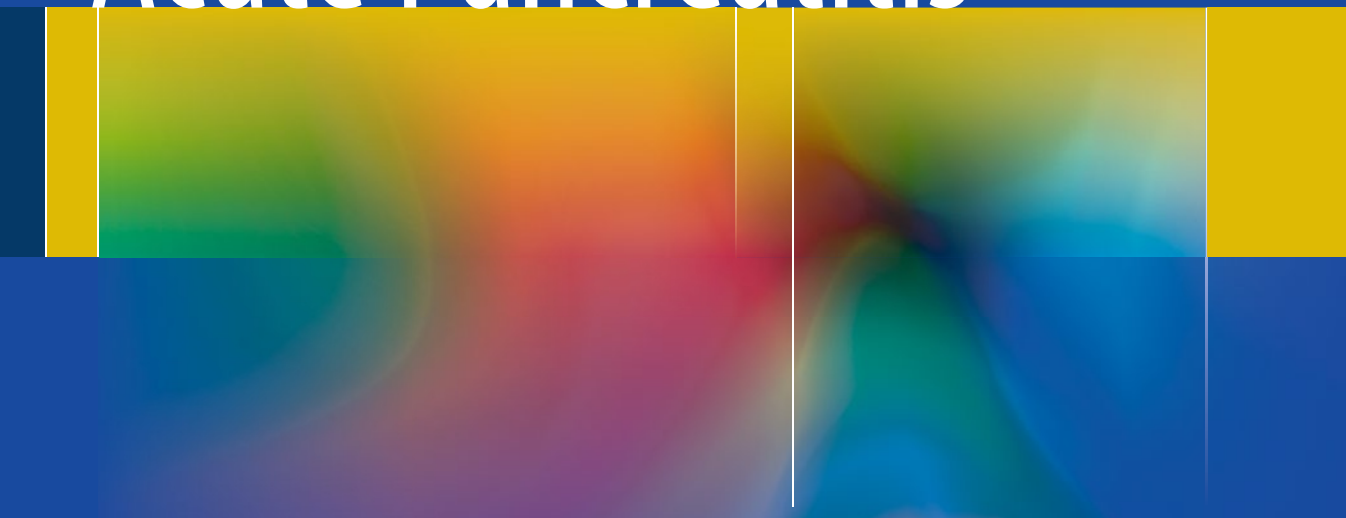
Prediction and Management of Severe Acute Pancreatitis



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Preface

Severe acute pancreatitis (SAP) is a devastating disease affecting thousands of patients annually and resulting in substantial morbidity, mortality, and healthcare costs. In fact, acute pancreatitis is currently the most common hospital discharge diagnosis for gastrointestinal disease in the United States. While most patients have mild pancreatitis and recover, the high morbidity and a mortality rate of 20 % make SAP among the most lethal of all gastrointestinal diseases.

In the last 20 years extensive progress has been made in identifying and treating SAP. These advances include more standardized definitions of disease, more careful long-term follow-up of patient outcomes, and the beginnings of evidence-based therapies to prevent mortality and severe complications. Randomized, controlled trials are increasingly being performed to evaluate interventions in this disease, and consensus about definitions and therapies are being offered by major medical societies. Given the significant pathologic burden and improved diagnostic and therapeutic modalities, it is an important time for a text on severe acute pancreatitis.

This textbook provides a comprehensive review of the subject and serves as an essential resource for practicing gastroenterologists, surgeons, radiologists, intensivists, hospitalists, pathologists, and trainees. It details the recent consensus guidelines updating the definition of pancreatitis and its complications. It summarizes the current prediction models for severe acute pancreatitis, including laboratory, clinical, and imaging parameters. Evidence-based guidelines of medical and surgical management of both the hospitalized and discharged patient are described, with recommendations from expert authors pertaining to various clinical situations. Finally, complications of acute pancreatitis and their management, including the use of cutting-edge minimally invasive therapies, are discussed.

We offer our deep gratitude to our colleagues who authored chapters for this text. Their devotion to the field of pancreatology and their determination to improve the outcomes of patients afflicted with acute pancreatitis are inspiring. In editing this work, we were consistently reminded of how fortunate we are to collaborate with such dedicated clinicians and researchers.

We would also like to thank our editors at Springer, specifically Diane Lamsback, whose patience and guidance were critical in completing this book.

We hope you find the following text enriching and rewarding as we continue to make progress in the management and treatment of this difficult disease.

Gainesville, FL, USA — Chris E. Forsmark
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Part I

Definitions of Severe and Necrotizing Pancreatitis

Revised Atlanta Classification of Acute Pancreatitis

1

Rupjyoti Talukdar and Santhi Swaroop Vege

Introduction

The introduction of the 1992 Atlanta Classification was a major milestone in the practice of pancreatology at that time [1]. The classification was aimed to define a common terminology and define the severity of the disease in a globally acceptable uniform manner. Even though it generated great enthusiasm initially, it was observed over the years that many issues pertaining to the disease were either not addressed or lacked clarity [2]. It was observed that over the past two decades, the terminologies from the Atlanta Classification were inappropriately used. For example, terms like pancreatic phlegmon and infected pseudocyst were still used, even after being abandoned in the Atlanta Classification. With generation of more data on the natural history and pathophysiology of the disease, and with development in cross-sectional imaging techniques, new terminologies like organized pancreatic necrosis, subacute pancreatic necrosis, necroma, and pseudocyst associated with necrosis came into existence [3]. These ambiguities called for a revision of the 1992 Atlanta Classification, which was long awaited in the pancreatology community. The process of revision was initiated in 2007 and after 5 long years of efforts that included modifications, revisions, and acquiring global consensus, the Revised Atlanta Classification was finally published in 2013 [4]. Table 1.1 shows the gross differences between the original and revised classification.

Objectives of Revision

The objectives of the revision of the Atlanta Classification were to (1) incorporate modern concepts of the disease; (2) address areas of confusion; (3) improve clinical assessment of severity; (4) enable standardized data reporting; (5) assist objective evaluation of new treatments; and (6) facilitate communication among treating physicians and different institutions.

However, the revision was not meant to be a management guideline, even though the definitions have potential to guide appropriate management strategies.

Methodology

The Revised Atlanta Classification resulted from an international, web-based, multiply reiterative process that began in 2007 at the Digestive Diseases Week. The process began

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Table 1.1 Changes made in the Revised Atlanta validation compared to the 1992 Atlanta Classification

1992 Atlanta Classification	Revised Atlanta Classification
• No defined threshold of amylase/lipase levels for the diagnosis of AP	• Elevation of serum amylase and lipase of greater than three times the upper limit of normal is required to make a diagnosis
• Inclusion of local complications and/or organ failure under the severe category	• The presence of local complications in the absence of persistent organ failure is categorized as moderately severe acute pancreatitis
• No distinction between transient and persistent organ failure	• Transient organ failure is defined as organ failure that resolves within 48 h • Persistent organ failure is defined as organ failure that persists beyond 48 h
• Nonuniform use in the classification for organ failure	• Organ failure should be defined according to the Modified Marshall scoring system • Gastrointestinal bleeding as an organ failure has been removed
	• Discrete definitions of local complications (acute peripancreatic fluid collections, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis)
• No distinction of peripancreatic collections with and without necrotic debris	• Terms like pancreatic abscess have been abandoned
• Local complications included necrosis, abscess, and pseudocyst	• Terms like "organized pancreatic necrosis," "subacute pancreatic necrosis," "necroma," and "pseudocyst associated with necrosis," pancreatic sequestration are now collectively termed as walled-off necrosis

with a meeting of 40 selected pancreatologists and pancreatic surgeons to agree on the process and areas of revision. A working group, consisting of three pancreatic surgeons, two pancreatologists, and one pancreatic radiologist, prepared an initial draft. This was the first working document that was circulated among the 40 participants; the document was revised according to their suggestions. This working draft was then sent electronically to all members of 11 national and international organizations interested in acute pancreatitis. The working group prepared a second working draft after discussing the modification suggested in the first draft and resent to the members. The process was repeated and a third draft was generated, which contained minor modifications and was submitted to Gut. Based on journal reviewers' comments, a fourth revision of the document was made in which the three-tier classification of severity was incorporated.

Definition of a Diagnosis of Acute Pancreatitis

According to the Revised Atlanta Classification, a diagnosis of acute pancreatitis (AP) can be made if two of the following three features are present, namely abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and characteristic findings of AP on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography. Acute pancreatitis runs a dynamic clinical course and levels of serum lipase and amylase tend to fall over time. Therefore, in patients presenting after a prolonged duration following onset of symptoms, serum lipase and amylase may not be greater than three times the upper limit of normal in spite of typical pancreatitis type abdominal pain. These are the patients in which CECT could help in making the diagnosis. In situations where a diagnosis can be satisfactorily made on the basis of pain and serum lipase/amylase, CECT should be reserved for potential future use when it can diagnose local complications and provide important leads for complication-specific management approaches.

Phases of Acute Pancreatitis

The natural course of AP runs through two overlapping but pathophysiologically discrete phases. The early phase, which usually runs for 1–2 weeks, is clinically marked by systemic inflammatory response syndrome (SIRS) that is triggered by the cytokine cascade released as result of local pancreatic inflammation [5–7]. Persistent and severe SIRS during this phase could lead to development of transient or persistent organ failure [8, 9]. Persistent organ failure, which is defined as organ failure lasting for greater than 48 h primarily determines the severity of AP in the first phase [6, 9, 10]. Acute pancreatitis is a dynamic disease and local complications do develop during this phase; however, they are not proportional to the extent of organ dysfunction, thereby negating them as the predominant determinant of severity during this phase [11, 12]. Therefore, imaging with CECT or MRCP is unlikely to be of benefit in assessment and prognostication in this phase.

In the second or late phase, which can run a protracted course of weeks to months, the additional determinant of severity besides persistent systemic inflammation is local complications. This phase is also marked by a compensatory anti-inflammatory response syndrome (CARS), which makes the patient prone to infections that in turn can further determine severity by contributing to organ dysfunction. Therefore, besides clinical monitoring a meticulous evaluation of the local complications by appropriate imaging also becomes essential during this phase. Distinguishing between the different types of local complications would not only help to prognosticate but will also aid in selecting the appropriate treatment modality.

Types of Acute Pancreatitis

Acute pancreatitis can be divided into two broad categories, namely interstitial edematous pancreatitis (IEP) and necrotizing pancreatitis (NP); and this definition is predominantly directed by the degree of enhancement of the pancreas on CECT imaging (Table 1.2).

Interstitial Edematous Pancreatitis

In IEP, which constitutes 80–90 % of AP, CECT shows a relatively homogenously enhanced pancreas with or without mild peripancreatic stranding or peripancreatic fluid collection (Fig. 1.1a, b). However, it is important to understand that confirmation of IEP is not an indication for CECT.

Necrotizing Pancreatitis

Necrotizing pancreatitis, on the other hand, is characterized by tissue necrosis within the pancreatic parenchyma and/or peripancreatic tissues (Fig. 1.2a–c). Necrosis is marked by lack of enhancement, which is a function of impaired or absent tissue perfusion. Involvement of the pancreatic parenchyma alone is exceedingly uncommon and in most of the cases both the pancreatic parenchyma and peripancreatic tissues are involved. Peripancreatic necrosis alone (which is as frequent as pancreatic necrosis) results in a less severe disease course compared to involvement of the pancreatic parenchyma, but higher morbidity compared to IEP. Pancreatic and peripancreatic necrosis usually evolves over the first week of the disease and might not be mature enough to be detected early on by imaging. This is more so for peripancreatic necrosis, which is essentially necrosis of peripancreatic fat, which has little radiologically detectable perfusion even in health [13–16]. After 1 week, the necrosis will gradually liquefy and contain both solid and liquid components, thereby resulting in a more heterogeneous appearance that would make radiological diagnosis evident. Therefore, a diagnosis of NP can be most reliably made after about 1 week of development of AP.

Infected Necrosis

Infection of necrotic pancreatic and/or peripancreatic tissues usually occurs after the first week of AP. Most of the current evidence failed to establish a positive correlation between the extent of necrosis and the duration of symptoms with development of infected necrosis [11, 17–19].

Table 1.2 Definitions and CECT appearance

Terminology	Definitions	CECT appearance
Interstitial edematous pancreatitis (IEP)	• Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis	• Pancreatic parenchyma enhancement by intravenous contrast agent • No findings of peripancreatic necrosis
Necrotizing pancreatitis	• Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis	• Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or • The presence of findings of peripancreatic necrosis
APFC (acute peripancreatic fluid collection)	• Peripancreatic fluid associated with IEP with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of IEP and without the features of a pseudocyst	• Occurs in the setting of IEP • Homogeneous collection with fluid density • Confined by normal peripancreatic fascial planes • No definable wall encapsulating the collection • Adjacent to pancreas (no intrapancreatic extension)
Pancreatic pseudocyst	• An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of IEP to mature	• Well circumscribed, usually round or oval homogeneous fluid density • No nonliquid component • Well-defined wall; that is, completely encapsulated • Maturation usually requires >4 weeks after onset of acute pancreatitis; occurs after IEP
ANC (acute necrotic collection)	• A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues	• Occurs only in the setting of acute necrotizing pancreatitis • Heterogeneous and nonliquid density of varying degrees in different locations (some appear homogeneous early in their course). • No definable wall encapsulating the collection • Location—intrapancreatic and/or extrapancreatic
WON (walled-off necrosis)	• A mature, encapsulated collection of pancreatic, and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotizing pancreatitis	• Heterogeneous with liquid and nonliquid density with varying degrees of loculations (some may appear homogeneous) • Well-defined wall, that is, completely encapsulated • Location—intrapancreatic and/or extrapancreatic • Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

Since development of infected necrosis has several therapeutic implications, it is essential to recognize it early [18]. The telltale sign of infected necrosis is the presence of extraluminal gas in pancreatic or peripancreatic tissues on CECT (Fig. 1.3a, b), although gas can be present without infection due to a communication with the gut. In such communications, one could presume infection still exists

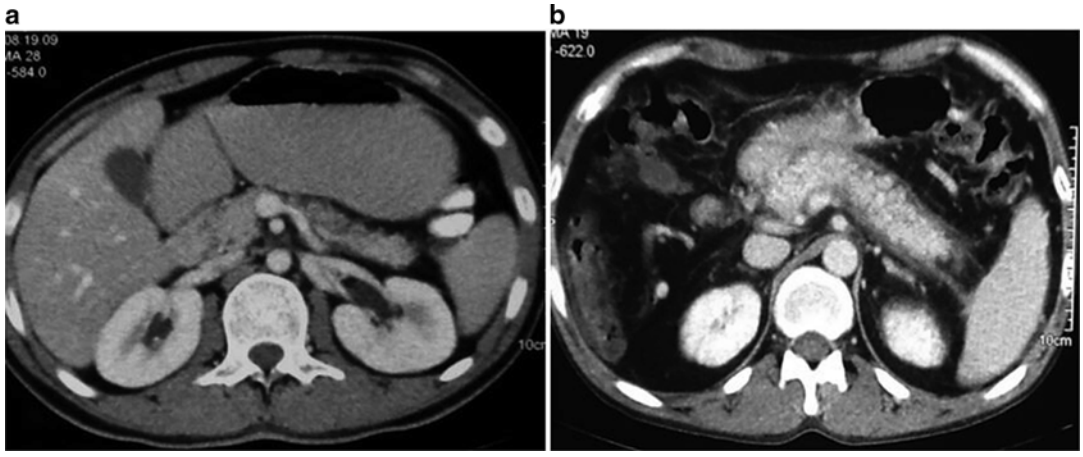

Fig. 1.1 Interstitial edematous pancreatitis with (**a**) peripancreatic fat stranding and (**b**) minimal peripancreatic fluid

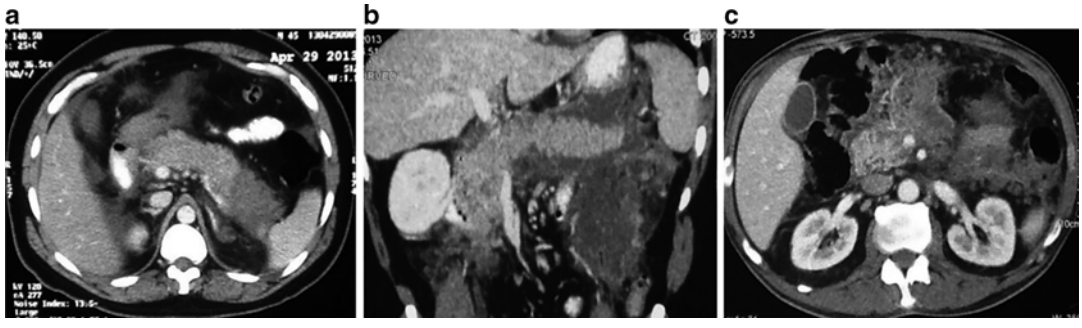

Fig. 1.2 Necrotizing pancreatitis showing (**a**) only pancreatic necrosis; and (**b**) only peripancreatic necrosis and (**c**) both parenchymal and peripancreatic necrosis

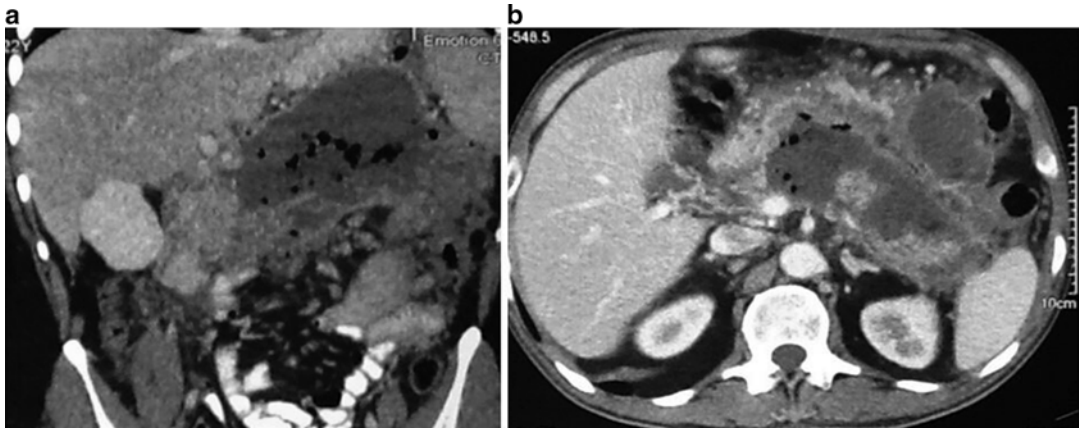

Fig. 1.3 Infected necrosis showing the presence of air within the necrotic areas

due to contamination with gut bacteria. Confirmation can be done by the presence of bacteria/fungi on gram staining or culture of image-guided FNA of necrotic tissue. It should, however, be borne in mind that FNA might not be always positive even in the presence of infection, and thus a negative aspirate should be interpreted with caution. The key to diagnosis of infected necrosis is a strong clinical suspicion based on signs of sepsis. Thus, FNA of necrosis is not being advocated routinely now. Infected necrosis can also result from interventions (percutaneous, endoscopic, and surgical) and has been shown to have adverse impact on morbidity and mortality [20].

Complications of Acute Pancreatitis

Complications of AP include organ failure, local and systemic complications.

Organ Failure

The Revised Atlanta Classification has recommended the use of the Modified Marshall scoring system (Table 1.3) to assess organ dysfunction and failure [21]. The Modified Marshall system assesses three organ systems that are usually involved by SIRS, namely respiratory, renal, and circulatory. A score of 2 or more in any one of these organ systems qualifies the diagnosis of organ failure. If organ failure persists for less than 48 h, it is termed as transient organ failure; and if at least or more than 48 h, then persistent organ failure. Involvement of one organ is defined as single organ failure while more than one organ is called multiorgan failure. The Modified Marshall system is simple, universally feasible and has an edge over the other commonly used system called sequential organ failure assessment (SOFA) [22], which also requires measurement of additional parameters like inotrope and respiratory support.

Local Complication

A better understanding of the natural history of AP and advancements in imaging have now enabled identification of morphological changes of AP in a more efficient manner. Accordingly, discrete types of local complications have been defined in the Revised Atlanta Classification.

Table 1.3 Modified Marshall scoring system[a]

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal[b]					
(serum creatinine, μmol/L)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dL)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)[c]	>90	<90, fluid-responsive	<90, not fluid-responsive	<90, pH <7.3	<90, pH <7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental oxygen (L/min)	*FiO_2 (%)*				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

[a]A score of 2 or more in any system define the presence of organ failure
[b]A score for patients with preexisting chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/L or ≥1.4 mg/dL
[c]Off inotropic support

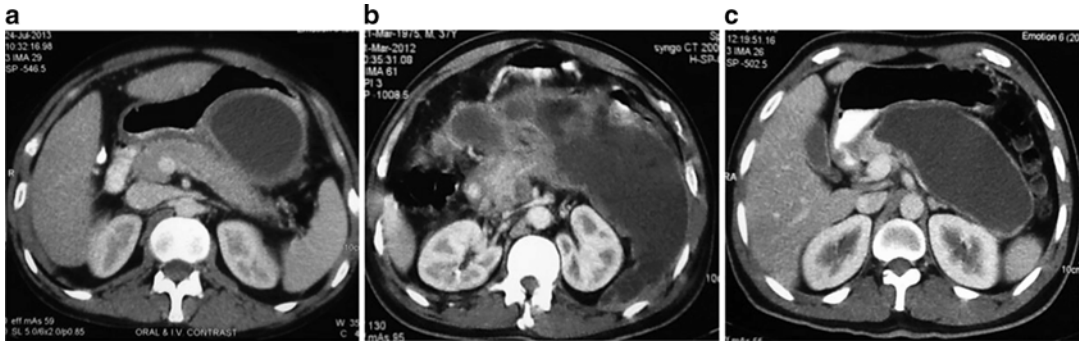

Fig. 1.4 Pictures of different types of fluid collections. (**a**) Pseudocyst. (**b**) ANC. (**c**) WON

These include acute peripancreatic fluid collection (APFC), pancreatic pseudocysts (Fig. 1.4a), acute necrotic collections (ANCs) (Fig. 1.4b), and walled-off necrosis (Fig. 1.4c) (see Table 1.2). Other local complications include gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis.

A major highlight of the revised classification is the CECT-based definitions of pancreatic and peripancreatic collections that distinguish between collections that contain only fluid content (APFC and pancreatic pseudocyst) and those that contain a solid component with or without a fluid component (ANC and WON) (see Table 1.2). APFCs are associated with IEP and often resolve spontaneously without intervention [16, 23]. These collections are confined to the fascial planes in the retroperitoneum and may be multiple. If an APFC persists beyond 4 weeks and acquires a well-defined wall, it is termed as a pancreatic pseudocyst. Pseudocysts are very uncommon, and specifically refer to the encapsulated fluid collections in the peripancreatic tissues. Even though pseudocysts may rarely involve the pancreatic tissue, these kind of collections are more likely to be ANCs; therefore, an MRI, EUS, or transabdominal ultrasound might be necessary to look for the presence of solid material that distinguish between ANC and a pseudocyst. The term pseudocyst should not be used if there is evidence of solid debris within the collection. Pseudocysts usually develop as a result of disruption of the main pancreatic duct or a side branch in the absence of necrosis. A pseudocyst may also result from a disconnected duct syndrome resulting from localized necrosis in the neck or body of the pancreas [24].

ANC is characterized by the presence of variable amount of solid and fluid components within the first 4 weeks of illness. ANCs may be pancreatic, peripancreatic, or both; and may appear multiple and loculated on CECT. It is important to interpret CECT findings of collections with caution in the first week of illness since CECT may not distinguish between APFC and ANC. MRI, EUS, or transabdominal ultrasound can be of help in distinguishing the two, if necessary. Otherwise, serial imaging can reliably confirm the diagnosis of ANC from the second week and beyond. An ANC may be associated with a disrupted pancreatic duct within the area of necrosis. The presence of a mature reactive wall around ANC defines it as a WON and this maturation usually occurs after 4 weeks from the onset of disease. WON may be single or multiple and involve areas even distant from the pancreas. ANCs and WONs are prone to develop infections.

The presence of the following features should prompt the caregiver to suspect development of local complications: (1) persistence of recurrence of abdominal pain; (2) increasing degrees of organ dysfunction; and/or (3) development of clinical signs of sepsis. The presence of any of these forms a definitive indication for a high-resolution cross-sectional imaging. Findings of cross-sectional imaging of pancreatic and peripancreatic collections should be described as shown in Table 1.4.

Table 1.4 Format to record morphologic features observed on CECT

1. Pancreatic parenchymal necrosis	None	<30 %	30–50 %	>50 %
2. Peripancreatic necrosis				
3. Pancreatic/peripancreatic fluid or collections				
(a) Location				
Intrapancreatic, location _____				
Peripancreatic, location _____				
(b) Characteristics of fluid				
Homogenous	Heterogeneous			
(c) Well-demarcated wall (*measure thickness in mm*)				
No	Yes			
(d) Extraluminal loculated gas bubbles				
No	Yes			
(e) Gas/fluid level				
No	Yes			
(f) Shape of collection				
Round or oval	Irregular			
4. Related extrapancreatic findings				
(a) Cholelithiasis				
(b) Choledocholithiasis				
(c) Extrahepatic biliary dilation				
(d) Portal venous thrombosis/obstruction				
Gastroesophageal varices				
(e) Superior mesenteric venous thrombosis/obstruction				
(f) Splenic vein thrombosis/obstruction				
Gastric varices				
(g) Arterial pseudoaneurysm				
Location and size: _____				
(h) Pleural effusions				
(i) Ascites				
(j) Inflammatory involvement of organs				
Stomach				
Duodenum				
Jejunum				
Colon				
Appendix				
Liver				
Kidney (right/left)				
Ureter (right/left)				
(k) Colonic necrosis				
(l) Signs of chronic pancreatitis—pancreatic calcification				
5. Unrelated intraabdominal or intrathoracic findings				
Describe findings _____				

Systemic Complications

This is defined as exacerbation of preexisting conditions like coronary artery disease, congestive cardiac failure, chronic obstructive pulmonary disease, diabetes, and chronic liver disease, precipitated by acute pancreatitis. It should be understood that persistent organ failure (as defined by the Modified Marshall scoring) inherent to the pancreatitis episode should

be considered as the primary determinant of severity and should not be defined as a systemic complication.

Definition of Severity of Acute Pancreatitis

The original Atlanta Classification classified AP into two severity types, namely mild and severe (presence of local complications and/or organ failure). However, it was observed over time that the group of severe AP was heterogeneous and encompassed patients who would have different clinical outcomes based on the type of complications. Most importantly, patients who had local complications but no persistent organ failure had low mortality but high morbidity. Furthermore, early stratification could guide the caregiver to triage the patients for early referral to advanced centers; ensure focused care to the priority problems; aid better communication with relatives; and provide homogeneous groups for comparative research. With these in mind, the three-tier category of severity of AP has been introduced, which categorizes severity of AP as mild, moderately severe, and severe. This definition of severity is determined by the presence or absence of organ failure, and local or systemic complications. It is therefore important to assess and record the duration of organ failure and also to perform a meticulous morphologic evaluation of the local complications.

Mild Acute Pancreatitis

This category is defined as acute pancreatitis without organ failure and local/systemic complications; and usually resolves within the first phase, with minimal morbidity and very rare mortality [25]. Patient will usually not require advanced pancreatic imaging for morphological assessment and can be discharged within a week.

Moderately Severe Acute Pancreatitis

This is defined as AP with transient organ failure and/or local complications and/or systemic complications, in the absence of persistent organ failure. In patients with moderately severe AP, the management strategy is guided by the type of local complications, the presence of symptoms and development of issues related to the defining local complications (e.g., infection of pancreatic and peripancreatic necrosis or bleeding from a pseudoaneurysm). Mortality is significantly less among these patients compared to severe acute pancreatitis [12, 26]; and many of them can be discharged in 2–3 weeks without major interventions. Other patients with symptomatic local complications might require prolonged hospitalization with or without major radiologic, endoscopic, or surgical interventions.

Severe Acute Pancreatitis

This category is characterized by the presence of persistent organ failure, irrespective of the time of development in relation to disease onset (i.e., early phase or late phase) [6, 8]. Persistent organ failure in the early phase of disease usually results from severe and persistent SIRS and can result in a mortality rate of 36–50 % [5, 6, 8]. Persistent organ failure that develops in the late phase of the disease is usually associated with infected necrosis or severe extrapancreatic infections, in addition to persistent SIRS. Mortality in this group of patients (infected necrosis with persistent organ failure) is high (43 %) [20]. It is essential to treat a patient with severe early and persistent SIRS even in the absence of organ failure as potentially severe disease.

How to Use the Revised Atlanta Classification in Clinical Practice?

The Revised Atlanta Classification was developed based on a web-based consensus process. The original drafts by the working group and subsequent additions from pancreatologists and pancreatic surgeons were based on both evidence from the literature and clinical experience and expertise. Since this classification has not stemmed out of results from a single focused multicenter prospective study, its validity in

clinical practice needs to be evaluated. The application of the revised classification in clinical practice and for research will necessitate precise use of the proposed definitions and documentation of the clinical events and test results in a meticulous manner. Figure 1.5a–c present an algorithmic approach on the use and interpretation of the various definitions as a function of dynamic progression of the illness. Table 1.4 depicts the manner in which CECT data should be documented.

Since the first week (early phase) of the disease is the phase of SIRS and associated organ failure, priority should be given to evaluation of organ dysfunction. Clinical and laboratory-based assessment gains importance in this phase. Even though local complications evolve during this phase, it is not mandatory to document these during the first

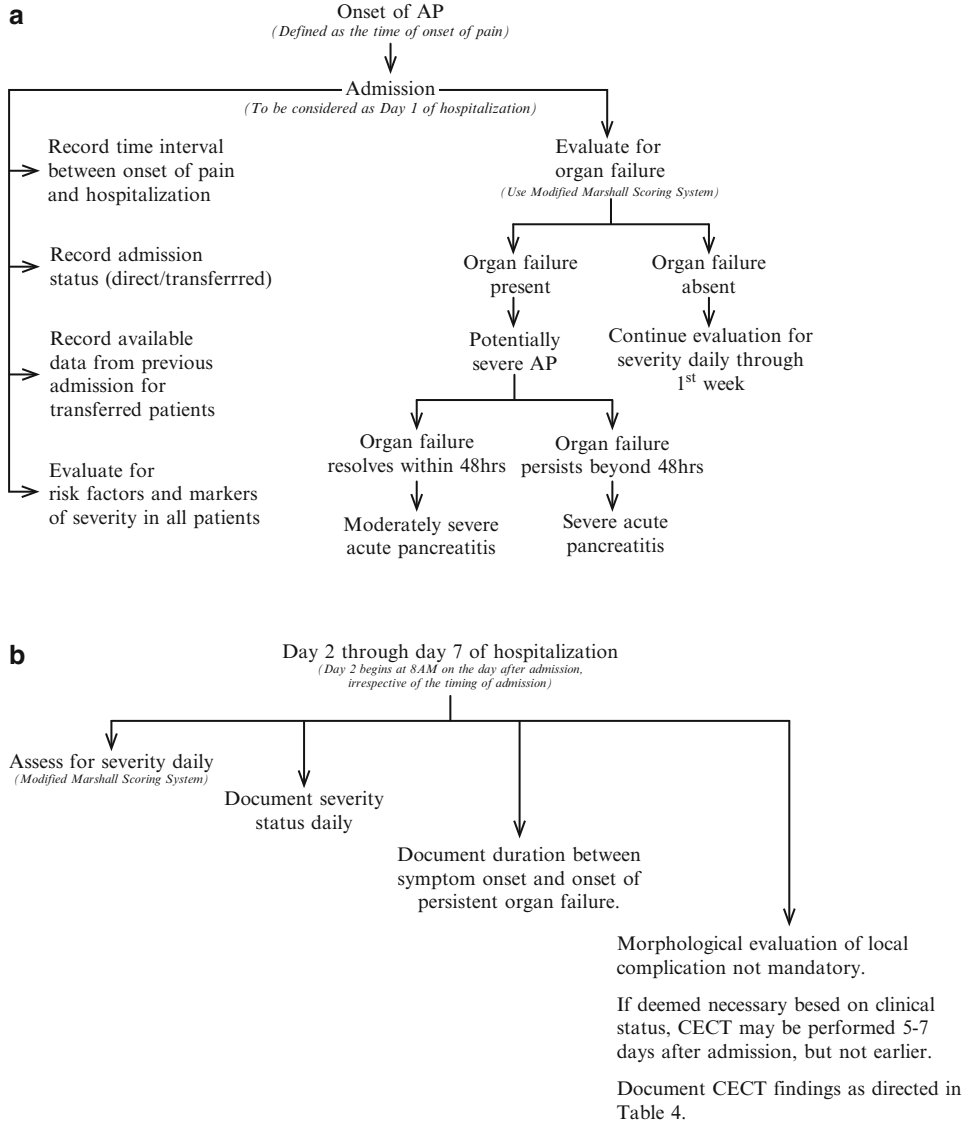

Fig. 1.5 Algorithmic approach to the utility of the Revised Atlanta Classification. (**a**) At admission. (**b**) During the early phase. (**c**) During the late phase . N.B.: Risk factors include age, body mass index, and comorbidities; clinically feasible severity markers at admission (and following 3 days) includes scoring systems like APACHE II, Ranson's, BISAP, HAPS, etc.; hematocrit; serial BUN; serum creatinine; pleural effusion or pulmonary opacities; serum CRP; procalcitonin. Serum amylase and lipase do not have any correlation with severity of acute pancreatitis; therefore, serial measurement should not be performed. Their use should be restricted to only making a diagnosis of acute pancreatitis

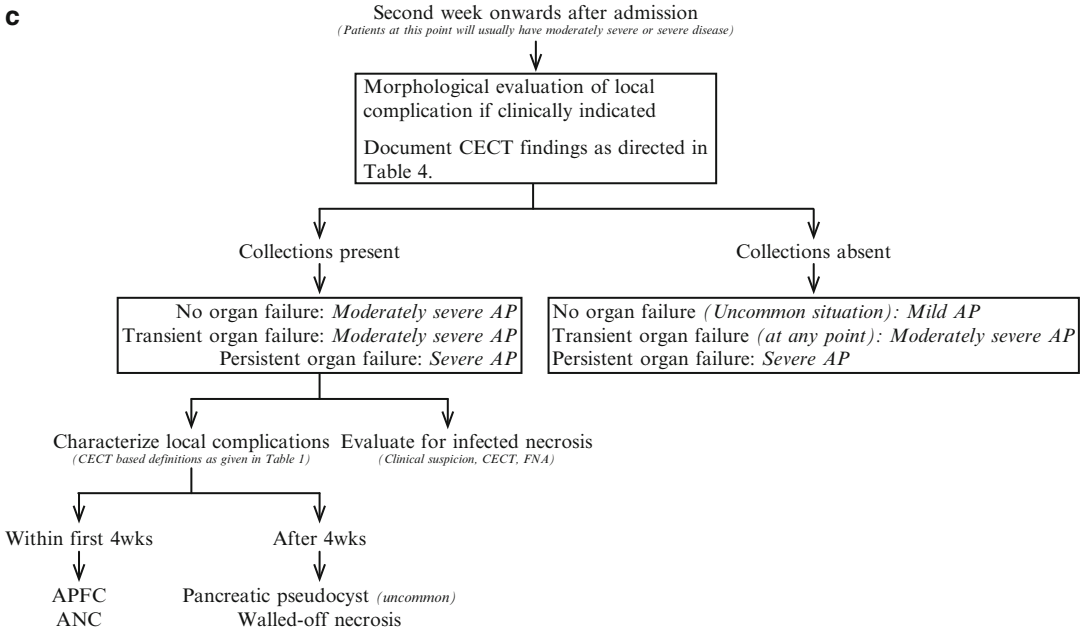

Fig. 1.5 (continued)

week since the extent of necrosis cannot be clearly defined during this phase, extent of necrosis does not correlate to severity of organ failure [11, 27] and no specific treatment is required for necrosis and collections during this phase. On the other hand, it becomes important to perform morphological evaluation for local complications and also assess for infection of the necrotic tissue during the late phase of the disease. Mortality in patients with organ failure and infected necrosis is much higher compared to patients with organ failure without infected necrosis [20].

Conclusion

The Revised Atlanta Classification of acute pancreatitis has addressed several areas of confusion and issues unaddressed in the 1992 Atlanta Classification. More plausible definitions of organ failure and local complication (including pancreatic and peripancreatic collections) have been proposed. Table 1.1 shows the revised nomenclatures as opposed to the terminologies used in the original Atlanta Classification. The severity of the disease has also been classified into three clinically relevant categories with discrete clinical outcomes. The new classification needs to be validated in large-scale multicenter prospective studies, which could possibly uncover inadvertently overlooked areas in the consensus process and thereby create scope for further improvement. It is expected that revised classification would soon emerge as the gold standard for evaluation of acute pancreatitis for decades to come.

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Organ Failure and Acute Pancreatitis

2

Colin D. Johnson

Since the beginning of this century, our understanding of the relationship between organ failure and acute pancreatitis has greatly improved. Organ failure is frequently observed in severe pancreatitis but it was not recognized that it is usually present early in the course of disease, often at the time of admission to hospital. We now know that this is the case. It has also become clear that a proportion of patients with organ failure improve rapidly in response to treatment and it is only those with persistent organ failure who are at risk of serious complications and death, and we are able to identify patients at risk of organ failure, and grade the severity of organ failure using objective scores.

We still do not have effective specific therapies for acute pancreatitis or for organ failure, other than general supportive measures. Our understanding of the pathophysiology remains limited, and we still lack basic and clinical research into the mechanisms of inflammation and how to manipulate them.

Diagnosis of Organ Failure

Acute pancreatitis is one of many conditions associated with organ failure. In the early 1990s, advances in critical care medicine were accompanied by descriptions of threshold values to define organ failure and systems for grading severity. Organ failure thresholds were incorporated into the definition of severe acute pancreatitis in the Atlanta classification [1], so it is not surprising that these thresholds closely match the thresholds adopted in critical care medicine. The publication by Marshall and colleagues [2] of a simple numerical scoring system to take account of the number and severity of organ failures offered the potential to categorize patients numerically. This system was modified as the SOFA score [3], which is better adapted for use in intensive care units. However, the potential application of this system to describe grades of severity in acute pancreatitis has not been widely adopted although the recent revision of the Atlanta classification published in 2013 [4] adopted the Marshall score in the definition of organ failure. See also Chap. 1. This revision does not take account of the severity of organ failure, which can be assessed and described numerically by the Marshall score (Table 2.1).

Assessment of Organ Failure in Acute Pancreatitis

Clinical research on the assessment of organ failure in acute pancreatitis has been heavily influenced by the use of a single threshold for organ failure in the original Atlanta definition. Most researchers have focused on the presence or absence of organ failure in relation to other

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Table 2.1 Modified Marshall Scoring System [2, 4] for organ dysfunction[a]

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal					
Serum creatinine, μmol/L	≤134	134–169	170–310	311–439	>439
Serum creatinine, mg/dL	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)[b]	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2

[a]A score of 2 or more in any system defines the presence of organ failure
[b]Off inotropic support

outcomes in acute pancreatitis. As the presence of organ failure was a defining feature of severe pancreatitis in the Atlanta definition, the demonstration of organ failure of any severity, and at any time, caused the patient to be allocated to the severe category. This has caused some confusion, particularly for those who failed to appreciate that the Marshall score (and Atlanta criteria) definition of organ failure included patients with lesser degrees of dysfunction, who did not require artificial ventilation, inotrope support, or renal replacement therapy.

Very few studies have attempted to explore the relationship between the severity of individual organ failures and other outcomes such as local complications and death. This may have hampered progress in our understanding of the pathophysiology of organ failure and pancreatitis, and it remains a potential research area of considerable interest. While it is clear that multiple organ failure puts the patient at greater risk of fatal outcome than a patient with only one organ failure [5, 6], I am aware of only six assessments of organ failure scores in acute pancreatitis. These mostly deal with comparisons of APACHE-II and other scores for the prediction of local complications or severe pancreatitis.

Glisic and colleagues studied 60 unselected patients and found significant correlation between the Bernard (Marshall) and the APACHE-II scores [7]. These also correlated well with C-reactive protein (CRP) levels. Dambrauskas and colleagues [8] and Mason and colleagues [9] studied 101 and 181 unselected patients, respectively. Both groups found that the Marshall score [2] or the logistic organ dysfunction score (LODS) [10] predicted outcomes such as death, pancreatic necrosis, infection, or the need for critical care equally as well as the APACHE-II score. Two reports from India [11, 12] describe 50 and 55 patients admitted to intensive care units. Both studies demonstrated the ability of the SOFA score to predict fatal outcome better than other score systems including APACHE-II and LODS.

All the above reports used organ failure scores to find a cutoff between patients with or without a particular endpoint. Only one study has attempted to relate the severity of organ failure to outcomes assessed in more than two categories. Mole and colleagues [13] analyzed data from a historic cohort of 276 patients with pancreatitis who had undergone early computed tomography (CT). They showed correlation between Marshall score and the modified CT Severity Index as well as with the number and extent of local complications. However, they noted a lack of association between organ failure score and the presence of necrosis >30 % of the pancreas. It seems likely there is a complex interaction between organ failure and the causes of necrosis, which may vary between individuals.

Dynamic Nature of Early Organ Failure

While application of the Atlanta classification confirmed that organ failure often occurred in patients with severe acute pancreatitis, the

mindset of clinical researchers before 2000 was heavily influenced by the desire to identify early signs of severity, and to predict patients likely to have severe acute pancreatitis. A variety of scoring systems was used for this purpose [14–16]. See also Chap. 7. In fact, these systems all measured physiological disturbance, and they owed their effectiveness to *detection* of patients with organ dysfunction, rather than *prediction* of those likely to develop organ failure or other complications.

Publication in 2001 of a large multicentre study conducted in the United Kingdom to investigate the effect of Lexipafant in "predicted severe" acute pancreatitis [17] revealed a number of important lessons. This study included patients within 72 h of onset, with APACHE-II score >6. The proportion of patients with organ failure was the primary endpoint. However, over 40 % of patients had organ failure at the time of entry to the study, and only a further 7 % developed new organ failure during the first week. It was not possible therefore to significantly influence the primary endpoint in that trial. Until this time, it had not been appreciated that organ failure during the first week of acute pancreatitis was usually already established shortly after admission to hospital. More importantly, this trial yielded sufficient data to enable the characterization of features of organ failure associated with a high risk of death.

Using data from a similar cohort, Buter and colleagues [18] had identified the persistence of organ failure at the end of the first week as a substantial adverse prognostic factor. More than half of their patients in that category had a fatal outcome whereas patients whose organ failure had resolved by that time were unlikely to die. In our analysis [19] of 290 patients with admission APACHE-II score of >6, we found that 44 % of patients had organ failure at the time of admission. Overall just over half the patients developed organ failure during the first week. Patients with organ failure that persisted for more than 48 h, that is, it was present on 3 consecutive days, had a mortality rate of 35 %. This was true both for those with organ failure at the time of admission or organ failure which developed later during the first week (Table 2.2). Patients who had no organ failure during the first week had a very low mortality rate. Since that observation, the association between persistent organ failure during the first week of pancreatitis and at least a 1 in 3 risk of death has been confirmed by others [20–22] (Table 2.3 and Fig. 2.1) and persistent organ failure has been adopted as the primary definition of severe acute pancreatitis in the recent revision of the Atlanta classification of acute pancreatitis [4].

Table 2.2 Relationship between presence and persistence of organ failure during the first week of acute pancreatitis and death [19]

	Survived	Died	Total
No organ failure	113	3	116
Of at entry			
Transient	59	1	60
Persistent	56	32	88
New of within 7 days			
Transient	11	0	11
Persistent	11	4	15

Table 2.3 Fatal outcome in patients with persistent organ failure during the first week of acute pancreatitis

Author	Patients	Persistent organ failure (%)	Died after persistent organ failure (%)
Johnson 2004 [19]	290	103 (36)	36 (35)
Mofidi 2006 [20]	759	89 (11)	37 (42)
Singh 2009 [21]	252	13 (5)	9 (69)
Thandassery [22]	114	43 (38)	18 (42)

The observation that persistent organ failure identifies a group of patients at high risk of death has had two consequences. First, it shifted the emphasis from attempts to predict which patients would subsequently be judged to have severe pancreatitis onto the identification of patients with organ failure, and the understanding that when this persisted for more than 48 h the patient already has severe acute pancreatitis. Second, some authors have sought to identify markers already present very early after admission, which identify patients who subsequently have persistent organ failure.

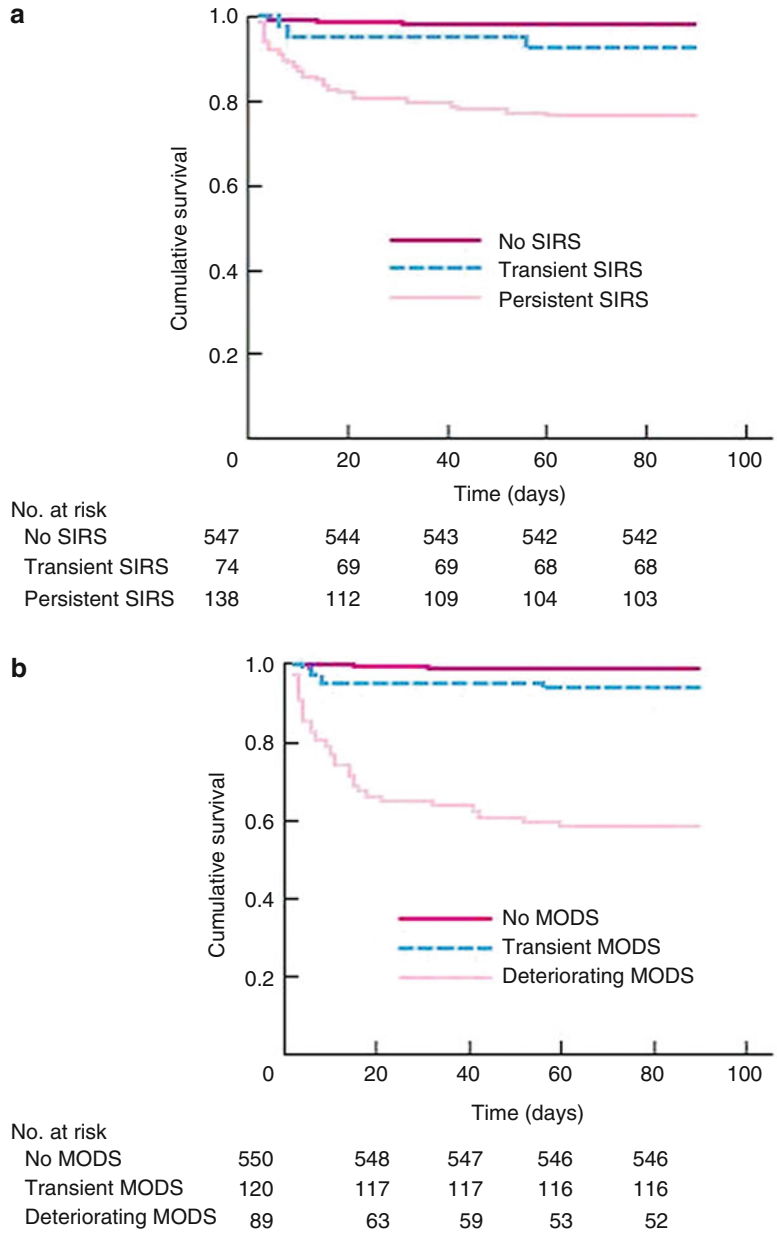

Fig. 2.1 Numbers at risk, and survival in patients with no, transient, or persistent SIRS (**a**) or organ failure (**b**). Reprinted with permission from Mofidi R., Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006; 93(6): 738–744. Copyright 2006 British Journal of Surgery Society Ltd. Published by John Wiley & Sons, Ltd.

