 151, 163), a few showing the majority of deaths within the rst 2 wk (67, 75), and others showing the majority of deaths after the rst 2 wk (59, 89, 135). These variations re ect a variety of in uences including percentage of very ill patients referred to a reporting hospital compared to patients admitted directly. Deaths within the rst 2 wk are generally attributed to organ failure; deaths after this interval are generally caused by infected necrosis or complications of sterile necrosis.

DIAGNOSTIC GUIDELINE I: LOOK FOR RISK FACTORS OF SEVERITY AT ADMISSION

Older age (>55), obesity (BMI >30), organ failure at admission, and pleural effusion and/or in ltrates are risk factors for severity that should be noted at admission. Patients with these characteristics may require treatment in a highly supervised area, such as a step-down unit or an intensive care unit.

Level of evidence: III

The importance of establishing risk factors of severity of acute pancreatitis at admission is several-fold: to transfer those patients who are most likely to have a severe episode to a step-down unit or an intensive care unit for closer supervision, to allow physicians to compare results of optimal therapy, and to facilitate the identi cation of seriously ill patients for inclusion in randomized prospective trials. A variety of potential risk factors have been investigated as follows.

It is intuitive that older individuals would have more severe pancreatitis because of comorbid disease. In many (50, 55, 60, 67, 70, 75, 83, 86 88, 91, 128) but not all (31, 46, 53, 61, 165, 168) reports, older age (generally ≥55 yr of age) has correlated with a more severe prognosis.

There have been a variety of studies that have sought to determine whether obesity is a risk factor for severity in acute pancreatitis (56 60, 75, 87, 88). A recent meta-analysis concluded that obese patients (de ned as those with a BMI >30) had more systemic and local complications but not greater mortality (57). In one recent report, the combination of APACHE-II and obesity (a classi cation termed APACHE-O) measured within the rst 24 h of admission improved the prediction of severity in patients with acute pancreatitis (58).

Several reports have pointed out that patients with organ failure at admission have a higher mortality than those who do not experience organ failure at admission (50, 61, 69, 71, 72, 83, 163). The progression of single organ failure to multisystem organ failure is a major determinant in the high mortality associated with organ failure at admission (83). Survival among patients with organ failure at admission has also been shown to correlate with the duration of organ failure (71, 72, 151). When organ failure is corrected within 48 h, mortality was close to 0. When organ failure persisted for more than 48 h, mortality was 36% (72).

Several reports have pointed out that a pleural effusion obtained on chest X-ray within the rst 24 h of admission correlates with greater severity in terms of necrosis or organ failure (84) or greater mortality (75, 86). Additionally, the presence of in ltrates on chest X-ray within 24 h has been associated with greater mortality (75, 85, 86).

Several reports have indicated that gender has no prognostic signi cance (31, 46, 73, 83, 87, 91, 165). Furthermore, etiology has also been shown to have no prognostic significance (46, 53, 60, 61, 75, 83, 87, 91, 168) other than one report that indicated that patients with alcoholic pancreatitis in their rst episode of pancreatitis have a greater need for intubation and greater prevalence of pancreatic necrosis (74).

In three reports (82, 83, 171), almost all deaths in acute pancreatitis occurred during the rst two episodes, fewer in the third episode. Studies in the future should stratify patients on the basis of number of prior episodes to con rm this observation. In one report (172), but not in another (83), a short interval between onset of symptoms and hospitalization correlated with more severe disease, presumably because abdominal pain was particularly intense among patients with early spread of in ammatory changes in the retroperitoneum and elsewhere that would cause early third space losses.

DIAGNOSTIC GUIDELINE II: DETERMINATION OF SEVERITY BY LABORATORY TESTS AT ADMISSION OR ≤48 H

The two tests that are most helpful at admission in distinguishing mild from severe acute pancreatitis are APACHE-II score and serum hematocrit. It is recommended that APACHE-II scores be generated during the rst 3 days of hospitalization and thereafter as needed to help in this distinction. It is also recommended that serum hematocrit be obtained at admission, 12 h after admission, and 24 h after admission to help gauge adequacy of uid resuscitation.

Level of evidence: III

The APACHE-II severity of disease classi cation system includes a variety of physiologic variables, age points, and chronic health points, which can be measured at admission and daily as needed to help identify patients with severe pancreatitis (1, 7, Table 6). A variety of reports have correlated a higher APACHE-II at admission and during the rst 72 h with a higher mortality (<4% with an APACHE-II <8 and 11 18% with an APACHE-II >8) (31, 46, 52, 72, 83, 128, 147). There are some limitations in the ability of the APACHE-II score to stratify patients for disease severity. For example, in one report, there was no sharp cutoff between interstitial and necrotizing pancreatitis (52). In three reports, APACHE-II scores were not statistically different among patients with sterile and infected necrosis (66, 83, 134). In one recent report, APACHE-II generated within the rst 24 h had a positive predictive value of only 43% and negative predictive value of 86% for severe acute pancreatitis as compared to the 48-h Ranson score of 48% and 93%, respectively (53). The advantage of the APACHE-II score was the availability of this information within the rst 24 h and daily (53). In general, an APACHE-II score that increases during the rst 48 h is strongly suggestive of the development of severe pancreatitis, whereas an APACHE-II that decreases within the rst 48 h strongly suggests mild pancreatitis.

Ranson signs have been used for many years to assess severity of acute pancreatitis but have the disadvantage of requiring a full 48 h for a complete evaluation. In general, when Ranson signs are <3, mortality is 0 3% (46, 86, 145); when ≥3, 11 15% (46, 86, 145); when ≥6, 40% (46). However, a more recent comprehensive evaluation of 110 studies concluded that Ranson signs provided very poor predictive power of severity of acute pancreatitis (173). In two studies,

Table 6. APACHE II Score APACHE II score = (acute physiology score) + (age points) + (chronic health points) Acute Physiology Score

		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Rectal temp (°C)	>41	39 40.9		38 38.9	36 38.4	34 35.9	32 33.9	30 31.9	<29.9
2	Mean arterial pressure (mmHg)	>160	130 159	110 129		70 109		50 69		<49
3	Heart rate (bpm)	>180	140 179	110 139		70 109		55 69	40 54	<39
4	Respiratory rate (bpm)	>50	35 49		25 34	12 24	10 11	6 9		<5
5	Oxygen delivery (mL/min)	>500	350 499	200 349		<200				
6	PO_2 (mmHg)					>70	61 70		55 60	<55
7	Arterial pH	>7.7	7.6 7.69		7.5 7.59	7.3 7.49		7.25 7.3	7.15 7.2	<7.15
8	Serum sodium (mmol/L)	>180	160 179	155 159	150 154	130 149		120 129	111 119	<110
9	Serum potassium (mmol/L)	>7	6 6.9		5.5 5.9	3.5 5.4	3 3.4	2.5 2.9		<2.5
10	Serum creatinine (mg/dL)	>3.5	2 3.4	1.5 1.9		0.6 1.4		<0.6		
11	Hematocrit (%)	>60		50 59.9	46 49.9	30 45.9		20 29.9		<20
12	White cell count (10^3/mL)	>40		20 39.9	15 19.9	3 14.9		1 2.9		<1

Age Points

Age	**Points**
<44	0
45 54	2
55 64	3
65 74	5
>75	6

Chronic Health Points

History of Severe Organ Insufficiency	**Points**
Nonoperative patients	5
Emergency postoperative patients	5
Elective postoperative patients	2

the Ranson score was the same in sterile and infected necrosis (66, 134).

There have been studies that have attempted to correlate severity of pancreatitis with one or more serum measurements that are available at admission. In one study, creatinine at admission >2.0 mg/dL and a blood glucose >250 mg/dL were associated with a greater mortality (39% and 16%, respectively) (46). In two additional studies, serum creatinine >2.0 mg/dL within 24 h of admission was also associated with a greater mortality (75, 86). In another study, serum glucose >125 mg/dL at admission correlated with a variety of parameters including longer hospital stay but not organ failure, length of intensive care, or mortality (140).

The addition of an obesity score to the standard APACHE-II (so-called APACHE-O score) appears to increase accuracy of APACHE-II for severity. In this scoring system, a point is added to the APACHE-II score when the BMI is 26 30 and 2 points are added when the BMI is greater than 30 (58).

In severe acute pancreatitis, there is considerable extravasation of intravascular uid into third spaces as a result of in ammatory mediators as well as local in ammation caused by widespread enzyme-rich pancreatic exudate. The reduction in intravascular volume, which can be detected by an increased serum hematocrit, can lead to decrease in the perfusion of the microcirculation of the pancreas and result in pancreatic necrosis. As such, hemoconcentration has been proposed as a reliable predictor of necrotizing pancreatitis (82). In this report, hematocrit ≥44 at admission and failure of admission hematocrit to decrease at 24 h were the best predictors of necrotizing pancreatitis. In another study, patients who presented with hemoconcentration and then had a further increase in hematocrit at 24 h were at particularly high risk of pancreatic necrosis, whereas 41% of patients whose hematocrit decreased by 24 h did not develop pancreatic necrosis (172). Other reports have not con rmed that hemoconcentration at admission or at 24 h is a risk factor for severe acute pancreatitis (44, 75). However, there is agreement that the likelihood of necrotizing pancreatitis is very low in the absence of hemoconcentration at admission (44, 82). Hence, the absence of hemoconcentration at admission or during the rst 24 h is strongly suggestive of a benign clinical course.

C-reactive protein (CRP) is an acute phase reactant. Plasma levels greater than 150 mg/L within the rst 72 h of disease correlate with the presence of necrosis with a sensitivity and speci city that are both >80%. Because the peak is generally 36 72 h after admission, this test is not helpful at admission in assessing severity (16, 77, 79).

A variety of additional tests, including urinary trypsinogen activation peptide, serum trypsinogen-2, serum amyloid A, and calcitonin precursors, have shown promise at admission in distinguishing mild from severe pancreatitis in many (77 80, 159) but not all (165) reports. None of these tests is available commercially.

DIAGNOSTIC GUIDELINE III: DETERMINATION OF SEVERITY DURING HOSPITALIZATION

Pancreatic necrosis and organ failure are the two most important markers of severity in acute pancreatitis. The distinction between interstitial and necrotizing pancreatitis can be reliably made after 2 3 days of hospitalization by contrast-enhanced CT scan.

Level of evidence: III

A. Imaging Studies

CONTRAST-ENHANCED CT SCAN. Many patients with acute pancreatitis do not require a CT scan at admission or at any time during the hospitalization. For example, a CT scan is usually not essential in patients with recurrent mild pancreatitis caused by alcohol. A reasonable indication for a CT scan at admission (but not necessarily a CT with IV contrast) is to distinguish acute pancreatitis from another serious intra-abdominal condition, such as a perforated ulcer.

A reasonable indication for a contrast-enhanced CT scan a few days after admission is to distinguish interstitial from necrotizing pancreatitis when there is clinical evidence of increased severity. The distinction between interstitial and necrotizing pancreatitis can be made much more readily when a contrast-enhanced CT scan is obtained on the second or third day after admission rather than at the time of admission (34). Additional contrast-enhanced CT scans may be required at intervals during the hospitalization to detect and monitor the course of intra-abdominal complications of acute pancreatitis, such as the development of organized necrosis, pseudocysts, and vascular complications including pseudoaneurysms.

Contrast-enhanced CT scan (and in particular contrast enhanced thin-section multidetector-row CT scan) is the best available test to distinguish interstitial from necrotizing pancreatitis. Interstitial pancreatitis is characterized by an intact microcirculation and uniform enhancement of the gland. Necrotizing pancreatitis is characterized by disruption of the microcirculation such that devitalized areas do not enhance. Whereas small areas of nonenhancement could represent intrapancreatic uid rather than necrosis, large areas of nonenhancement clearly indicate a disruption of microcirculation and pancreatic necrosis (33, 34, 38).

When there is signi cant renal impairment (generally a creatinine greater than 1.5 mg/dL) or history of signi cant allergy to contrast dye, CT scan should be performed without the use of IV contrast. Although the distinction between interstitial and necrotizing pancreatitis cannot be made in the absence of contrast enhancement, a nonenhanced CT scan provides some important information in accordance with Balthazar Ranson criteria for severity (Table 7). In general, the most severe acute pancreatitis, both in terms of organ failure and in the development of pancreatic necrosis, occurs in grade E pancreatitis. When IV contrast is used, a CT severity index can be used. This index assigns points on the basis of the CT grade (A E) and the amount of necrosis (none, less than 30%, 30 50%, greater than 50%). Patients with necrotizing pancreatitis have a higher morbidity and mortality than patients with interstitial disease (33, 34).

Table 7. Balthazar Ranson Criteria for Severity

CT Grade	Score	Necrosis	Score
A	0	None	0
B	1	One-third	2
C	2	One-half	4
D	3	>One-half	6
E	4		

A = normal; B = focal or diffuse enlargement of the pancreas; C = intrinsic pancreatic abnormalities associated with haziness and streaky densities representing in ammatory changes in the peripancreatic fat; D = single, ill-de ned uid collection; E = two or multiple uid collections.

There have been concerns in some animal studies that the use of IV contrast might accentuate the severity of acute pancreatitis. While there have been very few studies that have addressed this issue, two recent reports found no evidence that IV contrast resulted in extension of necrosis as visualized on subsequent CT scans (143, 174).

The determination that a patient has pancreatic necrosis has clinical implications because the morbidity and mortality of necrotizing pancreatitis is higher than that of interstitial pancreatitis. Furthermore, the determination that a patient has necrotizing pancreatitis may lead to treatment that is not necessary in interstitial pancreatitis. However, the extent of necrosis may not be as important in the morbidity and mortality of necrotizing pancreatitis as was once thought. While some series have shown a correlation between extent of necrosis and prevalence of organ failure (66, 69, 148, 161), others have not (50, 83, 111); similarly, while some series have shown a correlation between the extent of necrosis and the prevalence of infected necrosis (117, 161, 175), others have not (83, 91, 111); while one recent study has shown a correlation of extent of necrosis with mortality (161), others have not (83, 128, 138).