Significance of Persistent Organ Failure

Until 2004, early assessment of acute pancreatitis used multiple factor scoring systems during the 48 h after admission to hospital, in an effort to identify patients at high risk of complications and death. These "predicted severe" acute pancreatitis patients were in fact often already in established organ failure, and the delay of up to 48 h required to complete some of the scoring systems meant that by the time they were "predicted" to have severe acute pancreatitis they had in fact already fulfilled the criteria for severe pancreatitis that were adopted in 2012. Persistent organ failure defines severe pancreatitis immediately, often on the third day in hospital, which is a similar time scale to that required for the "prediction" given by the Ranson and Glasgow scores. The presence of organ failure based on routinely available clinical and biochemical findings immediately identifies patients at risk of severe outcome, but if the organ failure resolves within 48 h, severe pancreatitis has been avoided [4, 19]. Thus the emphasis has shifted from *prediction* of severe cases to the *identification* of those at high risk.

Currently it is not known whether treatment intervention during the 48-h window, with the aim of reducing the severity or resolving the organ failure, will have a consequential beneficial effect on mortality rates. Common sense would say that it should, but it may be that some patients recover from early organ failure because of some difference in their physiological response, rather than because of treatment given. Nevertheless, diagnosis of organ failure in any patient should of course prompt appropriate treatment to encourage resolution. At the time of writing, there is no evidence to confirm that supportive treatment can lead to resolution of organ failure and consequently reduced risk of death, mainly because treatments for pancreatitis and for organ failure are entirely supportive and it would be inappropriate to offer anything other than best supportive care. There is no specific agent that can reverse the physiological responses driving organ failure.

The physician dealing with patients with acute pancreatitis who have evidence of organ failure in the early days of the attack, must rely on basic supportive measures. These include provision of adequate inspired oxygen to maintain arterial oxygen tension, and adequate fluid infusion to maintain normovolemia, and hence normal tissue perfusion. It seems logical that this strategy should protect the respiratory, cardiovascular, and renal systems.

Early Warning, Systemic Response, and Organ Failure

The physiological response to acute injury is immediately manifest by change in parameters usually recorded as nursing observations (pulse rate, respiratory rate, blood pressure, temperature). These observations have been used in a variety of early warning scores (EWS) sometimes referred to as modified early warning scores (MEWS) [23–27]. Abnormal scores using these systems identify patients at the earliest phase of the physiological response, and therefore offer an opportunity to begin treatment before more severe irreversible changes have occurred. The value of such scores in acute pancreatitis has been investigated [28–30], and they do appear to provide an early screening tool to identify patients who ultimately develop organ failure. However this screening is relatively nonspecific, as it includes patients with minor abnormalities whose condition settles rapidly, either spontaneously or in response to initial supportive therapy.

More severe disturbance of these basic observations, with the addition of the white blood cell count as an acute marker of inflammation, has been identified in the definition of the systemic inflammatory response syndrome (SIRS) [31] (Table 2.4).

Patients who are progressing towards organ failure will first inevitably demonstrate at least

Table 2.4 Features of the systemic inflammatory response syndrome (SIRS) [31]

Core body temperature	>38 or <36 °C
Heart rate	>90 beats/min
Respiratory rate	>20/min or $PaCO_2$ <32 mmHg
White blood cell count (WBC)	>12,000 or <4,000 cells/mm^3

If SIRS is present for >48 h, the patient is likely to have severe pancreatitis

two features diagnostic of SIRS. However, patients who respond to initial treatment may not progress to organ failure and a SIRS response is less specific than the observed presence of organ failure. Mofidi and colleagues [20] have shown that an early SIRS response is predictive of subsequent organ failure in acute pancreatitis, and that if the SIRS response is present for more than 48 h, this identifies a high-risk group in the same way as persistent organ failure. In their study 25 % of patients with persistent SIRS eventually died, compared with 40 % of patients with persistent organ failure during the first week (see Fig. 2.1). We can conclude that an SIRS response, particularly if it is persistent, or if it fails to respond to initial aggressive supportive therapy, could be a useful marker for patients who will go on to persistent organ failure and who will therefore be at high risk of death.

This has important implications for the planning of therapeutic randomized trials. Most interventions designed to combat the physiological responses leading to organ failure would work better if given earlier, to prevent progression, rather than to reverse established organ failure. Depending on the proposed mechanism of action, and the anticipated effect of a new agent, it is now possible to select patients for study at a variety of time points, which will yield patient groups at different risk of organ failure and death. For example, selecting patients with SIRS, before any treatment, will include a substantial proportion that will respond to simple supportive measures and who have a relatively low mortality rate. Such criteria might be useful to select patients for a trial of an initial resuscitation strategy designed to prevent onset of organ failure. Patients who have SIRS that has persisted despite aggressive therapy represent a more selected group with a high risk of organ failure. This group might be suitable to investigate a specific agent designed to block progression towards organ failure. The percentage of patients developing persistent organ failure in each treatment group would be a suitable primary endpoint, as it is a surrogate marker for potentially fatal pancreatitis. Finally, if the agent being tested is thought to act by promoting a compensatory anti-inflammatory response, or by some other mechanism that can switch off persistent organ failure and thereby reduce the high mortality rate, it might be best to test that agent only in patients with persistent organ failure after 48 h of intensive supportive therapy.

Early Management to Minimize Organ Failure

The commonest organ failure seen in severe acute pancreatitis is respiratory, secondary to accumulation of fluid between the alveolar membrane and the capillaries in the lung. This leads to reduced gas transfer and low arterial oxygen tensions. For this reason, clinical practice is to provide oxygen supplements to patients from the time of admission until it is clear that they have mild resolving pancreatitis without evidence of organ failure. This approach is supported by expert consensus opinion [32].

Fluid Replacement

There is little good evidence to guide the administration of fluid during the first 24–48 h in hospital in patients with pancreatitis, especially those who do not have organ failure. See Chap. 8. It is sensible to ensure adequate volume replacement. Patients with severe pancreatitis may well have a fluid deficit, with loss of fluid from the circulation into the extracellular space leading to hemoconcentration. Baillargeon and colleagues [33] found that an admission hematocrit ≥47 % or failure of admission hematocrit to decrease at 24 h were risk factors for the development of pancreatic necrosis. However, these hematocrit values were not predictive of organ failure. Although the data are somewhat conflicting, others have reported similar data, with a stronger association between hemoconcentration and necrosis, than with organ failure [34–38]. Perhaps the weak association between hemoconcentration and organ failure may be due to variability in the fluid resuscitation provided to different patients.

The difficulty in evaluating descriptive cohort studies is that in the absence of a comparison group, it is impossible to know whether patients with a high volume infusion in the first 48 h have a poor outcome because they are ill and require high volume in fusion, or because the high volume infusion has been harmful. On the one hand, the most sick patients with early hypovolemia will require large volumes of fluid to restore circulatory parameters. Despite the effort to replace fluid into the circulation, these patients remain unwell and have poor outcomes. On the other hand, it may be that patients with less severe pancreatitis who receive large volumes of fluid are actively harmed by the addition of pulmonary edema to the existing tendency for fluid accumulation in the lungs. A small number of studies have tried to address this problem. For example, a study by Kuwabara and colleagues [39] in nearly 9,500 patients showed an association between higher fluid volumes in the first 48 h in hospital and fatal outcome and for the need for respiratory or renal support. The same study, however, showed that when fluid given in the first 48 h was expressed as a ratio to the total fluid given during hospitalization, a high ratio was associated with a reduced mortality. The authors concluded that either too much or too little fluid in the first 48 h can be harmful to the patient.

Warndorf and colleagues [40] in 2011 calculated the fluid volume infused on day one as a percentage of the volume infused over the first 3 days and divided their patients into three groups: those with more than 33 % infused on day 1 were designated early resuscitation and those with less than one-third on day 1 as late resuscitation. SIRS and organ failure were significantly lower in the early resuscitation group compared with the late resuscitation group, during the first 72 h in hospital.

There is evidence that too much fluid may be harmful. Mao and colleagues [41] found significantly worse outcomes in 36 patients with high volume replacement compared with 40 patients with lower volumes. However, the overall volumes infused in these groups were relatively high, and the low-volume group may in fact have been optimally replaced (Table 2.5).

Table 2.5 Outcomes in study by Mao and colleagues [41] comparing higher and lower volumes of fluid resuscitation

	Higher volume ($n=36$)	Lower volume ($n=40$)
Mean time to achieve hemodilution (h)	13.5	24
Mechanical ventilation	34 (94)	26 (65)
Abdominal compartment syndrome	26 (72)	13 (32)
Sepsis within 2 weeks	23 (64)	15 (37)
Death	11 (69)	4 (10)

Planning Fluid Therapy

Although the evidence reviewed above is difficult to interpret, there are some pointers to best practice in planning fluid replacement. There are three questions to answer in comparisons of different fluid therapies. What is the most appropriate fluid to use? What is the ideal rate of infusion and what targets should dictate infusion rate?

Choice of Fluid

Wu and colleagues [42] compared Ringer's lactate with normal saline for crystalloid infusion from the time of admission in 40 patients who received mean volume 4.3–4.5 L in the first 24 h. The group that received Ringer's lactate had significantly more patients (84 %) with reduction in SIRS and a lower mean CRP (51.4 mg/dL) compared with the saline group (0 and 104 mg/dL, respectively), but there was no difference in clinical outcomes. In another study, Du and colleagues [40] gave all patients Ringer's lactate with or without hydroxyethyl starch. There was no difference in clinical outcomes in these two groups.

Zhao and colleagues [40] used crystalloid fluid replacement with normal saline and compared

crystalloid only to a regime with additional hydroxyethyl starch. They found less intra-abdominal hypertension and improved circulatory parameters with the addition of colloid. However, general ITU experience with hydroxyethyl starch is that this fluid can increase mortality and it is not currently recommended for use in pancreatitis. Consensus recommendations at present are that fluid resuscitation early in the course of acute pancreatitis should be with Ringer's lactate [32].

How Much Fluid to Give

Because the evidence from observational studies is difficult to interpret, a causal relationship between high volume replacement and death cannot be assumed. Sufficient fluid should be given to reverse the abnormalities of circulation. In order to determine what is sufficient fluid volume, goal-directed therapy may be used. In this approach, the rate of infusion is determined by the degree of abnormality of circulatory parameters, in an attempt to restore normality as rapidly as possible.

Wang and colleagues [43] in 2013 conducted a randomized trial in patients admitted to ITU within 24 h of onset of symptoms. They allocated patients to receive Ringer's lactate and hydroxyethyl starch according to a volume replacement protocol in the control group ($n=68$), and two treatment groups that had infusion rate determined by early goal-directed therapy (64 patients had the same fluids as controls, 68 patients received control fluids plus fresh frozen plasma). The patients in the early goal-directed therapy groups were monitored and treated aggressively to achieve within 6 h a CVP of 8–10 mmHg, a mean arterial pressure >65 mmHg, urine output >0.5 mL/kg/h, and central venous oxygen saturation >70 %. Early goal-directed therapy was associated with significant reductions in number of days ventilated, number of days in ITU, and with lower numbers of patients with organ failure or fatal outcome (Table 2.6).

Table 2.6 Outcomes in a randomized trial [41] of early goal-directed therapy (EGDT) in patients who received Ringer's lactate and hydroxyethyl starch

	Control	EGDT 1	EGDT 2
Ventilated (days)	13	12.3	10.3
ITU (days)	20.6	18.6	15.4
ACS	18 (26)	14 (22)	12 (18)
MODS	20 (29)	18 (26)	16 (23)
Death	16 (23)	14 (22)	12 (18)

The critical factor to consider in circulatory resuscitation is probably to achieve adequate tissue perfusion. The circulatory parameters used to direct therapy in the above study are reasonable markers for good tissue perfusion, but this can be measured directly. Several studies have shown intestinal ischemia to be associated with poor outcome in severe acute pancreatitis. In the research setting, intestinal ischemia can be reliably identified by measurement of intestinal fatty acid-binding protein (IFABP). We have preliminary data that support a link between inadequate fluid replacement, severe pancreatitis, and higher levels of IFABP [44], and we conclude from those studies that adequate early fluid resuscitation is important. This must be carefully controlled because it is also necessary to avoid over infusion of fluid.

Ischemia of the gastrointestinal mucosa can be measured directly using gastric tonometry [45, 46]. There is little evidence to support its use in acute pancreatitis but this area deserves further investigation. Intestinal ischemia probably permits absorption of endotoxin, which contributes to excessive stimulation of the immune response, leading to SIRS and organ failure. If the intestinal mucosa can be restored to normal function by provision of adequate fluid and restoration of the circulation, then this has the potential to interrupt the cycle of progression towards organ failure. Gastric tonometry may therefore be a useful functional marker to guide the rate of fluid resuscitation.

Pain Relief

Pain relief is often neglected in discussions of the treatment of acute pancreatitis. Failure to relieve pain will have harmful effects in addition to the suffering of the patient, because abdominal pain

causes restriction of thoracic and diaphragmatic movement, with consequent impaired ventilation. This may hamper attempts to restore normal tissue oxygenation. The initial management of any patient with pancreatitis should include adequate analgesia.

With severe pain, opioid analgesia may be required. It is well established that morphine can cause increased pressure in the sphincter of Oddi. This has the theoretical risk of exacerbating the pancreatitis [47]. Many clinicians therefore choose synthetic opioids which have not been shown to stimulate contraction of the sphincter; pethidine causes less contraction, and may be safer [48]. One randomized pilot study showed better pain relief with the nonsteroidal anti-inflammatory drug, metamizole, than with regular subcuticular injection of morphine [49]. In practice at most hospitals in the United States, hydromorhpine is used, often in a patient-controlled anesthesia (PCA) approach. Ensuring adequate pain relief is the paramount concern, and it is advisable to consider the best route to deliver reliable plasma levels of analgesic agents. In patients who are nauseated or vomiting, or who have circulatory collapse, controlled intravenous infusion may be appropriate. Care should be taken to avoid respiratory depression, which could negate the benefit of good analgesia on respiratory function.

Computed Tomography and Renal Function

Current guidelines recommend avoiding early CT unless there is a positive indication. It is certainly not necessary to perform CT in all cases of pancreatitis. Indeed even in severe cases, most patients do not require CT during the first week [32]. CT may be required if there is an atypical presentation (raised amylase without pain) or delay in presentation (abdominal pain but amylase levels returning to normal). In addition, in a patient with an acute abdomen in whom there is diagnostic doubt, or when other abdominal catastrophes must be excluded, CT may be helpful. However, the intravenous contrast that may be used during CT can impair renal function, and indiscriminate use of CT increases the rate of renal failure and may prolong mean hospital stay [50]. For this reason, CT should be used with caution during the first week of admission and only for properly justified indications.

Specific Therapies

Pro-inflammatory Pathways

The pro-inflammatory pathways involved in the pathogenesis of SIRS, and its progression to organ failure, are complex. Some of the early signaling is mediated by interleukin 8 (IL-8), IL-1β, and IL-6 and the anti-inflammatory cytokines IL-2 and IL-10 [51]. These cytokine levels increase before rises in other markers of inflammation such as CRP. Platelet-activating factor (PAF) is well known as a mediator of the inflammatory response, leading to activation of platelets and neutrophils, and increasing endothelial permeability [17]. See Chap. 11.

Complement activation is involved in a variety of inflammatory diseases such as sepsis, and burns, which like acute pancreatitis have a vascular/capillary leak component. In these conditions activation of the complement and contact inflammatory cascades causes vascular leakage, tissue edema formation, and leads to hemoconcentration and hypovolemia. The activation of kallikrein plays a significant role in SIRS, and in severe cases, organ failure. Kallikrein is physiologically inactivated by complex formation with C1 inhibitor (C1INH) [52], which also inhibits activation of the complement and contact cascades at several points.

Anti-inflammatory Treatments

Development of specific treatments has been hampered by a lack of effective agents for clinical trials. To date there have been no clinical studies of blockade or antagonists of the interleukins known to be involved in SIRS in acute

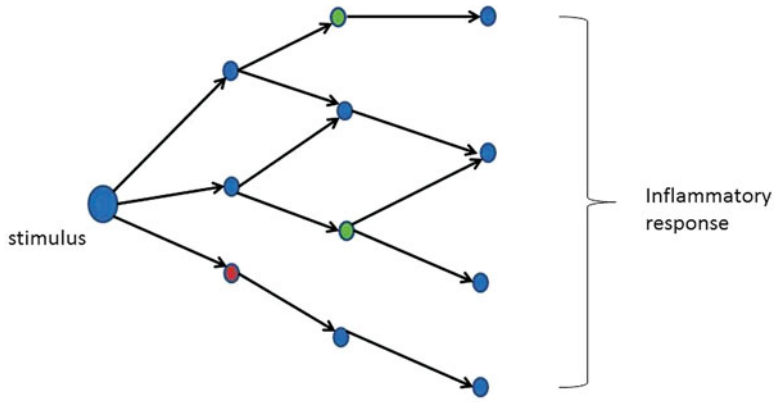

Fig. 2.2 Schematic representation of complex pathways in inflammation. The inflammatory stimulus (*blue*) activates a number of pathways. Blockade of one pathway (*red*) will have minimal effect. An agent with multiple sites of action (*green*) may be more effective. Combination of both agents will produce maximal effect

pancreatitis. This is true not only in pancreatitis but in the sepsis field in general.

Even when inhibitors of inflammatory mediators have been identified, it has proven difficult to demonstrate effectiveness in clinical trials. The most promising agent last evaluated in acute pancreatitis was the PAF antagonist, Lexipafant. This showed well in phase II studies, but a phase III study in the United Kingdom [17] failed to demonstrate effectiveness in patients recruited within 72 h of onset of symptoms. That trial showed some encouraging data with reduction in IL-8 levels in patients receiving active treatment and a reduction in mortality in a post hoc analysis of patients treated within 48 h of symptoms. However, for a variety of reasons a large multinational study of this agent failed to reach a conclusion, and further investigation has been abandoned.

It seems likely that in the complex physiological disturbances of severe acute pancreatitis, it will prove difficult to demonstrate effectiveness of single agent anti-inflammatory treatment. The multiple pathways involved in the inflammatory response suggest that blocking a single pathway may not be enough to prevent stimulation of the response via alternate routes (Fig. 2.2). This leads to the conclusion that combined therapies may be required, although such research is difficult to set up because of the many conflicting scientific and commercial interests that have to be reconciled.

However, as noted above, complement activation occurs in the SIRS response, and the inhibitor C1INH can block multiple sites in these complex pro-inflammatory pathways. The use of C1INH in other inflammatory conditions has been encouraging, without significant adverse effects [53], but there is only sparse uncontrolled evidence that this agent might affect the course of severe acute pancreatitis. In a pig model of experimental pancreatitis, C1INH improved hemodynamics and increased survival in treated animals compared to untreated controls [54–56]. Four clinical case reports describe resolution of severe acute pancreatitis within a few hours of treatment with C1INH [57–59].

In the only randomized evidence available, consecutive patients undergoing endoscopic sphincterotomy for common bile duct stones or benign papillary stenosis were randomly allocated to receive either C1INH (20 cases) or placebo (20 cases) 30 min before the procedure. The C1INH group had significantly lower serum amylase levels during the first 8 h after sphincterotomy [60]. A phase II study is now in progress to investigate the possibility that C1INH could ameliorate the inflammatory response and prevent progression from SIRS to organ failure in patients with pancreatitis who fail to respond to initial treatment.

Conclusion

The identification of organ failure is now central to the definition of severe acute pancreatitis. We know that some patients with organ failure improve rapidly in response to initial treatment, and these patients have a low mortality rate. Transient organ failure is a marker of moderately severe disease. If organ failure persists for more than 48 h, the patient has severe pancreatitis, and is at high risk (at least 35 %) of a fatal outcome.

Organ failure is preceded by a period of illness with a marked inflammatory response. If the criteria for SIRS are present, the patient is at risk of progression to organ failure, and every attempt should be made to restore normality as soon as possible. Unfortunately, there are no specific anti-inflammatory treatments currently available, and management relies entirely on supportive measures.

Development of effective treatments for SIRS and early organ failure will require targeting of multiple pathways, either with a versatile agent which can block multiple receptors, or by combinations of agents active at different sites.

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Sterile and Infected Pancreatic Necrosis

3

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Acute pancreatitis has become the most common reason to be hospitalized for a gastrointestinal disease in the USA, with nearly 275,000 admissions reported in 2009 resulting in a total cost of $2.6 billion [1]. While the majority of admissions are for mild acute interstitial pancreatitis, approximately 5–10 % of patients have acute necrotizing pancreatitis [2–6], with rates of 27–42 % reported in other studies [7, 8]. The discrepancy between rates of necrotizing pancreatitis across studies is likely due to the inclusion of transfer patients. Acute necrotizing pancreatitis is associated with significant mortality, ranging from 10–15 % in sterile pancreatic necrosis and approximately 20–30 % in those with infected pancreatic necrosis [9, 10]. However, mortality can be as high as 40 % in patients with concurrent multi-organ failure [6]. The incidence of infected necrosis in patients with necrotizing pancreatitis is approximately 30–45 % but has been decreasing for unclear reasons, which might include more widespread use and earlier administration of enteral nutrition, improved supportive care for patients with concurrent organ failure, and antibiotic treatment for extrapancreatic infections, which may reduce bacterial seeding of pancreatic necrosis [9, 11–13].

The 1992 Atlanta classification defined necrotizing pancreatitis as a diffuse or focal area of nonviable pancreatic tissue on contrast-enhanced imaging, typically associated with extrapancreatic fat necrosis, with non-enhancing pancreatic parenchyma > 3 cm in length or involving > 30 % of the pancreas [14]. However, over the years, small case series have reported on patients with extensive extrapancreatic necrosis but with preserved pancreatic parenchyma [15–17]. Pancreatic necrosis can involve both the pancreatic parenchyma and extrapancreatic tissues (most common), pancreatic parenchyma alone, or extrapancreatic tissue alone (least common). It is important to recognize that extrapancreatic necrosis alone has a lower mortality compared to parenchymal necrosis [17–19] unless the extrapancreatic necrosis becomes infected [18].

Given the deficiencies of the original Atlanta classification in 1992, particularly with regard to the characterization of pancreatic fluid collections, a revision of the Atlanta classification was undertaken in 2007 through the efforts of several expert pancreatologists and pancreatic societies. (See also Chap. 1.) The revised Atlanta classification was published in 2013 [20]. The revised criteria characterize the pancreatic and extrapancreatic collections that can form in necrotizing pancreatitis. In the first 4 weeks from the onset of symptoms, an acute necrotic collection (ANC) can form. This is defined as a non-organized collection that contains variable

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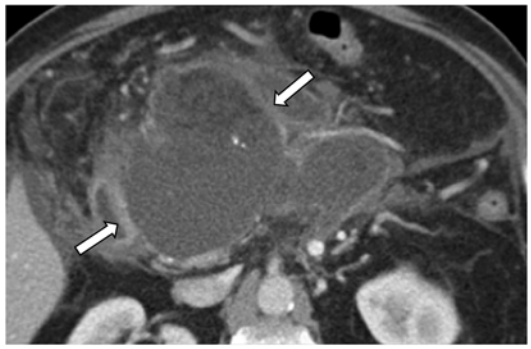

Fig. 3.1 CT image of walled-off pancreatic necrosis in the head of the pancreas with a completely encapsulated collection that is noted (*arrows*)

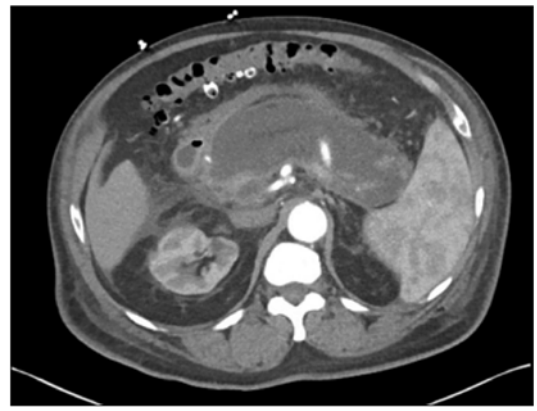

Fig. 3.2 Contrast-enhanced computed tomography images showing pancreas with lack of contrast enhancement. This CT was obtained on Day 3 in a 26-year-old male presenting with alcohol-induced acute pancreatitis

quantities of fluid and necrotic debris involving the pancreatic parenchyma and/or extrapancreatic tissues. However, solid debris may not be discernable on a CT scan and this can lead to an incorrect diagnosis of an acute fluid collection (AFC), which forms in the context of acute interstitial pancreatitis. Walled-off pancreatic necrosis (WOPN) is a mature, encapsulated collection consisting of variable quantities of solid necrotic tissue. Approximately 1–9 % of patients with acute necrotizing pancreatitis will develop WOPN in 4–6 weeks after the onset of symptoms [20]. On contrast-enhanced CT (CECT), WOPN is defined as a heterogeneous collection with liquid and non-liquid densities, and varying degrees of loculations, some of which can appear homogenous (Fig. 3.1). Both ANC and WOPN can become infected.

Diagnosis

Imaging

Cross-sectional imaging with CECT, or magnetic resonance imaging (MRI), is the imaging modality of choice for diagnosing necrotizing pancreatitis. (See also Chap. 6.) These imaging studies not only determine the presence and extent of necrosis but also local complications, including pseudoaneurysm, duodenal or biliary obstruction, presence of air bubbles indicating infection, and splanchnic thrombosis. CECT remains the gold standard for the diagnosis of pancreatic necrosis (Fig. 3.2). However, it can take several days for pancreatic necrosis to appear on imaging since the pancreas can often appear heterogeneous early in the course of disease. Over the first week, the area(s) of impaired perfusion become more demarcated on CECT. Dynamic CECT is currently recommended after 72–96 h of symptoms if a complication is suspected. Perfusion CT is another imaging modality used to diagnose necrotizing pancreatitis. However, unlike dynamic CTs, smaller amounts of contrast material (40–50 mL) are injected at a higher rate (4–10 mL/s) and at higher concentrations (350–370 mg/kg). Images of the pancreas are then obtained at multiple times. Perfusion CT software is used to calculate perfusion parameters and arterial input function. Perfusion CT has been shown to have a sensitivity of 100 % and specificity of 95.3 % for demonstrating pancreatic necrosis within 72 h of symptom onset but is not in widespread clinical use [21]. The advantage to using CECT includes its widespread availability, rapid scanning, and the ability to detect pancreatic necrosis. Disadvantages include exposure to ionizing radiation, contrast-induced nephrotoxicity, and inability to reliably detect necrotic debris in an ANC or WOPN [22].

MRI can also be used to diagnose pancreatic necrosis. Advantages to MRI include lack of ionizing radiation exposure and the ability to distinguish pancreatic necrosis without the administration of gadolinium using fat-suppressed

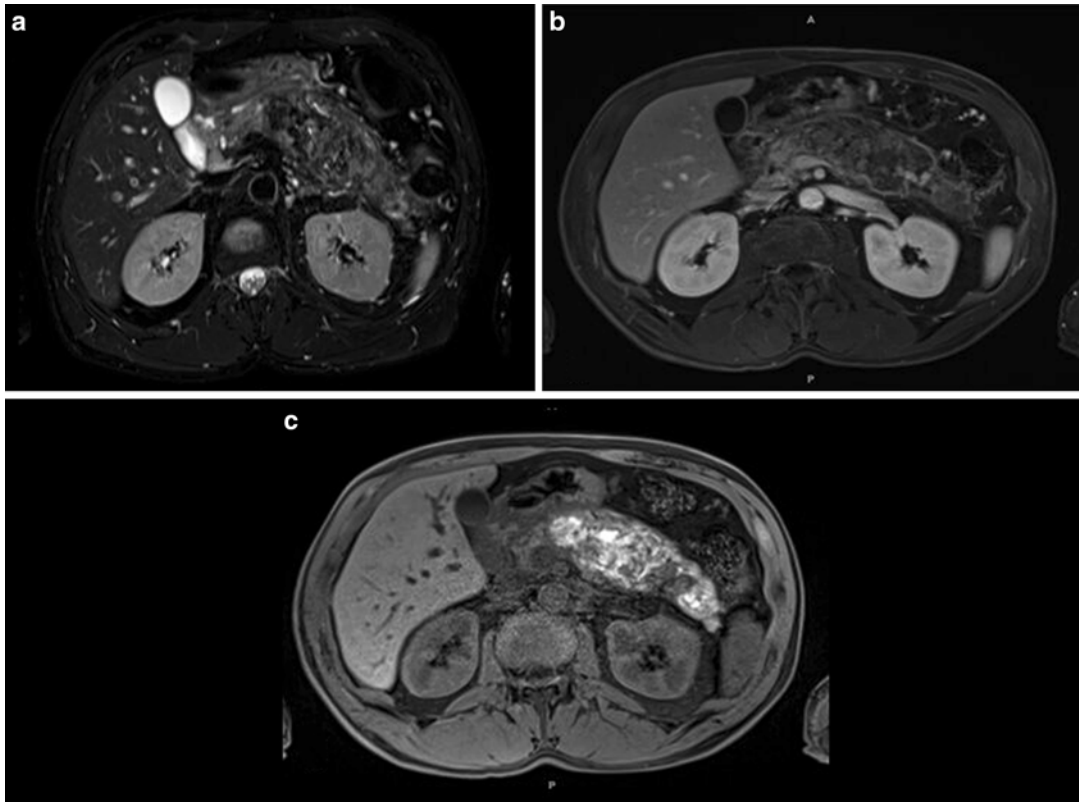

Fig. 3.3 MRI images of pancreatic necrosis in body and tail. (**a**) T2-weighted image. (**b**) T1-weighted image. (**c**) T1-weighted post-contrast image

T1-weighted images, which can be useful in patients with renal insufficiency. In addition, T2-weighted MRI is superior to CT for the evaluation of necrotic debris within pancreatic collections and extrapancreatic fat necrosis. Figure 3.3 shows T2- and T1-weighted MRI images of pancreatic necrosis. Figure 3.4 compares CT and MRI image of WOPN. MRCP also has the ability to delineate a pancreatic ductal disruption and evaluate for bile duct stones. Disadvantages include cost, lack of widespread availability, longer acquisition times, poor patient tolerance, and the contraindication of metallic foreign bodies, which includes coils and pacemakers [22–25].

Development of Infection

Infection of pancreatic necrosis most commonly occurs 2–4 weeks after the onset of acute pancreatitis, or at any point after the development of necrotizing pancreatitis [26, 27]. Pancreatic infection in patients with necrotizing pancreatitis is due to increased intestinal permeability and decreased immunity that occurs during severe acute pancreatitis, termed "gut barrier dysfunction," which results in the translocation of bacteria. Besselink et al. found that 72 (46.8 %) out of 154 patients with pancreatic parenchymal necrosis developed infected necrosis over a median of 26 days after admission [26]. This high rate of infected necrosis; however, may be partially explained by contamination after fine-needle aspiration (FNA), since all patients with suspected infected necrosis underwent FNA. Bacteremia was shown to be a risk factor in the development of infected necrosis (65 % versus 37.9 %, $p=0.002$). In 21 out of 51 patients, who had both bacteremia and infected necrosis, the same pathogen was isolated from both cultures of

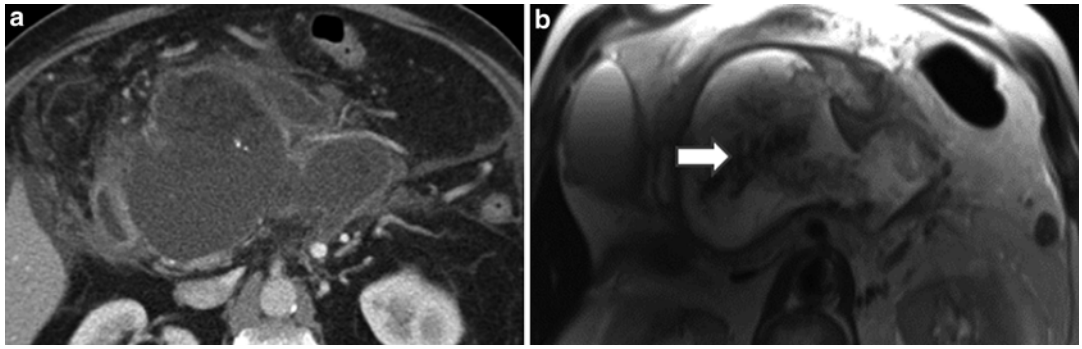

Fig. 3.4 (**a**) CT image of walled-off pancreatic necrosis. (**b**) MRI T2-weighted image of pancreatic necrosis. There is a encapsulated wall surrounding collection, which contains hypodense material (*arrow*)

the blood and pancreatic necrosis. They also reported that patients with extensive necrosis (>30 %) had a higher risk of developing infected necrosis [26]. Other studies have also shown a correlation between the presence and extent of pancreatic necrosis and infection [8, 12, 28].

Diagnosis of Infection

Infected pancreatic necrosis should be suspected if there is progressive clinical deterioration as evidenced by persistent systemic inflammatory response syndrome (SIRS) and/or worsening organ failure [29, 30]. According to the most recent American College of Gastroenterology guidelines on management of acute pancreatitis, infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who clinically decline or fail to improve after 7–10 days of hospitalization [31]. In a subset of patients, CT imaging will reveal air bubbles within a collection, which suggests the presence of gas forming organisms or the development of a fistulous tract between a pancreatic collection and the stomach, small bowel, or colon [29]. However, the presence of gas within pancreatic tissue occurs in a minority of patients (Fig. 3.5).

Approximately 25 % of patients presenting with acute pancreatitis develop extrapancreatic infections [26, 32]. Clinical studies have shown that infection of the pancreatic bed is the result of seeding from extrapancreatic infections, most commonly from the bloodstream [26, 33]. These extrapancreatic infections are more often polymicrobial compared to pancreatic infections that are monomicrobial [34]. Gram-negative bacteria are the predominant cultured organisms in pancreatic necrosis. However, the incidence of gram-positive organisms and yeast has been increasing, which is potentially due to the widespread use of broad spectrum antibiotics [33, 35–37]. *Candida* species are the most common isolated fungus in patients with necrotizing pancreatitis, followed by *Torulopsis* [38]. Studies have also revealed increased mortality in patients with pancreatic necrosis who develop fungal infection with *Candida* [37, 39].

There has been controversy with the routine use of FNA for diagnosing infected pancreatic necrosis [40, 41]. CT- or ultrasound-guided FNA has been shown to be a safe, effective, and accurate technique for diagnosing infected necrosis [42–44]. While the detection of infected necrosis can guide therapy and the appropriate use of antibiotics based on a sensitivity profile of organism(s) cultured from the aspirate, some argue that even if the aspirate is positive, the patient should not undergo intervention until 3–4 weeks after onset of disease, as debridement is then preferably delayed. The only widely accepted indication for early debridement is clinical deterioration. In addition, aspiration is not very accurate, with a reported sensitivity of 88 % and specificity of 90 % [43]. If the aspirate is

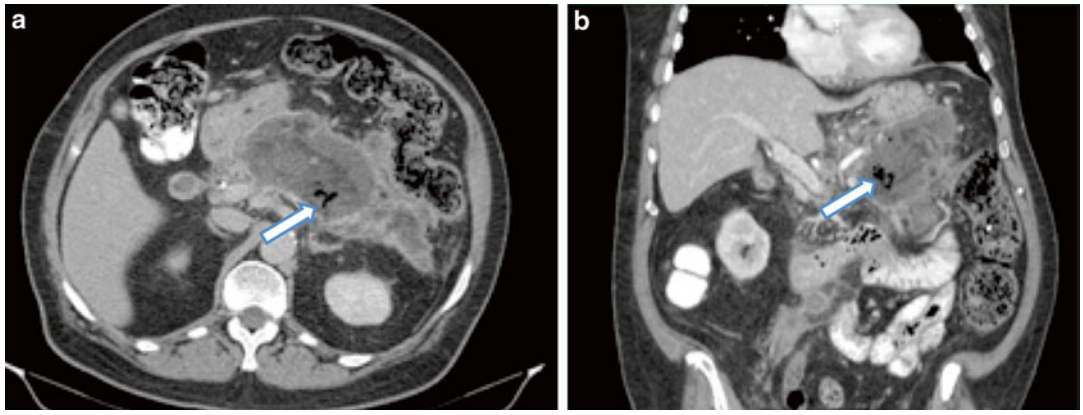

Fig. 3.5 CT exam revealing multiple foci of gas (*arrows*) within collection

negative for infection but the patient experiences clinical deterioration, then debridement is still indicated.

Management of Sterile and Infected Necrosis

The treatment of necrotizing pancreatitis has changed over the last two decades. Historically, patients with sterile and infected necrosis underwent open surgical necrosectomy at early stages of disease [45]. In recent years, the indication, timing, and approaches towards intervention have changed. With the advent of minimally invasive techniques, the mortality of patients with necrotizing pancreatitis has further decreased [9]. Figure 3.6 displays an algorithm summarizing the approach to intervention in necrotizing pancreatitis based on current evidence.

Aggressive but conservative supportive therapy is the mainstay treatment for patients with acute necrotizing pancreatitis. Aggressive intravenous fluid resuscitation is required to maintain adequate intravascular volume and end-organ perfusion. (See also Chap. 8.) The controversy lies in what is considered "aggressive" resuscitation. Despite the fact that this is recommended universally in the guidelines of experts and professional societies, there are few randomized trials to guide clinical decision making. One trial utilized a 2×2 factorial design where 40 patients were equally randomized to type of fluid administered as well as rate of infusion. The authors demonstrated significantly reduced C-reactive protein levels and prevalence of SIRS at 24 h in those randomized to lactated Ringer's compared to normal saline but found no difference in the rates of infusion due to a possible crossover effect [46]. Two retrospective studies demonstrated that early aggressive fluid resuscitation is associated with lower rates of SIRS, organ failure, and length of stay [47]. The primary criticism of retrospective studies is the concept of "reverse causation," where increased fluid was administered to patients with a greater severity of illness [48]. However, caution must be observed since aggressive resuscitation is associated with adverse outcomes due to third spacing of fluid. One study demonstrated that rapid hemodilution can increase the incidence of sepsis within 28 days and inhospital mortality in patients with severe acute pancreatitis [49]. There have not been any studies to date demonstrating that aggressive fluid resuscitation results in a reduced incidence of pancreatic necrosis. Supportive care for the treatment of organ failure should ideally be provided in intensive care units. Early nutritional support with enteral feeding is critical for providing sufficient caloric intake and to maintain the gut barrier, which reduces septic complications, including infected pancreatic necrosis, thereby reducing mortality, multi-organ failure, and the need for surgical intervention [50–52].

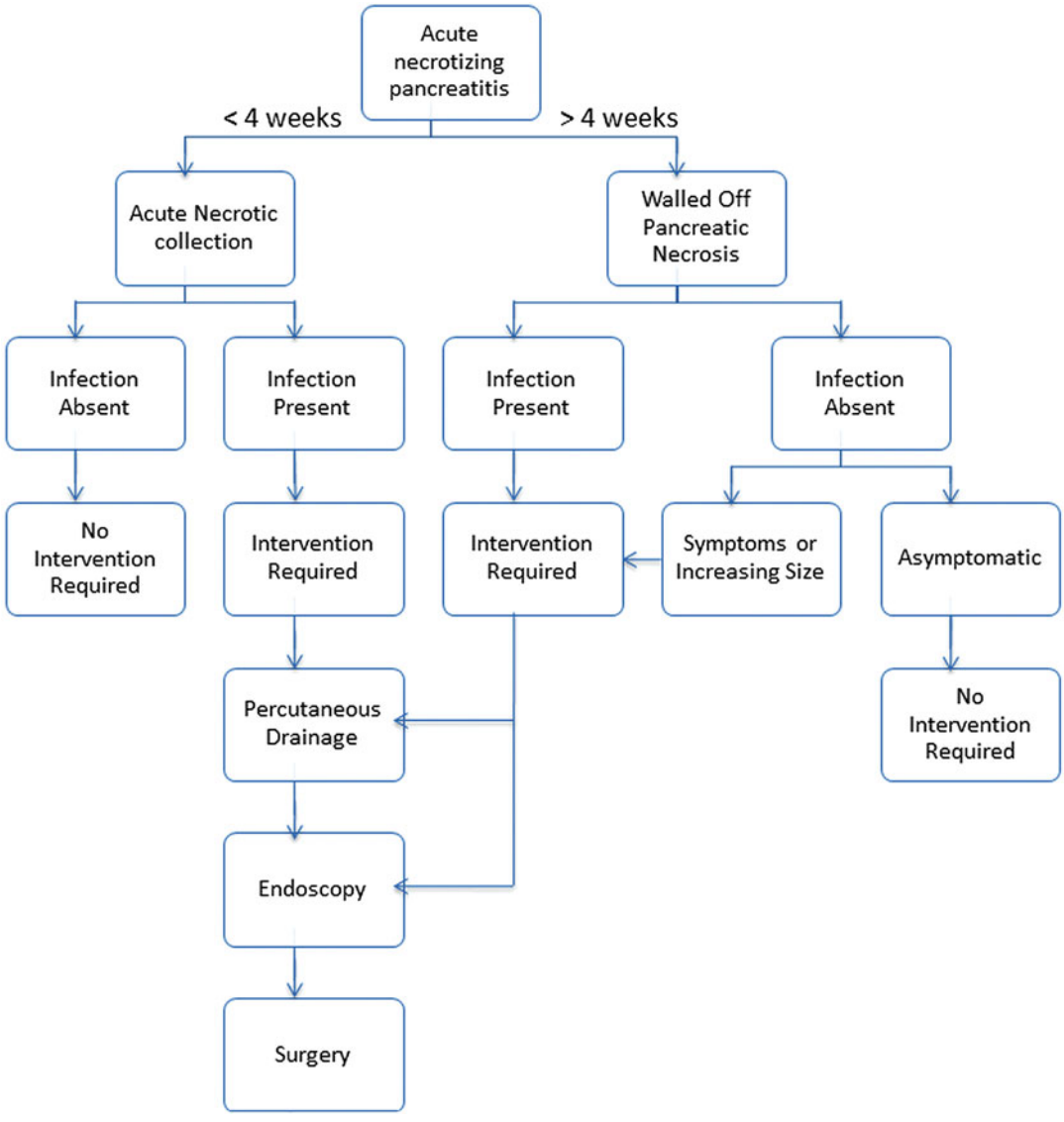

Fig. 3.6 Algorithm for the management of necrotizing pancreatitis

Sterile Necrosis

There has been a paradigm shift in the treatment of sterile necrosis. In patients with sterile necrosis and organ failure, surgical debridement was associated with increased mortality [53]. According to a recent consensus conference on necrotizing pancreatitis, sterile ANC do not necessitate early intervention [54]. Sterile asymptomatic WOPN also does not require intervention, as these collections can resolve spontaneously, although the rate of spontaneous resolution is not known. However, the presence of symptoms, including persistent abdominal pain and/or mechanical obstruction, e.g., gastric outlet obstruction or biliary obstruction, development of infection as well as increase in size of WOPN necessitates drainage and the methods used for drainage are similar to those used for infected necrosis.

Use of Prophylactic Antibiotics

The use of prophylactic antibiotics has been controversial. (See also Chap. 9.) Clinical trials in the 1970s did not show improvement in mortality with the use of prophylactic antibiotic use in patients with acute pancreatitis. However, these studies were criticized for the inclusion of patients with mild disease. In the 1990s, the use of prophylactic antibiotics was revisited with the advent of new antibiotics against enteric organisms. Studies showed an improvement in mortality in those presenting with acute necrotizing pancreatitis with the use of prophylactic antibiotics [55, 56]. However, in 2009, a large randomized multicenter trial of prophylactic antibiotics in 276 patients with pancreatic necrosis revealed no difference in the rates of infected necrosis, mortality, and operative necrosectomy [57]. Prior smaller randomized controlled trials revealed similar findings [27, 58]. De Vries et al. [59] evaluated the methodologic quality of randomized controlled trials of antibiotic prophylaxis in patients with severe acute pancreatitis in relation to their outcome. They showed an inverse relationship between the methodological quality and the impact of antibiotic prophylaxis [59]. A Cochrane review of the literature evaluated seven randomized controlled studies consisting of 404 patients found no benefit of antibiotics in preventing infected necrotizing pancreatitis or mortality. However, they reported that there was less mortality and less infected pancreatic necrosis in those receiving beta-lactams antibiotic prophylaxis, although this was not statistically significant [60]. Studies have also revealed that the use of prophylactic antibiotics, which include beta-lactams, have been associated with secondary fungal infections, as well as the selection of multiresistant organisms [35, 36, 61]. In these studies, the prevalence of secondary fungal infection ranged from 11–32 % [37, 61]. Based on the current literature, the use of prophylactic antibiotics in patients with pancreatic necrosis is not recommended. In clinical practice, if infection is suspected, it is reasonable to initiate antibiotics after obtaining blood and urine cultures as well as radiographs and when the results of these investigations become available, the decision to continue or discontinue antibiotics can be made accordingly.

Infected Necrosis

Prior to 1998, surgical management using open necrosectomy was the standard of care for managing infected pancreatic necrosis. In 1998, Freeny et al. [62] reported resolution of sepsis in 47 % of patients with infected necrosis after aggressive percutaneous drainage using multiple catheter(s) and lavage. However, the remaining 53 % of patients required an open necrosectomy and mortality was reported to be 12 % in the total cohort. In the last decade, data have suggested that patients with infected necrosis can be treated conservatively without compromising prognosis [63]. Early management of infected necrosis is similar to conservative approach of sterile necrosis in addition to antibiotics that penetrate the pancreas, e.g., carbapenems, quinolone, metronidazole, and high dose cephalosporins [12, 28]. Amphotericin B and fluconazole are appropriate antifungal agents, although amphotericin is considered first-line.

Open Necrosectomy

Open surgical necrosectomy, which was routinely performed early in the course of disease in order to remove infected pancreatic necrosis, has been associated with high morbidity and mortality as well as long-term pancreatic exocrine and endocrine insufficiency [64, 65]. (See also Chap. 16.) Throughout the years, the management of infected necrosis has been modified in several ways. First, it is now known that waiting 3–4 weeks after the onset of disease is associated with decreased complications as this allows for the encapsulation of ANCs into WOPN, which will improve conditions for intervention [66, 67]. Second, taking the "less is more approach" has been supported by several studies. A recent study by Garg and colleagues [68] compared conservative therapy to surgical therapy in 80 patients with infected necrotizing pancreatitis. Conservative therapy was defined as the use of antibiotics, enteral nutrition, support of organ failure, and percutaneous drainage of organized or walled-off collections if needed. Surgical therapy was defined as those who were treated with

surgical necrosectomy, lavage, and drainage. Patients underwent surgical intervention if they deteriorated despite aggressive conservative therapy. The mortality rates in patients who went to surgery immediately was 43 %, compared to a mortality rate of 28 % in patients whom were treated with conservative approach ($p=0.22$) A recent meta-analysis of eight studies comprising 324 patients revealed that 64 % of patients treated with the conservative approach had successful outcomes and a mortality of 12 % [69]. Third, as an alternative to open necrosectomy, minimally invasive approaches have become more accepted. These include percutaneous catheter drainage, minimally invasive retroperitoneal necrosectomies, including video-assisted retroperitoneal debridement (VARD), and endoscopic transluminal necrosectomy.

Percutaneous Drainage

The goal of percutaneous drainage is to drain infected fluid from an ANC or WOPN. Percutaneous drainage of pancreatic and extrapancreatic necrosis involves placement of single or multiple catheters that are typically upsized, irrigated, and manipulated. Freeny et al. [62] were the first to describe the treatment of acute necrotizing pancreatitis in 34 patients with image-guided percutaneous drainage as an alternative to surgical intervention. They used multiple large-bore catheters with vigorous irrigation to achieve successful percutaneous necrosectomy. The authors found that this approach resulted in postponing surgical intervention by median of 4 weeks, and prevented the need for surgery altogether in 47 % of patients. However, their approach required multiple procedures over time to achieve these outcomes. A recent systematic review of 11 studies with 384 patients evaluating percutaneous drainage for treatment of sterile and infected necrotizing pancreatitis found that 56 % of cases were successfully treated with percutaneous drainage and did not require surgical necrosectomy [70]. The size of the percutaneous drains inserted varied from 8 to 28 Fr. Recent prospective studies have confirmed these findings [9].

Percutaneous drainage is a simple procedure. It can be used in situations where a collection or a portion of a collection cannot be accessed endoscopically (e.g., left paracolic gutter extension). It can be used in critically ill patients as a bridge to surgery. It can also be used as a bridge to other minimally invasive surgical procedures. Disadvantages include limited access to the head collections, the necessity for multiple drain exchanges due to drain occlusion and/or repositioning, limited ability to remove necrotic material, and the development of fistulas between the collection and the drain tract exit site [38].

Minimally Invasive Retroperitoneal Necrosectomy

Minimally invasive retroperitoneal necrosectomy includes sinus tract endoscopy, laparoscopic transabdominal necrosectomy, and VARD. (See also Chap. 15.)

Sinus tract endoscopy involves serial dilations of tracts that have formed from previously placed percutaneous catheters under fluoroscopy in the operating room, followed by jet irrigation and lavage using an endoscope or nephroscope. Solid necrotic material is removed with an endoscope. This technique was initially reported by Carter et al. [71] and later by Connor et al. [72]. Mortality has been reported to range from 0 % to 25 % with a median of four procedures performed on each patient with infected necrosis [72].

VARD was initially described by van Santvoort et al. [73]. A percutaneous drain is initially placed in the (peri-) pancreatic collection through the left retroperitoneum. If there is no clinical improvement, then a 5-cm subcostal incision is made near the exit point of the percutaneous drain. The percutaneous drain is followed deeper into the necrotic collection. Under direct videoscopic visualization, further debridement is performed using a laparoscopic forceps. Advantages include the use of both the endoscopic and open approach, as well as removal of larger quantities of necrotic material when compared to the sinus tract endoscopy, thus reducing repeat procedures. However, disadvantages include the exposure to

ionizing radiation in the operating room as well as increased costs [73]. A recent prospective multicenter study evaluating the safety and efficacy of VARD reported bleeding and enteric fistulas in 7.5 % and 17.5 %, respectively, and a 30-day mortality of 2.5 % [74]. Since VARD utilizes percutaneous drainage, it carries the potential complication of an external pancreatic fistula. In addition, its use is limited in those with necrosis involving the head of the pancreas, where the application of percutaneous drainage is not amenable through the retroperitoneal approach.

Endoscopic Necrosectomy

In the 1996, Baron et al. [75] described an endoscopic method for draining WOPN employing a transmural approach through the posterior gastric wall or the medial wall of the duodenum. See also Chap. 14. A needle knife sphincterotome was utilized to gain access to the collection. The tract was then dilated using a hydrostatic balloon followed by the insertion of two 10-Fr, 3-cm double pigtail stents into the collection. Saline irrigation was performed in patients who developed infected necrosis using a nasobiliary tube. Over the years, the approach has been modified. Subsequently in 2000, Seifert et al. [76] published a case report of three patients using the direct retroperitoneal endoscopic approach to debride the necrotic pancreas. In the series of the three patients, transmural puncture created a fenetration, which was then dilated with 16-mm balloon, allowing for the advancement of the therapeutic gastroscope into the cavity. Endoscopic debridement was achieved using lavage and electrocautery [76]. The approach of direct entry into the necrotic cavity is known as direct endoscopic necrosectomy [77–79]. When compared to the conventional transmural endoscopic drainage for the treatment of WOPN, direct endoscopic necrosectomy achieved high rates of resolution, shorter length of hospitalization, and reduced rate of cavity recurrence [78].

With the advent of newer endoscopic techniques and modalities [74], the EUS-guided approach has been adopted to localize a site from the posterior gastric wall or medial wall of the duodenum to reduce the risk of complications and improve success rates [80, 81]. Endoscopic placement of transmural stents have been used to create a temporary fistula for drainage of pancreatic collections. Over the years, these stents have been modified. Prior studies used plastic stents for drainage of WOPN [78]. However, these stents are susceptible to obstruction, migration [82], and ineffective drainage, particularly for WOPN [83]. Belle et al. [84] reported a case report on their experience of using a partially covered self-expanding metal stent (SEMS) in patients with WOPN. The SEMS creates a wide diameter outflow tract for the drainage of solid debris and provides a port of access for further endoscopic interventions. Since then, several case reports detailing the use of fully covered SEMS in patients with WOPN have been promulgated [85, 86]. A novel fully-covered metal stent, named AXIOS, with bilateral flanges and a wider diameter, has been developed [87]. It has been reported to have easy deployment, and its large diameter permits faster drainage and allows for therapeutic interventions [88], which may include direct endoscopic necrosectomies.

The GEPARD study [81] was the first study to report the long-term outcomes of patients who undergo direct endoscopic necrosectomy. This retrospective study included 93 patients in six centers in Germany with mean follow-up of 6 years. These patients had infected WOPN and underwent endoscopic transmural necrosectomy every 1–4 days until the removal of all necrotic material. The authors reported an initial clinical success in 80 % of patients, and of these patients, 84 % had sustained clinical improvement after mean follow-up period of 43 months, and 10 % needing further endoscopic intervention. Major complications were seen in 26 % of cases, which included bleeding in 14 %, perforation in 6 %, air embolism in 2 %, and mortality in 7.5 % at 30 days. Gardner et al. [79] reported the results of the largest multicenter study evaluating direct endoscopic necrosectomy. A total of 104 patients underwent direct endoscopic necrosectomy for WOPN with the insertion of an endoscope across the cystgastrostomy or cystduodenostomy tract and removal

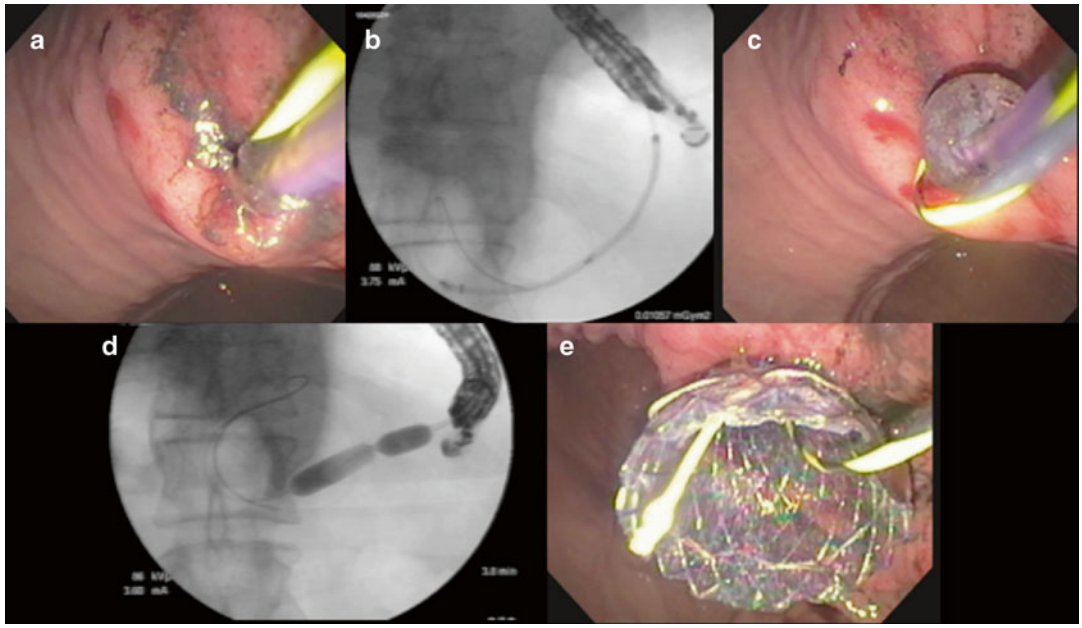

Fig. 3.7 Endoscopic drainage and necrosectomy. (**a**) Transmural puncture is performed under EUS guidance and a guidewire is advanced into the pancreatic cavity with the use of fluoroscopy. (**b**) Fluoroscopic evaluation of the guidewire into the fluid collection. (**c**, **d**) Balloon dilation of the tract with a 12- to 15-mm CRE balloon advanced over guidewire under fluoroscopic guidance in a 54-year-old male with acute necrotizing pancreatitis of unclear etiology. The waist of the balloon (*arrows*) defines the site of the cystgastrostomy. (**e**) Fully covered 22-mm diameter × 60-mm long esophageal metal (Tae Woong Medical) stent placed across the cystgastrostomy into the necrotic collection

of the necrotic debris. The overall success was reported to be 91.3 % in resolution of the WON and the mean duration to cavity resolution after initial resolution was 4.1 months. Complications included bacteremia/ infection (27 %), bleeding (20 %), perforation (13 %), and pneumoperitoneum (20 %). This large study showed that direct endoscopic necrosectomy is a successful alternative to surgical or percutaneous debridement for the management of WOPN. The disadvantages of this approach include the need for several procedures for successful debridement, the time-consuming nature of the procedure, and the need for specialized endoscopic expertise. Figure 3.7 demonstrates endoscopic drainage and necrosectomy. Figure 3.8 demonstrates endoscopic resolution of the necrotic collection.

The PENGUIN (Pancreatitis, Endoscopic Transgastric vs Primary Necrosectomy in Patients with Infected Necrosis) trial was a prospective, randomized trial evaluating 22 patients with infected WOPN who underwent percutaneous catheter drainage. If this failed, patients were randomized to endoscopic transgastric or surgical necrosectomy. The surgical necrosectomy consisted of VARD, or if not feasible, then laparotomy. They found that endoscopic transgastric necrosectomy was associated with significantly reduced IL6 levels, multi-organ failure, and external pancreatic fistulas when compared to the surgical necrosectomy [89].

Combined percutaneous and endoscopic drainage of WOPN was described by Ross et al. [90]. Patients in this study initially underwent a CT-guided placement of a percutaneous drainage catheter into the WOPN to remove necrotic debris. The catheters were irrigated three times a day. The patients were immediately transferred to the endoscopic suite where an endoscopic transmural drainage was performed with the utilization of two transenteric double-pigtail stents. The cystgastrostomy fistula redirects the

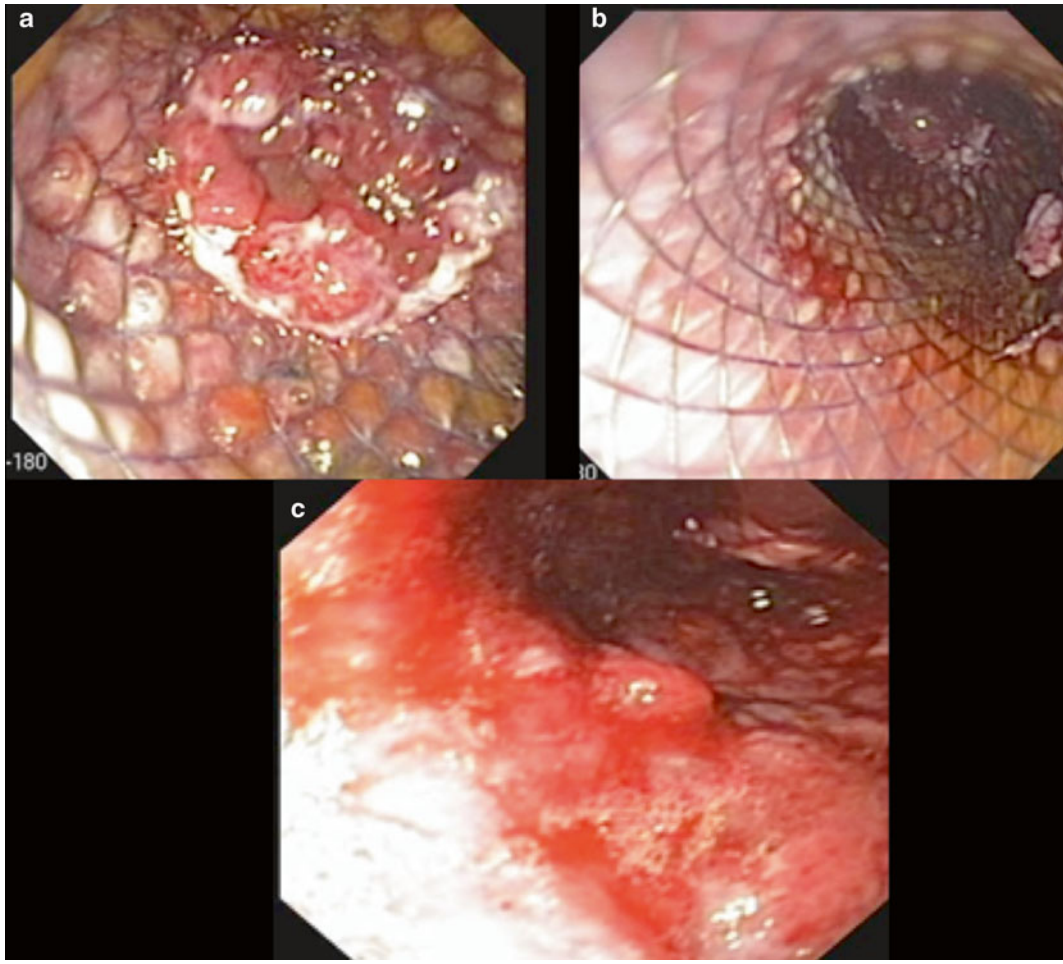

Fig. 3.8 Endoscopic resolution of the necrotic collection seen above

pancreatic secretions into the small bowel. The combined drainage technique avoids the utilization of large-diameter balloon dilation of the cystenterostomy, thereby reducing the risk of hemorrhage and free perforation into the peritoneum. The authors also reported a low rate of endoscopic reintervention with this approach, as well as absence of chronic pancreaticocutaneous fistula formation, which has been shown in patients with central gland necrosis and percutaneous drains [90]. This approach is associated with reduced length of hospitalization, radiological procedures, and number of ERCPs when compared to those who underwent percutaneous drainage only [91, 92]. However this approach may be limited to only a few centers nationwide, given that the coordination of percutaneous drainage through interventional radiology and endoscopic drainage immediately after may be difficult to arrange.

Step-up Approach

A landmark RCT performed by the Dutch Acute Pancreatitis Study Group [93] compared a minimally invasive technique with open necrosectomy. The inclusion criteria for this study were stringent. After screening 378 patients, 88 patients with confirmed or suspected infected

pancreatic necrosis were randomized to percutaneous drainage versus open necrosectomy. For those randomized to PD, if there was no clinical improvement in 72 h and if the position of the drains were inadequate, then a second drainage procedure would take place. If there was no clinical improvement in 72 h, then a "step-up" approach would include VARD with postoperative lavage or endoscopic drainage. The patients randomized to the step-up approach had lower rates of multisystem organ failure, major complications such as diabetes and need for pancreatic enzyme supplementation when compared to the open necrosectomy group. Mortality was not different between the two groups; however, the study was not powered to demonstrate a difference in mortality rates. This study has shifted the treatment paradigm away from invasive surgery and towards a minimally invasive approach for patients with infected ANCs [93].

Conclusion

There have been great advances in the diagnosis and management of necrotizing pancreatitis over the last decade. The first was the revised Atlanta classification, which refines the characterization of ANCs and WOPN. The second are the various modalities for the diagnosis of infected and sterile necrosis, which include dynamic CECT and MR imaging. The third is the shift in the management paradigm from surgical to conservative and minimally invasive approaches with the goal of delaying intervention until a collection becomes organized. Conservative management with intravenous fluids and enteral feedings continue to be the mainstay of therapy for patients with sterile and infected necrosis. Prophylactic antibiotics are not recommended in patients with pancreatic necrosis. In patients with sterile necrosis who remain asymptomatic, no intervention is required. However, patients who develop symptoms or infection, warrant intervention. The decision as to which approach to intervention to pursue should be guided by the presence of the adequate surgical, endoscopic, and/or radiological expertise. The optimal management of an infected ANC requires the minimally invasive step-up approach, which consists of percutaneous drainage initially followed by endoscopy and/or minimally invasive retroperitoneal necrosectomy if necessary. This has been associated with reduced rates of complications. Endoscopic therapy alone using direct necrosectomy or large-bore transmural metal stents has largely become the mainstay of therapy for patients with symptomatic and/or infected WOPN.

Conflict of interest. Vikesh Singh is a consultant for Abbvie, Santarus, D-Pharm, Novo Nordisk and Boston Scientific. The other authors have no disclosures.

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Evolving Definitions of Severe Acute Pancreatitis

4

John A. Windsor and Maxim S. Petrov

Introduction

Acute pancreatitis (AP) is a protean inflammatory disease with a wide range of severity and a highly variable course [1]. Patients with more severe disease still have an appreciable morbidity and mortality and are a significant clinical and economic challenge. Although the overall outcomes have improved over the last few decades, there remains no specific treatment targeting the outcome determining pathophysiology. This failure to develop specific treatments is in part due to misclassification error in clinical trials. The accuracy of most approaches to predicting the severity of AP is around 70 % [2], which means that 30 % of patients are not allocated correctly. There has also been a failure to understand the different types of definitions that exist in general, the fallacies that can befall definitions, and in particular the different ways that definitions are used in the AP literature. The aim of this chapter is to review some of the issues with the use of definitions and the evolution of definitions of AP severity and to indicate the future directions as a series of research priorities. Note that this chapter will address the definition of actual (present tense) severity, which can also be termed classification or staging, rather than the predicted (future tense) severity, which is the subject of Part II in this text.

Definitions: Types, Fallacies, and Attributes

Without delving too deeply into the semantics and philosophy of definitions, when considering how to define the severity of AP it is helpful to consider the type of definition that is most applicable. Aristotle made the distinction between a *nominal* definition, which explains what severe AP is, from a *real* definition, which would explain the essential nature ("essence") of severe AP. These are different from a *descriptive* definition that gives features of severe AP. A recent example of descriptive definitions is shown in Table 4.1, relating to the local complications of acute pancreatitis [3]. It is appreciated that these morphological and temporal definitions, particularly useful for reporting radiological imaging of acute pancreatitis, do not necessarily have a direct relationship with the severity of AP and may just be a consequence or epiphenomenon of the disease. Of more use in clinical practice, in defining the severity of AP, is an *intensional* type of definition, which specifies the necessary and sufficient conditions required to state that a patient has severe AP. This is in contrast to an *extensional* definition, which simply lists patients

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Table 4.1 Definitions of local complications of acute pancreatitis, based on morphological characteristics and time[a]

Content	Acute (<4 weeks, with no defined wall)		Chronic (≥4 weeks, with defined wall)	
	No infection	Infection	No infection	Infection
Fluid only	Acute peripancreatic fluid collection (APFC)	Infected APFC[b]	Pseudocyst	Infected pseudocyst[b]
Solid ± fluid	Acute necrotic collection (ANC)	Infected ANC	Walled-off necrosis (WON)	Infected WON

[a]Modified from the revised Atlanta classification [3]
[b]Infected acute pancreatic fluid collection and infected pseudocyst are not included in the revised Atlanta Classification [5]

with severe AP. Examples of both nominal and intensional definitions of severe AP include the classification of severity in the original [4] and revised Atlanta [5] classifications and the determinant-based classification [6].

Definitions can fail to have merit when they do not obey the accepted rules of definitions. In defining the severity of AP, published classification systems have fallen short in several typical ways, including the incorporation of non-essential attributes (e.g., the moderately severe category in the revised Atlanta classification includes patients who have an exacerbation of a pre-existing chronic illness); being overly broad or narrow (e.g., further clinical evidence has demonstrated that the severe category of the original Atlanta criteria includes subgroups of varying severity); not always being stated in positive terms (e.g., mild AP being defined as the absence of severity determinants); and by being obscure or ambiguous (e.g., necrosis including both pancreatic and peripancreatic tissue).

To be clinically useful the definition of AP severity should accurately distinguish the subset of patients, and ideally individual patients, for whom clinical benefit will derive by doing so. The more accurate the identification and definition of the patients with severe AP, the better will be the clinical decisions about treatment and research decisions about recruitment for trials. A sound definition of AP has important attributes which include being easily measured, having high clinical utility, being specific to AP, and are indexed to time and scientifically sound. The iterative nature of science means that the definition of severity should evolve with new scientific knowledge and for this reason definitions should always be considered "working" definitions.

The time dimension of definitions is also worth noting, since in any population of patients with AP and at any one time there will be a range of severities and over time the proportion of patients with severe AP will change. While definitions that yield the prevalence and incidence in populations are of value in clinical research, the clinician who is faced with management decisions about the individual patient in their care requires a responsive and accurate way to define disease severity, which also changes over time. Thus, the repeated definitions of the severity of AP in an individual patient are necessary, as this dynamic disease unfolds, to describe the severity of disease course.

Dimensions of Severity

Severity can be defined in different dimensions, dictating different definitions. These dimensions include defining severity in biochemical (e.g., greater proinflammatory response), clinical (e.g., more severe organ failure), pathological (e.g., extent of necrosis), outcome (e.g., longer hospital stay), or economic (e.g., cost of treatment) terms. Although not customary to do so, it is suggested that when defining the severity of acute pancreatitis the dimension(s) relevant to the requirements of the classification should be considered.

Previous Classifications of Severity

The first published classification of AP severity dates back to 1983 when an international meeting on classification of pancreatitis was held in

Cambridge [7]. See also Chap. 1. At that meeting it was agreed that acute and chronic pancreatitis are essentially distinct entities. Further, the Cambridge classification addressed the issue of severity by distinguishing "mild" and "severe" AP. The latter was defined as "multisystem failure and/or early or late local complications" and "mild" AP was defined as "no multisystem failure with uncomplicated recovery." The recognized local complications were pancreatic phlegmon, pseudocyst, and abscess.

One year later, a meeting in Marseilles gave special emphasis to the morphological features of AP [8]. "Severe" AP was defined as "extensive peri- and intra-pancreatic necrosis, parenchymal necrosis and hemorrhage, localized or diffuse" and "scarring and pseudocysts may persist." "Mild" AP was defined as "peripancreatic fat necrosis and interstitial edema, absence of pancreatic necrosis." Possible impairment of exocrine and endocrine function was also mentioned in the classification.

More details were added to the Marseilles classification at the meeting in Rome in 1988 [9]. These mainly related to pancreatic and peripancreatic collections in AP. As a result, the definition of "mild" AP remained unchanged, while the definition of "severe" AP was extended to "extensive peri and intra-pancreatic necrosis, parenchymal necrosis and hemorrhage, localized or diffuse, peripancreatic fluid collections, infection of necrosis, formation of pseudocysts or abscesses."

In 1992, the Atlanta symposium focused exclusively on AP and attempted to devise a classification of severity that would be suitable for both routine clinical practice and comparison of inter-institutional data [4]. The Atlanta classification adopted the same two categories for classifying AP severity and added some special definitions regarding acute fluid collection, pancreatic necrosis, pancreatic pseudocyst, and pancreatic abscess. It also recommended the use of predictive tools, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Ranson criteria. As a result, "severe" AP was defined as being "associated with organ failure (OF) and/or local complications, such as necrosis, abscess, or pseudocyst and characterized by three or more Ranson criteria, or eight or more APACHE II criteria" and "mild" AP as "associated with minimal organ dysfunction and an uneventful recovery, and it lacks the features of severe AP." This reveals a common mistake in equating classifying severity and predicting severity. Table 4.2 summarizes the entities that have been included in the definitions of "severe" AP in previous classifications of AP severity.

The original Atlanta classification was published in 1993 and the revised Atlanta definition was published in 2013. The revision of the Atlanta was a protracted process over 7 years and was not based on a systematic review of the evidence but relied primarily on a Web-based consensus building approach. This meant that the publishing journal had to do an unusually "extensive and diligent review process" [10]. And while the editorial committee acknowledged that many aspects of the manuscript remain debatable, particularly in areas where published data were scarce, the revised Atlanta manuscript is an advance in the field [10].

The major impetus to revising the original Atlanta classification has been the many advances in understanding the pathophysiology of AP, and, in particular, the role of systemic complications. While the original Atlanta definitions of "severe" AP included only the presence or absence of OF, it is increasingly recognized that the number of organs that fail, timing of onset, and duration of OF all relate to mortality. In particular, it has been shown that OF persisting beyond 48 h is associated with significantly increased mortality in patients with AP. The revised Atlanta classification states that only patients with persistent OF should be defined as having "severe" AP (see Table 4.2). This means that patients with local pancreatic complications, even infected pancreatic necrosis, which is an independent determinant of severe disease [11], are excluded from the definition of "severe" AP. From the first description of the severity of AP by Fitz in 1889 up until the original Atlanta classification of severity in 1993, a morphological component has always been included. While Fitz believed that the morphological features of severe disease were

Table 4.2 Entities included in the definition of "severe" acute pancreatitis in classifications of severity

Classification	Year (reference)	Local entities		Systemic entities		Other entities
Cambridge	1983 [7]	Pancreatic phlegmon Pancreatic pseudocyst Pancreatic abscess	and/or	Multisystem failure		–
Marseilles	1984 [8]	Peripancreatic necrosis Parenchymal necrosis Pancreatic hemorrhage Pancreatic scarring Pancreatic pseudocyst		–		–
Marseilles-Rome	1988 [9]	Peripancreatic necrosis Parenchymal necrosis Pancreatic hemorrhage Peripancreatic fluid collections Infection of necrosis Pancreatic abscess Pancreatic pseudocyst		–		–
Atlanta	1993 [4]	Pancreatic necrosis Pancreatic abscess Pancreatic pseudocyst	and/or	Respiratory failure Renal failure Shock Gastrointestinal bleeding Hypocalcemia Coagulopathy	and/or	APACHE II ≥ 8 Ranson ≥ 3
Revised Atlanta	2013 [5]	–		Persistent organ failure	and/or	Active intervention (late phase only)

evidence of pancreatic hemorrhage and disseminated fat necrosis, the morphological features of severe disease in the original Atlanta classification were pancreatic necrosis, abscess, and pseudocyst. Since then, a number of studies have demonstrated that infection of pancreatic necrosis rather than presence of necrosis per se is associated with high morbidity and mortality in patients with AP [12, 13]. These patients have significantly worse outcomes than patients with "mild" or "moderate" AP. Taking these arguments into account, it seems reasonable to consider infectious pancreatic complications in the definition of "severe" AP.

There is also concern about the category termed "moderately severe" in the revised Atlanta classification since it draws in a "mixed population of patients," including the full range of local complications (some of which are not determinants of severity), those with transient organ failure (which has not been shown to be an important determinant of severity) and all exacerbations of preexisting comorbidities (none of which are determinants of acute pancreatitis severity). This is in contrast to the "moderate" category of severity, which is derived from the coherent use of local and systemic determinants of severity and that provides an epidemiologically sound framework for the determinants-based classification (see below).

In addition to overlooking infected pancreatic necrosis as a determinant of severe disease, another important shortcoming of the revised Atlanta classification [5] is that it is strongly based on the notion of a biphasic disease course. As a result it recommends that clinicians use a different method of classification for the early phase and the late phase of AP. In the early phase of the disease, the classification of severity is to be based on the presence or absence of persistent OF. In the late phase, the classification of severity is to be based on the need for "active intervention

(operative, endoscopic, laparoscopic, or percutaneous) or other supportive measures (such as need for respiratory ventilation, renal dialysis, or nasojejunal feeding)" as well as the presence or absence of persistent OF. There are a number of potential drawbacks with this approach to defining severity:

1. The two-phase concept, which describes sequential phases and a bimodal mortality distribution [14], is simplistic and belies the complexity of AP pathophysiology. Recent evidence from other diseases, including severe trauma and septic shock, suggests that the two phases (proinflammatory and anti-inflammatory) can occur concurrently. There are also studies that demonstrate pancreatic infection can occur within the first week and that persistent organ failure can occur later, even in the absence of infection [15, 16]. Further, there is a lack of precision in the definition of these phases and a commentator has highlighted that there is also an intermediate [1]. The imprecision of the duration of the early phase as "within the first 1 to 2 weeks of onset" reflects the lack of consensus in the literature. A recent study of all deaths due to AP in Scotland over a 6-year period did not reveal a bimodal distribution of mortality [17].
2. The approach is not applicable to all patients with AP. Particularly, patients who only develop OF in the late phase and those who only develop pancreatic complications in the early phase are not taken into account by the revised Atlanta classification and are likely to be misclassified. The proportion of these patients is not negligible. A study from India of 59 patients with persistent OF found that 27 (46 %) developed it after 7 days of onset of AP [17], and an earlier study from Germany found infected pancreatic necrosis was present in 27 of 114 (24 %) patients during the first week of disease [15].
3. Using the need for intervention or supportive care as part of the definition creates significant variation since it is dependent on subjective clinical judement since there is a lack of international standardization of management, including the indications for endoscopic procedures, enteral nutrition, and criteria for admission to an intensive care unit (ICU) [18].
4. In order for the new radiological terms (e.g., "acute peripancreatic fluid collection," "acute post-necrotic collection," "walled-off necrosis") to gain clinical utility will require clinico-radiological correlation and agreement, and there will need to be consensus among radiologists for the adoption of them. Further revision is expected, illustrated by the proposal for a classification based on retroperitoneal extension [19].

Determinants-Based Classification of Severity

This classification system is based on factors that are causally associated with severity. These factors are called "determinants," and include both local and systemic determinants. The local determinant of severity is necrosis of the pancreas and/or peripancreatic tissue. This is covered by the term (peri)pancreatic necrosis. The systemic determinant of severity is OF due to AP. The definitions used for the categories of severity are based on attributes of the local determinants (absent, sterile, or infected [peri]pancreatic necrosis) and the systemic determinants (absent, transient, or persistent OF) as well as the possibility of their interaction (Table 4.3). These items have also been carefully defined by consensus and published [6].

Table 4.3 The four severity categories (mild, moderate, severe, and critical) of the determinants-based classification [6]

Determinants	No local complications	Sterile local complications	Infected local complications
No organ failure	Mild	Moderate	Severe
Transient organ failure	Moderate	Moderate	Severe
Persistent organ failure	Severe	Severe	Critical

The determinants-based classification has been presented, discussed, and debated in a number of international forums, including a global online survey [20] and a dedicated symposium at the 2011 International Association of Pancreatology meeting. It has also been independently validated in a prospective study from India [21]. For mortality, this study demonstrated that the four categories are significantly different: mild (0 %), moderate (3.6 %), severe (33.8 %), and critical (87.5 %). The study also highlighted the interaction of determinants by confirming that mortality more than doubles in the critical category of severity. Further, the study showed an accurate and incremental discrimination between all the four categories for other important clinical endpoints, including computed tomography severity index, need for percutaneous catheter drainage, need for surgical interventions, prevalence of blood infection, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, admissions and duration of stay in ICU, and total length of hospital stay.

Optimal Number of Categories in a Severity Classification

A question arises about the number of severity categories that are most useful in the clinical and research settings [22]. It can be argued that in the community setting a dichotomous (mild/severe) classification is sufficient as the priority is to identify patients for early transfer from those patients that can be managed in the local district hospital. In the teaching hospital, and in clinical research, setting two categories is inadequate since there is a need for greater discrimination. Patients with severe pancreatitis represent a heterogeneous population, with a wide spectrum of severity, and it was partitioned into three categories as a result of the approach taken to development rather than as an a priori decision. And it must be remembered that severity is by nature a continuum and not fundamentally categorical.

Comparison of Severity Classifications

A key question that arises is whether the performance of the determinant-based classification and the revised Atlanta classification is superior to the original Atlanta classification. In the first direct comparison of these classifications, the Pittsburgh group has demonstrated that this is so, and the original Atlanta can now be retired [23]. The retrospective study used collected data of three cohorts of patients from before the publication of the two new classification systems and examined five different outcomes, concluding that the two approaches are "comparable" and "complementary." However, they advised caution because of inherent biases, the low patient numbers in some categories, and because they are a specialized tertiary center with half of the cases being transferred from other hospitals and an overall mortality of a strikingly low 4 %. Further studies are required.

The novel metric to compare different approaches to classification is the "net reclassification improvement" (NRI) [24]. This defines the relative improvement in discriminating the event of interest after introducing a new classification scheme. The method requires constructing a reclassification table separately for patients with and without the nominated event (e.g., mortality or no mortality). It then quantifies the correct movement between the categories: upwards for event (i.e., mortality) and downwards for non-event (i.e., no mortality) (Table 4.4). Using the data on mortality presented by the authors of the Indian study [21], 31.0 % (9/29) of patients who died and 50.1 % (62/122) of patients who did not die were reclassified to either moderate or critical category (correctly or not) by employing the determinant-based classification (see Table 4.4). Applying the NRI formula that considers both those correctly reclassified as well as those incorrectly reclassified, a net 87.2 % (7/8 – 2/63) of the patients who died were reclassified appropriately with the use of the determinant-based classification in comparison with the

Table 4.4 Calculation of the net reclassification improvement (NRI) [24] for mortality in acute pancreatitis using the determinant-based classification of acute pancreatitis severity compared with the original Atlanta classification

		Mortality	No mortality	Total
Severity category	Mild	0	21	21
	Moderate	2	61	63
	Severe	20	39	59
	Critical	7	1	8
Total number		29	122	151
Reclassified (%)		31.0	50.1	81.1
Net correct classification (%)		87.2	84.3	
NRI[a]			1.715	

[a]NRI = (Prob [being correctly reclassified to a higher-risk category/event] – Prob [being incorrectly reclassified to a lower-risk category/event]) + (Prob [being correctly reclassified to a lower-risk category/non-event] – Prob [being incorrectly classified to a higher-risk category/nonevent])

original Atlanta classification and a net 84.3 % (61/63 – 1/8) of the patients who did not die were reclassified appropriately with the use of the determinant-based classification in comparison with the original Atlanta classification (see Table 4.4). The NRI of the determinant-based classification calculated by adding 0.872 to 0.843 (0.872 + 0.843 = 1.715). Given that the possible range of NRI is −2.0 to +2.0, the NRI of 1.715 indicates excellent discriminative ability of the determinant-based classification over the original Atlanta classification. When the revised Atlanta classification was compared with the original Atlanta classification, a net 40.2 % (27/67 – 2/63) of the patients who died were reclassified appropriately with the use of the revised Atlanta classification in comparison with the original Atlanta classification and a net 37.1 % (61/63 – 40/67) of the patients who did not die were reclassified appropriately with the use of the revised Atlanta classification in comparison with the original Atlanta classification. The NRI of the three category revised Atlanta classification calculated by adding 0.402 to 0.371 (0.402 + 0.371 = 0.773). The data presented above indicate that, while the revised Atlanta classification offers some improvement in comparison with the original Atlanta classification, the discriminative ability of the determinant-based classification appears to be superior to the one offered by the revised Atlanta classification.

Future Directions

The definition of severity should be based on factors that determine severity and so further improvements in the definition of severe AP will require a greater understanding on determinants of severity. These improvements will come from a clear identification of clinical research priorities, examples of which follow.

1. While pancreatic necrosis is accepted as a determinant of severity, there is no agreement as to the extent of hypoperfusion on CT scanning that is required to diagnose necrosis. One third of the global survey of pancreatologists considered that the diagnosis of necrosis on initial (early) CT required detection of *any* hypoperfusion and another one third considered that it needed hypoperfusion of more than 30 % of the pancreas [20]. Further radiological studies should define the protocol and criteria for the diagnosis of pancreatic necrosis on CT scan. This is important for determining the real prevalence of pancreatic necrosis and standardized reporting of clinical studies in AP.
2. Given that the development of pancreatic necrosis occurs over the first few days of admission to hospital [25], further research is required to determine the optimal timing of CT scanning to delineate the extent of pancreatic necrosis.

3. Given that MR is preferable for the estimation of the amount of solid necrosis within post-necrotic fluid collections, and that open MR scanners (three-sided and more useful in critically ill patients) are becoming more available, it is going to be necessary to determine whether MR scanning should be used as the imaging modality of choice. In that case we are going to need to determine whether contrast MR is as good or better than CT in determining hypoperfusion.
4. The presence of (peri)pancreatic necrosis is a significant determinant of severity, especially when infected. This presents a challenge for its diagnosis since CT scanning and fine needle aspiration for bacteriological culture are less frequently performed [1]. CT scanning is rarely required for the diagnosis of AP and it confers no advantage in predicting the severity of AP [26]. Fine-needle aspiration to diagnose infected pancreatic necrosis is rarely required as the decision for intervention is based primarily on the patient's clinical trajectory and not on the result of a bacteriological culture. These trends mean that another research priority is the identification of reliable and accurate surrogate markers of infected pancreatic necrosis.
5. There is no agreement about the relative importance of pancreatic necrosis and peripancreatic necrosis as determinants of severity. While the majority of patients with necrotising pancreatitis develop both pancreatic necrosis and peripancreatic necrosis, it is known that some patients develop pancreatic necrosis alone and others peripancreatic necrosis alone. There is a growing body of evidence that peripancreatic necrosis alone contributes to severity, but no study has directly compared it with pancreatic necrosis alone. Therefore, a clinical study is warranted to compare the outcomes of patients with peripancreatic necrosis alone versus those with pancreatic necrosis alone.
6. While the importance of OF in patients with AP has been well recognized since the Marseilles classification of severity in 1984, recent studies have demonstrated that the duration of OF rather than its mere presence or absence is of importance. However, those studies used an arbitrary threshold of 48 h or three consecutive days or more to define persistent OF. Further research is needed to establish a minimal clinically meaningful duration of OF. In particular, it is worth establishing the risk of mortality in patients with AP who have OF for two consecutive days or more, and whether it is significantly lower in comparison with those who have it for three consecutive days or more.
7. The contribution of the failure of individual organs to severity has not been determined, or whether the sequence of organ failure is important in determining severity. Further research is required in this area, as well.
8. There is also no agreement as to the best method for diagnosing OF. Half of the respondents to the global survey prefer to diagnose individual OFs separately using a certain threshold and half of them prefer to use a composite score (e.g., SOFA or Marshall) [20]. The use of a composite organ dysfunction score appears favorable from a research perspective, but further studies have to investigate whether it presents any advantages in routine clinical practice.
9. Further studies are also warranted to investigate the effect of timing of OF on outcomes in AP, in particular whether "early" OF is more ominous in comparison with "late" OF. The three single-center studies available in the literature are inconclusive and suffer from several important flaws. Further studies, preferably prospective studies from multiple international centers, are warranted to answer this important question.

Conclusion

Significant progress has been made in defining the severity of AP, and this will no doubt continue. Differences between current classifications are expected as they are derived by different methodologies and based on different concepts of the disease. Sound prospective validation and utility

studies are now required to provide confidence in both clinical and research settings that the definitions of AP severity have the necessary accuracy to improve decision making. In the words of a doyen of pancreatology, Charlie Frey, "the final test of the value of a particular classification system of pancreatitis will be whether it improves communication and advances our understanding of the disease and its management" [27].

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Part II

Predictors and Characteristics of Severe Acute and Necrotizing Pancreatitis

Clinical Predictors

5

Rawad Mounzer and Georgios I. Papachristou

Introduction

Acute pancreatitis is currently the leading cause of gastrointestinal-related hospital admissions [1]. Approximately 80 % of patients who develop acute pancreatitis, regardless of etiology, have mild disease. The remaining patients develop severe disease characterized by end organ failure and/or necrosis of the pancreatic parenchyma or peripancreatic fat [2–4]. In mild interstitial disease mortality is about 3 % and reaches 17 % in patients who develop gland necrosis [4]. Organ failure, a consequence of the systemic inflammatory response incited by an insult to the pancreas, is an integral part of the definition of severe disease. Patients who develop multisystem organ failure have significantly increased mortality rates sometimes surpassing 60 % [5–8].

Predicting disease severity in acute pancreatitis has been an area of increasing interest over the past few decades. This has been driven by the fact that acute pancreatitis is a highly variable physiologic process that can lead to a broad range of clinical outcomes. These outcomes range from mild, self-limited disease to a systemic inflammatory process that can progress to organ failure and mortality. Moreover, local complications can develop, including acute fluid collections, gland and peripancreatic necrosis, and portosplenomesenteric venous thrombosis. Infection of necrosed tissue, which can occur later in the disease course, contributes significantly to mortality [4, 7, 9]. Identifying patients at risk for these severe complications is therefore crucial for modifying clinical outcomes. The early recognition of disease severity enables clinicians to tailor medical management and transition patients to the appropriate level of care [4].

Risk Factors

A thorough clinical assessment plays a key role in the overall risk stratification of patients with acute pancreatitis as pre-existing clinical comorbidities serve as risk factors for the development of organ failure and mortality. *Obesity* is a comorbid condition that has been extensively studied as a risk factor for the development of both local and systemic disease complications

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[10–12]. Patients with a body mass index (BMI) >=30 have been shown to be at a significantly increased risk for organ failure, pancreatic necrosis, and mortality [10]. These observations have been supported by histological studies demonstrating that patients with a higher BMI, and therefore a higher percentage of intra-pancreatic fat, develop more severe disease. Additionally in vitro studies utilizing pancreatic acinar cells have demonstrated that unsaturated fatty acids induce the generation of inflammatory mediators that can ultimately lead to cell death. These findings suggest a role for lipotoxicity in propagating systemic inflammation [13].

Other risk factors that have been evaluated as clinical predictors of disease severity include age, sex, and medical comorbidities. In a large retrospective study, male sex, increased age (>65 years), and the number of chronic medical comorbidities were shown to be significantly associated with early mortality. The medical conditions found to predispose patients to early mortality included malignancy, heart failure, chronic kidney disease, and liver disease [14]. Increased age (>=70 years) was shown to be a significant risk factor for the development of organ failure and mortality in another retrospective study [15]. Moreover, patients who consume more than two alcoholic drinks per day are at an increased risk for developing pancreatic necrosis [16]. Although genetic testing is still not utilized in daily clinical practice, pilot studies have assessed several single nucleotide polymorphisms as risk factors for severe acute pancreatitis. A common polymorphism in the promoter of the monocyte chemotactic protein-1 (MCP-1) gene, namely the MCP-1-2518 G allele, has been shown to increase the risk for organ failure [17].

Clinical risk factors should thus be identified by means of a detailed history taking and physical examination. This provides the initial assessment and preliminary risk stratification in patients presenting with acute pancreatitis. Studies evaluating the ability of clinical assessment alone in predicting severe disease, found clinical judgment to have a high specificity with sensitivities, however, below 50 % [18, 19].

Clinical Scoring Systems

Following the initial clinical assessment, further risk stratification can then be implemented by utilizing clinical scoring systems for the prediction of disease severity. Over the past three decades, a myriad of such clinical scores have been developed and validated in different cohorts of patients with acute pancreatitis. Several of these scoring systems have been utilized to triage patients in clinical practice. Moreover, they have been used extensively in research to identify patients at risk for severe disease. Here we discuss the main clinical scoring systems available to date and review their performance characteristics (Table 5.1).

The first clinical scoring system for the prediction of disease severity in acute pancreatitis was developed by Ranson and colleagues in 1974. See also Chap. 7. This scoring system represented a landmark in the field as prior assessment of patients with acute pancreatitis was based solely on clinical judgment. The Ranson score incorporated objective laboratory and clinical data collected upon initial presentation and within the following 48 h [20, 21]. The 11 prognostic parameters utilized in the Ranson score were selected, based on a statistical analysis, from among 43 variables in a retrospective cohort of 450 patients. When evaluated in a study of 386 patients who presented with an initial attack of acute pancreatitis, a Ranson score of >=3 was found to be associated with a mortality of 15 %. A score of >=6 was associated with 40 % mortality [22]. A meta-analysis evaluating 110 clinical trials that utilized the Ranson score for predicting disease severity showed it to be a moderately accurate predictor with performance characteristics similar to those of clinical judgment [23]. The 48 h needed to complete the score also posed a significant limitation in that this time interval during the early stages of the disease course is critical for optimizing medical intervention and allocating patients to the appropriate level of care [4].

A more rigorous scoring system, the Acute Physiology and Chronic Health Evaluation II

Table 5.1 Clinical scoring systems, year of initial report, and associated parameters[a]

Scoring system	Year	Parameters
APACHE-II[b]	1989	*Admission & 48 h*: temperature, MAP, heart rate, respiratory rate, PaO_2, arterial pH, HCO_3, sodium, potassium, creatinine, hematocrit, WBC, Glasgow Coma Score, age, chronic health points
BISAP	2008	*Admission & 48 h*: BUN (>25 mg/dL), impaired mental status (Glasgow Coma Score < 15), SIRS (>=2), age (>60 years), pleural effusion
Glasgow	1984	*Admission & 48 h*: age (>55 years), WBC (>15,000/mL), glucose (>180 mg/dL), BUN (>45 mg/dL), PaO_2 (<60 mmHg), calcium (<8 g/dL), albumin (<3.2 g/dL), LDH (>600 IU/L)
HAPS	2009	*Admission & 48 h*: abdominal tenderness, hematocrit (>43 mg/dL for men or >39.6 mg/dL for women), creatinine (>2 mg/dL)
JSS	2009	*Admission & 48 h*: base excess (<=3 mEq/L), PaO_2 (<=60 mmHg or respiratory failure), BUN (>=40 mg/dL) or Cr (>=2 mg/dL), LDH (>=2x upper limit of normal), platelet (<=100,000/mm^3), calcium (<=7.5 mg/dL), CRP (>=15 mg/dL), SIRS (>=3), age (>=70 years)
Panc3	2007	*Admission & 48 h*: hematocrit (>44 mg/dL), BMI (>30 kg/m^2), pleural effusion
POP[b]	2007	*Admission & 48 h*: age, MAP, PaO_2:FiO_2, arterial pH, BUN, calcium
Ranson	1974	*Admission*: age (>55 years), WBC (>16,000/mL), glucose (>200 mg/dL), LDH (>350 IU/mL), AST (>250 IU/mL) *48 h*: hematocrit (decrease > 10 %), BUN (increase > 5 mg/dL), calcium (<8 mg/dL), PaO_2 (<60 mmHg), base deficit (>4 mEq/L), fluid sequestration (>6 L)
SIRS	2006	*Admission & 48 h*: temperature (<36 or >38 °C), heart rate (>90/min), respiratory rate (>20/min or $PaCO_2$ < 32 mmHg), WBC (<4,000/mm^3, >12,000/mm^3 or >10 % bands)

BMI body mass index, *WBC* white blood cell count, *BUN* blood urea nitrogen, *MAP* mean arterial pressure, PaO_2 partial pressure of oxygen, FiO_2 fraction of inspired oxygen, *LDH* lactate dehydrogenase, *CRP* C-reactive protein

[a]Scores are presented in alphabetical order. Reprinted from [40], with permission from Elsevier

[b]Parameter cut-offs were not indicated for the APACHE-II and POP scores due to the fact that these scores utilize value ranges

(APACHE-II), was subsequently developed in 1989 and has been utilized extensively in assessing disease severity in acute pancreatitis. In addition to encompassing a broad range of clinical data including vital signs, blood studies, and a neurologic assessment, the APACHE-II score also took into account chronic illness [18]. In contrast to the Ranson score, it can be calculated on admission and updated daily during the hospitalization, thus allowing for closer monitoring of the clinical course and response to therapy. The main drawbacks of the APACHE-II score are its complexity and the fact that it is not pancreatitis-specific, as it was designed for patients requiring critical care. Moreover, it is cumbersome to calculate on a daily basis and some of the variables incorporated into the score are not routinely recorded outside of the intensive care unit.

Another pancreatitis-specific score, similar to the Ranson score in that it requires 48 h to be calculated, is the Glasgow score [24]. In well-designed, prospective studies performed approximately 20 years ago, the Ranson, Glasgow, and APACHE II scoring systems were found to have similar accuracies in predicting severity in acute pancreatitis [18, 25, 26]. Following these studies, research on clinical scoring systems subsided for about a decade.

Scoring systems, however, have regained significant attention in recent years with a focus on the development of simple scores that are easy to calculate and apply clinically. The systemic inflammatory response syndrome (SIRS), based on four clinical parameters, has been long established as a physiologic clinical response that is induced by nonspecific insults to the body [27]. The four parameters include: temperature (<36 or >38 °C), heart rate (>90 beats/min), respiratory rate (>20 respirations/min or $PaCO_2$ < 32 mmHg), and white blood cell count (<4,000/mm^3,

>12,000/mm^3 or >10% bands). In recent years SIRS, which precedes the development of organ failure, has been further investigated as a prognostic clinical score in acute pancreatitis. In a prospective study of 121 patients with acute pancreatitis predicted to have a severe course of disease based on an APACHE-II score >=6, early organ dysfunction was found to be significantly associated with mortality. Moreover, the presence of SIRS (score of >=2) on admission, at 24 h, 48 h, and persistent SIRS (SIRS present throughout the initial 48 h), were also significantly associated with mortality [28]. A subsequent large retrospective study reaffirmed persistent SIRS to be strongly associated with mortality [29]. Given the readily available parameters used for calculating the SIRS score, its simplicity, ability to be calculated daily, and strong correlation with poor clinical outcomes, monitoring for the persistence of SIRS has been recommended in recent management guidelines for the prediction of disease severity in acute pancreatitis [30].