In one recent study among patients with greater than 50% necrosis, mortality was the same in sterile necrosis as compared to infected necrosis (142). It is dif cult to explain these differences among hospitals with similar expertise in the care of patients with acute pancreatitis. One possible explanation is that there is considerable variation in the number of patients with severe necrotizing pancreatitis who are referred to individual hospitals for specialized care. In recent series, among the total number of patients with severe pancreatitis who were cared for in referral hospitals, the median percentage of referred patients was 63% (range 32 73%) (55, 60, 62, 64, 68, 83, 106, 110, 138, 156, 161, 164). In some series (60, 62, 68), but not all (83, 138), patients who were transferred were more seriously ill than those who were admitted directly to the reporting hospital. The clinician should keep in mind that organ failure (and particularly multisystem organ failure) rather than the extent of necrosis appears to be a more important factor in the morbidity and mortality of acute pancreatitis.

Complications in acute pancreatitis that can be recognized on abdominal CT scan include pancreatic uid collections, gastrointestinal and biliary complications (such as obstruction of duodenum or stomach, in ammation of the transverse colon, and biliary obstruction), solid organ involvement (such as splenic infarct), vascular complications (such as pseudoaneurysms, splenic vein thrombosis with varices, portal vein thrombosis), and pancreatic ascites (33, 35, 90).

MAGNETIC RESONANCE IMAGING. Thus far, magnetic resonance imaging (MRI) has not been widely used in the care of patients with acute pancreatitis. While CT scan remains the primary imaging technique to evaluate patients with acute pancreatitis, recent reports have indicated that MRI has some advantages: the lack of nephrotoxicity of gadolinium as compared to an iodinated preparation used for contrast-enhanced CT scan, potential concerns regarding radiation exposure, the greater ability of MRI as compared to CT to distinguish necrosis from uid, and the overall reliability of MRI as compared to CT scan in staging the severity of acute pancreatitis and its complications (36 38). In one study, secretin-MRCP provided accurate identi cation of retained bile duct stones and pancreatic duct leaks (38). Disadvantages of MRI include lack of availability when urgently needed, variation in quality among centers, and the dif culty of supervising a critically ill patient undergoing MRI.

B. Organ Failure

It has already been noted that patients with organ failure at admission have a higher mortality than those who do not have organ failure at admission (50, 61, 69, 71, 72, 83, 163). It has also been determined that for patients who develop organ failure for the rst time after admission, mortality may be as high when organ failure is experienced at admission (71, 72, 83, 163). Hence, the development of organ failure, whether at admission or thereafter, implies a high mortality. The highest mortalities ($\geq$36%) are among patients with multisystem organ failure (83) and sustained organ failure (that is, organ failure lasting more than 48 h) (72). Because it is not clear at the onset of organ failure whether it is likely to be transient or sustained, patients who demonstrate signs of organ failure in accordance with the Atlanta Symposium (Table 4) require more diligent care in a specialized unit, such as an intensive care unit or step-down unit, until there is resolution or improvement.

It is recommended that a standardized organ failure score that strati es for severity (including need for pressor agents for shock, assisted ventilation for refractory hypoxemia, and dialysis for renal failure) be used to grade the severity of organ failure and results of therapy among institutions.

TREATMENT GUIDELINE I: SUPPORTIVE CARE

Supportive care with particular emphasis on measures that prevent hypoxemia and insure adequacy of uid resuscitation is a critical component in the care of patients with acute pancreatitis.

Level of evidence: III

Proper supportive care is invaluable in the treatment of acute pancreatitis. It is important to obtain vital signs at frequent intervals (such as every 4 h) and to obtain measurement of bedside oxygen saturation whenever vital signs are recorded. These measurements are of utmost importance during the rst 24 h of admission when the care of the patient can be fragmented. For example, in many hospitals it is not unusual for patients to be maintained in an emergency ward setting for prolonged intervals of time until a hospital bed becomes available. Under these circumstances, caregivers are usually attending to obviously critically ill patients, and supervision may be less focused on patients with acute pancreatitis who appear to be resting comfortably while receiving a parenterally administered narcotic agent every 2 4 h. The clinician should realize that hypoxemia and inadequate uid resuscitation may be unrecognized for prolonged periods of time unless vital signs, oxygen saturation, and uid balance are carefully monitored during the rst 24 h and each day thereafter as indicated. It is recommended that supplemental oxygen be administered during the rst 24 48 h, especially if narcotic agents are used to control pain. Supplemental oxygen should be continued until the clinician is fully satis ed that there is no further threat of hypoxemia. Blood gas analysis should be performed when oxygen saturation is $\leq$95% or when other clinical manifestations suggest the possibility of hypoxemia (including labored respiration or hypotension refractory to a bolus of IV uids). There is no speci c value of bedside oxygen saturation that correlates accurately with a PO_2 $\leq$60 mmHg.

Aggressive IV uid replacement is of critical importance to counteract hypovolemia caused by third space losses, vomiting, diaphoresis, and greater vascular permeability caused by in ammatory mediators. Hypovolemia compromises the microcirculation of the pancreas and is a major contributor to the development of necrotizing pancreatitis. Intravascular volume depletion leads to hemoconcentration (hematocrit $\geq$44), tachycardia, hypotension, scanty urine output, and prerenal azotemia. There is abundant experimental evidence that early aggressive uid resuscitation and improved delivery of oxygen prevent or minimize pancreatic necrosis and improve survival (176 178). Although comparable studies have not been carried out in clinical practice, there is widespread acceptance of the importance of aggressive uid resuscitation in acute pancreatitis. In one study, all patients who exhibited hemoconcentration at admission and whose hematocrit increased further after the rst 24 h (as a result of inadequate uid resuscitation) developed pancreatic necrosis (172). Clinically, the adequacy of uid resuscitation should be monitored by vital signs, urinary output, and decrease of hematocrit at 12 and 24 h after admission (particularly for patients with hemoconcentration at admission). Monitoring of central venous pressure is generally not required.

A second important consequence of hypovolemia is intestinal ischemia. There is evidence that ischemia increases intestinal permeability to bacteria, products of bacteria, and endotoxins. Translocation of bacteria is an important cause of secondary pancreatic infection. Translocation of bacterial products and endotoxins are also potent stimulants of cytokine release and increases in nitric oxide that contribute both to ongoing pancreatic injury and also to organ failure (particularly respiratory failure) (98 100, 179).