In light of this data, studies assessing medical intervention targeted at abrogating systemic inflammation were performed in an attempt to improve clinical outcomes. Early fluid resuscitation, for example, was shown to significantly reduce both SIRS and organ failure in patients with acute pancreatitis. This also led to significantly shorter hospitalizations and a decreased need for intensive care in these patients [31]. In a prospective pilot study, lactated Ringer's was found to be more effective than normal saline in reducing systemic inflammation [32].

SIRS has also been incorporated into a more recently developed clinical scoring system for predicting overall prognosis in acute pancreatitis. The Bedside Index of Severity in Acute Pancreatitis (BISAP) includes five clinical parameters, one of which is SIRS >= 2. These five parameters are: age >60 years, blood urea nitrogen >25 mg/dL, SIRS >= 2, impaired mental status with a Glasgow Coma Score <15, and presence of pleural effusions [33]. A BISAP score >=3, calculated within 24 h of admission, was shown to be significantly associated with both the development of organ failure and pancreatic necrosis in a large prospective study [34]. In a follow-up prospective study, the BISAP score had a similar accuracy in predicting the development of organ failure, pancreatic necrosis, and mortality when compared to the Ranson score and APACHE-II [35].

Panc 3, another simple clinical scoring system, was developed at about the same time as the BISAP score and included three clinical parameters (hematocrit >44 mg/dL, BMI > 30 kg/m^2, and pleural effusions), which had each individually been shown to predict severe disease [36]. The harmless acute pancreatitis score (HAPS) was also recently developed in Germany. This scoring system is unique in that it was designed to identify patients expected to have a mild course of disease. Moreover, it only incorporates three parameters: abdominal tenderness, hematocrit >43 mg/dL for men or >39.6 mg/dL for women and creatinine >2 mg/dL. In a prospective study that had a validation cohort, absence of these parameters identified patients with uncomplicated acute pancreatitis with a specificity of 97 % and a positive predictive value (PPV) of 98 % [37]. Other scoring systems that predict disease severity have also been recently reported including the pancreatitis outcome prediction (POP) score and the new Japanese severity score [38, 39]. The POP score incorporates six objectively weighted clinical variables obtained from patients admitted to the ICU [38]. The new Japanese severity score incorporates nine prognostic variables.

Overall, the studies performed to develop and validate the above mentioned clinical scoring systems are limited by heterogeneity between different populations and varying endpoints among the different studies. Some studies used the original Atlanta criteria for the assessment of disease severity, whereas others evaluated mortality. A recent large dual-center study, conducted to compare all available clinical scoring systems in two prospective cohorts of patients with acute pancreatitis, found all the above described clinical scoring systems to have comparable performance characteristics with only modest overall accuracies among all the scoring systems. Performance characteristics of the various scoring systems from the training cohort of this study are

Table 5.2 Comparison of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy determined by area under the curve (AUC) for each scoring system at the specified score cut-off. These values are obtained from the training cohort ($n = 256$) in this study[a]

Score	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
APACHE-II	7	0.84 (±0.11)	0.71 (±0.06)	0.49 (±0.11)	0.93 (±0.08)	0.77 (±0.07)
BISAP	2	0.61 (±0.20)	0.84 (±0.04)	0.54 (±0.10)	0.87 (±0.10)	0.72 (±0.10)
Glasgow	2	0.85 (±0.08)	0.83 (±0.07)	0.61 (±0.06)	0.95 (±0.05)	0.84 (±0.06)
HAPS	1	0.70 (±0.11)	0.53 (±0.21)	0.32 (±0.11)	0.85 (±0.13)	0.62 (±0.06)
JSS	2	0.59 (±0.13)	0.92 (±0.05)	0.70 (±0.16)	0.88 (±0.07)	0.76 (±0.07)
Panc3	1	0.76 (±0.15)	0.52 (±0.05)	0.34 (±0.11)	0.87 (±0.11)	0.64 (±0.06)
POP	9	0.57 (±0.15)	0.76 (±0.06)	0.43 (±0.16)	0.85 (±0.08)	0.67 (±0.09)
Ranson	2	0.66 (±0.09)	0.78 (±0.10)	0.49 (±0.17)	0.88 (±0.08)	0.72 (±0.06)
SIRS	2	0.70 (±0.18)	0.71 (±0.04)	0.43 (±0.10)	0.88 (±0.11)	0.70 (±0.10)

[a]Adapted from [40], with permission from Elsevier

presented in Table 5.2. Furthermore, combining these scoring systems in order of increasing complexity as part of predictive rules in an attempt to improve predictive accuracy yielded no significant improvement in their performance characteristics. This highlighted the limitations of clinical scoring systems in prognosticating disease severity and suggested that these scoring systems have reached their maximal predictive capacity. This may be due to the fact that in the majority of clinical scoring systems clinical parameters are converted from continuous to dichotomous values [40].

Laboratory Markers

Multiple laboratory markers have also been evaluated individually as predictive markers of disease severity including hematocrit, blood urea nitrogen (BUN), creatinine, and C-reactive protein (CRP) levels [4]. Serum hematocrit, which serves as a surrogate marker for intravascular volume, has been evaluated in several studies as a predictor of pancreas necrosis and organ failure [41–43]. Pancreatic necrosis has been attributed to an increase in vascular permeability; a consequence of the systemic inflammatory process that can be induced by pancreatic injury. This increase in vascular permeability leads to a decrease in intravascular volume, an increase in blood viscosity, and thus an impairment in microcirculation within the pancreatic parenchyma resulting in tissue necrosis [3, 4, 44, 45]. In a landmark study performed in 1998 comparing patients with pancreas necrosis to those with mild acute pancreatitis, both a hematocrit >=47 % on admission and failure to decrease the hematocrit within the first 24 h were both found to be significantly associated with the development of necrosis [41]. In a follow-up prospective study by the same group, a serum hematocrit of >=44 % upon admission and failure to decrease the hematocrit level with intravenous hydration within the first 24 were found to be significant predictors of both pancreas necrosis and organ failure [42]. In a subsequent prospective study of patients with a first attack of acute pancreatitis, hemoconcentration at different cut-off values was found to be significantly associated with length of hospitalization and length of ICU stay, but not with the development of organ failure or morality. Performance characteristics of hemoconcentration were comparable to the Ranson and Glasgow scores in this study [43].

BUN serves as another surrogate marker for intravascular volume and catabolic states. As such, the relationship between hemoglobin and BUN, as well as their performance characteristics, were evaluated in an observational study that incorporated retrospectively collected data from 69 hospitals in the U.S. Rising BUN levels within the first 48 h of hospitalization were found to be significantly associated with mortality. This relation-

ship, however, did not hold true for hemoglobin. BUN levels upon admission and changes in BUN over time were found to be independent predictors of mortality with each 5 mg/dL rise in BUN leading to an increase in the odds ratio for mortality of 2.2. When compared to other laboratory parameters (calcium, hemoglobin, creatinine, white blood cell count, and glucose) BUN was found to have the highest accuracy of predicting in-hospital mortality with an area under the curve (AUC) of 0.90 [46]. In patients with pancreas necrosis, elevated BUN correlated with both prolonged ICU stay and mortality [47]. An international multicenter validation study further supported the role of BUN in predicting mortality. A BUN >= 20 mg/dL upon admission was associated with an odds ratio of 4.6 for mortality. When BUN was measured serially during hospitalization, it was also found to be comparable to both creatinine and the APACHE-II score in predicting mortality with an AUC of 0.80. A decline in BUN of >=5 mg/dL with fluid resuscitation led to a significant decrease in mortality [48].

Comparison of admission hematocrit, BUN, and serum creatinine in a prospectively enrolled cohort of 129 patients found all three parameters to be significantly associated with pancreas necrosis. A peak serum creatinine >1.8 mg/dL during the first 48 h of hospitalization was associated with the highest odds ratio (OR) for the development of necrosis (OR = 35) [49]. A follow-up study revealed a lower sensitivity and PPV and comparable specificity and negative predictive value (NPV) for the prediction of pancreas necrosis [50]. The differences in these results have been attributed to differences in the populations between the two studies; the index study population had a higher prevalence of pancreas necrosis that was driven by a referral bias of transferred patients with more severe disease [51].

CRP is a widely available and inexpensive marker of systemic inflammation that has been studied as a predictor of disease severity in acute pancreatitis [52]. In a retrospective study, a CRP level measured at 48 h was found to be a moderately accurate prognostic marker for severe disease. CRP levels predicted the development of organ failure, pancreas necrosis, and inpatient mortality with AUCs ranging from 0.7 to 0.81. Cut-off values used for these endpoints were 190 mg/L, 190 mg/L, and 170 mg/L, respectively [53]. Urine trypsinogen-2, urine trypsinogen activation peptide, and interleukin-6 have also been evaluated for assessing disease severity in acute pancreatitis. These tests, however, have yet to be established in clinical practice [54, 55].

Radiographic Scores

Several radiographic scoring systems utilizing computed tomography (CT) have been proposed over recent years for the assessment of disease severity (Table 5.3). See also Chap. 6. The Balthazar CT score, the first radiographic score developed in 1985, graded severity based on the

Table 5.3 Radiographic scoring systems, year of initial report, and associated parameters

Radiographic score	Year	CT parameters
Balthazar Score [57]	1985	Gland enlargement, peripancreatic inflammatory changes, fluid collections, gas within or around the pancreas
CT Severity Index (CTSI) [62]	1990	Peripancreatic inflammation, pancreas necrosis, phlegmon formation
Extrapancreatic Score (EP) [60]	1985	Extrapancreatic findings
Extrapancreatic Inflammation on CT (EPIC) [61]	2007	Pleural effusion, ascites, retroperitoneal inflammation
Mesenteric Edema and Peritoneal Fluid (MOP) [59]	2003	Mesenteric edema, peritoneal fluid
Pancreas Size Index (PSI) [58]	1989	Anteroposterior dimensions of the pancreas head and body

presence or absence and number of fluid collections on initial non-contrasted CT. Patients found to have fluid collections on CT had a higher morbidity and mortality than those without [56, 57]. Other scoring systems based on non-contrasted CT scan findings include: the pancreatic size index (PSI), mesenteric edema and peritoneal fluid (MOP), extrapancreatic (EP), and extrapancreatic inflammation on CT (EPIC) scores [58–61]. The more recent CT severity index (CTSI) is based upon contrast-enhanced CT and thus incorporates inflammatory changes with the presence or absence of pancreatic necrosis to generate a numeric score [62]. In a large prospective study comparing the performance characteristics of CTSI (obtained within 48 h) to the Ranson, APACHE-II, and BISAP scores, these scores were found to perform comparably. The CTSI score, as expected, had the highest accuracy for predicting pancreatic necrosis [35]. More recently, a study evaluating the accuracy of several radiographic scoring systems, including the CTSI score on the day of admission to the BISAP and APACHE-II scores, found no significant differences in the prediction of disease severity or overall mortality. Based on the comparable performance characteristics found in this study, it was recommended that CT scans not be obtained upon admission for the purpose of assessing disease severity [63].

Conclusion

Despite extensive research over the past few decades, a highly accurate clinical scoring system, laboratory marker, or radiologic score for predicting disease severity in acute pancreatitis has yet to be developed. This likely reflects underlying deficiencies in the scientific and statistical processes used to develop these scores, as well as the complexity and heterogeneity of this disease. Overall, the above approaches can only predict severe disease with moderate accuracy. The authors' recommendations to clinicians are therefore to assess host risk factors (i.e., age, presence of obesity, alcohol use) and utilize laboratory values and simple scoring systems in the early phase of acute pancreatitis both for risk stratification upon admission and to assess the response to therapy within the first 24–48 h [30]. This is summarized as follows:

1. A BUN level of >=20 mg/dL upon admission, or failure to decrease after 24 h despite adequate resuscitation, places patients at significant risk for mortality.
2. A peak Cr level of >1.8 mg/dL within the first 48 h should raise concern for pancreatic necrosis, even in patients that do not require ICU admission.
3. Presence of systemic inflammatory response syndrome (SIRS score >=2) on admission and persistence of SIRS for 24–48 h despite adequate fluid resuscitation is highly predictive of the development of organ failure.

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Imaging Predictors

6

Thomas L. Bollen

Introduction

Acute pancreatitis is a common cause for hospitalization in the Western world. Fortunately, most patients with acute pancreatitis follow a mild clinical course without significant complications [1, 2]. Imaging in these patients is rarely necessary aside from establishing the cause of pancreatitis, i.e., an ultrasound on admission is often requested for assessment of biliary stones. However, about one-quarter of patients develop clinically severe acute pancreatitis accompanied by prolonged hospitalization with high morbidity and mortality rates [1–3]. These patients are responsible for most of the healthcare expenses in acute pancreatitis that include the need for repeated imaging. Despite increased knowledge of the pathophysiology and natural course of acute pancreatitis and notwithstanding the improvements in imaging techniques and critical care, mortality rates in severe acute pancreatitis have been unchanged. Given these differences in length of hospitalization and intensive care stay, the differences in morbidity and mortality and in healthcare costs, a continuous effort for more than four decades has been made to develop a prognostic multifactorial scoring system (based on clinical, biochemical, and/or imaging parameters) for accurate severity stratification, preferably during the first days of admission.

Early severity stratification is deemed important for several reasons. Identification of patients with the highest morbidity and mortality is critical because these patients may benefit most from timely transfer to the intensive care unit or tertiary referral centers for supportive treatment or for targeted therapy (i.e., endoscopic intervention or enteral feeding). In addition, stratification is essential for reliable interinstitutional comparison of new methods of therapy and for inclusion of patients in randomized trials [2, 4].

This chapter will review existing radiologic prognostic systems with their respective advantages and limitations and addresses imaging features of acute pancreatitis with an emphasis on the prognostic significance of specific findings that impacts patient management.

Overview of Imaging Modalities

Multidetector computed tomography (MDCT) is the most widely available imaging modality and is the standard for the evaluation of acute pancreatitis [2, 5]. Other imaging modalities that are used for evaluation of acute pancreatitis include endoscopic and transabdominal ultrasound and magnetic resonance imaging (MRI). Imaging in acute pancreatitis is performed for several reasons that include confirmation of the diagnosis, detection of gallstones or biliary

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obstruction, assessment of severity of disease, and evaluation of complications related to acute pancreatitis [5–7].

Ultrasound

Ultrasound has only limited value in the assessment of acute pancreatitis and its severity, because overlying bowel gas often obscures portions of the pancreas. However, ultrasound has a high sensitivity for detecting gallstones and is useful for follow-up of established pancreatic fluid collections [8].

Magnetic Resonance Imaging

The use of MRI in the assessment of acute pancreatitis and its complications is gaining increasing acceptance. Indeed, MRI offers similar diagnostic capabilities compared with CT with better depiction of stones in gallbladder or common bile duct and better evaluation of the pancreatico-biliary ductal system [8, 9]. Additionally, MRI is more accurate than CT in characterizing the content of peripancreatic collections that may aid in allowing appropriate drainage techniques to be used [10]. Disadvantages of MRI are its limited availability in an acute setting and that acquisition times are significantly longer than with MDCT.

Computed Tomography

MDCT is the primary imaging modality used in the evaluation of patients with acute pancreatitis. Morphologic changes of the pancreas and peripancreatic region are easily depicted on CT that allows for confirmation of the diagnosis, for assessment of disease severity, and for evaluation of local pancreatic and extrapancreatic complications [11]. A monophasic CT protocol after intravenous contrast administration is usually adequate for assessment of acute pancreatitis [12, 13]. Typically, scans are performed during the pancreatic phase (delay of 40–50 s) or portal venous phase (delay 60–70 s). Multi-phase studies are recommended in case of hemorrhage, ischemia, or suspicion of an arterial pseudoaneurysm [12, 13]. Major disadvantages of CECT remain the radiation exposure and the limited capability of differentiating fluid from necrotic material in peripancreatic collections [10].

Radiologic Scoring Systems

Scoring systems related to CT are the most studied imaging test in acute pancreatitis [14]. Since the introduction of CT for diagnosis and severity assessment of acute pancreatitis in the 1980s, many imaging-based systems have been developed. In this section, the most relevant scoring systems will be reviewed in order of year of development. Determinants of most radiologic scoring systems include pancreatic changes, peripancreatic features, and extrapancreatic features (Table 6.1). Severity assessment of acute pancreatitis by CT can be done using unenhanced (Schröder index, Balthazar grade, Pancreatic size index (PSI), MOP score, retroperitoneal extension grade, and EPIC score) or contrast-enhanced CT studies (CT severity index and Modified CT severity index).

Schröder Index

In 1985, Kivisaari and Schröder were among the first to develop a CT scoring system for severity stratification in acute pancreatitis based on pancreatic and extra-pancreatic findings [15]. The pancreatic CT findings include edema in part of the pancreas and edema of the entire pancreas. Extrapancreatic findings include peritoneal fluid, perirenal fat edema, mesenteric fat edema, pleural effusion, and bowel paralysis. Each of these findings was assigned one point with a maximum score of 7. A total score of <4 correlates with predicted mild acute pancreatitis, and a score of 4 or more with predicted severe acute pancreatitis. This scoring system is relatively easy to apply and practical even among patients with renal failure when no intravenous contrast medium agents

Table 6.1 CT determinants that constitute radiologic scoring systems

Pancreatic features
Subjective pancreatic enlargement
Pancreatic size index (PSI)[a]
Pancreatic parenchymal necrosis (presence and extent)
Peripancreatic features
Peripancreatic fat stranding
Peripancreatic fluid collection (presence and number)
Perirenal edema
Mesenteric inflammation
Retroperitoneal extension
Extrapancreatic features
Pleural effusion (presence, uni-, bilateral)
Ascites (presence and number of locations)[b]
Vascular complications (venous thrombosis, hemorrhage, arterial pseudoaneurysm)
Extrapancreatic parenchymal complications (infarction, hemorrhage, subcapsular fluid collection)
Gastrointestinal complications (ileus, signs of ischemia, perforation, marked bowel wall thickening, intramural fluid collection)

[a]PSI defined as multiplication of maximum anteroposterior measurement of the pancreatic head and body. A score of <10 cm^2 is regarded as predicted mild pancreatitis and ≥10 cm^2 is regarded as predicted severe pancreatitis [23]
[b]Ascites in either one of these locations: perihepatic, perisplenic, interloop, or in pelvis [41]

can be administered. Limitations are that the presence of peritoneal fluid (especially in female patients) and perirenal fat edema can be a normal finding (especially in the elderly).

Balthazar Grade

In 1985, Balthazar and colleagues developed a CT grading system based on the presence of pancreatic and peripancreatic changes into five grades of severity, ranging from Grade A (normal pancreas) to Grade E (inflamed pancreas with two or more fluid collections) (Fig. 6.1) [16, 17]. In their original report, Grade A and B correlated with mild uncomplicated clinical course with no mortality, whereas Grade D and E signified severe disease with 54 % morbidity and 14 % mortality [16, 17]. These results have been confirmed in subsequent studies by different groups of investigators [18–20]. The advantages of the Balthazar grading system are that it can be applied at any point during the patient's hospitalization and requires no iodinated contrast medium. Limitations are the subjective assessment of pancreatic enlargement

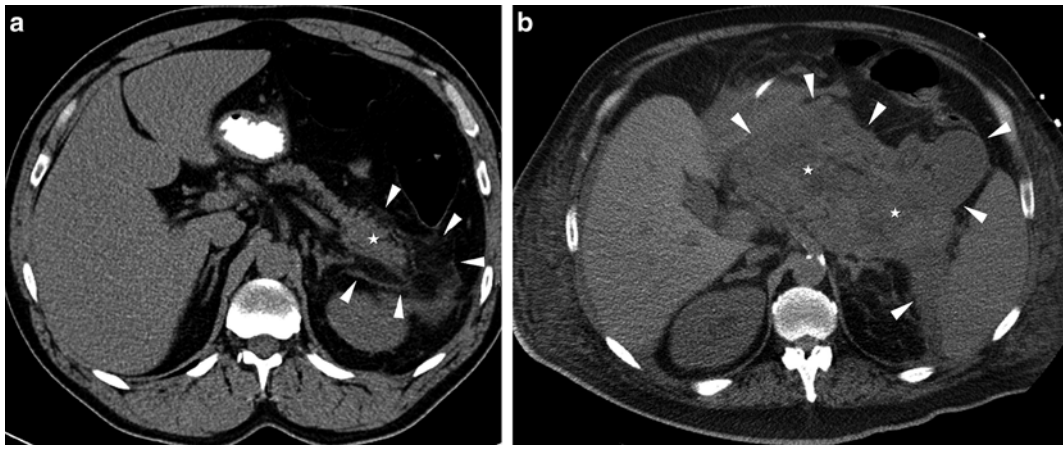

Fig. 6.1 (**a**) A 35-year-old man with acute pancreatitis (Balthazar Grade C). Unenhanced CT shows a swollen pancreatic tail (*white star*) with peripancreatic fat stranding (*arrowheads*). (**b**) A 56-year-old man with acute pancreatitis (Balthazar Grade E). Unenhanced CT shows a heterogeneous pancreas (*white stars*) surrounded by multiple peripancreatic collections (*arrowheads*)

(corresponding to Grade B), the arbitrarily chosen distinction between peripancreatic inflammatory changes ("fat stranding") and a peripancreatic collection (Grade C and D, respectively), and the need for counting peripancreatic collections (differentiating Grade D from Grade E), all of which are associated with moderate interobserver agreement. Some authors maintain that Balthazar grading system simplifies the retroperitoneal compartment rather than acknowledging the different components that constitute the retroperitoneum [21]. Another shortcoming (put forth by Balthazar himself) is that peripancreatic fluid collections (Grade D and E) have a variable natural history; in their study 54 % resolved spontaneously, whereas 46 % became infected necessitating intervention [16, 22].

Pancreatic Size Index

The PSI was first introduced in 1989 by London and colleagues [23]. The PSI (in cm^2) is calculated by multiplying the maximum anteroposterior measurement of the head and body of the pancreas resulting in an objective assessment of pancreatic enlargement (as opposed to subjective assessment in other CT scoring systems, such as Schröder index, CT severity index [CTSI], and modified CT severity index [MCTSI]). By using a cut-off of 10 cm^2 the authors found a sensitivity of 71 % and specificity of 77 % for clinically severe attacks [23]. In several other studies these results were confirmed [24, 25]. The underlying theory behind the PSI is that with increasing degree of pancreatic insult, the resultant swelling of the pancreas releases more toxic cytokines and pancreatic enzymes in the systemic circulation and peripancreatic area, respectively. Advantage of the PSI is the evaluation of only one parameter. Like other CT scoring systems, PSI measurement does not require the administration of intravenous contrast medium. Main limitation is that normal values of pancreatic size may vary considerably according to age and previous attacks.

Table 6.2 CT severity index

Characteristics	Points
Pancreatic inflammation	
Normal pancreas	0
Focal or diffuse enlargement of the pancreas	1
Peripancreatic inflammation	2
Single acute fluid collection	3
Two or more acute fluid collections	4
Pancreatic parenchymal necrosis	
None	0
Less than 30 %	2
Between 30 and 50 %	4
More than 50 %	6

CT Severity Index

The advent of incremental dynamic bolus CT technique and faster scanning equipment in the early 1990s resulted in considerable improvement of imaging assessment of acute pancreatitis; the use of intravenous contrast medium enabled to differentiate interstitial pancreatitis (with intact capillary network and homogeneous enhancement) from necrotizing pancreatitis (with portions of pancreas failing to enhance) [22]. In 1990, Balthazar made his CT grading system more sophisticated by incorporating the presence and extent of parenchymal nonenhancement (corresponding to parenchymal necrosis) by using intravenous iodinated contrast medium [22]. The resulting CT scoring system (CT severity index or CTSI) combines the Balthazar grade (0–4 points) with the extent of pancreatic necrosis (0–6 points) on a 10-point severity scale (Table 6.2). The calculated CTSI can then be subdivided in three categories (CTSI 0–3, 4–6, and 7–10; corresponding to predicted mild, moderate, and severe disease, respectively) that have subsequent increases in morbidity and mortality (Fig. 6.2). In the original study, patients with predicted mild disease (CTSI 0–3) had 8 % morbidity and 3 % mortality (of note, no mortality occurred in patients with CTSI 0–2), patients with predicted moderate severe pancreatitis had 35 % morbidity and 6 % mortality, and patients with predicted severe disease (CTSI 7–10) had

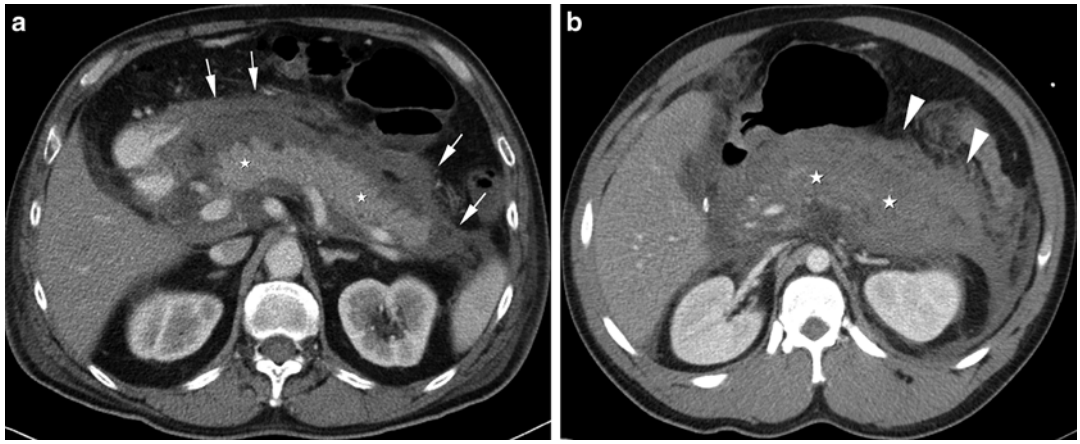

Fig. 6.2 (**a**) A 41-year-old man with acute pancreatitis (CTSI 4). Contrast-enhanced CT shows a normal enhancing pancreatic parenchyma (*white stars*) with more than two peripancreatic collections (*arrows*). (**b**) A 32-year-old man with acute necrotizing pancreatitis (CTSI 10). Contrast-enhanced CT shows extensive pancreatic nonenhancement (*white stars*), representing pancreatic necrosis. More than 50 % of the pancreatic volume is involved in the necrotic process. Peripancreatic collections (acute necrotic collections) are present (*arrowheads*)

92 % morbidity and 17 % mortality [22]. CTSI, of all radiologic scoring systems, is the most studied system, and many reports from different groups of investigators confirmed the utility of using CTSI in assessing patient outcomes [26–29]. However, some have found only a modest correlation between presence and extent of pancreatic necrosis and organ failure [30–32], between pancreatic necrosis and extrapancreatic parenchymal and vascular complications [33, 34], and between extent of parenchymal necrosis and clinical outcome (i.e., no significant differences in patient outcome are observed in patients with 30–50 % necrosis versus those with >50 % necrosis) [35]. Other limitations are the moderate interobserver agreement due to the specific categorization of the evaluation of pancreatic inflammation and necrosis and the need for intravenous contrast agent.

MOP Score

In 2003, King and co-authors tested a simple CT scoring system based on two CT features (mesenteric edema [MO] and peritoneal [P] fluid; resulting in the MOP score) in a cohort of patients [36]. MOP score correlated well with disease severity, especially when both features were present. This scoring system is appealing because it is simple and easy to evaluate even for non-radiologists, requiring no intravenous contrast medium. However, in the original study, patients were included of whom CT was performed up to 10 days after admission, limiting the predictive power of this scoring system.

Modified CT Severity Index

In 2004, Mortele and colleagues modified the existing CTSI accounting for the presumed shortcomings of this scoring system by incorporating extrapancreatic complications in the assessment and by simplification of the evaluation of peripancreatic collections and extent of parenchymal necrosis (Fig. 6.3) [26]. In the original study including 66 patients, the MCTSI, compared with CTSI, more closely correlated with patient outcome (length of hospital stay, need for intervention, and organ failure) with similar interobserver agreement [26]. In a larger cohort, these promising results could not be reproduced (no significant differences were observed between both CT scoring systems for the clinical parameters evaluated; intensive care stay, need for intervention, persistent organ failure, infected necrosis, severity of disease, and

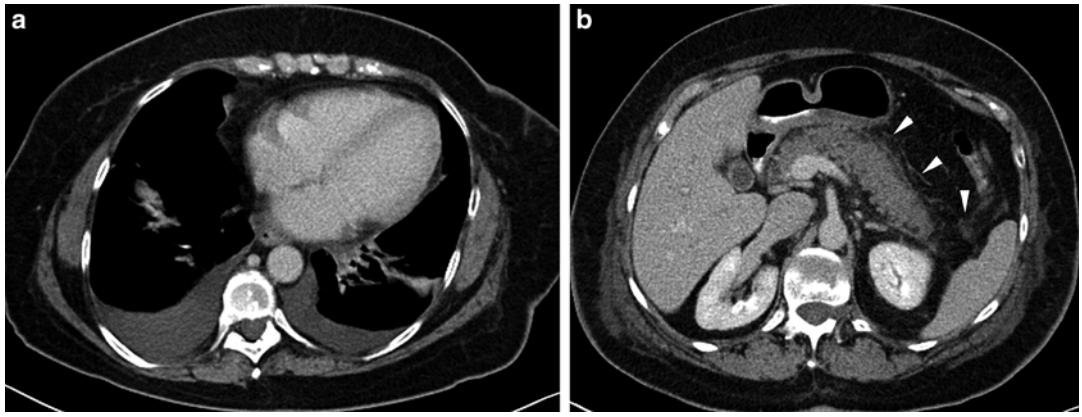

Fig. 6.3 A 65-year-old woman with acute interstitial pancreatitis (MCTSI 4). (**a**) Contrast-enhanced CT of the lung bases shows bilateral pleural effusion. (**b**) CT at the level of the pancreas shows a normal enhancing pancreatic parenchyma with little peripancreatic fat stranding (*arrowheads*). The CT severity index is 2 (predicted mild pancreatitis), while the modified CT severity index credits two extra points for pleural effusion (MCTSI 4, representing predicted moderate severe pancreatitis)

mortality) [37]. Possibly, because of the simplifications, the MCTSI may be easier to assess by less experienced readers.

Retroperitoneal Extension Grade

Traditionally, it was assumed that the retroperitoneum consisted of three compartments (anterior pararenal space, perirenal space, and posterior pararenal space) demarcated by three well-defined fascia (anterior renal fascia, posterior renal fascia, and lateroconal fascia). New anatomical insights are that each retroperitoneal fascia is composed of multiple layers (i.e., fused leaves of embryonic mesentery), creating potential spaces (the retroperitoneal interfascial planes) that may serve both as a reservoir for decompression of rapidly accumulating fluid collections (as in acute pancreatitis) and as a pathway for spread of an infiltrating neoplasm or inflammatory process [38–40]. In 2006, Ishikawa and collaborators used this new anatomic concept to design a CT grading system based on retroperitoneal extension of pancreatic fluid along the retroperitoneal interfascial planes on a 5-grade severity scale [21]. In their study, patients with Grade I–III (extension of pancreatic fluid from anterior pararenal space to the combined interfascial plane at the lower end of the perirenal space) had

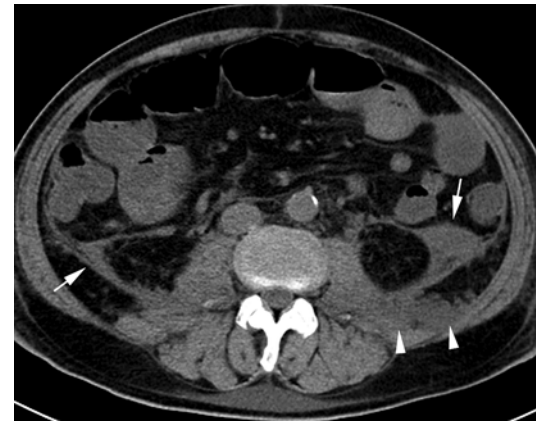

Fig. 6.4 A 49-year-old woman with acute pancreatitis (retroperitoneal extension grade V). Unenhanced CT shows extensive bilateral retroperitoneal inflammatory changes due to acute pancreatitis (*arrows*) with extension to the left posterior pararenal space (*arrowheads*), representing the highest grade of retroperitoneal extension (Grade V)

22 % morbidity and 0 % mortality, whereas patients with Grade IV–V (pancreatic fluid extending from the subfascial plane, located between the posterior pararenal space and the transverse fascia, into the posterior pararenal space) had 92 % morbidity and 39 % mortality (Fig. 6.4) [21]. This grading system can be assessed on unenhanced CT studies, but requires advanced radiologic interpretative skills and may not be easy to use for routine clinical practice.

EPIC Score

The latest CT scoring system is the ExtraPancreatic Inflammation on CT (EPIC score), developed in 2007, which measures exclusively extrapancreatic inflammatory changes hypothetically regarded as CT signs of systemic inflammation (presence of pleural effusion, ascites, and retroperitoneal and mesenteric inflammation on a 7-point severity scale) [41]. The EPIC score was validated in a small single-center study composed of 40 patients who received an abdominal CT within 24 h after admission and proved useful with an area under the receiver operating characteristics (AUC) curve for predicting severe disease and mortality of 0.91 (95 % confidence interval, 0.83–0.99) and 0.85 (95 % confidence interval, 0.71–0.99), respectively [41]. However, this study was biased towards inclusion of a high incidence of severe disease and high need for surgical intervention.

Value of Radiologic Scoring Systems for Severity Prediction

Since over four decades, an exhaustive search for the ideal scoring system has been undertaken to identify patients at risk for severe acute pancreatitis early in the disease process to guide patient triage and management, and to improve patient outcome. An ideal prognostic scoring system should be simple and easy to use in clinical practice, widely available, objective, reproducible, sufficiently accurate in differentiating mild from severe disease and applicable early in the disease process, preferably on day of admission, such that patients at risk for severe acute pancreatitis are more closely monitored or empirically treated (i.e., with tailored fluid resuscitation). Many clinical, biochemical, and imaging-based scoring systems have been developed but none fulfills all of the above-mentioned criteria. Several shortcomings are shared by all staging systems. The available staging systems were devised to identify groups of patients at risk of developing organ failure or clinically severe disease rather than identifying individual patients. Furthermore, about one fifth of patients with potentially fatal severe pancreatitis are inappropriately identified using the traditional scoring systems [42]. Indeed, scoring systems perform best at the extremes of the prediction range, while the discriminatory power is moderate at best in the middle prediction range (i.e., the range where the clinician needs most assistance). Also, the variable timing of patient presentation to the hospital affects the clinical, laboratory, and imaging parameters explaining the variability in scores obtained. Finally, scoring systems (radiologic and biochemical systems alike) do not correlate with the risk of particular extrapancreatic complications (e.g., abdominal compartment syndrome (ACS), bowel ischemia, or perforation or arterial pseudoaneurysm) and, therefore, fail to provide detailed information that impacts patient management on an individual basis.

Imaging-based systems have their specific shortcomings compared with clinical and biochemical scoring systems. It is commonly known that severe acute pancreatitis may run a highly variable clinical course; it may manifest early with SIRS, organ failure, and death in the first week or late with local complications demanding intervention [1, 2]. Biochemical scoring systems, compared with imaging-based systems, better correlate with early systemic effects of pancreatic injury (i.e., organ failure; the main determinant for severity of disease in the revised Atlanta Classification) and, thus, are better in predicting clinical severity early in the disease course. Conversely, radiologic scoring systems are best in predicting late local complications (infected necrosis, need for intervention) [37, 42]. Second, radiologic scoring systems are based on visual estimation and, therefore, are subject to variable interpretation, whereas most biochemical scoring systems are derived from objective parameters. Third, radiologic scoring systems do not account for patients preexisting clinical status; such as age, comorbid disease, and obesity which are well-known prognostic factors for morbidity and mortality. Institution of preventative measures requires early identification of patients with severe disease before the development of a complication. However, the timing of the CT scan in

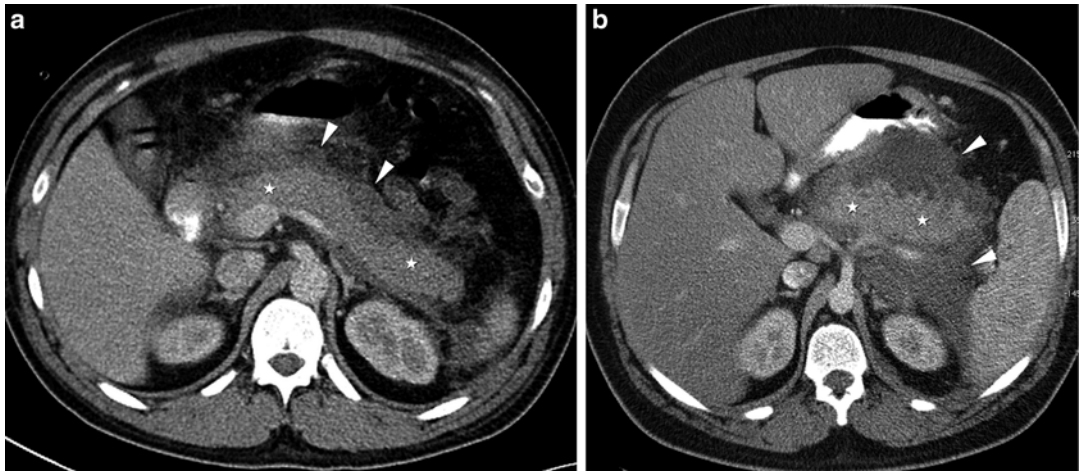

Fig. 6.5 Two different patients (**a**, **b**) with similar grades of severity but marked difference in magnitude of peripancreatic collections. (**a**) A 44-year-old man with limited peripancreatic collections (*arrowheads*). (**b**) A 37-year-old man with extensive peripancreatic collections (*arrowheads*). Both patients are appreciated with similar grades according to all radiologic scoring systems. *White stars* denote a normal enhancing pancreas in both patients

reports on the predictive power of radiologic scoring systems has varied from at admission to 10 days after admission [14]. Conversely, clinicobiochemical scoring systems are mostly tested early in the clinical course (within the first 24–48 h), i.e., in a timeframe where severity stratification is most useful. Finally, studies on imaging-based systems are biased toward more severe disease because patients with mild or minimal symptoms do not need cross-sectional imaging for clinical management while biochemical scoring systems are tested and applicable in all patients presenting with acute pancreatitis.

Reports on the discriminatory power of radiologic scoring systems all show a positive correlation between the scoring system studied and patient outcome. However, because of the profound lack of homogeneity in study design, differences in methodology used and the wide diversity in definitions for severe acute pancreatitis and clinical end points (e.g., variation in defining organ failure and systemic complications) comparison of these studies are rendered difficult [14]. A recent study comparing seven of the eight above-mentioned CT prognostic scoring systems on the day of admission accounted for these shortcomings by using definitions put forth by the working group on revising the Atlanta Classification [43]. This study did not detect significant differences between the studied CT scoring systems in predicting clinical severity or mortality (AUC ranging between 0.72–0.88 and 0.70–0.81, respectively). Moreover, CT scoring systems did not perform better than commonly used clinical scoring systems [43].

The use of early imaging for prognostication is limited by several factors: (1) In most imaging-based systems, the rating of peripancreatic inflammation and fluid is determined based on their presence rather than extent; the latter may vary considerably among patients appreciated with similar grades (Fig. 6.5). (2) Morphologic signs of severe disease are a time-dependent phenomenon. CT only takes a snapshot of a moment in time, while acute pancreatitis is a continuously evolving disease process. Consequently, patients may progress from mild to severe grades of CT severity. (3) Parenchymal necrosis may not be evident until after 24–48 h and, thus, may be underrated on early imaging (Fig. 6.6). (4) On the other hand, the presence and extent of parenchymal necrosis do not invariably correlate with organ failure and clinical severity, and (5) the evolution of CT findings does not always parallel the clinical course; CT may show little

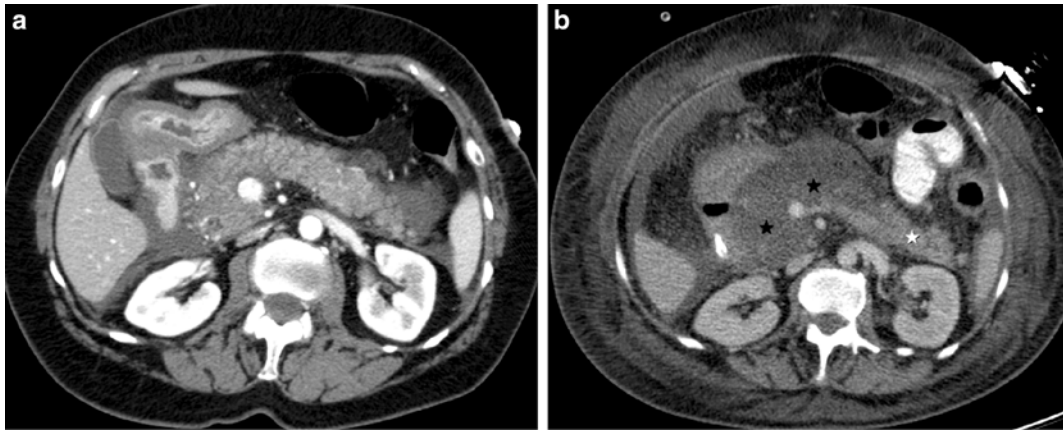

Fig. 6.6 A 47-year-old woman with false negative parenchymal necrosis on early CT. (**a**) Contrast-enhanced CT on day 1 shows a heterogeneous enhancing pancreatic parenchyma, but no apparent areas of nonenhancement. (**b**) Repeat CT was performed on day 4 showing clear nonenhancement of pancreatic head, neck and part of body (*black stars*), while the tail shows preserved enhancement (*white star*)

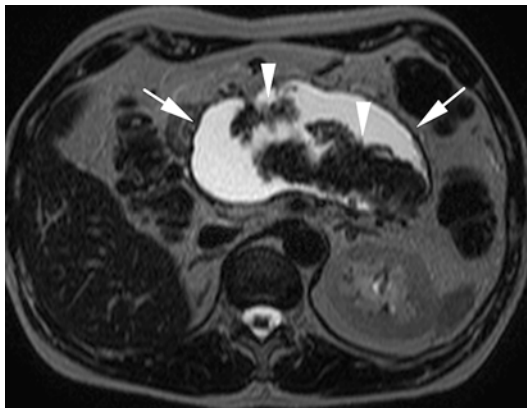

Fig. 6.7 A 50-year-old man with extensive necrosis and mild clinical symptoms. MRI was performed for continuing mild discomfort 6 weeks after an episode of acute pancreatitis. T2-weighted sequence shows a fully encapsulated collection (walled-off necrosis) in the pancreatic area (*arrows*) with dark material (*arrowheads*), representing necrotic pancreatic and peripancreatic tissue

morphologic signs of severe disease early in disease process (i.e., on day of admission) in patients who already have organ failure as sign of a severe attack. Conversely, imaging studies late in the disease process may show major morphologic changes (like extensive parenchymal necrosis and retroperitoneal collections) in patients who have only mild clinical discomfort (Fig. 6.7).

In summary, current evidence suggests that there is no role for radiologic scoring systems for prediction purposes. Additionally, given the high costs associated with acute pancreatitis [44], the radiation burden of (serial) CT [45, 46], and the lack of correlation between imaging utilization and patient outcome [46, 47], initial evaluation of a patient presenting with acute pancreatitis is best performed based on clinical assessment and biochemical scoring systems that better correlate with organ failure and systemic complications dominating the clinical picture in the first weeks after the initial attack. Performing a CT on admission (or within the first days after admission) is unlikely to affect patient management, unless a severe complication (like hemorrhage or bowel ischemia) is suspected or in case of a diagnostic dilemma. The decision about when to perform MDCT depends, therefore, on the overall clinical presentation. Unquestionably, the impact of CT is greater in the later phase of the disease process in patients who have predicted severe acute pancreatitis by clinical assessment or who fail to improve clinically despite conservative therapy when local complications (most commonly infection of parenchymal and peripancreatic tissues) predominantly dictate clinical management.

Prognostic Value of Specific Computed Tomography Findings

Morphologic findings of acute pancreatitis include necrosis of pancreatic parenchyma, peripancreatic inflammation with or without fluid and extrapancreatic retroperitoneal or subperitoneal fatty tissue necrosis, subsequent infection of pancreatic or extrapancreatic necrosis, vascular compromise of adjacent veins and arteries, extrapancreatic parenchyma complications, biliary complications, and gastrointestinal complications. Some of these findings or complications are detected on cross-sectional imaging only but nonetheless may harbor significant prognostic importance (Table 6.3). Given the aforementioned limitations of radiologic scoring systems, this section will review the key findings on cross-sectional imaging associated with prognostic significance, which may directly influence patient management.

Table 6.3 CT findings of complications in acute pancreatitis with clinical implications

CT findings	Clinical implications
Necrosis of pancreatic parenchyma: – Extended necrosis (>30 %) – Central gland necrosis	Increased risk for developing organ failure, infected necrosis, and higher need for intervention
Infected necrosis (gas bubbles in necrotic collections)	Institution of (empiric) antibiotics and/or intervention
Peripancreatic collections exerting mass effect on surrounding structures: – Biliary dilation – Obstructive hydronephrosis	If symptomatic, stent placement
Deep vein thrombosis of iliofemoral veins or pulmonary emboli/ infarction	Initiation of anticoagulant therapy
Hemorrhage/arterial pseudoaneurysm	Angiographic coiling/ embolization or surgical clipping
Cholecystitis or gallbladder perforation	Percutaneous drainage or surgical cholecystectomy
Bowel ischemia or perforation	Surgical resection
CT signs of abdominal compartment syndrome (ACS)	Percutaneous drainage of ascites (if present) or surgical decompression
Pulmonary complications: – Pleural empyema – Pulmonary infiltrate(s) – Pneumothorax	Initiation of antibiotics (empyema, pneumonia) or drain placement (empyema, pneumothorax)

Pancreatic Findings

Pancreatic Necrosis

Necrosis of pancreatic tissue signifies the most severe morphologic form of acute pancreatitis and represents the basis for most of the local complications [48]. Necrosis of pancreatic parenchyma results from severe disturbances in the pancreatic microcirculation and occurs early in the disease process [5, 22]. Generally, it is fully established by 72–96 h and tends to remain stable across time [5, 22, 49]. CECT is considered the noninvasive reference standard for diagnosing pancreatic necrosis. CECT is highly accurate in assessing parenchymal necrosis when performed after 72–96 h after symptom onset and when more than 30 % of pancreatic parenchyma is involved [5, 22]. Early CECT within 24–48 h of disease may miss the presence and extent of necrosis in about 30–40 % of cases [43]. Also, accuracy of pancreatic necrosis detection drops to about 50 % when small areas of pancreatic tissues are affected [5, 50]. Mortality rates in cases of pancreatic necrosis are about 20 %, as opposed to less than 5 % in patients without pancreatic necrosis [3]. Extended pancreatic necrosis (i.e., more than 30 %) is associated with SIRS, organ failure, and development of late local complications such as infection of necrosis [35]. Furthermore, patients with significant necrosis are prone to develop other infections (urinary, respiratory, and systemic infections) during both the early and late phases [51]. These infections complicate the clinical course of acute pancreatitis and prolong hospitalization. Some studies have shown that transparenchymal necrosis concerning the central area (pancreatic neck and/or body) or central gland necrosis also heralds prognostic significance because of the possible

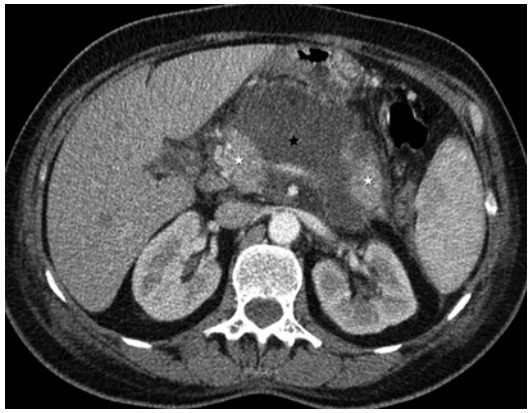

Fig. 6.8 A 42-year-old woman with central gland necrosis. Contrast-enhanced CT depicts necrosis of the neck and body of the pancreas (*black star*) among the viable pancreatic head and tail (*white stars*). This patient is at risk for having a pancreatic duct disruption with increased need for intervention

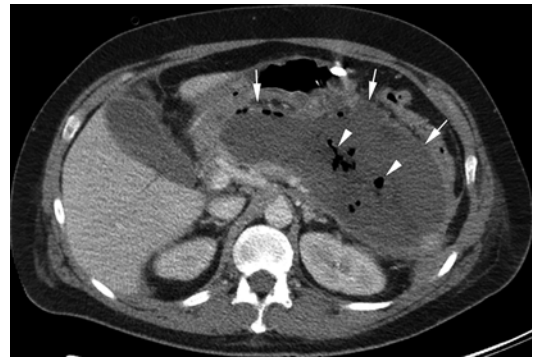

Fig. 6.9 A 51-year-old woman with infected necrosis. Contrast-enhanced CT performed on day 26 after symptom onset shows a nearly completely encapsulated necrotic collection (*arrows*) with impacted gas bubbles (*arrowheads*), virtually diagnostic for infection of necrosis

involvement of the pancreatic duct, resulting in the pancreatic duct disruption syndrome (Fig. 6.8) [52, 53]. In central gland necrosis, a viable pancreatic tail causes the ongoing secretion and extravasation of pancreatic fluid in the necrotic collection and peripancreatic area associated with increased need for percutaneous, endoscopic, or surgical intervention [53].