It is important to relieve abdominal pain with a parenterally administered narcotic medication. There is no evidence to suggest an advantage of any particular type of medication. The amount of narcotic agent and the frequency of administration should be monitored closely by experienced physicians. Many hospitals have a dedicated pain service staffed by experienced physicians. When abdominal pain is particularly severe, patient-controlled analgesia can be used. It is particularly important to obtain measurements of bedside oxygen saturation frequently whenever narcotic agents are administered to relieve pain.

TREATMENT GUIDELINE II: TRANSFER TO AN INTENSIVE CARE UNIT

Prompt transfer to an intensive care unit should take place for sustained organ failure. Transfer to an intensive care unit (or possibly a step-down care unit) should be considered if there are signs that suggest that the pancreatitis is severe or is likely to be severe.

Level of evidence: III

Evidence of organ dysfunction is the most important reason for prompt transfer to an intensive care unit. In particular, sustained hypoxemia, hypotension refractory to a bolus of IV uids, and possibly renal insuf ciency that does not respond to a uid bolus (such as a serum creatinine >2.0 mg/dL) warrant prompt transfer to an intensive care unit.

There are indications other than organ failure that should prompt consideration of transfer to an intensive care unit. One indication is the need for very aggressive uid resuscitation to overcome hemoconcentration, especially in an older person who may have underlying cardiovascular disease such that meticulous care will be required to gauge the amount of IV uids. Also, if a patient does not have hypoxemia but is showing signs of labored respiration, transfer should be considered to monitor pulmonary status carefully in anticipation of a need for intubation with assisted ventilation.

Additional danger signals that warrant close supervision by physicians and nursing staff in a step down unit but not necessarily urgent transfer to an intensive care unit include obesity (BMI >30), oliguria with urine output <50 mL/h, tachycardia with pulse >120 beats/min, evidence of encephalopathy, and increasing need of narcotic agents to counteract pain. The advantage of a specialized unit such as an intensive care unit is the opportunity of coordinated care under the direction of a multidisciplinary team with representation from pulmonary/critical care, gastroenterology, surgery, and radiology services. While an intensive care unit offers the best supportive treatment, including optimal uid resuscitation, monitoring for early signs of organ dysfunction, pressor agents for sustained hypotension, intubation and assisted ventilation for respiratory failure, and renal dialysis for intractable renal failure, there is currently no speci c treatment to counteract progressive organ failure.

TREATMENT GUIDELINE III: NUTRITIONAL SUPPORT

Whenever possible, enteral feeding rather than total parenteral nutrition (TPN) is suggested for patients who require nutritional support.

Level of evidence: II

In mild pancreatitis, oral intake is usually restored within 3 7 days of hospitalization, and nutritional support is not required. The exact timing of oral nutrition and the content of oral nutrition have not as yet been subjected to randomized prospective trials. In general, oral intake of limited amounts of calories is usually initiated when abdominal pain has subsided such that parenteral narcotics are no longer required, abdominal tenderness has markedly decreased, nausea and vomiting have ceased, bowel sounds are present, and the overall assessment of the physician is that the patient has improved. It has not been ascertained whether patients recovering from mild pancreatitis can safely receive a low-fat diet at the onset of oral nutrition rather than a diet of clear or full liquids prior to a low-fat diet. The need for dietary restriction of fat at the onset of nutrition has also not been evaluated. In interstitial pancreatitis, there is no role for pancreatic enzymes when the patient resumes an oral diet. However, in severe necrotizing pancreatitis (especially when most or all of the pancreas is necrotic but also when the body of the pancreas is totally necrotic such that enzymes from a remnant viable tail of the pancreas cannot gain access to the duodenum), it is prudent to provide potent oral pancreatic enzymes and then make an evaluation later in the recovery period whether or not the patient has pancreatic steatorrhea. Also, in subtotal or total pancreatic necrosis, it is prudent to use a proton pump inhibitor on a daily basis because of the likelihood that bicarbonate secretion by the pancreas is severely diminished rendering the patient susceptible to a duodenal ulcer.

In severe pancreatitis, nutritional support should be initiated when it becomes clear that the patient will not be able to consume nourishment by mouth for several weeks. This assessment can usually be made within the rst 3 4 days of illness. There is reason to believe that enteral feeding is preferable to TPN. First, there is compelling evidence that in severe acute pancreatitis gut barrier function is compromised resulting in greater intestinal permeability to bacteria (which may lead to infected necrosis) and endotoxins (which stimulate nitric oxide and cytokine production that contribute to organ failure) (98 100, 179). There is also evidence that there is a higher incidence of gastric colonization with potentially pathogenic enteric bacteria in severe disease that may also contribute to septic complications (130). Because

enteral feeding stabilizes gut barrier function, there has been considerable interest in the ability of enteral feeding not only to provide appropriate nutritional support, but also to prevent systemic complications and improve morbidity and mortality. Finally, there are numerous complications associated with the use of TPN (including line sepsis) that can be avoided by use of enteral feeding.

There have been a number of randomized prospective, but not double-blind, trials that have compared enteral feeding with TPN (92, 93, 95 97). All have included relatively few patients (median 33, range 17 53) that have differed considerably in entry criteria. There have been other methodologic concerns that have been well outlined in two meta-analyses (180, 181). In general, it is reasonable to conclude that enteral feeding is safer and less expensive than TPN, but there is not yet convincing ndings that there are major improvements in morbidity and mortality of acute pancreatitis.

The conclusions of the two meta-analyses, one of which reported on six studies (181) and the other on two of the six studies (180), were contradictory. In one, enteral nutrition was favored *versus* TPN (180); in the other, the interpretation was that there were insuf cient data to provide rm conclusions about the safety and ef cacy of enteral nutrition when compared to TPN (181). Additional studies will be required to determine the advantages of nasojejunal feeding *versus* TPN.

In one study, nasogastric feeding was found to be comparable to nasojejunal feeding in terms of safety, morbidity, and mortality (42). Additional studies will be required to determine the role of nasogastric feeding rather nasojejunal feeding for nutritional support. A major concern relates to stimulation of pancreatic secretion when feeding is introduced into the stomach or duodenum. There is evidence that intraduodenal feedings increase pancreatic enzyme synthesis (182) and secretion (183). The result may be an exacerbation of abdominal pain associated with a greater serum amylase (182).

A practical limitation of enteral feeding is that some patients do not tolerate the mechanical discomfort of a nasojejunal or nasogastric tube over extended periods of time. Thus the route of nutritional support must be tailored to the individual patient, and modi ed depending on the patient's response and tolerance.

TREATMENT GUIDELINE IV: USE OF PROPHYLACTIC ANTIBIOTICS IN NECROTIZING PANCREATITIS

The use of prophylactic antibiotics to prevent pancreatic infection is not recommended at this time among patients with necrotizing pancreatitis.