Infection of Necrosis

Necrosis of pancreatic parenchyma and peripancreatic fatty tissue serves as a nidus for bacterial superinfection, resulting in the most severe local complication in acute pancreatitis. Mortality rate in sterile necrosis is around 5–10 % and increases considerably when the necrosis becomes infected [3]. Indeed, infection of necrosis is a major prognostic risk factor in severe acute pancreatitis and sepsis-related multiple organ failure is the main life-threatening complication with a mortality rate up to 20–50 % [3]. On CECT, the presence of gas bubbles in an area of pancreatic and/or peripancreatic fatty tissue necrosis is virtually pathognomonic for the diagnosis of infected necrosis, especially in patients with clinical signs of infection (spiking fever, leukocytosis, elevated C-reactive protein, and/or (new onset) organ failure) (Fig. 6.9) [54]. In rare instances, gas bubbles can be seen in sterile collections associated with an enteric fistula. However, these patients often lack clinical signs of infection. Unfortunately, gas bubbles on CECT as sign of infected necrosis is only present in about 40 % of cases [54].

Peripancreatic Collections

In the more severe forms of acute pancreatitis peripancreatic (fluid) collections arise most commonly in the lesser sac, the retroperitoneum, and subperitoneal spaces of the mesenteries. According to the revised Atlanta Classification 2012, these are termed an acute peripancreatic fluid collection or pseudocyst in *interstitial* pancreatitis (collections contain fluid only) or acute necrotic collection or walled-off necrosis in *necrotizing* pancreatitis (collections contain a mixture of necrotic material and variable amounts of fluid) [48]. The natural history of these collections is highly unpredictable, ranging from spontaneous resolution in over half of cases, to persisting and increasing in size and giving rise to complications like secondary infection (in necrotizing pancreatitis, this is termed infected necrosis), mass effect on neighboring structures (e.g., biliary system resulting in biliary dilation, urogenital system resulting in hydronephrosis, venous system resulting in left-sided portal hypertension, splenomegaly and extensive collateral venous network when the portomesenteric

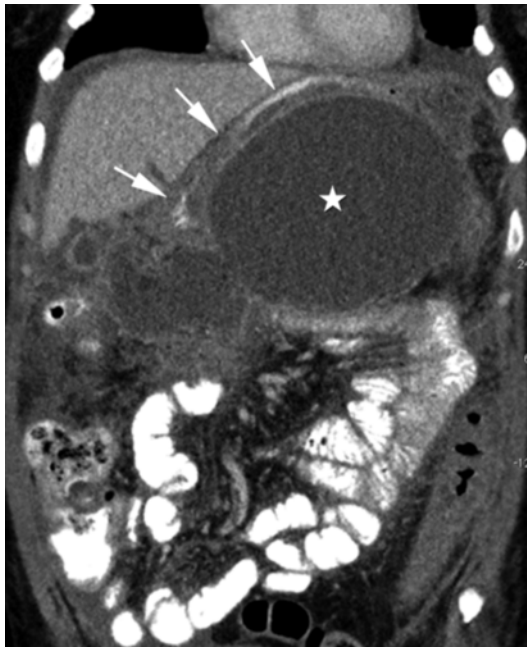

Fig. 6.10 A 49-year-old woman with large collection compressing the stomach. Coronal reformatted contrast-enhanced CT shows a large encapsulated necrotic collection (*white star*) exerting mass effect on the stomach (*arrows*), which is displaced medially and cranially

and splenic veins are involved, and gastric outlet obstruction), or rupture into the peritoneal cavity with development of acute peritonitis (Fig. 6.10) [5, 55, 56].

Extrapancreatic Findings

Vascular Complications

Vascular complications are common in patients with moderate severe and severe acute pancreatitis and include portomesenteric venous thrombosis, arterial pseudoaneurysm, and hemorrhage due to vessel erosion of arteries, veins, or small capillaries either through pancreatic enzymes or, iatrogenically, by surgical, endoscopic, or radiological drains.

Recent studies on splanchnic vein thrombosis report an incidence of about 50 % in patients with parenchymal necrosis, most frequently in the splenic vein, followed by portal and superior mesenteric vein (Fig. 6.11) [57, 58]. Most are

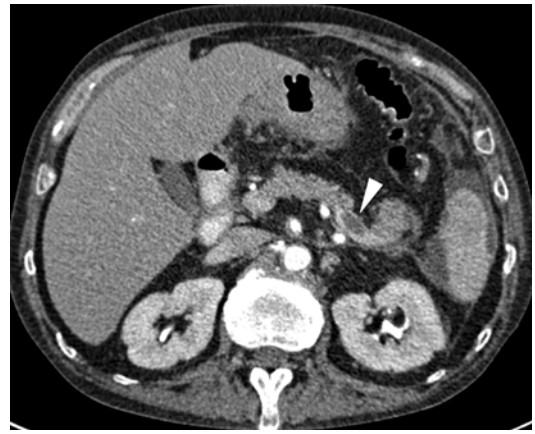

Fig. 6.11 A 56-year-old man with thrombus in the splenic vein. Contrast-enhanced CT depicts an intraluminal filling defect in the splenic vein (*arrowhead*), compatible with a thrombus. Usually, this is not an indication for initiation of anticoagulant therapy

asymptomatic, and spontaneous recanalization occurs in about one third of patients irrespective of the use of systemic anticoagulation. Reported complications include gastrointestinal bleeding and splenomegaly but are rare [59]. Current practice suggests that there is no need for initiation of anticoagulation unless there is propagation of thrombosis on serial CT scans [58]. In the literature, there is lack of data about the true incidence of deep vein thrombosis or pulmonary embolism on abdominal CT scans in acute pancreatitis. In the author's experience, this is rare and primarily seen in patients with severe necrotizing acute pancreatitis and prolonged hospitalization. However, opposed to portomesenteric vein thrombosis, the observation of intraluminal clots in the iliac or femoral vein necessitates the initiation of systemic anticoagulation to prevent a fatal outcome (Fig. 6.12).

Another vascular complication is the occurrence of an arterial pseudoaneurysm, which is often a late complication in acute pancreatitis, although rare (estimated incidence of less than 2 %) (Fig. 6.13) [60]. In order of frequency, the following arteries are involved: splenic artery, gastroduodenal artery, pancreaticoduodenal artery, gastric artery, hepatic artery, and others (superior mesenteric artery, jejunal or ileocolic artery) [60]. Generally, there is an indication for angiographic

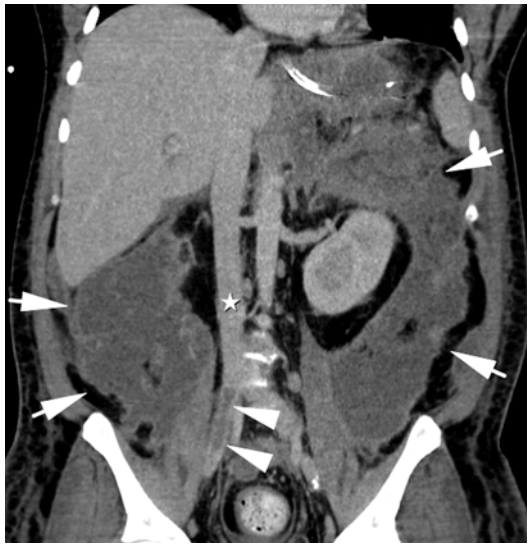

Fig. 6.12 A 43-year-old woman with thrombus in the right iliac vein during the course of acute necrotizing pancreatitis. Coronal reformatted contrast-enhanced CT depicts a large filling defect in the right iliac vein (*arrowheads*), diagnostic for deep vein thrombosis in a patient with necrotizing pancreatitis and extensive retroperitoneal collections (*arrows*). *White star* denotes the inferior vena cava. To prevent pulmonary embolism anticoagulant therapy is mandatory

embolization or coiling. Uncontrollable bleeding from a ruptured arterial pseudoaneurysm requires emergency surgical intervention.

Hemorrhage from erosion of a vascular wall may be a life-threatening complication if an artery is involved or may be an incidental finding in case of damage of small capillaries or veins. The vast majority of vascular complications are readily detectable on routine abdominal CT scans but some (e.g., small arterial pseudoaneurysms or insignificant hemorrhage) require a multiphasic scan protocol (including an unenhanced and arterial phase) for accurate detection [12].

Extrapancreatic Parenchymal Complications

Acute pancreatitis is capable of inflicting damage to adjacent parenchymal organs, like the spleen, liver, and kidneys, due to the central location of the pancreas in the upper abdomen and destructive nature of extravasated pancreatic enzymes. Splenic involvement in acute pancreatitis include hematoma, infarction, and perisplenic inflammatory fluid collections (sterile or infected) attributable to pancreatic secretions that dissect into the splenic hilum as the splenic capsule is continuous with the peritoneum covering the anterior surface of the pancreas (Fig. 6.14) [61, 62]. Similar complications may occur in the liver [63]. Renal involvement in acute pancreatitis includes perirenal fluid collections and parenchymal abnormalities (e.g., renal infarction) [33, 64]. Renal complications are most often an incidental finding and seem unrelated to the severity of pancreatitis. One renal complication with clinical impact is obstructive hydronephrosis as a result

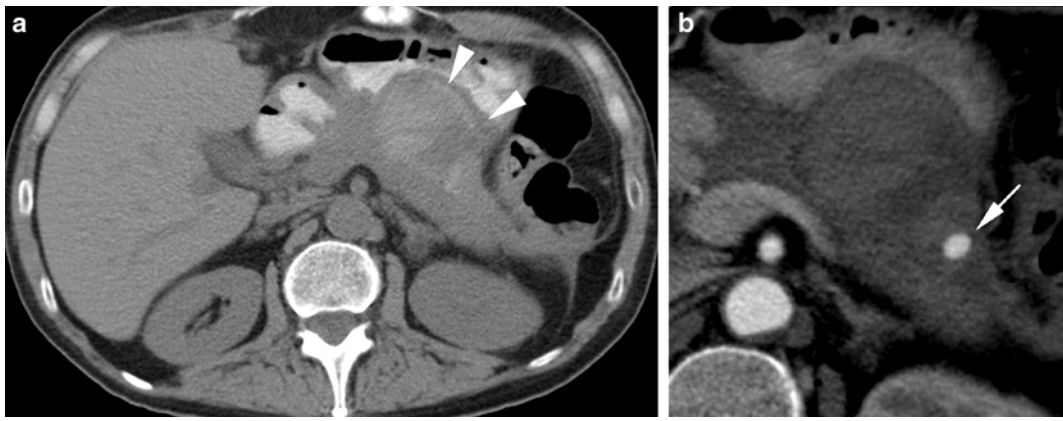

Fig. 6.13 A 40-year-old man with an arterial pseudoaneurysm after an episode of necrotizing pancreatitis. (**a**) Unenhanced CT shows a collection (*arrowheads*) with high density, suggestive of hemorrhage. (**b**) Contrast-enhanced CT in the arterial phase depicts a small arterial pseudoaneurysm (*arrow*) originating from the prepancreatic arcade. Pseudoaneurysm was successfully treated by embolization with platinum coils (not shown)

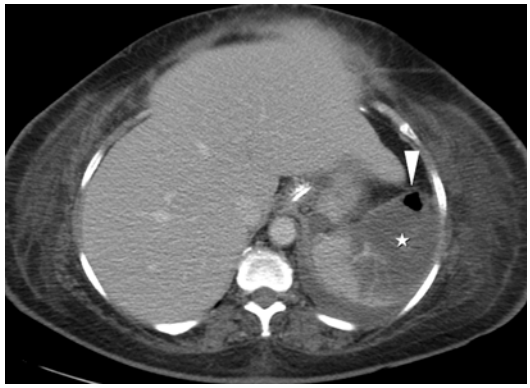

Fig. 6.14 A 61-year-old woman with splenic infarction and signs of infection (abscess) complicating acute pancreatitis. Contrast-enhanced CT shows an area of splenic infarction (*white star*) with a gas bubble (*arrowhead*) as a sign of a splenic abscess

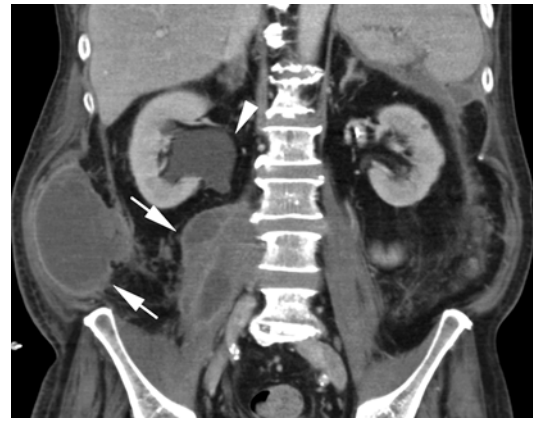

Fig. 6.15 A 72-year-old man with obstructive hydronephrosis of the right kidney due to extensive retroperitoneal collections. Coronal reformatted contrast-enhanced CT depicts a newly developed dilatation of the pyelocaliceal system of the right kidney (*arrowhead*), compatible with hydronephrosis due to obstruction by large retroperitoneal necrotic collections (*arrows*)

of eccentric compression of the proximal ureter by retroperitoneal pancreatic collections (Fig. 6.15) [65]. Most of the aforementioned complications lack any specific symptomatology, but are easily identifiable on CECT underlining the importance of CT for their diagnosis.

Biliary Complications

Concomitant acute cholecystitis and acute pancreatitis is a rare event [66] but development of acute cholecystitis during the course of acute biliary pancreatitis is not uncommon and is one of the reasons to perform a cholecystectomy shortly after an attack of acute biliary pancreatitis [67, 68]. Performing a cholecystectomy may be a surgical challenge, particularly in the presence of necrotic collections [69]. In these cases, percutaneous cholecystostomy may be an alternative treatment strategy. Assessment of gallbladder pathology can be difficult in the course of acute pancreatitis and findings on CECT may be helpful in the diagnosis and, thus, may directly influence patient management.

Direct extension of the inflammatory process to the duodenal wall and ampulla of Vater may result in transient inflammatory narrowing of the intrapancreatic segment of the common bile duct causing jaundice. Persistence of or development of jaundice a few weeks after the acute onset of pancreatitis, however, may indicate a more

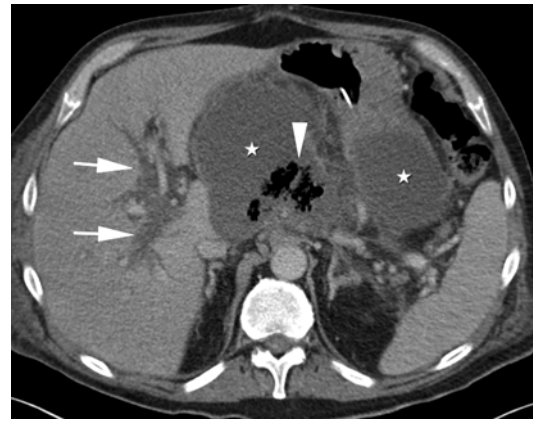

Fig. 6.16 A 76-year-old woman with infected necrotizing pancreatitis and biliary dilatation. Contrast-enhanced CT shows large necrotic collections (*white stars*) and impacted gas bubbles (*arrowhead*), indicative for infected necrosis. Also, dilatation of the intrahepatic bile ducts (*arrows*) is noted due to extrinsic compression of the common bile duct

significant complication such as a chronic obstruction due to a ductal stricture or compression of the common bile duct by peripancreatic collections (i.e., indication for endoscopic stent placement) [70]. CECT easily depicts biliary dilatation up to the level of obstruction (Fig. 6.16). Another severe, but extremely rare complication

is perforation of the gallbladder leading to biliary peritonitis [66]. CECT may diagnose this complication by depicting an interruption of the gallbladder wall with adjacent inflammatory fluid. Finally, erosion of the common bile duct wall by the inflammatory process may lead to a pancreaticobiliary fistula [71]. On CECT, the simultaneous presence of gas bubbles in the biliary tract and intrapancreatic collection is highly suggestive of a pancreatic choledochal fistula. Adequate drainage of the pancreatic/peripancreatic collection and bile duct is generally effective.

Gastrointestinal Complications

Involvement of gastrointestinal structures in acute pancreatitis is multifactorial and occurs primarily in necrotizing pancreatitis. Extravasated pancreatic enzymes may directly damage the gastrointestinal tract or may produce vascular thrombosis resulting in ischemic splanchnic injury. Also, early in the course of severe acute pancreatitis, hypovolemic shock with a splanchnic low flow state may occur because of inadequate fluid therapy and third-space loss responsible for further vascular compromise [72–74]. Rare but severe complications are perforation of the stomach (mainly the posterior wall of the stomach) and erosion of the medial wall of the duodenum in patients with pancreatic necrosis [75, 76]. A small but significant number of patients with necrotizing pancreatitis sustain ongoing abdominal pain, nausea, and inability to eat owing to centrally located pancreatic collections that displace and compress the stomach anteriorly giving rise to gastric outlet obstruction [77]. In these patients, endoscopic drainage may be indicated. The most severe small bowel and colonic complication in acute pancreatitis is ischemia and subsequent necrosis and perforation because of thrombosis of feeding or draining vessels in the mesentery (Fig. 6.17) [72, 73]. The usual sites of involvement of the colon are the transverse colon and the splenic flexure, because of their proximity to the pancreas, and the poor collateral flow [74]. These patients may present with prolonged ileus, gastrointestinal bleeding, and peritonitis along with features of necrotizing pancreatitis. Findings on CECT that are suggestive

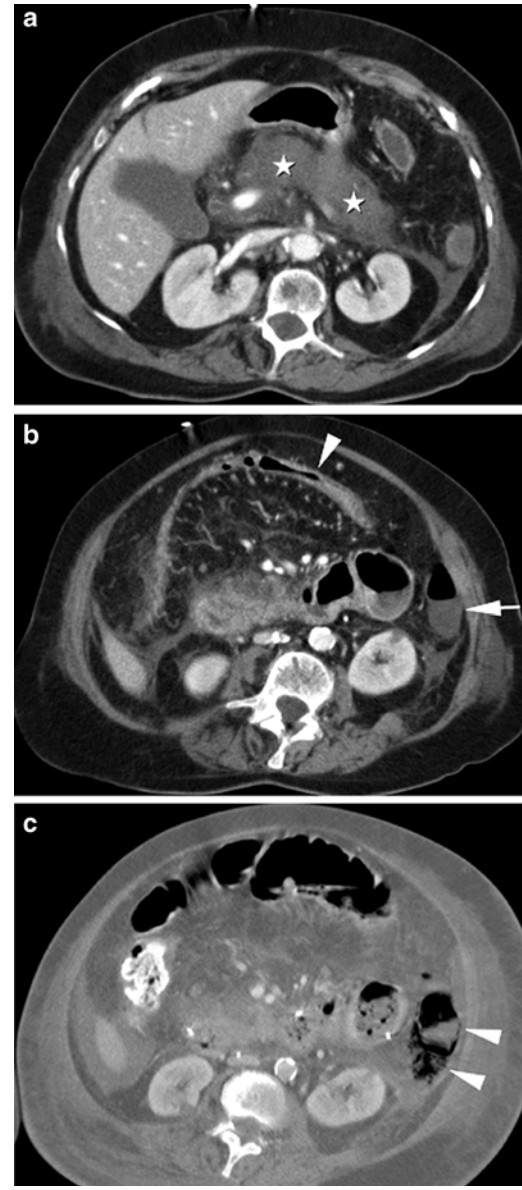

Fig. 6.17 A 58-year-old woman with bowel ischemia of descending colon complicating acute necrotizing pancreatitis. (**a**) Contrast-enhanced CT performed on day 2 after symptom onset shows extensive necrosis of pancreatic body and tail (*white stars*). (**b**) Same CT at a lower level shows normal enhancement of the bowel wall of the transverse colon (*arrowhead*), while the descending colon shows absent bowel wall enhancement indicative for ischemia, which was overlooked by the radiologist. (**c**) Repeat contrast-enhanced CT 24 h later for continuing severe sepsis depicts the development of gas in the bowel wall of the descending colon (pneumatosis intestinalis) and adjacent mesocolon (*arrowheads*) suggestive for bowel necrosis. Emergency laparotomy was performed which confirmed the CT findings

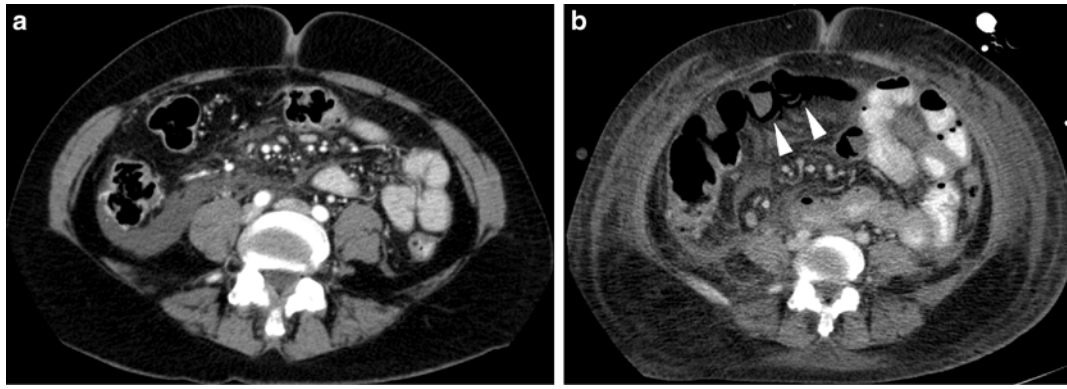

Fig. 6.18 A 47-year-old woman with development of ACS occurring early in the course of acute necrotizing pancreatitis (same patient as Fig. 6.6). (**a**) Contrast-enhanced CT (day 1) at the level of the umbilicus shows mesenterial and retroperitoneal inflammatory changes due to pancreatitis. Note, the normal configuration of the abdominal contour. (**b**) Repeat CT on day 4 shows a rounded appearance of the abdomen (round belly sign). Also note, pneumatosis intestinalis and absent bowel wall enhancement of ileal loops (*arrowheads*), indicative for small bowel ischemia. Patient underwent emergency laparotomy

for bowel necrosis are the presence of pneumatosis intestinalis, gas in the portomesenteric veins, diminished or absent bowel wall enhancement, clots or occlusion of feeding arteries, and free intraperitoneal gas (pneumoperitoneum; virtually diagnostic for a perforated hollow viscus). Identification of these CT signs is critical because intestinal ischemia has a very high mortality if not treated expediently. Other colonic complications with less clinical impact are ileus and fistula formation.

Abdominal Compartment Syndrome

ACS is caused by pathological elevation of intra-abdominal pressure in response to various diseases (including severe acute pancreatitis) leading to multiple organ dysfunction [78]. ACS is increasingly recognized in acute pancreatitis and since the condition is associated with high mortality, early diagnosis is imperative [79]. Usually, the diagnosis of ACS is straightforward by clinical assessment and intravesical pressure measurements; however, diagnosis may be delayed by interfering symptoms from the underlying illness. Abdominal CT scan may reveal subtle findings that include narrowing or collapse of the inferior vena cava, direct renal compression or displacement, bowel wall thickening with increased enhancement, bilateral inguinal herniation, elevated hemidiaphragm, and a rounded appearance of the abdomen (so-called "round-belly sign") [80, 81]. The "round-belly sign" is defined as abdominal distension with an increased ratio of anteroposterior-to-transverse abdominal diameter (ratio > 0.80). Especially, an increasing girth observed on serial CT scans performed at short intervals is worrisome (Fig. 6.18) [81]. Individually, these CT findings are neither specific nor sensitive, but when present in combination, radiologists should raise the possibility of this life-threatening complication and, in the proper clinical setting, should communicate the presence and significance of these CT findings to the referring clinician.

Miscellaneous Complications

Routine abdominal CT for acute pancreatitis can reveal some complications that may not always be clinically apparent. Among these are abdominal wall extension of infected collections (amenable for percutaneous drainage) and pulmonary complications such as pneumothorax, focal consolidations indicative for pulmonary infiltrates, pleural empyema, features of the adult respiratory distress syndrome, and pulmonary embolus or infarction (Fig. 6.19) [82].

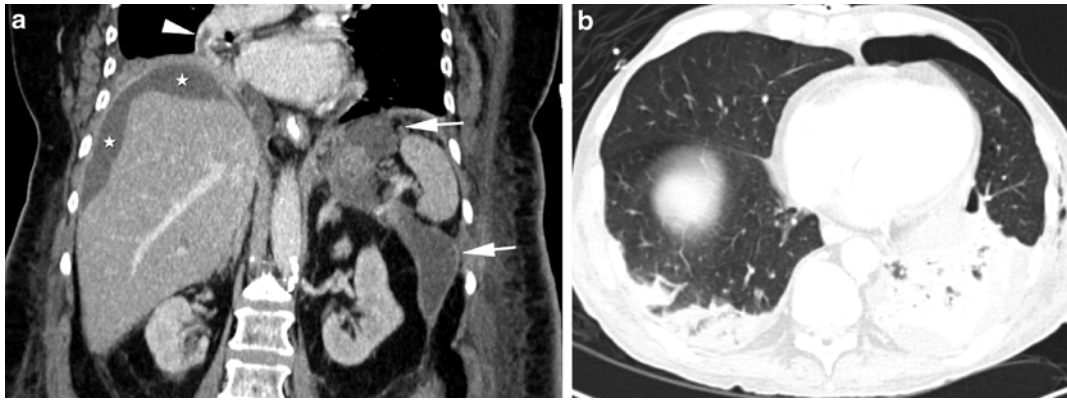

Fig. 6.19 Two different patients (**a**, **b**) with pulmonary complications during an episode of acute pancreatitis. (**a**) Coronal reformatted contrast-enhanced CT in a 69-year-old woman shows signs of acute necrotizing pancreatitis with necrotic collections in the left retroperitoneum (*arrows*) and perihepatic fluid (*white stars*). As incidental finding, a thrombus was noted in the right pulmonary artery (*arrowhead*). (**b**) CT at the lung bases in an 80-year-old man with acute pancreatitis, who experienced a sudden onset of dyspnea and fever, demonstrates a left-sided pneumothorax and bilateral consolidations in the lower lobes, indicative for pneumonia

Conclusion

Acute pancreatitis is a common but potentially devastating disease associated with significant morbidity, mortality, and public health impact in severe cases. Imaging-based predictive systems are useful for identifying groups of patients at risk for local complications or having severe disease rather than providing specific information changing clinical management on an individual basis. However, there are several individual CT features that may impact patient management significantly. Among these are the presence of significant necrosis (more than 30 %), especially in case of central gland necrosis (associated with increased need for intervention), imaging signs of infected necrosis (requiring empirical antibiotics or some kind of radiologic, endoscopic, or surgical intervention), massive hemorrhage or detection of an arterial pseudoaneurysm (indication for angiographic coiling or surgery), deep vein thrombosis (indication for anticoagulation), cholecystitis (amenable for percutaneous drainage), bowel ischemia or perforation (indication for surgery), and features of the ACS (requiring percutaneous drainage of ascites or surgery). The conveyance of these specific CT findings to clinicians caring for these challenging patients will have more clinical impact on patient management than providing any radiologic score.

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Predictive Scoring Systems in Acute Pancreatitis

7

Kavya M. Reddy and Bechien U. Wu

Acute pancreatitis is a disease of increasing annual incidence and that produces significant morbidity and mortality. The clinical course is highly variable, as many patients experience self-limited disease that requires only supportive measures. By contrast, others develop severe complications including death. In the United Sates, acute pancreatitis accounts for more than 330,000 hospital admissions per year and patients have an average hospital stay of 4 days [1]. Ten to twenty percent of patients develop persistent organ failure, and among this subgroup, mortality rate reaches 30 % [2]. For this reason, the ability to identify patients at risk for persistent complications such as persistent organ failure early in the disease course is critical in ensuring appropriate management and resource allocation.

Assessment of severity should start immediately with the initial clinical assessment. The objectives of initial clinical assessment are to establish the diagnosis of acute pancreatitis, evaluate potential etiologies, and perform risk stratification. Early risk stratification can help identify patients who are more likely to suffer complications such as organ failure and necrosis or infected necrosis. Patients determined to be at increased risk for morbidity and mortality from acute pancreatitis can then be triaged early to intensive care units and further be selected to undergo specific interventions. For instance, severe cases of pancreatitis may require imaging to evaluate for complications, pancreatic abscess, infected pancreatic necrosis, large pseudocysts, or acute cholangitis that may require interventions such as percutaneous drainage or ERCP.

Clinical scoring systems and laboratory markers function as prognostic indicators for acute pancreatitis; however, they do not measure severity directly. Measures of severity in acute pancreatitis were defined in the 2012 revised Atlanta classification system, which divides the disease into two phases—early and late. Mild acute pancreatitis is defined by the absence of organ failure, local or systemic complications, and resolution of disease within 1 week [3]. Moderate acute pancreatitis is defined by presence of transient organ failure, local complications, or worsening of comorbid diseases. Lastly, severe acute pancreatitis involves persistence of organ failure (signified by shock, respiratory failure, or end organ damage) for greater than 48 h and presence of local complications such as pancreatic or peripancreatic fluid collections, necrosis (sterile or infected), pseudocysts, and walled-off necrosis [3]. Studies using clinical scoring systems initially focused on mortality as the outcome of

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interest. However, recent data suggest that overall mortality has declined over the past several decades, and this has led to increasing debate over whether death remains the most appropriate outcome to use when predicting the outcome of acute pancreatitis.

Many studies have shown that it is critical to evaluate the patient immediately on presentation and the first 24 h after admission to the hospital for acute pancreatitis. Initial risk stratification should take place immediately and the patient should be reassessed again frequently during the first 24 h. In the retrospective cohort study conducted across 159 intensive care units in the United Kingdom, the median length of stay in the hospital prior to admission to the intensive care unit was 1 day and 22 % of the admissions to the ICU were on same as admission to the hospital [4]. Patients admitted to the ICU with severe pancreatitis have high morbidity and mortality compared to other ICU admissions, and early prediction of the severity can have important implications for management and timely intervention in the event of complications. Therefore, a prediction score that is sensitive and can be applied within the first 24 h of admission would be of great value to clinicians. These patients demand close monitoring for fluid status and nutrition, and improper triage due to underestimating the severity of acute pancreatitis may lead to inappropriate care of these patients and increased morbidity and mortality.

Historical Perspective

The first major advancement for predicting the severity of pancreatitis was the development of the Ranson criteria in 1974. Since then, multiple scoring systems have been developed which incorporate physiologic, laboratory, and radiographic parameters. New studies have also suggested the role of individual laboratory parameters in assessing disease severity such as blood urea nitrogen (BUN) and creatinine. In this chapter, we will summarize the current prediction models for severe acute pancreatitis as well as measurement of specific laboratory tests. We will also highlight the relative advantages and disadvantages of several of these models and markers which have been evaluated in several recent studies. The clinical scoring systems that will be discussed include the Ranson's score, the Glasgow criteria (also known as the Imrie score), APACHE-II, Systemic Inflammatory Response Syndrome (SIRS), Pancreatitis Outcome Prediction (POP), Bedside Index for Severity in Acute Pancreatitis (BISAP), the revised Japanese severity score (JSS), and Harmless Acute Pancreatitis Score (HAPS). The role of several laboratory markers and level of fluid sequestration in predicting outcomes in acute pancreatitis will also be discussed.

Ranson Score

Ranson's criteria were first developed in 1974 and are one of the earliest objective scoring systems to predict severity in acute pancreatitis. The criteria consist of five parameters measured at admission and six factors that are assessed during the next 48 h, looking at a total of 11 different components (Table 7.1). If the score is greater than or equal to 3, severe pancreatitis is likely, whereas it is unlikely with a score of less than 3 [5]. Percentage mortality has also been established based on the scoring system. A score of 0–2 has approximately 2 % mortality, a score of 3–4 has 15 % mortality, a score of 5–6 has 40 % mortality, and a score of 7–8 has 100 % mortality [5]. However, recent data suggests that overall mortality from acute pancreatitis has declined over the past several decades, which has led to increasing debate over whether death remains the most appropriate outcome to measure.

Ranson's criteria continue to be used since it is so well-established; however, there are two main problems with the score. First, it is cumbersome to use in routine clinical practice since there are multiple parameters that are needed that are not routinely calculated as well as the fact that it takes 48 h to complete. Secondly, the inability to calculate the score within the first 24 h misses a very important therapeutic window when risk-stratification should take place.

Table 7.1 Ranson's criteria

Criteria	Use	Advantages	Disadvantages	Score cutoff
At admission: age (>55 years), WBC (>16,000 mL^{-1}), glucose (>200 mg/dL), LDH (350 IU/mL), AST (>250 IU/mL) *At 48 h*: hematocrit (decrease >10 %), BUN (increase >5 mg/dL), calcium (<8 mg/dL), PaO_2 (<60 mmHg), base deficit (>4 mEq/L), fluid sequestration (>6 L)	At admission and at 48 h	Well established	Cumbersome Requires 48 h to complete	Score ≥3: severe pancreatitis likely Score <3, severe pancreatitis is unlikely Score 0–2 : 2 % mortality Score 3–4: 15 % mortality Score 5–6: 40 % mortality Score 7–8: 100 % mortality

Table 7.2 APACHE-II

Criteria	Use	Advantages	Disadvantages	Score cutoff
Temperature, MAP, heart rate, respiratory rate, PaO_2, arterial pH, HCO_3, sodium, potassium, creatinine, hematocrit, WBC, Glasgow Coma Score, age, chronic health points	At admission and at 48 h	Widely validated, can be calculated at any time	Cumbersome as all parameters are not routinely collected	Score ≥8 indicates severe disease

The original study detected the sensitivity of three or more criteria to predict severe disease to be 65 % with a specificity of 99 %, yielding a positive predictive value (PPV) of 95 % and a negative predictive value (NPV) of 86 % [6]. However, a meta-analysis of 12 published series using Ranson's criteria and encompassing 1,307 patients reported an overall sensitivity for predicting severe acute pancreatitis of 75 %, a specificity of 77 %, a PPV of 49 %, and an NPV of 91 % [6]. Therefore, many patients with a Ranson's score above 3 will not develop severe pancreatitis, emphasizing a high false-positive rate of Ranson's criteria [7]. Overall, Ranson criteria have been shown to be a good predictor of severity in acute pancreatitis with sensitivity, specificity, PPV, and NPV ranging from 67 % to 84 %, 76 % to 90 %, 49 % to 70 %, and 89 % to 95 %, respectively [7–10].

APACHE II

Currently, the most widely used index for early risk stratification in acute pancreatitis remains the APACHE II, which was originally developed for critically ill patients in intensive care units (Table 7.2) [11]. The score has 12 components and extra points based upon age and presence of chronic disease. This scoring system has been widely validated for predicting death in acute pancreatitis. The accuracy of this scoring system depends on the chosen cutoff value and time the score is calculated. When calculated at admission, the sensitivity of an APACHE II score of >7 to predict severe acute pancreatitis is 65 %, with a specificity of 76 %, a PPV of 43 %, and a NPV of 89 % [7]. Raising the cutoff to >9 improves the specificity and PPV but reduces the sensitivity [12, 13]. Overall, at 24 h, the sensitivity, specificity, PPV, and NPV of APACHE II range between 65 % and 70.3 %, 71.9 % and 81 %, 20 % and 67 %, and 80 % and 93 %, respectively [8, 14–16]. Many variations of the scoring system have recently been developed but overall, the advantages of using the APACHE II include the ability of the score to be calculated at any point in time during the patient's hospital stay and the ability to recalculate the score as conditions change.

Body mass index (BMI) score was recently added to APACHE II score, creating the

composite score (APACHE-O), which was shown to have greater predictive accuracy [17]. One point was added for a BMI of >25 to 30 and two points were added for a BMI > 30. With a cutoff score of 8, APACHE-O was shown to be a good predictor of severity during the first 24 h of hospitalization with a sensitivity, specificity, PPV, and NPV of 82 %, 86 %, 74 %, and 91 %, respectively [17]. In a prospective study looking at patients with a BMI > 30, the predictive values of APACHE-O and APACHE II were similar with AUC 0.895 and 0.893, respectively [18]. Several additional variables were added to APACHE II to improve its accuracy leading to the development of APACHE III. Both APACHE scoring systems use similar variables; however, they differ in the number of physiologic variables (12 for APACHE II vs. 17 for APACHE III) and the assessment of chronic health status [19].

The advantages of using the APACHE system as a predictive score are that it is widely validated and the score can be calculated at any time during a patient's hospital stay. In addition, the score can be recalculated as conditions change. There are also several disadvantages to using the APACHE II in a clinical setting. For instance, the score will likely require the use of an online calculator given the incorporation of multiple parameters. Furthermore, many of these parameters are not routinely collected.

Glasgow-Imrie Score

The modified Glasgow score was first developed in the mid-1980s and incorporates seven routinely calculated laboratory tests (white blood cell count, glucose, BUN, PaO_2, calcium, albumin, and LDH) as well as the patient's age (Table 7.3). In the original study, out of 405 episodes of acute pancreatitis, 72 % of patients had severity correctly predicted by the scoring system [20]. The original study included aminotransferase concentrations; however, this was found to not predict severity. Using eight factors, the scoring system was shown to correctly predict severity in 79 % of episodes and has since been widely validated. In a retrospective analysis of 126 cases of pancreatitis, the modified Glasgow score was found to be slightly inferior to Ranson's score with a sensitivity of 74.5 % and specificity of 71.1 % but had good discriminatory ability with AUC of 0.805 (0.724–0.886) [21]. Those with a score greater than or equal to 3 had statistically significant increase in mortality ($P = 0.001$) and median length of stay ($P = 0.003$) [21]. The modified Glasgow score seems simpler to calculate in comparison to Ranson's criteria and the APACHE II score. However, the score is similar to Ranson's criteria in that it was designed to be calculated at 48 h after admission.

Bedside Index of Severity in Acute Pancreatitis

Recently, a score known as the BISAP score has been developed for use in the first 24 h of admission (Table 7.4) [22]. The score was derived from a collection of data from 17,992 patients from 212 hospitals during the years of 2000 and 2001. The score was then validated in a population of 18,256 patients from 177 hospitals in 2004–2005. The score includes five factors and one point is assigned for each of the following factors during the first 24 h: BUN > 25 mg/dL, impaired mental status, SIRS (using the same criteria as the SIRS score), age >60 years, or the presence of a pleural effusion. Patients with a score of 0 had a mortality of less than 1 %, whereas patients with a score

Table 7.3 Glasgow-Imrie score

Criteria	Use	Advantages	Disadvantages	Score cutoff
Age (>55 years), WBC (>15,000 mL^{-1}), glucose (>180 mg/dL), BUN (>45 mg/dL), PaO_2 (<60 mmHg), calcium (<8 g/dL), albumin (<3.2 g/dL), LDH (>600 IU/L)	At admission and at 48 h	Simple to calculate	Requires 48 h to complete	Score >3 indicates severe pancreatitis

Table 7.4 BISAP

Criteria	Use	Advantages	Disadvantages	Score cutoff
BUN > 25 mg/dL, impaired mental status (Glasgow Coma Score <15), SIRS (≥2), age (>60 years), pleural effusion	Measured over 24 h	Straight forward calculation and can be calculated at any time during initial 24 h	Static measurement (does not incorporate changes over time)	Score ≥3 indicates severe disease

Table 7.5 SIRS

Criteria	Use	Advantages	Disadvantages	Score cutoff
Temperature <36 °C or >38 °C, HR >90/min, respiratory rate (>20 min^{-1} or $PaCO_2$ < 32 mmHg), WBC (<4,000 mm^{-3}, >12,000 mm^{-3} or >10 % bands)	Measured at any time	High sensitivity	Lacks specificity unless syndrome present for >48 h	Two of four SIRS criteria must be present

of 5 had a mortality rate of 22 %. In the validation cohort, the BISAP AUC was 0.82 (95 % CI 0.79–0.84) vs. APACHE II AUC of 0.83 (95 % CI 0.80–0.85); thus, the BISAP score was found to have a similar accuracy to the APACHE II score for predicting death [22]. The accuracy of this score was further validated in several prospective cohort studies [8, 23]. One study aimed to evaluate the ability of the BISAP score to predict mortality and found there to be a significant trend for increasing mortality with increasing BISAP score ($P < 0.0001$) [23]. Another validation study performed in 57 patients found the sensitivity and specificity of the BISAP score to be 75 % and 97.56 %, respectively [24]. The advantages of this scoring system include the simplicity of calculation and the ability to identify patients at risk of death even in the early phases of acute pancreatitis. The BISAP score, similar to most of the other scoring systems, has not been validated for predicting outcomes such as length of hospital stay, need for ICU care, or need for intervention. Furthermore, it is a static measure and does not incorporate changes over time.

Systemic Inflammatory Response Syndrome

Many studies have tried to determine whether the development of SIRS can be used to determine the severity of acute pancreatitis [25–27]. The SIRS criteria were first developed in the field of sepsis and diagnosis of the syndrome requires two of four criteria (Table 7.5) [28]. The criteria include a temperature of less than 36 °C (96.8 °F) or greater than 38 °C (100.4 °F), a heart rate greater than 90 beats/min, a respiratory rate greater than 20 breaths/min or an arterial partial pressure of carbon dioxide less than 32 mmHg, and a leukocyte count less than 4,000 cells/mm^3 or greater than 12,000 cells/mm^3 or alternatively the presence of greater than 10 % immature neutrophils (band forms). The presence of the syndrome during the first 24 h of admission has high sensitivity (85 %) for predicting organ failure and death (100 %), but lacks specificity for severe disease (41 %). Specificity was found to increase with duration of the syndrome and those patients with a higher number of criteria on day 1 had an increased risk for severe disease [27].

Harmless Acute Pancreatitis Score

The HAPS was developed in Germany to define and evaluate a simple clinical algorithm to rapidly identify patients with a first attack of acute pancreatitis that do not require intensive care unit level of care (Table 7.6). The score can typically be calculated within 30 min of admission and takes into account three parameters: lack of rebound tenderness or guarding, normal hematocrit, and normal serum creatinine. The prospective study included a cohort of 394 patients, and the score was later validated using a cohort of

Table 7.6 HAPS

Criteria	Use	Advantages	Disadvantages	Score cutoff
Abdominal tenderness, hematocrit (>43 mg/dL for men or >39.6 mg/dL for women), creatinine (>2 mg/dL)	Within 30 min of admission	Simple, high accuracy rate	Provider acceptance	Presence of all three criteria indicates severe disease

Table 7.7 POP

Criteria	Use	Advantages	Disadvantages	Score cutoff
Age, MAP, PaO_2:FiO_2, arterial pH, BUN, calcium	Within first 24 h	Increased sensitivity	Burdensome to calculate	Score from 0 to 40 which correlates with a % mortality

452 patients [29]. The score was able to identify a harmless course in 200 of 204 patients (98 %), and in both the initial and validation study, the HAPS score correlated with a non-severe disease course ($P < 0.0001$). Another study in Sweden looked to evaluate the reproducibility of this scoring system outside of the original study. Five hundred thirty-one patients with acute pancreatitis were included; of the 353 patients who had a HAPS score calculated, 79 were predicted to have a non-severe course [30]. Only 1 of 79 developed severe acute pancreatitis. The validation study found the HAPS score to have high specificity 96.3 % (95 % CI 93.1–100) for predicting a non-severe course of acute pancreatitis and a PPV of 98.7 % (95 % CI 93.1–100) [30]. The score seems to be advantageous in its simplicity, time of administration, and accuracy rate. However, it seems unlikely that providers will accept this score as the sole measure in their clinical practice to triage patients into severe and non-severe cases.

Pancreatitis Outcome Prediction Score

Another study that sought to develop a new and more sensitive outcome prediction score was based on 159 intensive care units in the United Kingdom and included 2,462 patients with severe acute pancreatitis [4]. This retrospective cohort study developed the POP score, which is a composite of demographic, physiologic, and biochemical data collected within the first 24 h of ICU admission (Table 7.7). The score consists of six variables—arterial pH, age, BUN, mean arterial pressure, PaO_2/FiO_2 ratio, and total serum calcium (listed in order of decreasing impact). These six factors were used to develop this multivariate prognostic score, which ranges from 0 to 40 points. In comparison to other prognostic models, the AUC (95 % confidence interval) of the final score in all admissions was 0.853 (0.838–0.866) compared with 0.670 (0.651–0.688) for the seven available modified Glasgow criteria and 0.804 (0.787–0.820) for the APACHE II score [4]. Though these initial results found the POP score to be statistically superior to other models, calculation of the score seems much more burdensome and further validation studies are needed.

Panc 3 Score

The Panc 3 score was developed for the Emergency Room setting to allow for rapid and accurate prediction of severity on presentation of acute pancreatitis (Table 7.8). The three risk factors used in this score included a serum hematocrit greater than 44 mg/dL, a BMI greater than 30 mg/kg, and a chest X-ray which revealed a pleural effusion [31]. Test-operating characteristics and likelihood ratios were computed for each risk factor using the patients originally sampled in each of the studies ($n = 393$) and for validation, the study examined the score's ability to predict severe acute pancreatitis among 238 patients at University of North Carolina at Chapel Hill (UNC) hospitals. Analysis revealed that the Panc 3 score is easy to use and accurate for the

Table 7.8 Panc 3

Criteria	Use	Advantages	Disadvantages	Score cutoff
Hematocrit (>48 mg/dL), BMI (30 kg/m^2), pleural effusion	Use on admission	Easy to use, accurate	Needs validation	Presence of all three criteria indicates severe pancreatitis

Table 7.9 JSS

Criteria	Use	Advantages	Disadvantages	Score cutoff
Prognostic criteria: base excess (≤3 mEq/L), PaO_2 (≤60 mmHg or respiratory failure), BUN (≥40 mg/dL) or Cr (≥2 mg/dL), LDH (≥2 × upper limit of normal), platelet (≤100,000 mm^{-3}), calcium (≤7.5 mg/dL), CRP (≥15 mg/dL), SIRS (≥3), age (≥70 years)	At admission and at 48 h	Well established	Cumbersome	Severe pancreatitis if ≥3 of nine prognostic criteria
CT grade (contrast):			Takes 48 h to calculate	CT grade:
1. Extrapancreatic progression of inflammation: Anterior pararenal space: 0 point Root of mesocolon: 1 point Beyond lower pole of kidney: 2 points				1 + 2 = total score Total score = 0 or 1, Grade 1 Total score = 2, Grade 2 Total score = 3 or more, Grade 3
2. Hypoenhanced lesion of the pancreas Localized in each segment or only surrounding the pancreas: 0 point Extends to two segments: 1 point Occupies ≥2 whole segments: 2 points				CT grade ≥2 severe pancreatitis

prediction of severe acute pancreatitis. In the validation set of data, when all three of these findings were present and the pretest probability of pancreatitis was between 12 and 25 %, the post-test likelihood of severe disease was 99 %. Furthermore, the serum hematocrit was also identified as the strongest predictor of severe disease [31].