Level of evidence: III

In recent years, there have been six randomized, prospective, but not double-blind, studies that have evaluated the role of antibiotics in preventing pancreatic infection (112 114, 120 122). The number of patients randomized in each study was small (median 60, range 23 102). Five of these studies used IV antibiotics (112 114, 120, 122) and one used selective decontamination of the digestive tract (121). Among these studies, three (113, 120, 121) demonstrated a decrease in infected necrosis with the use of prophylactic antibiotics, and two did not (112, 122). None showed a convincing decrease in mortality. There have been two meta-analyses: one (184) evaluated three of these studies (112, 114, 120) and a fourth that was published in German; the other (185) evaluated two studies (112, 120) and the same article published in German. The conclusion reached in one (185) was that antibiotic prophylaxis signi cantly reduced mortality, and in the other that antibiotics reduced pancreatic infection (184).

More recently, a multicenter, double-blind, placebo-controlled study on the effectiveness of cipro oxacin and metronidazole in reducing morbidity and mortality concluded that there was no difference in the rate of infected necrosis, systemic complications, or mortality in the two groups (111). While the numbers in this study were also relatively small (76 patients in all), this remains the only placebo-controlled, double-blind trial that has evaluated this important problem.

A recent editorial concluded that a de nitive answer would require larger studies with improvement in study design pertaining to the standardization of feedings, length of antibiotic therapy, and improved strati cation based on predictors of severity (186). The editorial also pointed out an increasing concern that the use of potent antibiotics may lead to a superimposed fungal infection. This risk appears to correlate with prolonged use of antibiotic therapy (62 64). While the prevalence of fungal infection among patients with necrotizing pancreatitis in recent studies has been 9% (range 8 35%) (62, 64, 65, 91, 110, 119, 187), it remains unclear whether mortality is signi cantly higher when there is superimposed fungal infection. Some reports indicate a greater mortality (63, 65, 91, 116), whereas others do not (62, 64, 115, 119, 187). It also remains unclear which patients should receive prophylaxis with antifungal agents.

Until further evidence is available, prophylactic antibiotics are not recommended in necrotizing pancreatitis. There is no indication for routine antibiotics in patients with interstitial pancreatitis.

It should be understood that during the rst 7 10 days, patients with pancreatic necrosis may appear septic with leukocytosis, fever, and/or organ failure. During this interval, antibiotic therapy is appropriate while an evaluation for a source of infection is undertaken. Once blood and other cultures (including culture of CT-guided ne needle aspiration) are found to be negative and no source of infection is identi- ed, our recommendation is to discontinue antibiotic therapy. It should also be understood that patients with necrotizing pancreatitis may appear clinically septic at various intervals during a prolonged hospitalization. Antibiotic therapy is appropriate for these patients while a thorough investigation for a source of infection takes place. If appropriate cultures,

including imaging-guided ne needle aspiration of pancreatic necrosis, are found to be negative, antibiotic therapy should be discontinued.

TREATMENT GUIDELINE V: TREATMENT OF INFECTED NECROSIS

CT-guided percutaneous aspiration with Gram's stain and culture is recommended when infected necrosis is suspected. Treatment of choice in infected necrosis is surgical debridement. Alternative minimally invasive approaches may be used in selected circumstances.

Level of evidence: III

Approximately 33% of patients with necrotizing pancreatitis develop infected necrosis, usually after 10 days of illness (62, 66, 68, 83, 91, 111, 113, 117, 118, 120, 121, 147, 159, 169, 170). Most patients with infected necrosis have systemic toxicity (including fever and leukocytosis) that is either documented from the time of admission or develops at some time after admission. As many as 48% of patients with infected necrosis have persistent organ failure, either documented initially at admission or sometime after admission (83). Because the elevations in white blood count and temperature may be identical in sterile and infected necrosis (188), and because organ failure may occur in a substantial percentage of patients with both sterile and infected necrosis (45% *vs* 62% in one series) (83), it is impossible to distinguish these conditions clinically unless CT scan shows evidence of air bubbles in the retroperitoneum. The distinction between sterile and infected necrosis is an important concern throughout the course of necrotizing pancreatitis, but particularly during the second and third weeks, when at least one-half of cases of infected necrosis are documented (47, 117, 126, 159, 170).

The technique of percutaneous aspiration (usually by CT guidance) has proven to be safe and accurate in distinguishing sterile from infected necrosis (47, 89, 117, 120, 126, 170, 188) except possibly during the rst week of illness (117). For this reason, when infected necrosis is suspected on the basis of systemic toxicity and/or organ failure, CT-guided percutaneous aspiration for Gram's stain and culture is recommended (2 4, 6 13). The initial aspiration is usually performed during the second or third week of illness. If this aspiration is negative for bacteria or fungi, it is generally recommended that patients with persistence of systemic toxicity undergo CT-guided percutaneous aspiration every 5 7 days to identify instances of infected necrosis that develop at a later time (or conceivably may have already developed but were not diagnosed at the time of a prior aspiration).

If CT-guided percutaneous aspiration reveals the presence of Gram-negative organisms, choices for antibiotic treatment include a carbipenem, a uoroquinolone plus metronidazole, or a third generation cephalosporin plus metronidazole pending results of culture and sensitivity. If Gram's stain reveals the presence of Gram-positive bacteria, a reasonable choice is vancomycin until results of culture and sensitivity are determined.

The standard of care for infected pancreatic necrosis is surgical debridement unless patients are too ill to undergo surgical intervention (47, 55, 89, 111 113, 116, 120, 121, 156, 164, 169, 189). Guidelines (2, 4, 6, 7) and review articles (9 12) have generally suggested that surgery be performed promptly or have left unsaid the exact timing of surgery. However, one recent guideline speci ed that surgical debridement be performed for patients with infected necrosis who are septic (3). In addition, a review article suggested that the initial treatment for infected necrosis for patients who were clinically stable should be a 3-wk course of antibiotics prior to surgery to allow the in ammatory reaction to subside and the infected process to become better organized (10). The role of prolonged antibiotic therapy prior to surgical debridement in infected necrosis requires further study. The timing of surgical debridement (whether promptly after initiation of antibiotic therapy or after a delay of several weeks) is generally determined by the pancreatic surgeon.

The concept that infected pancreatic necrosis requires prompt surgical debridement has also been challenged by anecdotal reports of patients who have been treated by antibiotic therapy alone (131, 132) and by one report (126) of 28 patients with infected necrosis treated prospectively with antibiotics rather than urgent surgical debridement. In this report, there were two deaths among 12 patients who eventually required elective surgical intervention, and also two deaths among 16 patients who were treated with long-term antibiotic therapy without eventual surgical debridement. It is also noteworthy that in one prior study (131), two of six patients treated with prolonged antibiotics without surgery died. Additional studies will be required to determine the bene t of prolonged antibiotic therapy without surgery.

The types of surgery that have generally been recommended have included necrosectomy with closed continuous irrigation via indwelling catheters (47, 55, 89, 104, 110, 112, 119, 156, 164, 169), necrosectomy and open packing (89, 104, 116, 119, 156, 164, 169), or necrosectomy with closed drainage without irrigation (89, 106). There have not been randomized prospective trials comparing these procedures. All are generally considered to provide equal bene t in skilled surgical centers.