Japanese Severity Score

The original Japanese severity scoring system (1999) incorporated 18 prognostic factors, which made the assessment extremely complicated (Table 7.9). Furthermore, the CT grades included in the scoring system were based on plain CT and thus did not accurately reflect the prognosis of acute pancreatitis. For this reason, the scoring system was revised in 2008. In the New Japanese criteria, severity assessment can be made according to both prognostic factors and the contrast-enhanced CT grade. Prognostic factors consist of the following nine items: (1) base excess (BE) ≤3 mEq/L or shock: (systolic blood pressure ≤80 mmHg), (2) $PaO_2 \leq 60$ mmHg (room air) or requiring respirator management, (3) BUN ≥ 40 mg/dL (or creatinine [Cr] ≥2.0 mg/dL) or oliguria after fluid replacement, (4) lactic dehydrogenase (LDH) ≥2 times of upper limit of normal, (5) platelet count ≤100,000 mm^{-3}, (6) Ca ≤ 7.5 mg/dL, (7) C-reactive protein (CRP) ≥15 mg/dL, (8) number of positive measures in SIRS criteria ≥3, and (9) age ≥70 years [32]. Patients who satisfy three or more of the nine items are assessed as having severe acute

pancreatitis. The contrast-enhanced CT grade incorporates the extent of extrapancreatic progression of inflammation and of hypoenhanced area of the pancreas that suggests the presence of ischemia or necrosis. A CT grade of 2 or higher indicates a severe case of pancreatitis [32]. The predictive value of the revised JSS was validated in a large scale study in Japan including 17,901 patients which were able to show a significant increase in the odds ratio for mortality with increasing prognostic factor score. Area under the ROC was 0.798 (95 % confidence interval 0.775–0.821). Thus, the prognostic score factor was found to have good predictive value for in-hospital mortality in acute pancreatitis. The score is pretty well established like many of the other scoring systems, but is quite cumbersome and difficult to calculate quickly at the bedside. Furthermore, many of the prognostic criteria are labs that do not result immediately and the score can thus take up to 48 h to calculate.

Overall Comparison of Clinical Scores

A recent study compared these nine existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Clinical data were collected from two prospective cohort studies, a training cohort from the Severity of Acute Pancreatitis Study conducted at University of Pittsburg Medical Center, and a validation cohort from Markers of Severity in Acute Pancreatitis study conducted at Brigham and Women's Hospital. Both centers utilized the same diagnostic criteria for acute pancreatitis and nine clinical scores were calculated at admission and at 48 h [33]. The scores included APACHE-II, BISAP, Glasgow, APS, JSS, Panc 3, POP, Ranson, and SIRS. The primary outcome measure was development of persistent organ failure which was defined as cardiovascular, pulmonary, or renal failure lasting for 48 h or more. A set of 12 predictive rules were developed that combined the various scoring systems in order of increasing complexity. The results showed that patients with organ failure had higher scores across all scoring systems compared to those without organ failure. Also, existing scoring systems showed moderate accuracy. The Glasgow score was found to be the best classifier at admission with AUC of 0.84 in the training cohort and 0.74 in the validation cohort. At 48 h, the best scoring system was JSS, with an AUC of 0.84 in the training cohort and 0.79 in the validation cohort. The study also found that serum levels of creatinine and BUN were similar in their ability to predict organ failure. The 12 predictive rules that combined scoring systems proved to increase accuracy to 0.92 in the training cohort and 0.84 in the validation cohort [33].

Imaging-Based Prediction/Severity Scores

There have also been severity scores based on imaging findings in acute pancreatitis. For example, a CT severity score (the Balthazar score) was developed in 1990 and was based on a combination of CT grade of pancreatitis as well as peripancreatic inflammation, phlegmon, and degree of necrosis seen on initial CT [34]. Patients with grade A–E pancreatitis were assigned a score of 0–4 plus an additional 2 points for necrosis up to 30 %, 4 points for necrosis from 30 to 50 %, and 6 points for necrosis greater than 50 %. The study found that there was a 23 % mortality rate and an 82 % complication rate in patients with any degree of necrosis. However, in patients without necrosis, mortality rate was 0 % and complication rate was 6 %. Furthermore, the study found that serious complications occurred in patients with more than 30 % necrosis. Patients with a high CT severity index (score 7–10) had 92 % morbidity and 17 % mortality rate, whereas patients with a low CT severity index (2) had 2 % morbidity and no mortality [34]. A large retrospective study of 268 patients was performed and reported that a CT severity index of >5 strongly correlated with mortality ($P = 0.0005$), longer hospital stay ($P < 0.0001$), and need for necrosectomy ($P < 0.0001$) [7].

Routine Laboratory Tests

Many serum markers have also been identified as possible prognostic indicators for severity in acute pancreatitis, including serum hematocrit, creatinine, and BUN levels (Table 7.10). See also Chap. 4. Laboratory tests allow clinicians to monitor a patient's initial response to treatment. Several small studies suggested that hemoconcentration, or an elevated hematocrit at admission, was a predictor of pancreatic necrosis [35, 36]. One such study was a prospective cohort study by Brown and colleagues, which found that patients with more severe disease may show hemoconcentration with hematocrit values >44 %. The study also found that failure of this to decrease at 24 h was a good indication of pancreatic necrosis and predictor of organ failure [36]. However, the accuracy of hematocrit to predict pancreatic necrosis was not confirmed in several external validation studies [37–39].

Early changes in serum creatinine levels, specifically within the first 48 h, have also been associated with the development of pancreatic necrosis [40]. However, serial measurement of BUN levels seems to be the most useful laboratory test for determining death. A large retrospective cohort study looked at data from 69 hospitals and examined the relationship between early trends in BUN and hemoglobin [41]. Compared to five other laboratory markers that were examined (hemoglobin, calcium, leukocyte count, creatinine, and serum glucose), BUN had the highest area under the curve for predicting mortality at admission, at 24 h, and at 48 h [41]. The accuracy of measure serial BUN levels has been validated using data from three independent prospective cohort studies [42].

Inflammatory markers such as CRP have also been studied as potential predictors for the outcome of acute pancreatitis. CRP is an acute-phase reactant produced by the hepatocytes and its synthesis is induced by the release of interleukin-1 (IL-1) and 6 (IL-6). Serum CRP peaks on day 3 after the onset of pain and is a useful predictor of severity in acute pancreatitis 48 h after the start of symptoms but not in the early phases [43]. A systematic review showed that the sensitivity of CRP at 48 h for severe pancreatitis was 80 % with a specificity of 76 %, a PPV of 67 %, and a NPV of 86 %, which are comparable to other predictive scores [7]. The advantages of CRP measurement include its low cost and availability; however, its usefulness is limited by the poor predictive value during the initial phases of acute pancreatitis.

Many other serum markers such as procalcitonin, polymorphonuclear elastase, IL-6, and IL-8 have been identified as potentially valuable predictors of severity in acute pancreatitis [43]. Urinary trypsinogen-activation peptide (TAP) has also been shown to accurately predict severity of pancreatitis 24 h after symptom onset [44]. However, the use of these serum markers has been limited by their availability in North America.

The American Gastroenterological Association (AGA) has issued guidelines for

Table 7.10 Comparing serum markers

Laboratory tests	Use	Advantages	Disadvantages
Blood urea nitrogen	Level at admission and increase over 48 h	Accurate, inexpensive, widely available	Not specific to one disease process
Serum creatinine	Initial increase within 48 h predictor of severity	Inexpensive, widely available	Need 48 h to assess
C-reactive protein	Levels >150 at 48 h predictor of severity	Widely available	Peaks 48 h after onset of illness
Inflammatory biomarkers (procalcitonin, polymorphonuclear elastase, interleukins 6 and 8)	Higher levels associated with severity of outcome	High accuracy early in disease	Not widely available
Urine trypsinogen activating peptide	Urine spot measurement	High accuracy 24 h after symptom onset	Not commercially available

assessing the severity of pancreatitis. The recommendations start with the clinician and their ability to assess severity of disease by the presence of organ failure and local complications (pseudocyst, necrosis, or abscess). The AGA recommends the APACHE II score as the preferred predictor of severe disease (using a cutoff of ≥8) [45]. Those with actual or predicted severe disease and those with other severe comorbid conditions should be considered for triage to an intensive care or intermediate medical care unit. In patients with predicted severe disease (i.e., APACHE II score of ≥8) and those with evidence of organ failure within the initial 72 h, rapid-bolus CT should be performed after 72 h of illness to assess the degree of pancreatic necrosis. CT should be used selectively based upon clinical features in patients who do not meet these criteria. The guidelines also suggest that laboratory tests can be used as an adjunct to clinical judgment, multiple factor scoring systems, and CT to guide initial triage decisions. Of all laboratory tests, a serum CRP level of >150 mg/L at 48 h is preferred [45].

Fluid Sequestration

Many early studies seemed to suggest early and aggressive fluid therapy to improve clinical outcome in acute pancreatitis; however, more recent studies have failed to demonstrate improved outcomes and some have suggested potentially worse outcomes. Amount of fluid sequestration has been identified as another factor that may predict outcomes in acute pancreatitis. De-Madaria and colleagues collected data on 403 patients admitted at two different hospitals and the amount of fluid sequestered at 48 h was calculated by subtracting the total amount of fluid administered and lost during the first 48 h of hospitalization [46]. The study was also able to identify factors associated with increased fluid sequestration. Increased fluid sequestration was shown to be associated with pancreatic necrosis, acute fluid collections, persistent organ failure, and increased length of stay.

Conclusion

Diagnosis of pancreatitis has always been clinical and based on elevations in amylase and lipase; however, severity of elevation in pancreatic enzymes does not necessarily correlate with disease severity. Multiple scoring systems have been developed to predict severity in acute pancreatitis, some more cumbersome and accurate than others. As highlighted in the recent study by Mounzer and colleagues [33], the existing clinical scoring systems each performed with moderate accuracy in their ability to predict persistent organ failure. Their method of developing 12 predictive rules to combine these scores further improved the accuracy to predict severe pancreatitis; however, this method too is cumbersome and not easily applicable in clinical practice. Of the risk factors that correlate with severe disease, the ones that are simple and easy to obtain include BMI, age, hematocrit, BUN, and presence of pleural effusions on a chest X-ray. Furthermore, since hemoconcentration itself has been shown to be an accurate predictor of necrosis and organ failure, serial BUN measurements seem to be a valuable routine laboratory marker for following disease progression. It seems that many of the scoring systems will not consistently be accepted into clinical practice since most are quite cumbersome to calculate. Physicians will likely continue to utilize their clinical judgment and individual laboratory markers that are easy to obtain to assess severity in pancreatitis.

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Part III

Medical Management of Severe and Necrotizing Acute Pancreatitis

Fluid Resuscitation in Acute Pancreatitis

8

Kartik Sampath and Timothy B. Gardner

Introduction

Acute pancreatitis is a common inflammatory condition of the pancreas often resulting in considerable morbidity and mortality. Its incidence is increasing, with over 200,000 annual hospitalizations reported in the United States [1, 2]. In addition, despite the increasing disease incidence, the overall mortality rate from acute pancreatitis has remained at approximately 5 % [3–7].

In the past, several pharmacological therapies have been proposed for treating acute pancreatitis; however, the majority of medications have demonstrated no proven clinical benefit in randomized controlled trials. Agents directed at reducing pancreatic secretions, including histamine-2 blockers like cimetidine, glucagon, atropine, somatostatin and its analogue octreotide, do not reliably affect morbidity or mortality [8–12]. Antiprotease therapy with aprotinin and gabexate mesilate is equally ineffective, as is therapy with lexipafant, a platelet-activating factor antagonist [13–15]. Alternatively, there have been medications validated for preventing pancreatitis in susceptible populations; for example, the use of rectal indomethacin to prevent post-ERCP pancreatitis in high-risk patients [16].

Except in very specific circumstances, such as gallstone pancreatitis complicated by choledocholithiasis with subsequent biliary obstruction and need for early ERCP or proven infected pancreatic necrosis requiring antibiotic therapy and debridement, the overriding principle in treating inpatients with acute pancreatitis is supportive therapy [17, 18]. Timing and use of parenteral versus enteral feeding, preventing infected necrosis with the control of metabolic derangements, and therapy of late complications are all important components of management.

This discussion will focus on the role of fluid resuscitation in acute pancreatitis. There is universal agreement that fluid loss must be corrected to ensure optimal patient outcomes, especially early in the disease process. However, currently there are limited animal and few prospective human studies which have attempted to further define the role of fluid resuscitation in acute pancreatitis. For example, what is the optimal resuscitative fluid? Is there a role for colloid solutions? To what clinical marker should resuscitation be targeted? Which is the best time to start such fluids and in what group of patients?

In this review, the physiology of the pancreatic microcirculation and the pathophysiologic alterations that occur in acute pancreatitis will be

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highlighted. Animal studies addressing issues of fluid resuscitation will be discussed, as well as the current and future status of human trials. Finally, the article will highlight the updated current American College of Gastroenterology expert recommendations regarding fluid resuscitation. We hope that this review will provide a broad overview of this often overlooked topic and stimulate new interest and exploration into this important area of gastroenterology.

Search Methods

A Medline/PubMed search was performed with manual cross-referencing (January 1966–November 2013). Search topics included "fluid resuscitation and acute pancreatitis," "fluids and acute pancreatitis," "pancreatic microcirculation," "vascular anatomy of the pancreas," "pancreatic necrosis," "hemoconcentration and acute pancreatitis," and "acute pancreatitis." Recent technical guidelines from the major gastroenterology societies were also evaluated. Original papers and reviews were included. The English translation of all foreign language papers was used.

The Pancreatic Microcirculation

The arterial supply to the pancreas is derived from the two main proximal trunks of the aorta—the celiac trunk and superior mesenteric artery. The splenic and common hepatic arteries (as well as the left gastric artery which does not supply the pancreas) arise from the celiac trunk. The splenic artery gives rise to the penetrating branches of the body and tail of the pancreas, while the common hepatic artery, via its branch the gastroduodenal artery, supplies the pancreatic head through the anterior and posterior superior pancreaticoduodenal arteries. The anterior and posterior inferior pancreaticoduodenal arteries, arising from the superior mesenteric artery, supply the head and neck of the pancreas, and form vascular anastomoses with the superior pancreaticoduodenal arteries. This vascular network features extensive collateralization, thus ensuring adequate pancreatic tissue perfusion [19].

From these large arteries arise the interlobular arteries, which run within the pancreas often parallel to the pancreatic ducts. The interlobular arteries give rise to the pancreatic microcirculation, a vast network of capillaries and venules which supply the pancreatic acinus with a rich blood supply [20].

The basic microscopic vascular unit consists of an exocrine lobular plexus with multiple, fine capillaries that receive one or more vessels from the interlobular arteries [21]. The capillaries tend to vary in size, with the smaller diameter vessels displaying a preference for the central lobule. These capillaries are to a significant degree more permeable than end blood vessels in other organs, owing to a significant degree of fenestration [22].

The pancreatic islet cells receive the vast majority of the arterial blood supply, up to 20 times more than the acinus [23]. Since the capillaries first meet the islet cells and then extend to the acinus, the acinar cells are exposed to high levels of endocrine hormones. The pancreatic capillaries are highly permeable to allow integration of the endocrine and exocrine tissues, and are quite responsive to pro-inflammatory cytokines. For example, insulin has been shown to enhance pancreatic exocrine secretion, as has somatostatin. Thus, the endocrine hormones do appear to have a regulating effect on the exocrine pancreas, the so-called insulo-acinar interaction [24]. The major goal of this autoregulation is to sustain a constant level of pancreatic blood perfusion, with the lower limit of normal being 40 mL/min per 100 g of tissue [20].

Each lobular plexus then drains via one or more efferent venules to the interlobular veins. The interlobular veins drain into the portal system via the splenic and superior mesenteric veins. The venous blood flow then enters the portal circulation via the portal vein.

Acute Pancreatitis and the Pancreatic Microcirculation

Alteration to the pancreatic microcirculation plays a central role in the pathogenesis of acute pancreatitis. In fact, disturbed pancreatic microcirculation is an important step in the

transformation from acute self-limited (interstitial edematous) pancreatitis to severe, necrotizing pancreatitis [25–28]. Alteration in the pancreatic microcirculation can occur from one of several causes including hypovolemia, increasing capillary permeability, and hypercoagulability causing microthrombi, among others. The generation of oxidative-free radicals with subsequent capillary endothelial damage has also been implicated. This alteration in microcirculation increases the degree of pancreatic ischemia, irrespective of etiology, thus exacerbating the systemic inflammatory response syndrome and leading to multisystem organ failure.

In response to pancreatic acinar cell injury, multiple pro-inflammatory cytokines and vasoactive mediators, including tumor necrosis factor alpha, histamine, bradykinin, IL-1, IL-2, IL-6, platelet-activating factor, and endothelin-1, are recruited to the pancreatic microcirculation and delivered to the acinar cells [29–31]. One of the effects of this onslaught of inflammatory mediators is to increase the vascular permeability of the capillaries [32–37]. The decrease in endothelial tone causes significant extravasation of both interstitial fluid, leading to acute edematous changes around the acinus, and inflammatory cells [38]. The invasion of inflammatory cells into the acinar cell further perpetuates the degree of pancreatic damage. Once this damage to the pancreatic microcirculation has been initiated, it is very difficult to reverse the process, with, for example, aggressive fluid resuscitation [39].

In contrast to interstitial edematous pancreatitis, necrotizing pancreatitis results in a progressive reduction of the number of perfused capillaries following acinar cell injury [25, 40]. In rabbit models, this process can occur within 30 min of onset of acute pancreatitis, and by 3 h, only very limited circulation via single capillaries is often present [41].

In addition to increasing vascular permeability as a means of inducing pancreatic ischemia, capillary vasoconstriction has also been implicated. In a study of rats with sodium taurocholate-induced pancreatitis, arterial constriction of up to 79 % occurred within minutes of cellular injury [42]. Vasoconstriction thus appears to be an early event in acute pancreatitis, and there does not appear to be a correlation between total pancreatic blood flow and regional pancreatic perfusion [43].

Hypercoagulability leading to microthrombi formation also contributes to pancreatic ischemia and subsequent necrosis [44]. Levels of procoagulant factors such as fibrinogen, D-dimer, and platelets all are increased in acute pancreatitis, likely triggered by inflammatory mediators [45, 46]. The possibility of ischemia-reperfusion injury, with generation of free radicals within the microcirculation, has also been proposed as another detrimental event [47–49]. Support for free-radical injury as a pathophysiologic event in acute pancreatitis is provided by evidence showing improved outcomes in animal models using antioxidant therapy [50].

There are also profound disturbances in the larger pancreatic vessels, which can lead to downstream effects on the pancreatic microcirculation. Often this disturbance is secondary to arterial vasospasm, causing decreased perfusion of the pancreatic capillary bed. For example, Takeda et al. [51] demonstrated in 102 patients with acute necrotizing pancreatitis that vasospasm detected on angiography of the intrapancreatic and extrapancreatic arteries corresponded with the necrotic region of the pancreas. The extent of the ischemic change was correlated with the extent of the poorly perfused area of the pancreas and the subsequent mortality rate.

In summary, the capillary-rich pancreatic microcirculation plays a vital role in modulating the severity of acute pancreatitis. Decreased blood flow via increasing capillary permeability, vasospasm, and the formation of microthrombi has been implicated as a major contributor to the development of necrotizing pancreatitis.

Fluid Resuscitation and Acute Pancreatitis: Animal Studies

Multiple animal studies have addressed ways to combat increasing capillary permeability, vasospasm, and the formation of microthrombi through a variety of mechanisms including

endothelin and platelet activating factor receptor antagonists, IL-1 antagonists, ICAM-1 antibodies, somatostatin, bradykinin antagonists, TNF-α antagonists, heparin, and endothelial nitric oxide synthase among others [15, 30, 31, 52–60]. Investigators have also employed high-volume hemofiltration and other blood purifying techniques in an attempt to reduce circulating inflammatory mediators [61, 62]. For the purposes of this chapter, these studies will not be discussed. Instead we will focus on the limited animal studies, which specifically address fluid resuscitation, including those utilizing colloid solutions, as a means of maintaining pancreatic blood perfusion in acute pancreatitis.

The goal of intravenous fluid resuscitation in acute pancreatitis is to adequately perfuse the pancreatic microcirculation so that pancreatic necrosis and its subsequent complications can be minimized or even prevented [18, 63–66]. This is an essential component of treatment for this disease, irrespective of the degree of pro-inflammatory mediators involved in its pathophysiology. In fact, in a canine model it was demonstrated that the detrimental effects of acute pancreatitis on cardiovascular function are related solely to hypovolemia and reduced cardiac filling and not to humoral or reflex effects induced by the disease [67].

In two animal studies, fluid resuscitation without regard to type of fluid showed improvements in circulation and survival. Juvonen and colleagues, using a pig model of Na-taurocholate-induced pancreatitis, demonstrated that the signs of splanchnic hypoperfusion can be prevented with fluid resuscitation [68]. Pigs were divided into four groups: (1) pancreatitis, (2) control, (3) pancreatitis and fluid resuscitation to keep the pulmonary capillary wedge pressure at 5–6 mmHg, and (4) control and fluid resuscitation as in group 3. Splanchnic perfusion was assessed by means of the local PCO_2 gap with intestinal tonometer, oxygen delivery and consumption, lactate production, and blood flow. The investigators found that the PCO_2 gap increased and portal venous blood flow decreased in pigs with acute pancreatitis, but did improve significantly with resuscitation. Niederau et al. [69] has also demonstrated in a choline-deficient, ethionine-supplemented diet mice model that hydration by subcutaneous fluid markedly improved survival and normalized the hematocrit without having significant biochemical or morphologic alterations.

Crystalloid resuscitation has been studied only sparingly in animal studies of acute pancreatitis. Knol et al. [70] evaluated the effect of low and high infusion rates of lactated Ringer's solution in 14 dogs with bile-trypsin pancreatitis. They found that pancreatic blood flow decreased to a greater extent in the low infusion group compared to the high infusion group. Similar findings were found in pancreatic oxygen consumption. However, vigorous fluid resuscitation did not completely reverse the pathologic process. Crystalloid resuscitation with a balanced salt solution adequately restored plasma volume, supported tissue perfusion, and prevented excessive hemodilution without detrimental effects on pulmonary pressures or oxygenation in a canine model of acute hemorrhagic pancreatitis [71]. Kerner and colleagues [33], using a rat model, demonstrated that pancreatic microvascular perfusion failure was aggravated by arterial hypotension but attenuated by treatment with high-volume crystalloid resuscitation.

Two studies using hypertonic saline have demonstrated benefit in acute pancreatitis [72, 73]. Using intraperitoneal injection of 20 % L-arginine, acute pancreatitis was induced in 32 Sprague–Dawley rats. The rats were divided into four groups of eight animals each: (1) controls, (2) pancreatitis without intervention, (3) pancreatitis plus intervention with 0.9 % normal saline 2 mL/kg at 24 and 48 h, and (4) pancreatitis plus intervention with 7.5 % hypertonic saline 2 mL/kg at 24 and 48 h. The results demonstrated that animals who received hypertonic saline showed significantly less pancreatic damage (acinar loss, inflammatory infiltrate, fibroblast proliferation, adipose involvement) than those animals treated with normal saline and those without fluid intervention [72]. Intratracheal hypertonic saline has also been shown to mitigate the neutrophil-mediated pulmonary insult subsequent to pancreatitis by the same investigators [73].

The majority of animal studies dealing with fluid resuscitation have used colloid solutions, most notably dextran, and generally found improved outcomes compared with crystalloid resuscitation. One suspected reason for improved outcomes with colloids has been that they are not as permeable to leakage in the pancreatic microcirculation compared with crystalloids. By remaining in the luminal environment, circulatory blood flow is better maintained, and inflammatory mediators are less able to access the acinus. Schmidt et al. in 1993 compared 46 ceruleinic-pancreatitis rats who received intraaortic bolus infusions (2 mL/kg) of either lactated Ringer's, 7.5 % sodium chloride and 10 % dextran 60,000, 7.5 % sodium chloride and 10 % dextran 500,000, or 0.9 % sodium chloride and 10 % dextran 500,000 at 30, 60, 80, and 150 min after induction of pancreatitis. The investigators found that mortality rates, histopathologic scores for acinar necrosis, and pathologic activation of trypsinogen were significantly lower in the high-dose dextran groups [74]. A follow-up study performed by the same group in 70 Wistar rats using six different dextrans compared with lactated Ringer's alone verified these findings [75]. Multiple other investigators have additionally demonstrated the beneficial effect of various dextran formulations on the outcomes in acute experimental pancreatitis [76–80].

Alternative types of infusions have also been employed. Purified bovine hemoglobin, a hemoglobin-based oxygen carrier, was demonstrated to improve pancreatic microcirculation assessed by leukocyte adherence and decrease tissue damage compared with normal saline in a rodent model [26, 81]. In addition, fresh frozen plasma in a rat model given in a continuous infusion did improve 72-h survival compared to crystalloid and colloid in acute hemorrhagic pancreatitis [82].

This expands to concepts of rates of fluid administration, duration of fluid administration, and furthermore what type of fluid is most opportune for these patients. Recent studies over the past 5 years have been conducted to attempt to address these issues.

Fluid Resuscitation and Acute Pancreatitis: Human Studies

Despite the universally accepted paradigm that aggressive resuscitation is critical for the treatment of acute pancreatitis, few human studies have addressed the specifics related to optimal fluid administration. Recently, there have been published human studies which sought to evaluate specific fluid resuscitation strategies, including the most appropriate prognostic biomarkers of adequate fluid resuscitation, the optimal volume of fluid resuscitation, the optimal type of fluid (colloid vs. crystalloid vs. other), the optimal timing of resuscitation in the course of pancreatitis, and finally prognostic markers for complications secondary to resuscitation.

The importance of aggressive fluid resuscitation has received increased attention based on the work by Banks and colleagues who have stressed the role of early and/or sustained hemoconcentration in predicting poor outcomes. The original study found that hemoconcentration with an admission hematocrit ≥47 % or failure of admission hematocrit to decrease at approximately 24 h was strong risk factors for the development of pancreatic necrosis [83]. Multiple subsequent studies have validated these findings, although the ability of an elevated admission hematocrit to predict necrosis and/or organ failure has not been shown to be as robust as in the original Banks paper [84–87].

The Banks group did perform a retrospective study to determine whether fluid resuscitation could prevent pancreatic necrosis among patients with hemoconcentration at the time of admission [88]. In 39 patients, they found that while fluid resuscitation with crystalloid solution was not shown to prevent necrosis, all patients with inadequate fluid resuscitation as evidenced by persistence of hemoconcentration at 24 h developed necrotizing pancreatitis. In a retrospective study published only in abstract form, under resuscitation, especially early in the hospital course, has been blamed for the failure of acute pancreatitis mortality to significantly decline in recent decades [89].

One retrospective evaluation of 99 patients with severe acute pancreatitis in Sweden determined that patients receiving 4,000 mL or more of fluids during the first 24 h ($n=32$) developed more respiratory complications (66 % vs. 53 %; $P<0.001$) as compared to patients who received less than 4,000 mL of fluid [90]. Need of intensive care was also more common in the group with higher volume replacement during the first 24 h after admission (47 % vs. 20 %; $P<0.001$). The fluid supply mainly consisted of crystalloids during the first 24 h, but within the first 72 h, 56 % (51/91) of the patients received both crystalloids and colloids and the most frequently administered colloid was albumin ($n=27$). There was no ascribed difference in patient outcomes based on the extent of fluid resuscitation. Mao and colleagues have also reported improved survival rates by controlling the amount of fluid resuscitation within the first 72 h in 83 patients with severe pancreatitis [91].

De-Madaria and colleagues performed a prospective cohort study, consisting of 259 patients, investigating fluid administration amount over the first 24 h and outcomes including persistent organ failure, and acute fluid collections [92]. Cohort patients were retrospectively stratified into subgroups including the low-volume group (receiving less than 3.1 L), intermediate-volume group (3.1–4.1 L), and a high-volume group (receiving greater than 4.1 L). The intermediate fluid resuscitation group had the best overall outcomes. The low-volume group comparatively had a moderately lower organ failure risk (OR 4.1). Conversely, the high-volume group was noted with the highest risk for persistent organ failure (OR 9.1) and acute collections (OR 2.3). We suspect these results carry an inherent bias due to severe pancreatitis associated with oliguria and hypotension, respectively, requiring aggressive fluid administration. Further sub-analysis revealed patients with SIRS had increased risk for persistent organ failure (OR 5.4) and acute fluid collections (OR 3.2). Hemoconcentration was also associated with an increased risk for developing fluid collections (OR 3.0).

With regard to fluid type and outcomes, a phase-1 study evaluated 13 patients with severe, non-biliary pancreatitis who underwent isovolemic hemodilution exchange with 6 % dextran 60 [77]. Independent from the exchange, patients received lactated Ringer's solution to maintain a CVP at 6 ± 2 mmHg. Whole blood (750–1,500 mL) was exchanged for dextran 60 over a period of 45–75 min and hematocrit was maintained at a mean of 30 % via autotransfusions of packed red cells. Patients were evaluated with CT scans for necrosis. The authors concluded that the procedure was safe, and two patients required surgical necrosectomy and one patient died. Interestingly, 10 of the 13 patients indicated pain relief during hemodilution in the absence of specific analgesics, which the authors felt could be explained by improvements of pancreatic perfusion at the time of hemodilution.

Only one other human study using dextran in acute pancreatitis has been reported. Wang and colleagues in China evaluated 32 patients with severe acute pancreatitis who were treated with 0.5–1 mg/kg day of dexamethasone for 3–5 days and 500–1,000 mL/day of dextran 40 for 7 days, in addition to standard therapy [93]. No control group was used. Of the 32 patients, 27 patients resolved with nonsurgical treatment, while 5 patients underwent necrosectomy, and 4 patients expired. The authors concluded that dexamethasone and dextran 40 block the pathologic process of severe acute pancreatitis through inhibition of inflammatory mediators and improvement of microcirculation disorders, respectively. A prospective study by Leese et al. enrolled 202 consecutive patients with acute pancreatitis and randomized two groups—one to receive 2 units fresh frozen plasma daily for 3 days, the other group to receive standard volume resuscitation. No difference in patient outcomes was reported [93].

As part of further investigation into fluid type, Wu and colleagues evaluated the efficacy of lactated Ringer's solution as the fluid option for treatment of acute pancreatitis. The utility of this fluid strategy may be related to the suspected complications of hyperchloremic non-anion gap acidosis from aggressive normal saline administration. Animal models study had investigated the role of increased systemic acidosis as a

predisposition to increased zymogen activation and accelerated risk for increased severity pancreatitis [94]. The concept to using a more pH-balanced solution may curb pro-pancreatitis processes, thus potentially improving clinical outcomes.

The 40 patient study represented a double-blinded randomized controlled study, with 4 treatment arms including: early goal-directed fluid therapy (defined as greater than one third of fluid within the first 24 h) versus standard fluid administration groups, which were further randomized to receive normal saline versus lactated Ringer's [94]. Major outcomes measured were 24-h SIRS criteria and serum CRP levels. Compared to the normal saline treatment arm, the lactated Ringer's treatment group was associated with SIRS frequency reduction, (84 % vs. 0 %, $P=0.035$). The lactated Ringer's treatment group also noted lower CRP levels (51.5 vs. 104 mg/dL, $P=0.02$). However, due to study size, the study goals were not achieved with regard to evaluating early goal directed versus standard fluid therapies. Furthermore, the study revealed significant reductions in acidosis as evidenced by bicarbonate serum levels. The study verified through a prospective randomized controlled trial approach the clinical utility of lactated Ringer's as the fluid type of choice for acute pancreatitis.

As aggressive fluid administration becomes well established, focus shifts towards the optimization of fluid administration rate. A retrospective study by Warndorf et al. in 434 patients sought to assess the efficacy of early fluid resuscitation on patient acute pancreatitis outcomes [95]. Patients were stratified into early (defined as greater than or equal to one third of total 72 h fluid resuscitation during the first 24 h) versus late fluid resuscitation. Primary outcomes assessed included SIRS frequency, organ failure, and death. Compared to late resuscitation, SIRS frequency was reduced at 24 h (15 % vs. 32 %, $P=0.001$), 48 h (14 % vs. 33 %, $P=0.001$), and 72 h of admission (5 % vs. 10 %, $P<0.05$). There was also a lower rate of admission to the intensive care unit (6–17 %, $P<0.001$) and reduced length of hospital stay (8 vs. 11 days, $P=0.01$). Subgroup analysis revealed pronounced improvement with acute pancreatitis in the interstitial state versus severe disease. Similarly, in patients with severe established disease, the authors concluded there is likely no significant role for aggressive fluid administration.

In contrast, a study by Mao et al. concluded that in patients with severe AP, rapid hemodilution was associated with increased sepsis and mortality [96]. The 115 patient prospective randomized controlled study with treatment arms consisting of rapid hemodilution defined as achieving an hematocrit less than 35 % within 48 h of admission, versus slow hemodilution defined as an hematocrit greater than 35 %. The results revealed early incidence of sepsis in the rapid hemodilution group (7.4–10.2 days), and over the first 28 days, the incidence of sepsis was higher in the rapid hemodilution group compared to slow hemodilution group (78.6 % 57.6 %). Overall survival rates were lower in the rapid hemodilutional group (84.7–66.6 %, $P<0.05$).

The study was performed to target a hematocrit lower than 35 % in the rapid hemodilution group and 35 % or higher in the slow hemodilution group over the first 72 h. In contrast to this approach, we recommend that fluid administration be adjusted and targeted not to a particular hematocrit level, but rather to target to more reflect fluid resuscitation markers such as adequate urine output; stabilization of blood pressure and heart rate; normalization of central venous pressure; and a modest decrease in hematocrit. Additionally In this study, fluids were administered over 72 h, with most of the fluid provided during the second 24-h period. As has been shown in our research, the best outcomes are obtained when more that one third of the 72-h fluid total is given in the first 24 h.

These recent studies indicate the utility of aggressive early fluid administration. The risks of this strategy relate to potential fluid sequestration and overload, which can lead to poor patient outcomes. In this regard, targeting aggressive fluid resuscitation to an ideal receiving target patient population would be beneficial. A retrospective study by De-Madaria sought to evaluate risk factors for fluid sequestration [97]. The 403 patient study revealed a median net 48-h fluid sequestration of 3.2 L. Regression model analysis revealed

association with younger age, alcoholic etiology, increased hematocrit, and SIRS associated with higher sequestration levels. Furthermore, elevated fluid sequestration was association with increased hospital stay, rates of fluid collection, and persistent organ failure. This study represents further progressive efforts towards ascertaining and developing individualized fluid resuscitation protocols for the purpose of optimizing safe and effective aggressive fluid administration in the context of acute pancreatitis management.

Current Clinical Recommendations

A summary of recommendations in regard to fluid resuscitation in acute pancreatitis from prominent recent review articles is highlighted in Table 8.1 based on studies referenced in Table 8.2. These studies in total serve to advocate for aggressive fluid administration during the first 24 h of acute pancreatitis admissions. Furthermore, they advocate the use of lactated Ringer's as the fluid of choice for resuscitation purposes.

The American College of Gastroenterology has provided recommendations regarding fluid resuscitation for acute pancreatitis in part due to the recently published human studies [98]. Current recommendations state that aggressive hydration with 250–500 mL/h of crystalloid solution should be provided for patients without cardiovascular or renal comorbidities. Furthermore, the most beneficial time of hydration is in the first 12–24 h of presentation, with little potential benefit after 24 h. Currently, there is a conditional recommendation to utilize lactated Ringer's as the fluid type of choice. Goals of fluid resuscitation should aim to decrease BUN, with reassessment every 6 h to gauge the efficacy of fluid administration.

A summary of recommendations in regard to fluid resuscitation in acute pancreatitis from prominent recent review articles is highlighted in Table 8.1.

Conclusion and Future Directions

Aggressive fluid resuscitation in acute pancreatitis is a universally recommended and accepted paradigm. Additionally, recent studies support the use of aggressive fluid administration within the first 24 h utilizing lactated Ringer's solution.

Table 8.1 Fluid resuscitation recommendations from recent reviews of acute pancreatitis

Author	Journal	Initial resuscitation recommendation[a]
Tenner et al. [98]	Am J Gastroenterol, 2013	Aggressive hydration (250–500 mL/h) Bolus administration for severe volume depletion Lactated Ringers preferred Target fluid resuscitation to BUN Assess fluid requirements within 6 h of admission, and for next 24–48 h
Talukdar et al. [99]	Curr Gastroenterol Rep, 2011	Early management of severe acute pancreatitis
Pandol et al. [29]	Gastroenterology, 2007	Severe volume depletion: 500–1,000 cm^3/h Non-pancreatic fluid loss: 300–500 cm^3/h No volume depletion: 250–350 cm^3/h
Forsmark et al. [100]	Gastroenterology, 2007	Vigorous fluid resuscitation Urine output ≥0.5 mL/kg body weight/h
Whitcomb [101]	New Engl J Med, 2006	Fluid bolus to achieve hemodynamic stability followed by 250–500 mL/h of crystalloid
Banks et al. [63]	Am J Gastroenterol, 2006	Aggressive IV fluid replacement
Vege et al. [102]	JAMA, 2004	Aggressive fluid resuscitation
Tenner [18]	Am J Gastroenterol, 2004	At least 250–300 cm^3/h for 48 h

[a]Assuming normal-sized individual without cardiac, pulmonary, or renal compromise

Table 8.2 Human fluid resuscitation studies in acute pancreatitis

Author	Journal	Title
De-Madaria et al. [97]	Clin Gastroenterol Hepatol, 2013	Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis
Warndorf et al. [95]	Clin Gastroenterol Hepatol, 2011	Early fluid resuscitation reduces morbidity among patients with acute pancreatitis
De-Madaria et al. [92]	Am J Gastroenterol, 2011	Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study
Wu et al. [94]	Clin Gastroenterol Hepatol, 2011	Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis
Wall et al. [103]	Pancreas, 2011	Decreased morbidity and mortality with acute pancreatitis related to aggressive intravenous hydration
Gardner et al. [104]	Pancreatology, 2009	Faster rate of initial fluid administration in severe acute pancreatitis diminishes in-hospital mortality
Eckerwall et al. [90]	Clin Nutr, 2006	Fluid resuscitation and nutritional support during severe acute pancreatitis in the past: what have we learned and can we do better?
Tenner [18]	Am J Gastroenterol, 2004	Initial management of acute pancreatitis: critical decisions during the first 72 h

As evidenced by recent human studies, unequivocal randomized studies related to fluid resuscitation will be a challenge, due to the varying severity of pancreatitis and subsequent individualized fluid requirements. Carefully designed large-volume human clinical trials using varying fluid solutions and rates, stratifying pancreatitis severity, identifying optimal target populations with emphasis on patient monitoring and safety should be conducted. Until these trials are completed, the optimal treatment recommendations and suitable patient populations with regard to fluid resuscitation will not be clearly defined.

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Antibiotic Therapy

9

Wesley Leung and Andres Gelrud

Introduction

Acute pancreatitis is a condition involving acute inflammation of the pancreas that results in considerable morbidity and 10–40 % mortality [1]. There are two major forms of acute pancreatitis: interstitial (about 80 % of cases) and necrotizing (about 20 %). Acute necrotizing pancreatitis usually runs a severe course and can be sterile or infected. Although patients with sterile pancreatic necrosis may have a severe course and die, infection of the nonviable necrotic pancreatic tissue usually portends a worse prognosis. Previous studies have shown that the extent and infection of pancreatic necrosis correlate with the development of organ failure and mortality in acute pancreatitis [2, 3]. The incidence of infected pancreatic necrosis (IPN) in patients with necrotizing pancreatitis has remained stable (around 30 %) during the last two decades [4, 5]. The peak incidence of infected necrosis is between 2 and 4 weeks after onset of disease [6] and is the cause of most of the late mortality during the course of acute pancreatitis [7].

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In addition to IPN, patients with acute pancreatitis may have extra pancreatic infectious complications such as pneumonia, cholangitis, bacteremia, and urinary tract infections that are often hospital-acquired. The early course of severe acute pancreatitis (SAP) may present with signs of systemic inflammatory response syndrome (SIRS): fever, leukocytosis, tachycardia, tachypnea and may be indistinguishable from infectious complications of pancreatitis or sepsis syndrome.

Given the poor prognosis of IPN, it would be helpful to be able to prevent it. Whether antibiotics can prevent IPN and can thus improve patient survival is controversial. In this chapter, we review the studies that have investigated which antibiotics penetrate sufficiently well into pancreatic necrosis and whether antibiotic treatment in patients with sterile and IPN is of clinical benefit.

Diagnosis of Infected Necrosis

The gold standard for the differentiation between interstitial pancreatitis and necrotizing pancreatitis remains contrast-enhanced computed tomography (CECT). See also Chap. 3. However, CECT is not always a helpful tool for diagnosing infection. Infected necrosis is typically suspected when there is persistent sepsis, new-onset sepsis, or progressive clinical deterioration (i.e., signs of sepsis) despite maximal support in the second phase of the disease, without another source of

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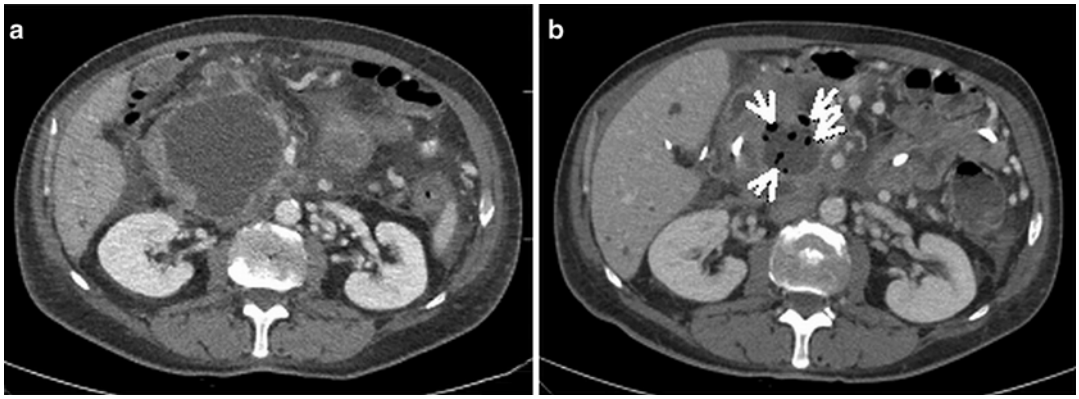

Fig. 9.1 A 67-year-old man admitted to the hospital with biliary pancreatitis. (**a**) Abdominal CT scan 2 weeks after presentation, based on pancreatic fluid collection a nasojejunal feeding tube was placed for enteral feeding. (**b**) Four weeks after initiation of jejunal feeding, patient called complaining of fever and diaphoresis for the past 2 days. Repeat CT scan revealed decreased size of the collection with extensive air bubbles (*arrows*). The patient was started on antibiotics and laparoscopically debrided

infection. A pathognomonic sign of infected necrosis is the presence of peripancreatic or intrapancreatic gas bubbles in a collection on CECT (Fig. 9.1), although this is present in only a minority of patients. Otherwise, there is no specific feature on CECT that is able to distinguish between infected or sterile necrosis. The gold standard for the detection of IPN is ultrasound-guided or CT-guided percutaneous aspiration of suspected pancreatic fluid collections with bacteriologic sampling (gram stain and cultures with sensitivity). The utility of this technique will be discussed later in this chapter.

Epidemiology

The microbial pathogens that cause IPN in necrotizing pancreatitis are predominantly gut-derived, including *Escherichia coli, Pseudomonas, Klebsiella,* and *Enterococcus*. Approximately 75 % of infections are monomicrobial. Fungal infection and infection with gram-positive organisms are uncommon but occur more frequently in the setting of prophylactic antibiotic use for SAP, especially when used for more than 10–14 days. The incidence of fungal infections in necrotizing pancreatitis is approximately 9 %, and it is not clear if this is associated with higher mortality [8].

Pathogenesis

Various theories have been proposed as to how pancreatic necrosis becomes infected. First, previous studies in SAP have shown gut mucosal defenses against bacterial translocation become impaired [9, 10]. Second, disturbed gastrointestinal motility may lead to bacterial overgrowth and failure of the structural mucosal barrier, which may lead to increased gut permeability. These events may result in the process of bacterial translocation—bacteria cross the gastrointestinal mucosal barrier and invade the systemic compartment [11, 12]. Bacterial translocation is thought to be the mechanism causing most infections in acute pancreatitis. Therefore, antibiotics aimed at preventing bacterial translocation and subsequent infections have been widely studied over the last two decades.

Pancreatic Penetration of Antibiotics

Because of the consistency of pancreatic necrosis, few antibiotics are able to penetrate the dead pancreatic tissue when given intravenously. However, antibiotics that effectively penetrate viable but not necrotic pancreatic tissue may at least achieve high microbicidal levels in adjacent tissues [13–15].

In addition, high circulating levels may also prevent infection via hematogenous and lymphatic routes [16]. Whether there is a benefit to a specific class of antibiotics has been extensively studied. Multiple studies have evaluated the penetration of antibiotics in the human pancreas with variable results [17–29]. Most studies utilized a parenteral route of antibiotic administration, which seems appropriate for a patient with acute pancreatitis. Eight studies measured the presence and concentration of the antibiotic in pancreatic secretions, obtained either on endoscopic retrograde cholangiopancreatography (ERCP) or after stimulation via a pancreatic fistula [17–23]. In the remaining studies, antibiotic concentrations were measured in pseudocysts [29] and pancreatic tissue [28]. Tissue samples were obtained from patients with different pancreatic diseases and different degrees of inflammation (acute pancreatitis, chronic pancreatitis, pancreatic carcinoma). Human studies have shown that the antibiotic concentration depends on the degree of inflammation, with higher levels in acute pancreatitis compared with controls [26].

Based on these studies, it is possible to classify antibiotics into three groups with regard to their efficacy in the pancreas: Group A, substances with low tissue concentrations that were below the minimal inhibitory concentrations of most bacteria found in pancreatic infection (aminoglycosidase, netilmicin, tobramycin); Group B, antibiotics with pancreatic tissue concentrations that were sufficient to inhibit some, but not all, bacteria in pancreatic infection (mezclocillin, piperacillin, ceftizoxime, cefotaxime); and Group C, substances with high pancreatic tissue levels, as well as high bactericidal activity against most of the organisms present in pancreatic infection (ciprofloxacin, ofloxacin, imipenem-cilastatin).

Preventing Infection in Sterile Necrosis

Experimental Studies

Various experimental studies using different animal models have investigated the effect of prophylactic antibiotics for the prevention of pancreatic infection in acute pancreatitis. Using a perfusion model in cats, Widdison et al. [30] studied the effect of cefotaxime, administered 12 h after the induction of acute experimental pancreatitis. Their group found cefotaxime reached bactericidal levels in pancreatic tissue and juice and significantly prevented pancreatic infection. The effect of piperacillin given immediately after experimentally induced acute pancreatitis in rats was studied by Araida et al. [31] and found a positive effect both on the infection and survival rate. The effect of intravenously administered cefotaxime and imipenem plus the effect of complete gut decontamination in a duct hyperstimulation model in the rat was studied by Foitzik et al. [32]. Neither treatment had a positive effect on survival. Pancreatic bacterial counts, on the other hand, were significantly reduced by imipenem, but not by cefotaxime. A study from the same group [37] and identical model investigated the effect of imipenem and ciprofloxacin but increased the antibiotic treatment from 4 to 7 days. An increased survival rate was observed in this study possibly related to increased duration of therapy. Both antibiotics reduced early and late septic pancreatic complications.

Human Studies

Over the years, there has been controversy surrounding the use of antibiotics in pancreatic necrosis. Three randomized studies were published in the 1970s, in which ampicillin or a placebo was given to less than 200 patients who had acute pancreatitis (only 1 patient died and 26 had infectious complications) [33–35]. All studies showed ampicillin had no beneficial effect on the clinical course of the disease [33–35]. For many years, this conclusion led to the impression that antibiotic prophylaxis was of no benefit in pancreatitis. However, these studies had various limitations. First, ampicillin has a modest activity against Gram-negative microorganisms, which are common in pancreatic infection. Second, ampicillin achieves poor penetration in pancreatic tissue [36] and in pancreatic fluid [18]. Third, the severity of acute pancreatitis in these studies

was low [33–35], resulting in insufficient statistical power [16].