More recently, several additional procedures have been introduced that are less invasive than standard open surgical debridement of infected necrosis. These techniques have generally been reserved for patients with infected pancreatic necrosis who are too ill to undergo prompt surgical debridement (such as those with organ failure and/or serious comorbid disease). The rst technique is minimally invasive retroperitoneal necrosectomy (55, 101, 102, 116, 156), which uses a percutaneous technique to gain access to the necrotic area, dilatation of the tract to a 30-French size, an operating nephroscope for piecemeal retrieval of solid material, irrigation with high volume lavage, and placement of catheters for long-term continuous irrigation. This technique requires

general anesthesia and has not been compared in a prospective fashion to more traditional surgical debridement. Another technique is laparoscopic necrosectomy with placement of large caliber drains under direct surgical inspection. This technique presumably has less physiologic stress and may have fewer complications than open surgical debridement (190 194). This technique has not been compared in a prospective fashion to open surgical debridement.

A third technique is percutaneous catheter drainage of infected necrosis (89, 103, 124, 131, 132, 137, 169, 195). The results from this technique have been encouraging, either as a temporizing measure until the patient has stabilized suf - ciently to undergo surgical necrosectomy or as de nitive therapy that completely eradicates infected necrosis after several weeks or months. This technique has not been compared to surgical debridement and requires a dedicated team of skilled radiologists who are willing to place at least one or more large bore drains, be available at all times for supervision of irrigation of catheters, exchange or upsizing of catheters because of inadequate drainage of infected material, and placement of new catheters as indicated. Finally, endoscopic drainage, as applied to sterile necrosis, may occasionally be applicable to selected patients with infected necrosis, but should be approached with caution (166, 195) (see Treatment Guideline VI).

A pancreatic abscess (whether in the form of an infected peripancreatic pseudocyst or late liquefaction of an area of pancreatic necrosis) generally takes place after 5 wk in a patient who is in the recovery phase of acute pancreatitis. Mortality of a properly treated pancreatic abscess is very low. Appropriate treatments include surgical drainage, percutaneous catheter drainage, or possibly endoscopic drainage (196).

TREATMENT GUIDELINE VI: TREATMENT OF STERILE NECROSIS

Sterile necrosis is best managed medically during the rst 2 3 wk. After this interval, if abdominal pain persists and prevents oral intake, debridement should be considered. This is usually accomplished surgically, but percutaneous or endoscopic debridement is a reasonable choice in selected circumstances with the appropriate expertise. Pancreatic duct leaks and stulas are common and may require endoscopic or surgical therapy.

Level of evidence: III

Organ failure occurs in at least 48% of patients with sterile necrosis (66, 83). Until the past 10 15 yr, surgical debridement was favored in patients with sterile necrosis with persistent organ failure with the view that removal of the necrotic material would improve chances of survival. There is now an increasing consensus that patients with sterile necrosis should continue to be managed medically during the rst 2 3 wk for the following reasons. First, 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 debridement (55, 60, 68, 107 109, 138). Secondly, when sterile necrosis is debrided surgically, a common sequela is the development of infected necrosis and the need for additional surgery (55, 91, 112, 138, 160). In at least one report, patients so treated had a very high mortality (138). Finally, in one randomized prospective trial that compared early to late surgery in a small number of patients with sterile necrosis, there was a trend to greater mortality among those operated on within 4 days (105).

The concept of removing necrotic tissue in severe sterile necrosis in an effort to overcome organ failure may still be valid when a less invasive technique is used. Such a technique is minimally invasive retroperitoneal surgery, which has been used in sterile necrosis as well as infected necrosis (55, 102, 156). Minimally invasive surgery within the rst 2 3 wk of severe sterile necrosis has not been compared prospectively with the continuation of medical therapy and thus far is an evolving technology that has been restricted to research centers.

If surgery is delayed for at least 2 3 wk, the diffuse in ammatory process in the retroperitoneum resolves considerably, and gives rise to an encapsulated structure that envelops the necrotic pancreas and peripancreatic area (166). This structure has frequently been called organized necrosis. By this time, organ failure has usually subsided, and many patients are now asymptomatic and do not require additional therapy. Those that are symptomatic generally have persistence in temperature and leukocytosis suggesting the possibility of infected necrosis, nausea or vomiting indicating compression of stomach or duodenum, or abdominal pain especially after eating as a result of greater pressure within organized necrosis caused by extravasation of uid from residual normal pancreatic parenchyma in the remnant tail of the pancreas. Patients who remain symptomatic require decompression of organized necrosis, either by surgical, percutaneous, or endoscopic techniques. More than one technique is often necessary in an individual patient. Management of patients with pancreatic necrosis is complex and is optimally provided by a multidisciplinary team at a center with expertise in all specialties dealing with pancreatic disease.

Surgical management involves debridement of the necrotic material, evacuation of the uid within the organized necrosis, and if a suitable capsule is present, creation of an anastomosis to the posterior wall of the stomach or to a Roux-en-Y loop of jejunum. This can be done by traditional open or by a newer laparoscopic approach. Percutaneous management of organized necrosis can be performed but requires aggressive management including placement of one or more large bore drains, aggressive lavage, and repositioning of catheters as necessary, and in some cases sinus-tract endoscopy (89, 103, 124, 131, 132, 137, 169, 195). Endoscopic debridement can be considered when the organized necrosis is rmly adherent to the wall of the stomach (or duodenum) and when endoscopic ultrasound reveals no intervening vessels (197). The technique includes puncture of the intervening gastric

(or duodenal) wall with an instrument introduced through a duodenoscope or echo-endoscope, followed by endoscopic balloon dilation to enlarge the opening, retrieval of necrotic material and evacuation of uid, often requiring direct endoscopic entry into the cavity and mechanical evacuation of solid contents, and insertion of double pigtail catheters between the stomach (or duodenum) and the cavity to maintain drainage. Repeated endoscopic debridements and/or prolonged nasocystic lavage of the cavity are often required (166, 196). While this technique appears to have a high success rate in limited reports, complications including infection and need for surgery have been noted in up to 37% of cases (166, 196). Endoscopic debridement should be performed at medical centers with extensive expertise in pancreatic therapeutic endoscopy. The major concern with any nonoperative technique is the potential for incomplete evacuation and secondary infection of residual necrotic material.

On very rare occasions, sterile pancreatic necrosis requires urgent surgical treatment even during the rst several weeks of illness (2, 4). One indication is the development of an abdominal compartment syndrome. This is manifested by marked abdominal distention with increase of intra-abdominal pressure. Laparotomy with decompression can be life saving. The second is the development of severe abdominal pain suggestive of intestinal perforation or infarction caused by extension of the in ammatory exudate to either the colon or small bowel. A third indication is the development of severe bleeding from a pseudoaneurysm. An appropriate way to document the presence of a pseudoaneurysm is contrast-enhanced CT scan. If a pseudoaneurysm is discovered, the treatment of choice is angiographic insertion of a coil to embolize the pseudoaneurysm. Surgery is required if this technique fails (35, 198).

Pancreatic duct leaks and/or main pancreatic duct disconnection (disconnected duct syndrome) may occur in one-third or more of patients with pancreatic necrosis, either spontaneously or as a result of debridement procedures (195, 199, 200). Duct leaks may be associated with worse outcomes (199), and present substantial acute and long-term management problems including recurrent uid collections, pancreatic ascites, pleural effusions, or pancreatic-cutaneous stulas. Management of pancreatic duct leaks requires expertise and cooperation of endoscopy, surgery, and radiology. Medical treatment is aimed at minimizing pancreatic secretion, including nasojejunal tube feeding or total parenteral nutrition, antisecretory therapy with octreotide, or repeated or chronic drainage procedures. Duct leaks can be identi ed by ERCP or by MRCP with secretin stimulation (38). ERCP should be performed for patients with evidence of persistent or symptomatic pancreatic duct leaks, and at centers with experience in pancreatic endotherapy.

Endoscopic treatment of a pancreatic duct leak includes placement of a pancreatic stent, preferably bridging the leak when the main pancreatic duct is in continuity (200 202). Endoscopic pancreatic duct stent placement in the setting of organized necrosis or larger or debris- lled pseudocysts should generally be accompanied by direct drainage of the necrotic cavity by another route as already described; placement of pancreatic stents alone during acutely evolving pancreatic necrosis is considered experimental at the current time, with concern about colonization with bacteria and infection of otherwise sterile necrosis (203). Closure of duct leaks with stents is successful in about two-thirds to three-quarters of cases, depending on a number of factors including site and size of duct disruption, superinfection, downstream obstruction as a consequence of pancreatic stricture or stone, whether the leak can be bridged, and the presence of the disconnected duct syndrome (200 202). Closure of refractory pancreatic stulas by injection of cyanoacrylate glue by endoscopic or percutaneous routes has been reported (196). Disconnected duct syndrome occurs when there is a wide gap in the main pancreatic duct, usually due to necrosis that cannot be bridged by a stent. In such cases, eventual surgical resection of the upstream remnant tail of the pancreas or internal drainage via Roux-en-Y anastamosis is often required (204).

TREATMENT GUIDELINE VII: ROLE OF ERCP AND BILIARY SPHINCTEROTOMY IN GALLSTONE PANCREATITIS

ERCP is indicated for clearance of bile duct stones in patients with severe pancreatitis, in those with cholangitis, in those who are poor candidates for cholecystectomy, in those who are postcholecystectomy, and in those with strong evidence of persistent biliary obstruction. ERCP should be performed primarily in patients with high suspicion of bile duct stones when therapy is indicated. Routine ERCP should be avoided in patients with low to intermediate suspicion of retained bile duct stones, who are planned to have cholecystectomy. EUS or MRCP can be used to identify common bile duct stones and determine need for ERCP in clinically ambiguous situations.

Level of evidence: I

Gallstones are suspected as a cause of acute pancreatitis when there are elevations of liver chemistries (particularly ALT $\geq$3 times the upper limit of normal) (205, 206), when gallstones are visualized, and to a lesser extent when the common bile duct is found to be dilated on the basis of ultrasound or computerized axial tomography (39, 207). Gallstones can be documented within the common bile duct with accuracy similar to ERCP by EUS (39, 205, 207 226), with somewhat lower accuracy by MRCP (227 233), and by intraoperative cholangiography at the time of laparoscopic cholecystectomy (234 237). Identi cation of a biliary etiology of acute pancreatitis is important because recurrent episodes will occur in one-third to two-thirds of these patients in follow-up periods of as short as 3 months unless gallstones are eliminated (238, 239).

The role of urgent ERCP and biliary sphincterotomy in gallstone pancreatitis has been the subject of three published randomized controlled studies. These studies have compared early ERCP with biliary sphincterotomy with delayed or selective ERCP (240 242). Inclusion criteria and presence of bile duct stones vary considerably among these trials. Two of the trials (240, 242), but not the third (241), showed a signi cant bene t for early sphincterotomy and stone

extraction, primarily in patients with severe acute pancreatitis and those with ascending cholangitis. Meta-analysis of randomized controlled trials including an additional unpublished abstract suggested that early intervention with ERCP in acute biliary pancreatitis resulted in a signi cant reduction in complication rate and nonsigni cant reduction in mortality (243). Subsequent meta-analysis limited to the three published trials concluded that endoscopic sphincterotomy signi cantly reduced complications in severe but not mild gallstone-associated pancreatitis but did not reduce mortality in mild or severe disease (244). There is insuf cient evidence to draw any conclusions about hospital stay and cost. One interpretation is that there is a strong correlation between persistent biliary obstruction and more severe disease (245). Hence, common bile duct stones were seen more often in the two positive studies (240, 242) than in the negative study (241). Retained common bile duct stones could lead to organ failure by causing ascending cholangitis or by causing intensi cation of the pancreatitis if a gallstone is blocking the pancreatic duct. Overall, these studies suggest that ERCP and biliary sphincterotomy is indicated (preferably within 24 h of admission) for patients with severe biliary pancreatitis with retained common bile duct stones and for those with cholangitis.

In the majority of patients with mild biliary pancreatitis, bile duct stones have passed by the time cholangiography is considered, such that routine ERCP prior to cholecystectomy is unnecessary and adds avoidable risk (246 250). For example, in a randomized trial in patients with mild gallstone pancreatitis with high suspicion of persisting common bile duct stones (elevated serum bilirubin, dilated common bile duct, or persistent hyperamylasemia) but without cholangitis, selective postoperative ERCP and CBD stone extraction was necessary in only approximately one in four such patients, and was associated with a shorter hospital stay, less cost, no increase in combined treatment failure rate, and signi cant reduction in ERCP use compared with routine preoperative ERCP (251). Thus, patients with resolving mild acute pancreatitis can undergo laparoscopic cholecystectomy with intraoperative cholangiography, and any remaining bile duct stones can be dealt with by postoperative or intraoperative ERCP, or by laparoscopic or open common bile duct exploration, depending on local expertise and access to referral centers in cases of unsuccessful ERCP.

During the course of biliary pancreatitis, progressive increases in serum bilirubin and other liver function tests and persistent dilatation of the common bile duct are strongly suggestive of common bile duct obstruction by gallstones (251 254). In this circumstance, it is reasonable to proceed directly to ERCP. In clinical practice, if there is intermediate concern regarding the possibility of a retained common bile duct stone, and the patient is not felt to be a good candidate for cholecystectomy with cholangiogram within the near future, EUS or MRCP can be performed to assess for presence of bile duct stones and determine need for ERCP. EUS is generally considered to be the most accurate method to detect bile duct stones; sensitivity of MRCP for small bile duct stones is lower, especially for those that are impacted at the ampulla (229, 230). EUS or MRCP are also useful to determine need for ERCP in patients who are pregnant, or in whom ERCP would be high risk or technically dif cult due to reasons such as severe coagulopathy or altered surgical anatomy. In critically ill patients, EUS can be performed at the bedside. The limitations of this technique include availability and operator-dependency. The limitations of MRCP include variable quality, dif culty in performing this procedure in critically ill or uncooperative patients, and contraindications such as presence of pacemakers or cerebral aneurysm clips.