Since the 1990s, there have been numerous prospective, randomized trials that have evaluated the use of prophylactic antibiotics in SAP. Unfortunately, the design, methodological quality, and most importantly, outcome of the included studies vary widely [37]. An attempt to summarize these studies in a systematic review (from 2006) concluded prophylactic antibiotics decreased mortality in severe pancreatitis, but not the rate of IPN [38].

However, more updated meta-analyses (from 2010) did not demonstrate a significant beneficial effect of antibiotic prophylaxis (except when imipenem was used) on infection of pancreatic necrosis and mortality [39, 40] with the number needed to treat of 1,429 for one patient to benefit [41]. It remains uncertain if a subgroup of patients with SAP (such as extensive necrosis with organ failure) may benefit from antibiotics, but large studies with sufficient statistical power required to determine whether any benefit exists will be difficult to perform.

Based on the current literature, use of prophylactic antibiotics to prevent infection in patients with sterile necrosis (even predicted as having severe disease) is not recommended. In addition, current guidelines do not recommend routine antibiotic prophylaxis [42, 43]. Overall, there has been a decrease in incidence of infected necrosis among patients even in the placebo arms of trials (15–20 % of cases with necrosis), consistent with findings from contemporary cohort studies [44]. Further casting doubt on the benefit of prophylactic antibiotics is recognition that it can be associated with the selection of resistant organisms and the development of fungal infection [45–47].

Prevention of Fungal Infections

Prevention of fungal infections in patients with sterile pancreatic necrosis is also not recommended. Although it was suggested that fungal infection may be a more common cause of mortality in acute pancreatitis, further study has not confirmed this finding [48]. It is unclear if the mere presence of candida within pancreatic necrosis indicates only colonization. Furthermore, candida infection may go unrecognized and untreated due to false negative microbiological sampling.

Gut Decontamination and Probiotics

There is one successful randomized controlled, clinical trial that used selective decontamination of the bowel, targeting both bacteria and fungi, in order to prevent infected necrosis [49]. Because of the decreased morbidity and mortality in this trial in patients with SAP who had undergone selective decontamination, further study in this area is needed. With regard to probiotics, they should not be given in SAP. Although earlier trials suggested a benefit, a very well-conducted, randomized controlled clinical trial demonstrated increased mortality [50]. This lack of benefit has also been shown in a recent meta-analysis [51].

Antimicrobial Therapy in Infected Necrosis

Rather than preventing infection, the role of antibiotics in patients with necrotizing pancreatitis is now to treat established infected necrosis, or to treat other hospital-acquired infections in these often critically ill patients. The dogma that IPN requires prompt surgical debridement has also been challenged by multiple reports and case series showing that antibiotics alone can lead to resolution of infection and, in select patients, avoid surgery altogether [52–55]. A study by Garg et al. reported 47/80 patients with infected necrosis over a 10-year period who were successfully treated conservatively with antibiotics alone [55]. The mortality in the conservative group was 23 % as compared with 54 % in the surgical group. The same group published a meta-analysis of eight studies involving 409 patients with infected necrosis of whom 324 were successfully treated with antibiotics alone [56]. Overall, 64 % of the patients with infected necrosis in this meta-analysis could be managed by conservative

antibiotic treatment with 12 % mortality, and only 26 % underwent surgery. Thus, a select group of relatively stable patients with IPN can be managed by antibiotics alone, without requiring percutaneous drainage. However, it should be cautioned that these patients require close supervision and percutaneous or endoscopic necrosectomy should be considered if the patient fails to improve or deteriorates clinically. We suggest using imipenem or meropenem for patients with suspected infected necrosis based on their high pancreatic tissue levels and bactericidal activity against most of the organisms present in pancreatic infection. Whenever clinically feasible, radiological, endoscopic, and surgical interventions for infected necrosis are postponed until there is sufficient encapsulation and demarcation of the infected peripancreatic or pancreatic collections, generally 4 weeks after onset of symptoms [57]. A discussion of these interventions is given in other chapters.

Role of CT-Guided FNA

The technique of computed tomography-guided fine needle aspiration (CT FNA) has proven to be safe, effective, and accurate in distinguishing infected and sterile necrosis [43, 58]. As patients with either infected necrosis or sterile necrosis may present similarly with leukocytosis, fever, and organ failure [59], it is impossible to separate these entities without needle aspiration. Historically, the use of antibiotics is best established in clinically proven pancreatic or extrapancreatic infection, and therefore CT FNA should be considered when an infection is suspected. An immediate review of the Gram stain will often establish a diagnosis. However, it may be prudent to begin antibiotics while awaiting microbiologic confirmation. If culture reports are negative, the antibiotics can be discontinued.

There is some controversy as to whether a CT FNA is necessary in all patients. Although use of CT FNA is recommended in some guidelines [42] and complications such as bleeding and exacerbation of acute pancreatitis are rare [60, 61], CT FNA is performed only in a minority of centers. To assess compliance with guidelines in Germany, for example, only one third of senior gastroenterologists said that they used the procedure [62]. In addition, FNA is associated with a risk of false-negative results, since a negative fine-needle aspiration does not confidently exclude infection [63]. Finally, in many patients, the CT FNA does not influence the management in patients with suspected infected necrosis [64]. Increased use of conservative management and minimally invasive drainage has decreased the use of FNA for the diagnosis of IPN [65]. Many patients with sterile or infected necrosis either improve quickly or become unstable, and decisions on intervention via a minimally invasive route will not be influenced by the results of the aspiration. A consensus conference concluded that FNA should only be used in select situations where there is no clinical response to antibiotics, such as when a fungal infection is suspected [65].

Therapy for Extrapancreatic Infections

Extrapancreatic infections such as bloodstream infections, pneumonia, and urinary tract infections occur in up to 20 % of patients with acute pancreatitis and increase mortality twofold [57, 66]. If sepsis is suspected during the course of pancreatitis, it is reasonable to start antibiotic therapy while waiting for culture results. If culture results are negative, then antibiotics should be discontinued to reduce the risk of fungemia, or *Clostridium difficile* infection.

Conclusion

Management of infectious complications of SAP remains complex and challenging despite major advances in the field over the last two decades. In summary, quinolones and carbapenems are the antibiotics with optimal pancreatic tissue penetration and bactericidal activity against most of the organisms present in pancreatic infection. With regard to prevention of infection of necrosis, routine antibiotic or probiotic prophylaxis is

not recommended. In cases of suspected IPN or sepsis, antibiotic therapy should be initiated while the source of the infection is being investigated [51]. However, once blood and other cultures are found to be negative and no source of infection is identified, antibiotics should be discontinued. A select group of relatively stable patients with IPN can be managed by antibiotics alone without requiring percutaneous drainage or necrosectomy. However, these patients should be closely monitored for failure to improve or clinical deterioration, in which case more aggressive therapy will be warranted.

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Nutrition in Severe Acute Pancreatitis

10

Kishore Vipperla and Stephen J. O'Keefe

Introduction

A variety of factors such as alcohol and gallstones predispose to the premature activation of the pro-enzymes within the acinar cells in the genetically susceptible individuals causing enzymatic destruction of pancreatic tissue or "autophagia" and inflammation known as acute pancreatitis (AP). AP represents a hypercatabolic metabolic state marked by high caloric and nitrogenous demand from the acute inflammatory and reparative processes. Nearly 80 % of AP patients have mild to moderate disease that resolves uneventfully within 3–5 days with bowel rest and supportive care, but ~20 % have severe AP (SAP) disease complicated by severe systemic inflammatory response syndrome (SIRS), multiorgan failure (MOF), and local complications such as necrotizing pancreatitis associated with mortality as high as 40 % [1]. Interestingly, while bowel rest is probably essential in the early treatment phase of SAP, delay in enteral feeding of these very sick patients is associated with increased morbidity and mortality, possibly because of complications arising from gut stagnation. Better understanding of the underlying pathophysiologic mechanisms and the unique nutritional challenges faced during the treatment of the SAP patients is crucial to provide the essential nutritional support; preserve the gut function and splanchnic metabolism; and potentially modulate the systemic inflammatory response through enteral feeding.

Physiology of Pancreatic Secretion

Proteolytic enzymes synthesized within the pancreatic acinar cells are secreted in their inactive forms (e.g., trypsinogen) that are activated in the intestinal lumen by the enterokinase, an intestinal brush border peptidase. Pancreatic juice is secreted at a basal rate (~20 %) and further stimulated by meals (~80 %) in three interrelated phases: cephalic, gastric, and intestinal phases [2]. In the "cephalic phase" mere sight of food, chewing, and swallowing cause pancreatic secretion mediated by direct vagal cholinergic stimulation of the acinar cells. In the "gastric phase" mechanical distention caused by the ingested food provides a major stimulus for pancreatic enzyme

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secretion in addition to the gastric acid secretion mediated by a gastropancreatic vagovagal reflex. Finally, in the "intestinal phase" passage of acidic gastric contents through the pylorus incites the maximal stimulatory phase of pancreatic secretion mediated by complex neural (cholinergic excitation of the entero-pancreatic reflex) and humoral (cholecystokinin [CCK] and secretin) pathways. CCK is released from the duodenal I-cells in response to peptides, amino acids, and fatty acids that are present in the chyme and is mediated by vagal neurotransmitters such as acetylcholine, gastrin-releasing peptide (GRP), and vasoactive intestinal peptide (VIP). Secretin is released by the duodenal mucosa in response to the acidic chyme and is the major mediator of pancreatic water and bicarbonate secretion. Importantly, when the undigested nutrients reach the terminal ileum pancreatic secretions are suppressed through a negative-feedback mechanism known as "ileal brake" that is mediated by the release of enteroendocrine gut peptides such as glucagon-like peptide-1 (GLP-1) and peptide-YY (PYY) [3]. Importantly, the rate of gastric emptying and duodenal delivery of nutrients, as well as their physicochemical characteristics (i.e., the proportion of fat, carbohydrate, and protein content), determine the duration and composition of the pancreatic secretory response.

Pathophysiology of Acute Pancreatitis

The inflammatory cascade of events in AP is believed to be triggered by the intracellular influx of calcium with inappropriate activation of the pancreatic zymogen (pro-enzyme) resulting in pancreatic parenchymal proteolysis or "autophagia" [4]. Pancreatic acinar cell injury results in activation of the periacinal myofibrocytic nuclear factor-kappa B (NF-κB) and mitogen-activated protein (MAP) kinase pathways that generate a flood of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins (IL)- IL-1b, IL-17, and IL-18 [5]. Subsequent IL-6 release and cytoattraction of neutrophils amplify this cytokine cascade. Activation of one of the cytokines, endothelin-A, causes arterial vasoconstriction and ischemic death of pancreatic as well as the intestinal tissue [6]. The fluid sequestration or "third spacing" secondary to pancreatic inflammation decreases the intravascular volume compromising tissue perfusion and microcirculation that further exacerbates the ischemic injury. Besides the local inflammation in the pancreatic bed, the proinflammatory cytokines released into the blood circulation can cause systemic inflammation and organ failure. The consequent SIRS escalates and manifests as acute respiratory distress syndrome (ARDS, from bronchial mucosal injury) and bowel ischemia that compromises the gut mucosal defense barrier causing bacterial translocation and systemic infections. To make matters worse, prolonged fasting can be detrimental as lack of luminal nutrients further aggravates the already disturbed gut function and splanchnic metabolism.

Nutritional Support in AP

The initial treatment of AP is focused on symptomatic control of nausea and abdominal pain using narcotic analgesics and antiemetic agents; aggressive fluid resuscitation and restoration of electrolyte balance; and initiation of specific treatment addressing the inciting etiological factor [7]. Nutritional support is a key supportive measure that serves two important purposes. First, nutrients provide the building blocks for the tissue repair and healing. Secondly, enteral nutrition can potentially improve the clinical outcomes of SAP by preserving the gut function and modulating the systemic inflammation and preventing organ failure, which are associated with high morbidity and mortality. The disease severity, determined by the severity and duration of symptoms, laboratory and radiographic evidence of organ failure, and stability of hemodynamic parameters, dictates the timing and mode of nutrition (Fig. 10.1). Most importantly, resting the bowel to avoid or minimize pancreatic secretion during AP has been the standard of care.

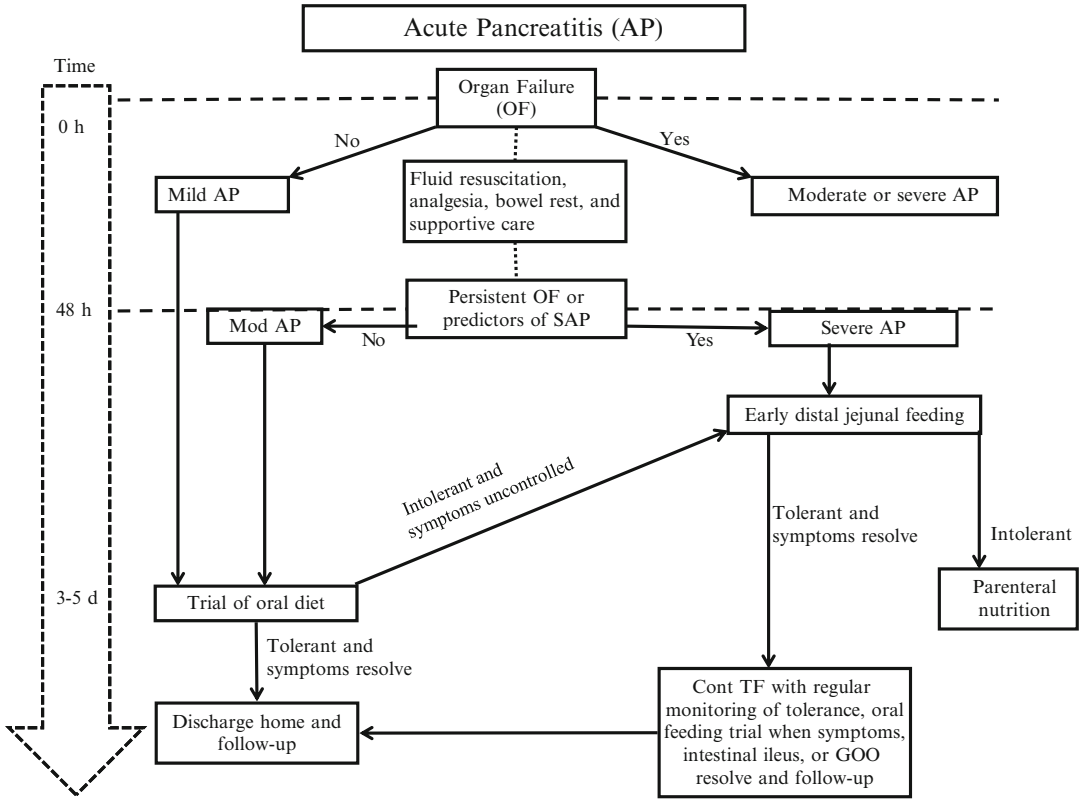

Fig. 10.1 Nutritional support in acute pancreatitis. Bowel rest is important during the first 48 h. Oral feeding can be initiated at 3–5 days in mild to moderate AP patients when symptoms resolve. Enteral feeding can be begun as early as 48 h after the initial resuscitation period in predicted severe AP patients in an effort to preserve gut mucosal function and splanchnic metabolism and modulate the inflammatory cascade to mitigate SIRS, OF, and high morbidity and mortality associated with severe AP

Nutrition can be held for up to a week without significant malnutritional consequence in patients with mild AP, but early enteral feeding should be started when AP is predicted to be severe or associated with complications such as necrotizing AP in order to sustain these profoundly catabolic hypermetabolic states and to maintain gut function and prevent ileus, stagnation, and bacterial overgrowth [8]. Risk stratification and prediction of severity of AP earlier in the course are very helpful in determining the timing and mode of nutritional support. Hence, the conventional practice of prolonged fasting patients with moderate to SAP for "pancreatic rest" has transformed into one where earlier enteral feeding is being advocated in anticipation of better clinical outcomes.

NPO-Pancreatic Rest

Nil per os (NPO) or bowel rest has been the cornerstone of AP treatment traditionally based on the assumption that ingestion of food stimulates pancreatic secretion and worsens leakage of enzymes that aggravate the pancreatic injury and inflammation [9]. Resting the pancreas is expected to decrease pancreatic secretion and mitigate the inflammation and pain, but strong evidence to prove the merits of the concept of "pancreatic rest" is lacking. On the other hand, AP is often associated with delayed gastric emptying and intestinal ileus that cause anorexia, abdominal pain, nausea, and vomiting that prevent the patient from tolerating oral fluids and diet.

However, depriving these patients of the essential nutrients during a highly catabolic process aggravates the nitrogen loss and is likely detrimental to the healing and repair of the inflamed pancreas. In addition, starvation compromises the mucosal integrity and promotes bacterial overgrowth due to diminished intestinal motility. An impaired mucosal defense barrier increases the gut permeability to inflammatory cytokines and intestinal bacterial translocation that worsen the SIRS. The fact that the enteric microorganisms are commonly isolated from infected pancreatic necrosis further underscores the risk of early bacterial translocation in AP. Unfortunately prophylactic antibiotics have not proven to be effective in decreasing the infection risk. Hence, oral or enteral nutritional support should be provided as soon as possible to preserve the gut function.

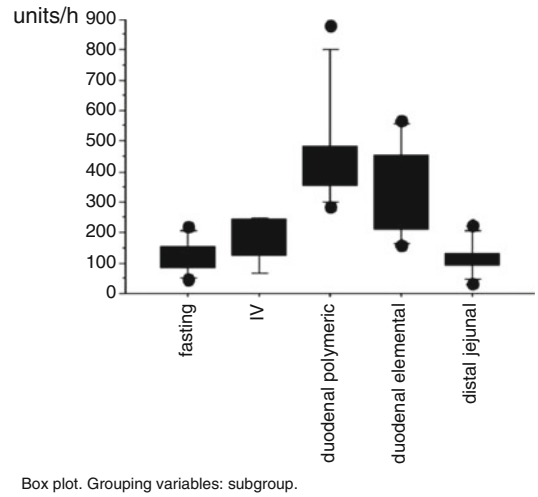

Fig. 10.2 The effect of site of nutrient delivery on trypsin secretion. Reprinted with permission from from O'Keefe S. Physiological response of the human pancreas to enteral and parenteral feeding. Curr Opin Clin Nutr Metab Care 2006; 9(5)

How Can We Safely Rest the Pancreas?

The pancreas continues to produce "basal secretion" that is rich in bicarbonate and fluid by volume and poor in protein enzyme output during an AP episode in spite of absolute bowel rest. An ideal nutrition support for AP should minimally stimulate pancreatic secretions or perhaps suppress them and yet be able to provide the required energy and protein. While only PN can completely avoid pancreatic stimulation, all forms of oral and conventional enteral feeding have been shown to stimulate pancreatic secretion to some degree in human studies [10]. The meal composition (i.e., proportion of fat, carbohydrate, and protein) and site of nutrient delivery influence the composition and duration of pancreatic secretion. High-fat diet stimulates pancreatic secretion through CCK and infusion of an elemental diet containing low fat and free amino acids was shown to reduce the pancreatic secretion by ~50 % when compared to a polymeric diet containing intact protein [10]. Trypsin secretion was shown to be lower with increasing distance of the tip of the feeding tube from ligament of Trietz (LOT) favoring distal jejunal feeding over gastric feeding for the least stimulation of pancreatic secretion (Fig. 10.2) [11]. Infusion of enteral feeding into the mid-jejunum at 60 cm distal to the LOT has been shown to have no stimulatory effect on the pancreas when compared to the infusion in the proximal duodenum, which resulted in fourfold increase in basal trypsin secretion [12]. Bypassing the oral, gastric, and intestinal phases of pancreatic secretion probably explains the lack of stimulatory effect of EN delivered to distal jejunum. Besides avoiding the stimulation of pancreatic trypsin secretion, delivery of EN into the mid-distal jejunum has been shown to activate the intestinal inhibitory peptide-mediated "ileal-brake" as evidenced by significantly elevated serum GLP-1 and PPY levels, but not CCK, as noted on measurement of these gut peptides in response to distal jejunal feeding [11]. These observations strongly support distal jejunal feeding as the most rational form of nutritional support in SAP.

Enteral Feeding

The concept of nutritional support in AP has evolved significantly in the past two decades with a growing understanding of early inflammatory mechanisms in AP and fascinating evidence on improved survival and reduced rate of complications with early initiation of oral or enteral feeding. Consequently, there has been a gradual shift in the treatment approach from recommendation of strict NPO to that of early EN with the expectation of being able to suppress the systemic inflammatory response. Sound evidence from several randomized controlled trials (RCTs) and meta-analyses comparing the outcomes of EN to PN in AP has clearly shown the superiority of EN in decreasing mortality, infectious complications rate, MOF, and length of hospitalization [13, 14]. The beneficial effects of EN have been ascribed to its ability to prevent mucosal atrophy and maintain the integrity of gut barrier. Avoidance of central venous access catheter-associated risks such as blood stream infections and vascular thrombosis, PN-related metabolic complications such as hyperglycemia, and importantly affordability of EN support at ~15 % cost of PN make EN a more attractive form of nutrition. EN was shown to be safe, effective, and even better in terms of mitigating the inflammatory effects of AP when compared to PN in mild-moderate as well as SAP [15, 16].

Route of EN

Severe abdominal pain, nausea, vomiting, and ventilator support requiring sedation in the ICU preclude oral feeding in patients with SAP. EN can be provided via nasogastric (NG), nasoduodenal, or nasojejunal (NJ) feeding. Gastric feeding is relatively easy and facilitates early enteral nutrition as nasogastric feeding tube placement is a simple procedure and can be performed at bedside. Eatock et al. and Kumar et al. have demonstrated in their RCTs that both gastric and jejunal feeding routes are well tolerated, and there was no significant difference between these groups in terms of mortality, length of hospital stay, infectious complications, or MOF [17, 18]. Eatock et al. compared the inflammatory responses and clinical course between NG versus NJ feeding of objectively graded SAP patients and found NG feeding as simple, cheap, and as good as NJ feeding as no significant differences were noted in the APACHE II scores, C-reactive protein levels, analgesic requirement, and mortality [17]. However, these studies failed to investigate the importance of pancreatic rest as both forms of feeding were stimulatory and positioning of the jejunal tube well down the jejunum was not proven. A systematic review noted nasogastric feeding to be safe and well tolerated with no difference in mortality or tolerance found between the NG and NJ groups, though it was acknowledged that a well-powered RCT is needed for a more conclusive and firm evidence [19]. However, the need for frequent gastric suctioning for delayed gastric emptying and/or gastric outlet obstruction from compression by duodenal swelling makes gastric feeding ineffective and even potentially dangerous by increasing the risk of aspiration of gastric contents. Further, the theoretical risk of pancreatic stimulation still exists with NG feeding.

Distal jejunal (DJ) feeding has been shown to be more effective than PN in delivering the nutrition and at the same time allowing the pancreas to rest [20]. In patients having gastric outlet obstruction from pancreatic inflammation or fluid collection related duodenal compression, a nasogastrojejunal (NGJ) tubing system, a double lumen tube with proximal gastric decompression, and distal jejunal feeding ports can be used to serve both the purposes without the need for two separate tubes [21]. When gastric decompression is not needed, a NJ feeding tube is usually placed under endoscopic or fluoroscopic guidance to infuse the nutrients far (~40 cm) beyond the LOT [22]. Only well-trained gastroenterologists or radiologists can place a NJ feeding tube successfully, which makes jejunal feeding a less readily available option with potential delays in "prompt or early" nutrition in some cases. In many centers, nasoduodenal feeding tubes are placed by

nursing teams, as the primary method of enteral feeding. Patients who require surgical intervention for AP-related complications could have a surgical enterostomy tube (jejunostomy) placed at the same time when the need for prolonged EN is anticipated.

Timing of EN (Window of Opportunity)

The first priority is to resuscitate the patient to maintain intravascular volume and prevent renal failure. Depending on the patient's preexisting nutritional state, nutritional support should not be delayed beyond 5–7 days of fasting to suppress severe net nitrogen losses, which can be as high as 20–40 g/day [23]. Evidence from studies on EN in critically ill patients with head injuries, burns, trauma, and postoperative and other non-pancreatitis-related medical problems have suggested benefits of reduced length of stay and delayed infectious complications when patients were fed within 36 h compared to those who received it after 36 h [24]. In a systematic review of RCTs comparing EN and PN in mild and SAP, significant differences between the two forms of feeding in terms of reductions in MOF, pancreatic infectious complications, and mortality were observed only in those who had their EN administered within 48 h of admission [25].

Although observational studies have shown that early enteral feeding is associated with better outcome, the best timing of enteral feeding in the AP patients has not yet been studied in large RCTs [8]. The current recommendation of "early EN" is based on the assumption of exploiting the "window of opportunity" during the initial course of disease when luminal nutrients reinforce the gut function and splanchnic metabolism to potentially ameliorate the SIRS [26]. It is still unclear whether interventional feeding is better than no feeding, or whether slow (trophic) feeding is as good as full feeding in the initial management, bearing in mind that most cases of SAP nowadays are obese [8].

Composition of EN

The average daily nutrition requirement in an adult is 25–35 kcal/kg of energy and 0.8–1.5 g/kg of protein. Despite the fact that the disease produces accelerated catabolism, there is no evidence that feeding at higher rates improves outcome, as energy stores in all but the previously malnourished can cover excess loss. Peptide-based formulas with low fat (long-chain fatty acids/LCFA) and isotonic solutions are ideally fed into the jejunum. Tube feeds are generally categorized into elemental, semi-elemental, and polymeric or standard formulas based on the characteristics of their individual carbohydrate, fat, and protein nutrient components. Elemental formula is a completely predigested formula consisting of amino acids, simple sugars, and essential fatty acids. Semi-elemental formula contains peptides, glucose polymers, and medium-chain triglycerides that are easier to digest compared to standard polymeric formulas, which contain non-hydrolyzed proteins, complex carbohydrates, and long-chain triglycerides. Earlier studies used (semi) elemental formulas based on the knowledge that they stimulate pancreatic secretions less than the polymeric formulas [27]. However, recent meta-analysis comparing polymeric and (semi) elemental feeds in patients with AP did not find any difference in the risk of intolerance to feeding, infectious complications, or death [28]. Despite these results, we prefer to use semi-elemental formulae because our studies have shown that pancreatic insufficiency can result from SAP and we want to ensure what is delivered is absorbed [27].

Tolerance of Tube Feeding

In general, enteral feeding is simple to use and safe. Although diarrhea is common in all ICU patients, EN is rarely the cause. Other medications such as antibiotics, sorbitol, and fiber deficiency are more common causes. Importantly, dysbiosis (disturbed microbiotal composition and their beneficial metabolites such as short

chain fatty acids) of the colonic microbiota as a result of fasting, use of proton-pump-inhibitors, and antibiotics is believed to be an important factor responsible for the diarrhea in these sick patients. Interestingly, diarrhea in the critically ill patients was shown to improve with fiber supplementation that had the potential to improve the microbial mass and function [29]. The other limitations of enteral feeding are intolerance and complications that are commonly associated with the feeding tube such as nasopharyngeal discomfort and mucosal erosions, otitis media, sinusitis, esophageal erosions, and acid reflux. In the case of NG feeding, gastric residual volumes (GRV) are measured every 4 h as a measure of tolerance to feeding. GRV <500 mL is an acceptable mark of continuation or advancement of rate of feeding, considering the significantly higher risk of aspiration noted beyond this mark [30]. The risk of aspiration, which is greater for NG than NJ mode of feeding, can be minimized by elevation of the head of the bed by 30–45º, confirmation of the position of the tip of the feeding tube by abdominal radiographs when dislodgement is suspected, gross inspection of the tracheal aspirates for presence of tube feeds in the intubated patients, and consideration of using a prokinetic agent (e.g., metoclopramide).

Maintenance of Tube Feeding

Certain maintenance and monitoring measures are paramount for the best performance of the feeding tubes. Nasal feeding tube must be secured properly using a device such as a "nasal bridle" to prevent accidental dislodgement. The tubes need to be flushed with 30 mL of tap water once every 4–6 h (now easily programmable on infusion pumps) to minimize the risk of clogging from congealed feed. Most importantly, the feeding tubes must be reserved for feeding. If alternative delivery is impossible, medications should be carefully administered as crushed or liquid preparations via the G-port, but should never be administered through the J-port. GRV should be <500 mL for medication deliver through the G-port. Kinking of the enteral feeding tube within the intestinal lumen can often present as "clogging" that does not respond to declogging maneuvers. Abdominal radiograph should be obtained to identify kinking that can be resolved by slowly withdrawing the J-tube until flow is restored.

Feeding must be initiated at a slow rate and then gradually advanced as tolerated. In either NG or NJ feeding, generally a liquid elemental nutrient formula can be initiated at 25 mL/h for the first 24 h, and then gradually advanced by 25 mL/h daily over the next 2–3 days to achieve the final goal rate calculated to provide 25 kcal energy/kg ideal body weight/day. Having said that, lower rates of feeding throughout the acute episode may be optimal, as it preserves gut function and reduces side effects. In the case of NGJ system, the gastric port (G-port) is connected to a low-pressure (50 mmHg) intermittent suction while feeding is started until the GRVs drop below 500 mL/4 h, whence the G-port can be clamped and monitored as described above.

Enteral feeding is continued until the patient's clinical condition improves and appetite returns. Tolerance of <10 % of the goal rate of feeding can be considered a failure of enteral feeding. Failure to tolerate EN requires consideration of PN for nutritional support in the second week.

Immunonutrition and Probiotics

Enrichment of enteral feeding formulas with glutamine, arginine, omega-3 fatty acids, antioxidants such as vitamins and micronutrients (concept of "immunonutrition") in order to boost the gut immune system has garnered significant research attention. While experimental models revealed promising observations, small-scale clinical studies in humans have yielded mixed results and a recent systematic review has not found any benefits of immunonutrition in clinical outcomes of AP in terms of incidence of MOF, length of hospitalization, or mortality [28]. Similarly studies on probiotic and prebiotic supplementation purported to reduce small intestinal bacterial overgrowth, reinforce the gut barrier, and modulate gut immunity have also resulted in inconsistent results. Importantly, mortality was shown to be higher (16 % vs. 6 %) in a RCT

that evaluated the effectiveness of multispecies probiotic prophylaxis in predicted SAP patients [31]. While these results are difficult to explain, they exemplify the critical state of the GI tract in severe disease and the need to be cautious and always avoid excessive forced feeding. Overall, the evidence recommends against probiotic prophylaxis in SAP and there is no strong enough evidence to recommend immunonutrition for the routine management of SAP.

Parenteral Feeding

PN was conceptualized as an ideal way to deliver nutrients to meet the high metabolic demands of AP, as it does not stimulate pancreatic secretion and thereby offering a more practical method of resting the pancreas. But bypassing the entero-pancreatic axis nutrient assimilation and providing intravenous glucose disturb the glucose metabolism causing hyperglycemia, hyperinsulinemia, and insulin resistance, resulting in higher rate of complications. Experimental and clinical data suggest that PN is associated with stronger proinflammatory responses, impaired cellular and humoral immunity, compromised gut defense barrier, increased bacterial translocation, and risk of systemic infections [32]. More importantly, the lack of intestinal luminal nutrients from fasting while receiving TPN has grave consequences in the form of gut mucosal atrophy and dysfunction of gut immune system, with suppression of Th_2 response and activation of adhesion molecules, increased neutrophil adherence, migration, and activation systemically causing end-organ damage such as ARDS [33]. Bowel rest also impairs intestinal blood flow and gut motility potentiating the risk of small intestinal bacterial overgrowth, bacterial translocation, and endotoxemia in the setting of increased intestinal barrier permeability [34]. Acute pancreatitis and PN are known to increase intestinal production of IL-6, associated with intestinal barrier dysfunction, and increase the risk of sepsis from enteric organisms/colonic microbiota.

In addition, the inherent risks associated with the central venous access catheter used for administering the PN such as of bleeding, bloodstream infections, and venous thromboses make it a poorer option. Serum electrolytes potassium, magnesium, and phosphorous and calcium need to be monitored closely and corrected appropriately while receiving PN.

Overall, an overwhelming body of evidence argues against general use of PN support and it should be reserved for patients who have failed enteral feeding and are becoming nutrient-depleted. In practice, PN is rarely needed when a NGJ tube can be placed and managed appropriately by experienced personnel.

Conclusion

- Bowel rest allows the inflamed pancreas to rest, but delay in enteral feeding can compromise the gut mucosal integrity, promote bacterial overgrowth and translocation, and exacerbate the systemic inflammation and risk of infection. Moreover, starvation aggravates the negative nitrogen balance and catabolism, thus impairing tissues healing and repair.
- PN provides the protein and nutrients for tissue repair without stimulating the inflamed pancreas. However, PN exacerbates systemic inflammatory responses, gut mucosal atrophy, and the risks of central venous catheter-related thrombosis and septicemia, and PN-associated metabolic complications (e.g., hyperglycemia) can outweigh the benefits of nutrition support.
- EN offers the advantage of delivering the nutritional support while it preserves gut mucosal integrity, supports splanchnic metabolism, and thereby potentially mitigates the systemic inflammatory response. Moreover, it avoids the complications of parenteral nutrition and causes minimal stimulation of pancreatic secretion by distal jejunal feeding.
- In general, recommendations for mode of nutritional support depend on the underlying nutritional state, the severity of pancreatitis,

and existence of complications. Early organ failure correlates well with mortality in SAP, and there is evidence that early slow (25 cm^3/h) enteral feeding may prevent progression of organ failure. Overfeeding from EN or PN introduces further complications and must be avoided in SAP.

- Oral feeding trials can be initiated within 3–4 days of supportive care and bowel rest in AP patients with mild to moderate disease severity.
- Early enteral feeding (within 48 h of onset of pain) may improve outcome in patients with significant symptoms and laboratory and radiographic evidence of SAP by suppressing systemic inflammation and organ failure, but RCT are needed to confirm this.

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Pharmacologic Therapy

11

Walter G. Park

Introduction

Acute pancreatitis is one of the most common gastrointestinal diseases, with a continuum of severity [1]. Mild pancreatitis is self-limiting and exists when there is no evidence of organ failure and/or pancreatic necrosis. Moderate severe pancreatitis is defined by local complications without persistent (>48 h) organ failure. Severe pancreatitis occurs when persistent organ failure develops [2]. Mild acute pancreatitis is the most common clinical presentation with moderate morbidity and negligible mortality. In contrast, severe acute pancreatitis occurs in up to 20 % of patients and is associated with significant morbidity and mortality [3].

Because of this difference in morbidity and mortality, the benefits of pharmacologic therapy will have the greatest impact in patients with severe acute pancreatitis. For mild disease, it may further reduce the development of organ failure and local complications. It may lead to earlier feeding, less narcotic pain medication use, and shorter hospitalization. For severe disease, it may alter the natural history, including the development of chronic pain, chronic pancreatitis, and hospital-related mortality.

Non-pharmacological interventions, including appropriate IV fluid administration (Chap. 8), antibiotic use (Chap. 9), and timely nutrition (Chap. 10), have already been discussed.

There is currently no U.S. Food and Drug Administration (FDA) approved pharmacological therapy for the treatment of acute pancreatitis. This chapter has three objectives (Table 11.1). The first objective will review key aspects of the pathophysiology of acute pancreatitis to highlight potential targets for pharmacologic intervention. The second objective will review pharmacologic therapies that have been evaluated. The third objective will highlight potential novel targets for future development.

Pathophysiology Overview: Potential Therapeutic Targets

When considering pharmacological therapies for acute pancreatitis, it is helpful to briefly outline the current pathophysiological framework for acute pancreatitis (Fig. 11.1). The primary site of injury occurs at the acinar cell from aberrant trypsin activity. Whether the mechanism is mechanical, metabolic, and/or genetic, the insult injures the acinar cell by blocking normal secretory activity [4]. Specifically, normal apical exocytosis is blocked and basal exocytosis (which under normal circumstances is constitutively blocked) now occurs. During this period of

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Table 11.1 Three objectives of this chapter

1. Review key pathophysiological aspects of acute pancreatitis to highlight potential pharmacological interventions
2. Summarize past clinical trials/studies of pharmacological agents studied for acute pancreatitis
3. Define potential novel targets for future development

dysregulation, the inactive trypsinogen within these secretory vesicles converts into active trypsin within the acinar cell. The actual site of intracellular activation remains elusive but proposed compartments include lysosomes/endosomes, autophagic vacuoles, and secretory granules. The immune system plays a pathophysiologic role in this early cascade that includes accelerating injury by stimulating zymogen activation within the acinar cell or limiting injury by degrading zymogens that are inappropriately released from the basolateral membrane of the acinar cell [5].

Acinar cell injury with inappropriate and excess leakage of activated enzymes subsequently induces local inflammation by various mechanisms. Activated proteases damage the vascular endothelium leading to microcirculatory injury. Leukocytes arrive via chemoattraction from increased vascular cell adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1) expression. The complement system is also activated and contributes to further injury. Both activated pro-inflammatory and anti-inflammatory cytokines lead to propagation of acinar cell injury and local inflammation. Specific pro-inflammatory cytokines include interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and platelet-activating factor (PAF). Specific anti-inflammatory cytokines include IL-2, IL-10, and IL-11. Other inflammatory mediators include arachidonic acid metabolites, reactive oxygen metabolites, and nitric oxide.

Unabated local inflammation can lead to systemic inflammation. The mechanism for this transition is thought to occur when activated pancreatic proteases reach the liver via the portal vein and induce hepatic injury. Hepatic injury stimulates the Kupffer cells (macrophages) within the liver to further activate pro-inflammatory cytokines and mediators triggering a systemic response. This clinically correlates with development of the systemic inflammatory response syndrome—a sensitive predictor for severe acute pancreatitis [6]. Acute phase proteins including C-reactive peptide and IL-6 are systemically released contributing to multi-organ failure. Bacterial translocation via the intestine occurs later in the course of disease leading to infected necrotizing pancreatitis.

The immune system plays a significant pathophysiological role in this disease. The initial inflammatory response in acute pancreatitis is characterized by up-regulation of ICAM-1 and neutrophil recruitment. Consequently, ICAM-1 deficiencies and neutrophil depletion in animal models have demonstrated a reduction in acute pancreatitis severity [7]. Regulating the degree of macrophage activation, which in turn induces more cytokine and inflammatory mediators such as TNF, IL-1B, IL-6, monocyte chemotactic protein (MCP)-1, and PAF may represent another pharmacological target to arrest local inflammation. Previous animal model studies have shown macrophage depletion to protect against experimental pancreatitis [8]. Certain subsets of activated T cells also appear to be important for progression to severe acute pancreatitis. Subsequent depletion may prevent progression to systemic disease [9].

More germane to severe acute pancreatitis are the extra-pancreatic immune responses that may be targeted for pharmacological intervention. Pancreatic necrosis, particularly when infected, is a major cause of morbidity and mortality. Control of bacterial translocation from the intestine may be regulated by toll-like receptors (TLRs), other nucleotide-binding domain and leucine-rich repeat-containing molecules, and dendritic cells [10]. Previous animal models have shown TLR4 deficiency to be associated with less severe forms of pancreatitis [11]. The role of TLRs is complex and incompletely understood, as various polymorphisms in TLRs have been associated with increased susceptibility to acute pancreatitis [12]. A better understanding of the regulatory role of the immune system within these local and systemic

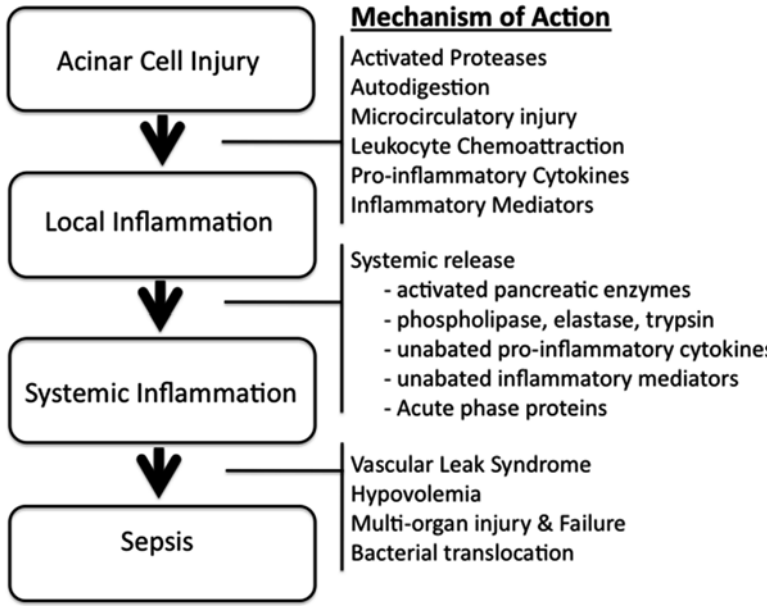

Fig. 11.1 Mechanisms of action involved in the pathophysiology of severe acute pancreatitis

inflammatory mechanisms that give rise to severe acute pancreatitis may lead to effective pharmacological intervention.

The complement system also appears to significantly contribute to the pathogenesis of acute pancreatitis. While complex and incompletely understood, it appears to be activated early in acute pancreatitis and to a greater extent in severe acute pancreatitis. Evidence of an activated complement system leading to severe pancreatitis is demonstrated by the observation of elevated C3a and sC5-9 levels in severe acute pancreatitis [13]. The elevation of C5a is particularly interesting because while it is commonly recognized as a potent pro-inflammatory mediator, it has demonstrated anti-inflammatory properties in experimental acute pancreatitis [14]. In such models, the use of a soluble complement receptor-1 demonstrated decreased leukocyte adhesion leading to a less severe course of acute pancreatitis [15].

The Kallikrein-Kinin system may also be involved in the pathogenesis of acute pancreatitis [14, 16, 17]. This poorly understood system involves the release of biologically active peptides, including bradykinin and kallidin. The pancreas has one of the highest tissue concentrations of these peptides compared to other organs. These peptides mediate large and small artery vasodilation and increase vascular permeability in the capillaries. This may facilitate capillary leakage and the pro-inflammatory mechanisms of acute pancreatitis. These peptides may also affect the afferent nervous system and may play an important role in pain development during acute pancreatitis. The development of kallikrein inhibitors may lead to decreased tissue damage, sepsis, and pain.

While many questions remain, our understanding of the pathophysiology of acute pancreatitis has advanced significantly. Beginning with acinar cell injury, this increased understanding has delineated a complex and interrelated system that includes a broad array of immunological mediators that define the course of disease. This framework provides a rational-based foundation toward developing therapeutic interventions for preclinical and clinical studies. As our understanding increases further, the number of potential pharmacological targets will also increase giving further hope for novel treatments. The subsequent section will review previously studied pharmacological agents in clinical studies.

Pharmacological Agents: Previous Clinical Studies

Based on the understood pathophysiology of acute pancreatitis and promising observations in preclinical studies, several clinical studies of pharmacological agents for acute pancreatitis have been performed. These studies can be categorized by the purported mechanism of intervention within the pathophysiological framework including anti-secretory agents, protease inhibitors, immunomodulators, anti-inflammatory agents, and antioxidants (Table 11.2) [18, 19].

Anti-secretory Agents

A long-time initial management principle of acute pancreatitis involves no per oral intake to minimize pancreatic secretions. Consequently, pharmacological agents that decrease pancreatic secretions have been studied in human clinical trials beginning in the late 1970s. Some of the first reported clinical trials involved the use of glucagon [20–22]. These included three randomized trials of sample sizes ranging between 22 and 69 patients with variable severity and etiologies of pancreatitis. No difference in mortality and relevant morbidities such as pain and length of stay was observed. Atropine and calcitonin

Table 11.2 Summary of pharmacological agents studied in clinical trials for acute pancreatitis

Pharmacological agent	Study design	Sample size	Outcomes assessment	Citation
Anti-secretory agents				
Glucagon	RCT[a]	22–69	No significant benefit	[20–22]
Atropine	RCT	51	No significant benefit	[23]
Calcitonin	RCT	94	No significant benefit	[24]
Somatostatin	RCT/meta-analysis	50–703	Possible less morbidity in SAP[b]	[26–31]
Octreotide	RCT/meta-analysis	19–948	Mixed results. Possible less morbidity in SAP	[31, 32, 34–40]
Protease inhibitors				
Aprotinin	RCT	48–105	No consistent significant benefit	[44–46]
Gabexate mesilate	RCT/meta-analysis	42–898	No consistent significant benefit	[31, 50, 52–54, 106]
Nafomostat (with antibiotics)	RCT	51–78	Mortality benefit for SAP by CRAI[c]	[56–59]
Immunomodulators				
Lexipafant	RCT	50–290	No consistent significant benefit	[62–64]
Dotrecogin alfa	RCT	32	No significant benefit	[68]
Antioxidants				
Combinations[d]	RCT	39–53	No significant benefit	[70–72]
Glutamine	Meta-analysis	505	Mortality benefit in patients on TPN	[75]
Anti-inflammatory				
Indomethacin	RCT	30	No significant benefit	[78]

[a]Randomized controlled trials
[b]Severe acute pancreatitis
[c]Continuous regional arterial infusion
[d]*n*-Acetylcysteine, vitamin C, vitamin A, selenium, and vitamin E

have also been studied, each in a randomized controlled trial, without benefit compared to placebo [23, 24].

Produced in the gastrointestinal tract, somatostatin is thought to have several beneficial effects in acute pancreatitis. These include inhibiting exocrine pancreatic secretions, reducing splanchnic blood flow, stimulating the hepatic reticuloendothelial system, and modulating the cytokine cascade [25]. Somatostatin has been well studied as a pharmacological agent in human clinical trials for acute pancreatitis [26–30]. While there is slight variability in the dose and duration of somatostatin, four different randomized controlled trials of 50–100 patients failed to show a clinically significant benefit with somatostatin treatment.

One particular study by Planas and colleagues focused specifically on patients with severe acute pancreatitis in the intensive care unit [30]. They randomized 50 patients to somatostatin for 10 days versus placebo in an unblinded fashion. While there was no difference in mortality or length of stay, they observed a reduction in the need for surgery for local complications (45.8 % vs. 86.4 %; $p=0.005$). A meta-analysis that included seven additional non-English publications (three were abstracts and half of which were not randomized) reported an overall mortality benefit with somatostatin for severe acute pancreatitis with an odds ratio (OR) of 0.36 (95 % CI: 0.20–0.64). Interestingly, this analysis did not find a correlating significant decrease in complication rates with somatostatin use. Further, the authors describe assessing for heterogeneity in their methods section, but did not report it in the results or discussion raising a concern regarding the validity of these results [31].

Octreotide is a synthetic analogue of somatostatin that can be given both by intravenous infusion (IV) and subcutaneously (SC). There are several clinical trials that have studied its efficacy for acute pancreatitis [32–38]. The first several studies were small and while they showed no mortality benefit, there was suggestion of decreased severity, local complications, and earlier return to oral intake [32, 34, 35, 39]. Uhl and colleagues published the largest clinical trial of 302 patients with moderate-severe pancreatitis from 32 centers and no clinical benefit was observed [36]. In a much smaller study by Paran and colleagues of 50 patients with severe acute pancreatitis, a significant reduction in sepsis (24 % vs. 76 %, $p=0.002$), acute respiratory distress syndrome (28 % vs. 56 %, $p=0.04$), hospital stay (20.6 days vs. 33.1 days, $p=0.04$), and mortality (2 deaths vs. 8 deaths, $p<0.019$) was reported [37]. More recently Yang and colleagues randomized 161 obese patients (BMI > 25) with mild pancreatitis to octreotide IV infusion for 3 days versus placebo and reported a risk ratio of 0.27 (95 % CI: 0.1–0.69) for developing severe pancreatitis. They also reported a difference in local complications in favor of octreotide treatment (4.9 % vs. 19 %, $p=0.006$) [38]. Although a meta-analysis performed by Andriulli and colleagues [31] suggests a mortality benefit for severe acute pancreatitis (OR 0.57 [95 % CI: 0.35–0.88]), another more recent meta-analysis [40] that limited their estimate to four higher quality studies [30, 34, 36, 37] did not show any benefit in sepsis, complication rates, or mortality. However, one of the four studies [30] did not specifically look at octreotide but somatostatin.

Although studied over the past 30 years, the use of anti-secretory agents, specifically somatostatin and octreotide, has produced inconsistent results. There appears to be no benefit in mild acute pancreatitis. For severe acute pancreatitis, the reported benefits remain inconclusive such that it is not currently recommended in clinical practice [3, 41].