Biliary sphincterotomy rather than cholecystectomy may be appropriate for proven mild biliary pancreatitis, especially in elderly patients who are poor candidates for surgery because of severe medical comorbidity, patients in whom cholecystectomy must be delayed because of local or systemic complications of pancreatitis, or because of pregnancy (255 258). The role of biliary sphincterotomy when biliary pancreatitis is strongly suspected but not proven has not been fully characterized. Some studies have suggested the effectiveness of endoscopic biliary sphincterotomy in these circumstances in preventing further episodes of acute biliary pancreatitis. These uncontrolled case series mostly suggest a reduction in the frequency of attacks of pancreatitis, although recurrent bile duct stones or acute cholecystitis may still be a problem in the future (255 264). Before considering an empiric biliary sphincterotomy for recurrent pancreatitis with or without abnormal liver function tests, the clinician must be aware of the possibility of an alternative etiology, such as sphincter of Oddi dysfunction, especially in women, young or middle-aged patients, and patients who are postcholecystectomy, or do not have clearly documented gallstone disease. Empiric biliary sphincterotomy and even diagnostic ERCP in patients with recurrent pancreatitis, and especially those with suspected sphincter of Oddi dysfunction, are associated with signi cantly greater risk of post-ERCP pancreatitis, and are less likely to be of therapeutic bene t than for patients with biliary pancreatitis (246 250). ERCP in such patients may be best approached in the context of a more comprehensive evaluation using other imaging techniques including MRCP and EUS, and risk of post-ERCP pancreatitis may be reduced by placement of a temporary small-caliber pancreatic stent (207, 265).

A summary of the recommendations for use of ERCP, EUS, and MRCP in patients with acute biliary pancreatitis is shown in Table 8.

SUMMARY

The diagnosis of acute pancreatitis requires two of the following three features: 1) characteristic abdominal pain, 2) serum amylase and/or lipase $\geq$3 times the upper limit of normal, and 3) characteristic ndings of acute pancreatitis on CT scan.

Risk factors of severity of acute pancreatitis at admission include older age, obesity, and organ failure. Tests at

Table 8. Suggested Indications for ERCP, EUS, and MRCP in Patients with Acute Biliary Pancreatitis

Urgent ERCP (Preferably Within 24 h of Admission):
Severe pancreatitis (organ failure)
Suspicion of cholangitis
Elective ERCP with Sphincterotomy:
Imaging study demonstrating persistent common bile duct stone
Evolving evidence of biliary obstruction (such as rising liver chemistries)
Poor surgical candidate for laparoscopic cholecystectomy
Strong suspicion of bile duct stones postcholecystectomy
Endoscopic Ultrasound or MRCP to Determine Need for ERCP:
Clinical course not improving sufficiently to allow timely laparoscopic cholecystectomy and intraoperative cholangiogram
Pregnant patient
High-risk or difficult ERCP (*e.g.*, coagulopathy, altered surgical anatomy)
Uncertainty regarding biliary etiology of pancreatitis

admission that are also helpful in distinguishing mild from severe acute pancreatitis include APACHE-II score ≥ 8 and serum hematocrit (a value <44 strongly suggests mild acute pancreatitis). An APACHE-II score that continues to increase for the first 48 h strongly suggests the development of severe acute pancreatitis. A CRP >150 mg/L within the first 72 h strongly correlates with the presence of pancreatic necrosis.

The two most important markers of severity in acute pancreatitis are organ failure (particularly multisystem organ failure) and pancreatic necrosis. Contrast-enhanced CT scan is the best available test to distinguish interstitial from necrotizing pancreatitis, particularly after 2–3 days of illness. Mortality of sustained multisystem organ failure in association with necrotizing pancreatitis is generally $>36\%$.

Supportive care includes vigorous fluid resuscitation that can be monitored in a variety of ways including a progressive decrease in serum hematocrit at 12 and 24 h. Supplemental oxygen should be administered during the first 24–48 h, bedside oxygen saturation monitored at frequent intervals, and blood gases obtained when clinically indicated, particularly when oxygen saturation is $\leq 95\%$.

Transfer to an intensive care unit is recommended if there is sustained organ failure or if there are other indications that the pancreatitis is severe including oliguria, persistent tachycardia, and labored respiration.

Patients who are unlikely to resume oral nutrition within 5 days because of sustained organ failure or other indications require nutritional support. Nutiritional support can be provided by TPN or by enteral feeding. There appear to be some advantages to enteral feeding.

Patients with acute pancreatitis caused by gallstones, who are strongly suspected of harboring common bile duct stones on the basis of organ failure or other signs of severe systemic toxicity (marked leukocytosis and/or fever), require evaluation for the presence of choledocholithiasis, preferably within the first 24 h of admission. ERCP with endosocopic biliary sphincterotomy and stone removal are indicated for patients with cholangitis, severe acute pancreatitis, or high clinical suspicion or definitive demonstration of persistent bile duct stones by other imaging techniques. Expectant management with interval cholecystectomy including intraoperative cholangiogram is appropriate for most patients with mild to moderate pancreatitis and an improving clinical course. Routine precholecystectomy ERCP is not recommended in patients with biliary pancreatitis. In ambiguous cases, where available, evaluation for bile duct stones can beperformed by endoscopic ultrasound or MRCP.

The use of prophylactic antibiotics in necrotizing pancreatitis is not recommended in view of a recent prospective randomized double-blind trial that showed no benefit and in view of the concern that the prolonged use of potent antibiotic agents may lead to the emergence of resistant Gram-positive organisms and fungal infections in the necrotic pancreas. It is reasonable to administer appropriate antibiotics in necrotizing pancreatitis associated with fever, leukocytosis, and/or organ failure while appropriate cultures (including culture of CT-guided percutaneous aspiration of the pancreas) are obtained. Antibiotics should then be discontinued if no source of infection is found.

CT-guided percutaneous aspiration with Gram's stain and culture is recommended when infected pancreatic necrosis is suspected. Treatment of choice of infected necrosis is surgical debridement. The timing of surgery is left to the discretion of the pancreatic surgeon. Patients who are medically unfit for open surgical debridement can be treated with less invasive surgical techniques, radiologic techniques, and, at times, endoscopic techniques in medical centers with these capabilities.

Treatment of sterile pancreatic necrosis is generally medical during the first several weeks even in the presence of multisystem organ failure. Eventually, after the acute inflammatory process has subsided and coalesced into an encapsulated structure that is frequently called organized necrosis, debridement may be required for intractable abdominal pain, intractable nausea or vomiting caused by extrinsic compression of stomach or duodenum, or systemic toxicity (fever and/or intractable malaise). Debridement can be performed by surgical, endoscopic, or radiologic techniques.

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APPENDIX

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