Protease Inhibitors

The use of protease inhibitors for treating acute pancreatitis has been proposed and reported in clinical studies as far back as nearly 50 years ago [42]. The rationale stems from premature and excess protease activation within the pancreatic parenchyma leading to autodigestion and subsequent inflammation. While endogenous inhibitors exist to mitigate these events, clinically severe disease occurs when these defense

mechanisms are overwhelmed leading to a systemic inflammatory response syndrome.

Aprotinin, a bovine pancreatic trypsin inhibitor, was one of the first protease inhibitors described for treating acute pancreatitis in humans with reported benefit in mortality [42–44]. However, subsequent studies have failed to repeat such a benefit. Baldin and colleagues randomized 55 patients with severe acute pancreatitis to peritoneal lavage of aprotinin and reported no difference in mortality or other relevant clinical outcomes [45]. Berling and colleagues also studied peritoneal lavage delivery of aprotinin in 48 patients with severe acute pancreatitis. Despite reporting less necrosis in the aprotinin-treated group, they observed no difference in mortality [46]. In further studying this difference in necrosis, they observed a reduction in complement activation with aprotinin. Specifically, the treated groups had relatively less C3a and more C1 inhibitor plasma levels [47]. They also observed no difference in the plasma levels of leukocyte proteases and postulated that this may explain the lack of mortality benefit with aprotinin given as a peritoneal lavage. Recently, Smith and colleague reviewed the literature and concluded that aprotinin may still have a role in treating acute pancreatitis because the previous studies were not adequately powered, and that aprotinin was not given in high enough doses to produce sufficient inhibitory activity [48].

In contrast to aprotinin, gabexate mesilate is a smaller protease inhibitor that has been studied in humans based on promising preclinical studies [49]. Early clinical studies including a small controlled trial of 42 patients suggested a trend towards a mortality benefit [50, 51]. However, larger randomized controlled trials including a multi-center study that randomized 223 patients with moderate to severe acute pancreatitis found no clinical benefit [52, 53]. Two different meta-analyses published in 1998 and 2003 reiterate this finding of no mortality benefit [31, 54]. The earlier meta-analysis, however, did observe a decreased complication rate and less surgery. Despite the overall lack of reported benefit, interest in gabexate persists with a recent small study suggesting a benefit by delivering it through a continuous regional arterial infusion [55].

Nafomostat is a relatively new protease inhibitor studied for treating acute pancreatitis. This synthetic protease inhibitor has a broad spectrum of enzyme inhibitory activity that is up to 100 times more potent than gabexate [49]. The design of human clinical studies has been different from aprotinin and gabexate. These studies have included antibiotics, severe acute pancreatitis patients, and delivery of nafomostat by continuous regional arterial infusions (CRAI). This relatively invasive technique delivers a higher concentration of drug through a catheter that is placed into major arterial branches (celiac axis and/or superior mesenteric artery) and must be performed by an interventional radiologist.

Takeda and colleagues first described a clinical trial of 53 patients with severe acute pancreatitis using nafomostat. One group of patients was given peripheral nafomostat and antibiotics (imipenem) intravenously greater than 8 days from symptom onset. The second group was given nafomostat by CRAI with peripherally administered antibiotics to a group that presented less than 7 days from symptom onset. The third group gave both nafomostat and antibiotics by CRAI to a group of patients who presented within 7 days of onset. They reported a progressive mortality benefit from group 1 to 3 (44 % vs. 14 % vs. 7 %) and the development of necrosis (50 % vs. 23 % vs. 0 %) [56]. Takeda and colleagues reported a subsequent study that demonstrated earlier CRAI of nafomostat (<48 h compared to >72 h) was associated with improved mortality (3.2 % vs. 26.3 %) [57]. Imaizumi and colleagues studied 51 patients with severe acute pancreatitis and reported that CRAI compared to non-CRAI delivery of nafomostat and antibiotics was associated with decreased need for surgery and improved mortality [58]. A more recent study of 78 randomized patients between CRAI nafomostat and antibiotic to just antibiotics showed improved mortality (5 % vs. 23 %) and decreased need for surgery [59].

Among the three most studied protease inhibitors (aprotinin, gabexate, and nafomostat), the

most promising outcomes data is associated with nafomostat. However, these studies with nafomostat are relatively small, involve the use of antibiotics, and require a relatively invasive procedure. At this time, none of these medications are accepted as part of standard clinical care for treating severe acute pancreatitis. Further study with nafomostat via CRAI may prove promising.

Immunomodulators

As discussed above, the pathophysiology of acute pancreatitis begins in the acinar cell and if left uncontrolled triggers an immunological cascade that leads to systemic inflammatory response syndrome and sepsis. Consequently, pharmacologic interventions that may mitigate this cascade have been studied for treating severe acute pancreatitis. These include lexipafant, a platelet activation factor inhibitor, and dotrecogin alfa, a genetically engineered activated protein C.

Under physiological conditions, endothelial cells, macrophages, neutrophils, and platelets produce platelet-activating factor (PAF) during the normal course of inflammation leading to platelet aggregation, hypotension, and vascular leak. Preclinical studies of acute pancreatitis have demonstrated a significant role for PAF in the pathophysiology of acute pancreatitis and the use of a PAF blocker to mitigate disease [60, 61]. Lexipafant is a PAF antagonist that has been studied in several clinical trials in humans.

The first clinical trial randomized 83 patients with acute pancreatitis, of whom 29 had severe acute pancreatitis. Lexipafant was administered intravenously on a daily basis (60 mg) for 3 days. While no significant difference in mortality was observed, a significant decrease in organ failure at day 3 in the treatment arm was reported [62]. Another study randomized 50 patients with severe acute pancreatitis with the treatment arm receiving 100 mg daily for 7 days. The treatment group had significantly less organ failure, with a trend toward a reduction in mortality and SIRS [63]. The largest randomized study to date was performed by Johnson and colleagues randomizing 290 patients with severe acute pancreatitis (APACHE > 6) with the treatment group receiving 100 mg daily for 7 days starting within 72 h of symptom onset. No significant difference in organ failure reduction or local complications was observed. The authors concluded that lexipafant alone was not sufficient to ameliorate severe acute pancreatitis [64].

Dotrecogin Alfa is an analogue of endogenous protein C that has demonstrated a mortality benefit in severe sepsis [65]. Endogenous protein C is synthesized in the liver and it inhibits thrombin generation and facilitates thrombolysis. Lower levels of activated protein C are associated with higher mortality in acute pancreatitis. Preclinical studies in acute pancreatitis show improved tissue histology, decreased rates of infection, and lower serum markers of inflammation. Activated protein C may mitigate severe acute pancreatitis by several immunomodulatory mechanisms—regulation of leukocyte endothelial interaction, improved intestinal microcirculation, and regulation of mitogen-activated kinases [66]. The first report of benefit using dotrecogin alfa in acute pancreatitis involved two case reports [67]. A subsequent pilot study of 32 patients with severe acute pancreatitis was studied. These patients received dotrecogin alfa within 96 h of symptom onset. No clinically significant difference in this pilot study was observed [68].

While modulating the immune system in acute pancreatitis as a pharmacological strategy is gaining more interest as knowledge of the pathophysiology unfolds, these recent targets, while promising in preclinical studies, have yet to translate into clinical practice [10].

Antioxidant Agents

Within the last decade, several clinical trials studying the benefit of antioxidant agents for acute pancreatitis have been published. The basis for this involves the recognized role of reactive oxygen species and cellular injury without immediate detoxification. Antioxidant agents that have been studied include a variety of different compounds including *n*-acetylcysteine, methionine, beta-carotene, selenium, ascorbic acid, and

alpha-tocopherol. Preclinical studies in acute pancreatitis demonstrate chemically reduced levels of glutathione and increased levels of oxidized glutathione suggesting a benefit with antioxidant intervention [69].

Three different clinical trials have been recently published on this topic. Siriwardena and colleagues reported a randomized controlled trial of 43 patients with predicted severe acute pancreatitis. The treatment group received intravenous *n*-acteylcysteine, selenium, and vitamin C. They demonstrated that serum levels of antioxidants increased and markers of oxidative stress decreased in the treatment group. The primary outcome was the development of organ dysfunction for which no difference was observed [70]. In another study of 53 patients, the treatment group received vitamin C, *n*-acetylcysteine, and a tablet of multiple antioxidants (antoxyl-forte). No significant difference in length of stay or complications was observed [71]. The final study randomized 39 patients with acute pancreatitis to receive vitamins A, C, and E within 96 h of symptom onset and observed no significant difference in organ dysfunction [72]. While this may be another example of a disconnect between preclinical evidence and clinical studies, it is possible that these studies, being all fairly small, were not powered enough to detect a real difference.

In severe acute pancreatitis, there is significant catabolic stress and active nutrient repletion is associated with a mortality benefit. The use of antioxidants for treating acute pancreatitis falls within an evolving proposed concept of "pharmaconutrition"—that nutrients can provide benefit beyond repletion of a deficiency [73]. Glutamine is a potent antioxidant that plays an important role in enterocyte, lymphocyte, macrophage, and neutrophil development. Consequently, it has been studied as a treatment for acute pancreatitis. Xue and colleagues randomized 80 patients to receive alanyl-glutamine dipeptide intravenously for 10 days starting either on the day of admission or at hospital day 5 (there was no placebo group). Complications, length of stay, need for surgery, and mortality were decreased in the early administration group [74]. Asrani and colleagues performed a meta-analysis of randomized controlled trials of glutamine use for acute pancreatitis. They identified 12 studies of 505 patients with acute pancreatitis. They reported a mortality benefit (RR 0.3; 95 % CI 0.15–0.6), reduced infectious complications (RR 0.58; 95 % CI 0.39–0.87) but no difference in length of stay. Interestingly, the benefit of glutamine use was observed in only patients who received total parenteral nutrition. Patients receiving enteral nutrition did not benefit from additional glutamine supplementation [75].

Anti-inflammatory

Since acute pancreatitis is primarily characterized by a state of acute inflammation leading to cellular injury, anti-inflammatory medications have been studied including indomethacin. The mechanism of action involves inhibition of phospholipase A2 activity, cyclooxygenase activity, and mediation of neutrophil endothelial interactions [76]. Preclinical animal studies have demonstrated a benefit with indomethacin [77]. Human studies, however, have yet to validate a clear benefit with the exception of post-ERCP pancreatitis (PEP). Ebbehoj and colleagues randomized 30 patients with acute pancreatitis with the treatment group receiving 50 mg of rectal indomethacin twice a day. The only outcomes reported were decreased pain and opiate use [78]. Elmunzer and colleagues recently demonstrated in a large multi-center study of 602 patients at high risk for developing PEP that one dose of rectal indomethacin after the procedure reduced the incidence of pancreatitis [79]. While this suggests that indomethacin may have a therapeutic role in preventing acute pancreatitis, there is a lack of clinical data to support its efficacy in patients outside of PEP.

Pharmacologic Therapies for PEP

PEP is a common cause of acute pancreatitis. Fortunately, the vast majority of cases do not evolve into severe disease. Aside from the possibility that the mechanism of PEP is unique

Table 11.3 Summary of pharmacological agents studied in clinical trials for post-ERCP pancreatitis

Pharmacological agent	Study design	Sample size	Post-ERCP pancreatitis rate	Citation
Anti-secretory agents				
Somatostatin	RCT[a]	160	Treatment: 2.7 %, placebo: 10 %[b]	[80]
Somatostatin/diclofenac	RCT	540	Treatment: 4.7 %, placebo: 10.4 %[b]	[81]
IV Octreotide	RCT	202	Treatment: 2 %, placebo: 9 %[b]	[82]
Protease inhibitors				
Nafomostat	RCT	608	Treatment: 5.1 %, placebo: 13 %[b]	[85]
Ulinastatin	RCT	406	Treatment: 2.9 %, placebo: 7.4 %[b]	[84]
Immunomodulators				
IL-10	RCT	137	Treatment: 10 %, placebo: 24 %[b]	[86]
	RCT	305	Treatment: 15 %, placebo: 14 %	[87]
Anti-inflammatory				
Prednisone	RCT	200	Treatment: 12 %, placebo: 7.9 %	[90]
Hydrocortisone	RCT	120	Treatment: 1.6 %, placebo: 11.9 %[b]	[91]
Indomethacin	RCT	602	Treatment: 9.2 %, placebo: 16.9 %[b]	[79]
Antioxidants				
n-Acetylcysteine	RCT	256	Treatment: 12.1 %, placebo: 9.6 %	[92]
Allopurinol	RCT	200	Treatment: 12 %, placebo: 7.9 %	[90]
Smooth muscle relaxant				
Glyceryl nitrate	RCT	806	Treatment: 4.5 %, placebo: 7.1 %	[94]

[a]Randomized controlled trial
[b]Statistically significant

compared to other known etiologies, it has been a popular focus for studying various pharmacological agents for prevention of acute pancreatitis. Since the incidence of pancreatitis episodes can be more easily predicted (i.e., the day of ERCP), clinical trials are relatively easier to perform with the primary outcome being the development of acute pancreatitis. Further, the design of providing a therapy before potentially inducing pancreatitis is more similar to preclinical study designs to suggest more direct translatability. Besides the trial involving rectal indomethacin mentioned above, other pharmacological agents will be briefly reviewed [79].

Active clinical trials in preventing PEP have been ongoing for the past two decades and include many of the pharmacologic agents described above (Table 11.3). These trials tend to be larger because enrollment is more predictable. Among anti-secretory agents, somatostatin with and without diclofenac and octreotide have been studied in randomized controlled trials. Bordas and colleagues randomized 160 patients and found a PEP rate of 10 % in the placebo group compared to 2.5 % in the somatostatin-treated group. In subgroup analysis, this benefit was observed in those patients undergoing sphincterotomy [80]. In a more recent study by Katsinelos and colleagues, somatostatin was added to diclofenac in a randomized study of 540 patients. The overall PEP rate was 7.2 % with the placebo-treated group experiencing a 10.4 % rate compared to the combination-treated group of 4.7 % [81]. It is unclear from this study whether one drug primarily accounts for the benefit. Thomopoulos and colleagues demonstrated a positive benefit with a 24-h infusion with octreotide in a randomized trial of 202 patients [82]. Treated patients had a PEP rate of 2 % compared to 9 % in the placebo group.

Among protease inhibitors, gabexate mesilate, ulinastatin, and nafomostat have been studied in this population [83–85]. Tsujino and colleagues randomized 406 patients to IV infusion with ulinastatin versus placebo before ERCP. The ulinastatin group had a PEP rate of 2.9 % that was significantly lower than 7.4 % in the placebo group [84]. Park and colleagues randomized 608

patients to three different groups: control group, IV nafomostat 20 mg, and IV nafomostat 50 mg before ERCP. While they reported a benefit with nafomostat-treated groups compared to controls, the higher dose did not further protect those patients at high risk for PEP [85].

Among immunomodulators, recombinant IL-10 has been studied with early promise followed by lack of validation in subsequent studies. Deviere and colleagues randomized 144 patients to receive IL-10 infusions compared to placebo with an observed protected effect [86]. A subsequent trial by Sherman and colleagues failed to show a benefit at an interim analysis of 305 randomized patients and terminated the study [87]. Although benefit with the use of non-steroidal anti-inflammatory medications including indomethacin and diclofenac have been observed, the use of steroids have had mixed results [79, 88, 89]. Brudzynska and colleagues randomized 300 patients to prednisone, allopurinol, or placebo before ERCP and found no protective benefit against PEP [90]. In a smaller randomized study of 120 patients, 100 mg of hydrocortisone prior to ERCP reduced PEP from 11.9 % in the placebo group to 1.6 % in the treated group suggesting a significant benefit [91]. Antioxidant therapy with *n*-acetylcysteine and allopurinol has been studied in relatively large randomized trials with no reported protected benefit [90, 92]. Nitroglycerin products to reduce sphincter hypertension have demonstrated benefits in smaller studies without subsequent validation in larger randomized trials [93, 94].

The search for a pharmacological agent for treating human acute pancreatitis has been fairly extensive. The historical arc for most of these agents is one of promise from preclinical studies, followed by a few promising small pilot clinical trials. Most, however, have failed to be validated at larger studies. Meta-analyses have been more positive about various agents, but this may reflect a weighting bias towards smaller and unpublished studies. In PEP, there are more positive clinical trial data for various pharmacological agents. Most, however, have yet to be accepted in standard clinical practice. In non-PEP as well, there is no current pharmacologic agent that has successfully navigated its way into clinical practice [3, 41]. While some of these agents including nafomostat and glutamine may merit further clinical study, the future may lie in novel agents.

Future Targets: Opportunities for Therapeutic Development

Despite previous efforts, there are promising opportunities for therapeutic development. Specifically, strategies that target and alter the activities of key immune cells may provide potential therapeutic benefit as demonstrated in preclinical studies. In acute pancreatitis, macrophages can play both a pro-inflammatory and anti-inflammatory role. Various modifiers such as IL-4 and IL-13 have demonstrated capacity to convert pancreatitis-activated macrophages (M1) into reparative macrophages (M2). Hemin-activated macrophages express high levels of hemoxygenase-1 (HO-1) that in turn promotes production of anti-inflammatory agents including carbon monoxide and biliverdin. These agents induce IL-10, IL-22, and p38 MAPK. Introduction of hemin-activated macrophages protects against experimental pancreatitis [10, 95]. In humans, HO-1 levels are upregulated in acute pancreatitis and that ex vivo treatment of patient blood with Panhematin, an FDA-approved medication for acute intermittent porphyria, can prime HO-1 production [96]. Habtezion and colleagues have shown that Panhematin given before experimental pancreatitis upregulates hemin-activated macrophages and leads to less pancreatic injury. More importantly, they have shown in their experimental model that if given after pancreatitis develops, in both early and late stages of disease, Panhematin treatment ameliorates the extent of pancreatitis-related injury [97].

Another perhaps underappreciated immune-related target involves the kallikrein-kinin and complement systems. As mentioned above, severe acute pancreatitis is associated with elevated C3a and sC5-9 levels [13]. The C1 esterase inhibitor (C1 INH) physiologically inhibits a variety of plasma proteolytic enzymes including the activated C1 complex and kallikrein [98].

In experimental models of acute pancreatitis, C1 INH given before the onset of pancreatitis demonstrated a potential protective benefit [99]. In particular, C1-INH may have a protective benefit in severe acute pancreatitis [100]. In small human studies, the use of C1-INH concentrate has demonstrated some protective benefit in acute pancreatitis [101, 102]. Pharmacological targets of the complement system have already been developed in other diseases that may have utility in acute pancreatitis. One example includes recombinant C1-INH that is currently available in Europe for the treatment of hereditary angioedema [103]. Another example is eculizumab, which is a monoclonal antibody that binds with high affinity to complement protein C5 preventing generation of the terminal complement complex C5b-9. It is currently approved for treating paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome [104].

Some potentially novel pharmacologic agents are being studied in PEP given some of the advantages in clinical trial design. Fluhr and colleagues recently published their design for a randomized controlled trial of IV magnesium to prevent PEP. Intra-cellular calcium release plays an important role in initiating protease activation. Magnesium is a calcium antagonist and counteracts calcium signaling. This study intends to randomize 502 patients to IV magnesium 60 min before and 6 h after ERCP or placebo [105].

Conclusion

Although there have been some positive studies of various pharmacological agents, the vast majority have failed to demonstrate a consistent benefit in large validation studies such that there is no current drug recognized for use in clinical practice for treating acute pancreatitis. Perhaps, one of the major reasons for this relates to differences between promising preclinical studies in experimental pancreatitis and human clinical trials. Besides the question of whether these models accurately reflect human disease, most preclinical studies administer the medication prior to pancreatic injury such that the medication in question provides a protective effect. In the clinical situation, the drug of interest is tested when the injury has already occurred and the inflammatory cascade associated with pancreatitis has begun.

With some drugs including nafomostat and glutamine requiring further validation and potential novel drugs to be tested hopefully soon, the design of future clinical trials needs to be reconsidered. Going forward, we need to design clinical trials that administer treatment within 24 h (or as soon as possible) from symptom onset. Even earlier delivery may be key (i.e., within 4 h of arriving into the ER), akin to treatment of ST-elevation myocardial infarctions where time to catheterization is now part of clinical practice. This will maximize any candidate drug's potential to interrupt the inflammatory cascade and injury. A continued focus of trials on predicted severe disease will more likely identify a candidate treatment, as trials that include patients with mild pancreatitis require larger sample sizes to detect a meaningful difference. To minimize heterogeneity, clinical trials should also standardize eligibility, supportive treatment approaches, and outcomes. Eligibility for severe disease as well as clinically relevant outcomes should adopt standards set forth by the revised Atlanta classification [2]. Clinically meaningful primary outcomes primarily include mortality, the development and resolution of organ failure, SIRS, sterile and infected necrosis, and other local complications. Important secondary outcomes include the length of stay, the amount of pain medication required, quality of life, and cost of care.

Despite past shortcomings of studied pharmacological agents, there remains promise in discovering and developing an effective pharmacological therapy for acute pancreatitis. The lessons learned from past clinical trials along with increased understanding of the immune system in this disease provide meaningful direction for substantial progress. When, not if, such a discovery occurs, it will fundamentally change our current management paradigm from one of supportive therapy to abortive therapy.

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Part IV

Interventional Management of Severe and Necrotizing Acute Pancreatitis

Management of Ductal Leaks

12

Michael C. Larsen and Richard Kozarek

Introduction

The development of acute pancreatitis is primarily caused by local enzyme activation and acute cytokine release in response to some form of insult to the pancreas. Early signs and symptoms of this inflammatory process include abdominal pain, ileus, and potentially a systemic inflammatory response syndrome (SIRS), and acute respiratory distress syndrome (ARDS). Depending on the severity of the insult, pancreatic tissue apoptosis or necrosis ensues. Perpetuation of the disease process may be the result of infection of necrotic tissue or an ongoing leak secondary to disrupted ductal epithelium from the inflammatory process [1–4]. Pancreatic trauma can also lead to an acute leak and traumatic pancreatitis. In the instance of penetrating trauma, this can lead to an acutely ill patient as compared with a clinically well patient after surgical trauma with a percutaneous drain left in place [5].

The potential manifestations of pancreatic leaks are multiple. Pancreatic leaks or fistulas are traditionally classified as internal or external [3, 6]. External leaks represent pancreaticocutaneous fistulas and are most typically iatrogenic in etiology. Internal leaks present in a myriad of different forms and include pancreatic ascites, pleural effusions, pseudocysts among others [4, 7]. The prognosis and management of pancreatic leaks varies based on the clinical manifestations of the leak.

Epidemiology

The incidence and prevalence of pancreatic duct leaks has not been thoroughly studied and remains unclear. However, up to 40 % of patients with acute pancreatitis will develop some type of acute fluid collection [8]. Only a small percentage of these patients will go on to develop a true pseudocyst or fistula. It appears that the etiology of pancreatitis is not important in determining whether a leak will ensue, but it is the severity of the insult that matters. Gallstone pancreatitis is, however, the most common cause of severe acute pancreatitis. One clinical entity that is known to involve high rates of pancreatic duct leaks is walled-off pancreatic necrosis (WOPN). In numerous studies WOPN patients have been shown to have disconnected duct syndrome (DDS) in 35–70 % of cases. It is unclear whether this ductal disruption is the cause of or a result of the WOPN [6, 9, 10].

Clinical Features

The symptoms and clinical manifestations of ductal leaks depend on multiple factors. The main determinants include the leak's location

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Table 12.1 Manifestations of pancreatic duct leaks

Internal fistula
– Peripancreatic fluid collection
– Pseudocyst
– Pancreatic ascites
– High amylase pleural fluid
– Pancreaticoenteric/biliary/bronchial fistula
– Walled-off pancreatic necrosis (WOPN)
– Smoldering pancreatitis
External fistula
– Pancreaticocutaneous fistula

within the gland, the size of the leak, and the body's ability to contain the leak's output (Table 12.1). Other factors include bacterial translocation, endotoxin release, extraluminal enzyme activation, and superinfection. Patients range from being completely asymptomatic to experiencing debilitating pain and potentially severe sepsis and other serious complications from resultant fluid collections. Signs and symptoms can include pain, nausea, vomiting, tachycardia, ileus, and hypotension [11, 12]. Certainly the severity of the pancreatitis that causes or results from the leak has the most bearing on the patient's initial symptoms and clinical course; later on the characteristics of the leak and the associated complications play the biggest role. The classic manifestation of a pancreatic duct leak is the formation of a pseudocyst, but other possibilities include walled-off pancreatic necrosis, pancreatic ascites, pleural effusions, and even pericardial effusions (Fig. 12.1).

The size of pancreatic duct leaks is highly variable and can range from a small trickle to high-grade output. The size of the leak does not necessarily correlate with the severity of the resulting symptoms and complications. Low-grade leaks typically result in intrapancreatic fluid collections, which can be asymptomatic or lead to a smoldering pancreatitis. This can be associated with variable degrees of pancreatic necrosis, which can in turn lead to multisystem organ failure or local and systemic infections [6, 13–15]. High-output leaks can similarly lead to pancreatic necrosis, but can also result in large peripancreatic or remote abdominal fluid collections, pancreatic ascites, high amylase pleural effusions, or have mediastinal involvement.

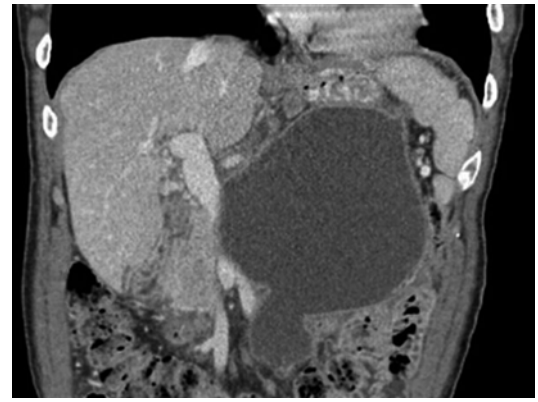

Fig. 12.1 Patient with severe acute pancreatitis with large pancreatic fluid collection

Leaks originating from the duct in the head of the pancreas can have a variety of manifestations. The leaking pancreatic fluid can be walled-off by the body and localized to the right upper quadrant. Collections in this location can impinge upon or fistulize to multiple different organs in this area. These collections can press on the common bile duct leading to biliary obstruction, jaundice, elevated liver function tests, or even cholangitis. Collections that impinge upon the duodenum or gastric outlet can lead to post-prandial pain, post-prandial nausea and vomiting, early satiety, and potentially gastric outlet obstruction. Leaks from the pancreatic head can also result in fluid tracking along the psoas and develop pelvic fluid collections. This fluid can even track into the scrotum and buttocks [16]. Often, pancreatic head leaks result in right pararenal fluid collections as well.

Leaks that develop in the pancreatic tail often result in left upper quadrant or perisplenic fluid collections [3, 17]. Collections that develop in this area can fistulize to the ligament of Treitz or the transverse colon [18–20]. Fluid from the tail can also track into the retroperitoneum and lead to acute pararenal or pelvic fluid collections. Alternatively, this fluid can track up into the thorax and develop high amylase pleural effusion [21–24]. Symptoms vary based on the location of the fluid collection but can include left upper quadrant pain, nausea, post-prandial pain, shortness of breath, or sepsis in the event of a colonic fistula.

Leaks originating in the genu or body of the pancreas often create fluid collections in the lesser sac. Necrotizing pancreatitis with walled-off pancreatic necrosis frequently results in leaks in this area in the form of DDS [3, 25–29]. Unfortunately, CT and other imaging studies are poor at differentiating WOPN from a pseudocyst and therefore most collections occurring in this area should be regarded as possible WOPN [4, 30–32]. Similar to patients with pancreatic tail leaks, body leaks can also create pleural effusions, pericardial effusions, and even pancreaticobronchial fistulas [3, 33]. Patients with pancreatic body leaks can also develop pancreatic ascites [6, 21, 23, 34]. Patients with pancreatic ascites will experience abdominal pain and increased abdominal girth, potentially with shortness of breath from pressure on the diaphragm and occasionally spontaneous bacterial peritonitis.

Diagnosis

In order to manage pancreatic duct leaks one must first successfully make the diagnosis. In the past this was commonly done with ERCP, which can also be therapeutic. However, the advent of excellent cross-sectional imaging and the risk of pancreatitis associated with ERCP have moved the use of ERCP to primarily therapeutic purposes. In the right clinical setting the uses of abdominal ultrasound, pancreatic protocol CT, secretin-MRCP (S-MRCP), and aspiration of fluid collections are often successful at making the diagnosis [3, 8, 35–39] (Table 12.2).

Table 12.2 Diagnosis of pancreatic leaks

External fistula
– Pancreatogram through JP or IR drain
– Persistent high amylase output through JP or IR drain
Internal fistula
Pleural effusion
– CXR, abdominal, and thoracic CT
– High amylase with aspiration
Pancreatic ascites
– Ultrasound, CT, or MR of abdomen
– High amylase with paracentesis
Pseudocyst
– CT, MRI, EUS, ERCP
WOPN
– CT, MRI, EUS
Duct disruption
– ERCP or S-MRCP

The diagnosis of an external pancreatic fistula is typically straightforward as long as the diagnosis is considered. A patient with persistent output from a JP drain after pancreatic surgery or peripancreatic surgery should have the fluid checked for amylase levels, which will be elevated in the setting of a pancreatic leak [40]. Inadvertent damage to the pancreas during peripancreatic surgery is far more common than damage to the stomach or colon. Also, in patients with variable output of clear pancreatic juice following percutaneous drainage of a pseudocyst or peripancreatic fluid collection, one can consider contrast injection through the drain to assess for a pancreatogram, which confirms the diagnosis. These tests should also be considered in patients with percutaneous output of clear fluids after a penetrating injury.

For making the diagnosis of an internal fistula, a pancreatic protocol CT is typically the best initial diagnostic test for patients with smoldering or severe pancreatitis [41]. If a fluid collection is seen in this type of clinical picture, it can generally be diagnosed as a leak. However, leaks are implied rather than defined by CT and sequential scans with evidence of enlarging collections may be needed for diagnosis. CT is also an imperfect test because it often overestimates the fluid component of a cyst and therefore can misdiagnose WOPN as a pseudocyst [9]. Historically, ERCP has been used to diagnose leaks; however, the S-MRCP may now frequently be used in its place as it has been shown to be able to characterize an active leak and minimizes the potential complications associated with ERCP, such as worsening pancreatitis [37–39, 42]. S-MRCP is also able to diagnose DDS, which is a situation where ERCP alone will not be able to control the problem.

The diagnosis of a pancreatic leak is most commonly considered when a patient presents with typical clinical picture of pancreatitis followed by persistent or recurrent symptoms. However, it is far more difficult when a patient

without a known history of pancreatitis is found to have a pancreatic or peripancreatic cyst. In this situation chronic pancreatitis changes such as parenchymal or ductal calcifications can suggest the diagnosis. Also, a uniform appearance, lack of cyst calcifications, and a thick outer rind can suggest a pseudocyst. Endoscopic ultrasound can often provide better characterization of the cyst and can allow for fine-needle aspiration to sample cyst fluid for amylase, CEA, and cytology, which can help differentiate pseudocysts from cystic neoplasms [43].

Management

Historically, the management of pancreatic duct leaks was typically surgical. Medical or conservative management with gut rest, TPN, and octreotide has been shown to be beneficial in some patients, although refractory cases are quite common, particularly in the setting of a high-volume leak. The advent of ERCP has allowed endoscopists to place transpapillary stents to facilitate leak closure [44] (Fig. 12.2).

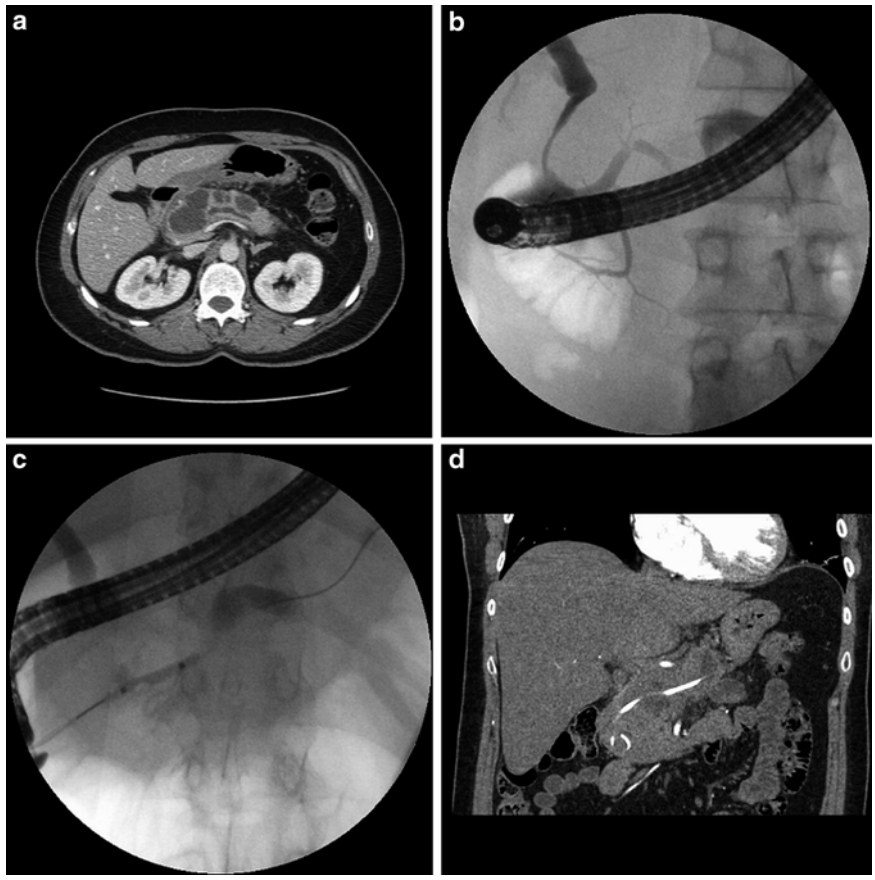

Fig. 12.2 Patient with acute biliary pancreatitis with subsequent development of multiple intrapancreatic fluid collections and symptoms of smoldering pancreatitis. Ductal disruption and downstream ductal stenosis treated with balloon dilation and stent placement. (**a**) CT with intrapancreatic fluid collections. (**b**) Pancreatogram demonstrating ductal leak. (**c**) Balloon dilation of stricture. (**d**) CT with stent post-ERCP

This intervention combined with other therapeutic endoscopy techniques has allowed many patients to avoid surgery.

Having the ability to place a pancreatic duct stent does not mean that one must provide endotherapy whenever the possibility of a pancreatic leak is entertained. Patients with pancreatic leaks are best served by a team including interventional radiologists, pancreaticobiliary surgeons, and endoscopists [1, 3, 45]. Ideally, the interventional plan should be developed in a collaborative way and involve high-quality cross-sectional imaging in the form of CT and/or MRI to map the leak and its complications. The main contraindication to ERCP in the setting of a leak is the inability to provide endotherapy as in that situation the unsuccessful intervention may lead to infection of the previously sterile fluid collection and subsequently result in the need for drainage or possibly surgery [32]. One example of such a situation is DDS, where the role of ERCP to treat this condition is limited while injection of the pancreatic duct can result in infection of preexisting sterile fluid collections. Furthermore, many patients with pancreatic leaks will experience resolution of their leaks without any intervention. For instance, the majority of low-volume leaks after pancreatic surgery are easily controlled with a JP drain and will spontaneously close over days to weeks [23, 46].

While not all patients with a pancreatic duct leak require intervention, a large number will benefit from endotherapy, percutaneous drainage, or surgical interventions. Indications for interventions include enlarging fluid collections despite conservative management, symptomatic or infected fluid collections, external fistulas, and recurrent pain or pancreatitis during recurrent attempts at refeeding [41].

Pancreatic Ascites

Patients with pancreatic ascites typically present with abdominal distention and abdominal pain. The diagnosis can be made by measuring the levels of amylase and lipase in paracentesis fluid; very high levels confirm the diagnosis. This manifestation typically occurs in the setting of a large volume pancreatic leak which the body has failed to contain. Pancreatic ascites have been historically managed primarily by making the patient NPO with TPN and octreotide with the addition of paracentesis and thoracentesis if a pleural effusion is also found. If the patient did not respond to this conservative management a salvage operation was performed. In this setting pancreatic resections carry an 8–11 % mortality and the leaks have a 15 % recurrence rate [41].

Given the high mortality and recurrence rates with surgical interventions for pancreatic ascites endotherapy is an attractive alternative. Our group was the first to demonstrate that the placement of a transpapillary pancreatic duct stent via ERCP was an effective treatment in this setting [34]. These results have been confirmed in several other studies [47–50]. It has also been shown that placing the stent across the ductal disruption optimizes the likelihood of a therapeutic response.

The mechanism by which pancreatic stenting is effective in the setting of pancreatic ascites is by returning flow of pancreatic juices into the duodenum rather than through the leak, therefore allowing the leak to heal. The stent bypasses upstream barriers to ductal flow such as the sphincter, or inflammatory strictures in the duct. This approach will not be effective if the pancreatic ascites are the result of DDS. In DDS a section of the pancreas has been completely separated from the head of the pancreas, making a stent across the ampulla ineffective and surgery has historically been recommended [41, 50].

Pseudocyst

Pseudocysts are the most common presentation of a pancreatic duct leak and can typically be diagnosed by high-quality cross-sectional imaging. Characteristics of pseudocysts include a well-formed, thick capsule and a homogenous internal fluid component. Pseudocysts either

represent an ongoing ductal leak or the after effect of a healed leak. Unfortunately, it has become clear that cross-sectional imaging is ineffective at differentiating between a true pseudocyst and evolving necrosis or WOPN [32]. CT imaging tends to overemphasize the fluid component of these cystic lesions and can miss areas of necrotic tissue and debris. Therefore, the treatment of peripancreatic collections should not be taken lightly and is best handled by a team including gastroenterologists, interventional radiologists, and surgeons [1, 3, 45]. A clinical history of severe acute pancreatitis should suggest that resultant fluid collections have a high likelihood of representing WOPN. The management of pseudocysts and WOPN differs significantly and patients with WOPN treated as pseudocysts can have severe complications [32]. The management of WOPN is covered in other chapters in this book.

Historically, symptomatic or non-resolving pseudocysts were treated with open surgery with cyst-enteric or cyst-gastric anastomoses and complex cysts were further treated with drainage [52–55]. However, surgery had a 25–30 % rate of morbidity and a 2–5 % 30-day mortality as well as a 10–20 % recurrence rate [40, 55–57]. Because of these high rates of complications most centers have moved to laparoscopic surgical procedures if surgery is performed, and an insistence on preoperative ERCP or MRCP [56, 58–60]. Furthermore, many centers have moved to nonsurgical management of pseudocysts either with endoscopic or interventional radiology drainage.

The first description of endoscopic drainage of pancreatic pseudocysts was in 1975 by Rogers who used a transgastric needle to drain a pseudocyst, although this collection did recur rapidly [61]. Not long thereafter our group published the first description of using electrocautery to fistulize pseudocysts into the stomach, demonstrating a permanent cure in three out of four patients [62]. While the procedure has been enriched to some degree since then, the basics remain the same. The endoscopist must first establish access to the cyst cavity with a needle-knife sphincterotome or a 19-gauge EUS needle. Patients should receive pre-procedural antibiotics. Previously the initial access incision was enlarged with electrocautery, but now most endoscopists use hydrostatic balloons of varying diameters for this purpose. Once the cystogastrostomy or cystenterotomy has been dilated, most endoscopists will place two or more double pigtail stents or varying sizes across the defect to maintain the patency of the fistula to allow for complete resolution of the pseudocyst [63–70]. Double pigtail stents are typically used for this situation in order to reduce the risk of migration [71]. After drainage the patient is followed with imaging such as CT until complete resolution of the cyst, at which point the stents are removed. Alternatively, stents can be left indefinitely, particularly in the setting of DDS [72, 73]. ERCP can be done at the same time as pseudocyst drainage to characterize ductal anatomy and place a stent if a persistent leak is identified [1, 5].

With the advent of EUS, many have advocated for EUS as the preferred choice to initiate pseudocyst drainage. For patients who have concomitant gastric varices it is generally preferred to utilize EUS so that intervening blood vessels can be identified and avoided. EUS also allows for endoscopic drainage, even in cases where a bulge within the gastrointestinal lumen cannot be identified on endoscopy [68, 70, 74–76]. With the first generation of linear echoendoscopes, the working channel diameter was only 2.8 mm, which limited the size of stents that could be inserted; therefore, initially, most endoscopists would exchange the echoendoscope for a duodenoscope after a wire was advanced into the cyst cavity. New therapeutic linear scopes have a larger 3.7-mm diameter channel, which allows for placement of up to 10-Fr stents. Antillon et al. were the first to publish a series demonstrating that single-step EUS pseudocyst drainage was safe and had good efficacy [77]. Kahelah et al. evaluated EUS-guided drainage by following 99 patients undergoing pseudocyst drainage, 46 with EUS and 53 without. Patients who had a visible bulge in the GI tract had drainage without EUS, while those with no bulge had EUS-guided drainage. They demonstrated no difference in efficacy or safety between the groups suggesting that non-EUS-guided drainage remains a reasonable choice for the right patient [78].

Another technique that can be used instead of, or in addition to, transmural drainage of pseudocysts is transpapillary drainage of pseudocysts. Multiple published series have demonstrated the effectiveness of placing stents into the pseudocyst cavity through the major or minor papilla [45, 79–81]. Stents can either be placed into the cavity itself or across the leak within the pancreatic duct. Trevino et al. demonstrated that this method of stenting can also be used to improve the success of transmural drainage as a combination approach [82].

An alternative to endoscopic or surgical treatment of pseudocysts is percutaneous drainage. This method has been shown to be up to 90 % effective for the treatment of pseudocysts [83]. The administration of subcutaneous octreotide to patients who underwent percutaneous drainage has been demonstrated to reduce the amount of time to pseudocyst resolution [84]. The main downside to percutaneous drainage is the high rates of development of percutaneous fistulas. One way to reduce this risk is with concomitant transmural drainage, as has been demonstrated for the treatment of WOPN [85]. In the event of a percutaneous fistula, salvage transmural drainage through a combined interventional radiology and endoscopic procedure has been shown to be effective [86]. The main situations where percutaneous drainage is preferred include patients who are symptomatic but have immature fluid collections and patients who are not surgical candidates and have fluid collections that are not adjacent to the gastrointestinal tract.

It remains unclear whether one method of pseudocyst drainage is superior as no large randomized trials have compared the different options. Recently, Varadarajulu et al. published the results of a randomized controlled trial comparing surgical and endoscopic pseudocyst drainage techniques. In this study 20 patients underwent surgical drainage and 20 underwent endoscopic drainage. Both methods demonstrated excellent success at initial resolution of the pseudocyst in all patients, and only one patient had recurrence in the surgical group and none in the endoscopic group. Patients in the endoscopic group had decreased hospital stay, decreased healthcare costs, and improved physical and mental health [87]. The same group previously published a retrospective study also comparing surgical and endoscopic methods and again showed no difference in efficacy, but decreased costs and hospital stay in the endoscopic group [69]. Several studies have compared EUS and non-EUS-guided transmural drainage and have generally demonstrated that patients with a bulge in the gastrointestinal tract seen can be drained by EUS or non-EUS methods without significant differences [78]. However, if no bulge is seen then EUS drainage will generally be successful, while non-EUS drainage should not be attempted without good cross-sectional imaging to direct therapy. Varadarajulu et al. randomized patients to EUS or EGD drainage and found that all 14 EUS drainages were successful, while only 5 of 15 patients randomized to EGD drainage were done successfully; all 10 EGD failures were crossed-over to EUS drainage with a successful outcome [88]. Park et al. published the results of another randomized trial that showed similar results with eight patients with no bulge crossing over to successful EUS drainage, with all patients in the study having eventual successful drainage [89]. In a study published by Fockens et al., the use of EUS changed management in 37.5 % of pseudocyst drainages because of a multitude of unexpected findings [90].

In summary, endoscopic treatment of pancreatic pseudocysts appears to be effective, with a 94 % initial success rate, 90 % cyst resolution rate, and a 16 % recurrence rate with a 20 % complication rate and mortality rate less than 1 % [91]. Outcomes are different based on the etiology of fluid collections [32]. EUS drainage is preferred and is required if no bulge is seen within the gastrointestinal tract. Because of the risk of adverse events, endoscopic drainage is best done in settings with significant experience and a multidisciplinary team. Alternative drainage options include surgery or percutaneous drainage.

Pancreatic Fistula and Trauma

Pancreaticoenteric fistulas occur in a variety of situations, including erosion of pseudocysts, WOPN, or percutaneous drains into neighboring structures. These fistulas can occur in the setting of acute or chronic pancreatitis. Often, these fistulas can present as spontaneous, rapid resolution of fluid collections and require no treatment. However, a stenosis can develop at the site of ductal disruptions, which may result in relapsing attacks of pancreatitis. Fistulization into the bile duct may result in cholestasis or cholangitis, while fistulas into the colon may result in recurrent sepsis.

Our group has now treated more than 30 patients with pancreaticoenteric fistulas. In our initial series of eight patients with pancreaticoenteric fistulas, three healed after transpapillary stenting, three healed after downsizing or removal of an external drain that had eroded into a loop of bowel, and two required surgical intervention [92]. Biliary fistulas will generally heal with simultaneous biliary and pancreatic duct stents if DDS is not present [93]. An alternative treatment for pancreaticocolonic fistulas is diverting ileostomy. This intervention reduces bacterial translocation and resultant sepsis [94].

Acute abdominal trauma can also result in pancreatitis and pancreatic duct leaks and fistulas. This can result in a wide variety of manifestations and symptoms may be masked by other injuries. Pancreatic injury occurs in 55 % of blunt trauma and 8 % of penetrating abdominal injuries. Pancreatic injury is associated with up to 30 % mortality and 45 % morbidity [95]. Therefore, pancreatic injury should be considered in all cases of severe abdominal trauma. In pancreatic trauma the integrity of the main pancreatic duct is the most important determinant of prognosis. Unfortunately, CT imaging is very poor at diagnosing pancreatic injuries, with a sensitivity of roughly 50 %. However, ERCP has been shown to be very accurate at diagnosing pancreatic trauma [96].

The high mortality associated with pancreatic injury and worse prognosis with later diagnosis have led some to propose early ERCP if there is any suspicion of pancreatic injury. Kim et al. diagnosed abnormal pancreatograms in 14 of 23 patients with acute abdominal trauma. Eight of these patients had complete transections, which were treated with surgery, three had main pancreatic duct leaks that were confined to the parenchyma and treated with stenting, and three branch leaks were successfully treated conservatively. The authors concluded that early ERCP was beneficial in patients with possible pancreatic duct injury [97]. Bhasin et al. reported the successful endoscopic treatment of 9 of 11 patients with pancreatic trauma with transpapillary stenting, nasopancreatic drain, or cystogastrostomy, with the other two patients requiring surgery for complete transections [98]. Other small series have also demonstrated that minor ductal trauma can be treated with pancreatic stenting [5, 51]. However, higher-grade trauma still generally requires emergent surgical intervention.

While ERCP does provide the benefit of potentially intervening in some pancreatic injuries, it does expose patients to the risk of procedural pancreatitis and can be limited by the endoscopists' ability to cannulate the pancreatic duct. MRCP and S-MRCP may be an improved modality to define which patients will have the greatest benefit from therapeutic ERCP while avoiding the potential complications of ERCP for those who will not require endotherapy. MRCP has the additional benefit of being able to image the parts of the pancreas that are proximal to any ductal disruption and are therefore not visible on ERCP [37–39]. It remains unclear which modality is superior for evaluating potential pancreatic injury and further research is necessary.

External Fistula

External pancreatic fistulas are typically iatrogenic in etiology. The most common situations in which they arise are percutaneous drainage of pancreatic fluid collections such as WOPN or after pancreatic surgery. The likelihood of developing an external fistula increases greatly if percutaneous drainage is performed in the setting of DDS [85].

Patients undergoing surgery for non-pancreatic indications may develop pancreaticocutaneous fistulas if unintended trauma to the pancreas occurs [1, 3, 6, 45]. Penetrating abdominal trauma is a non-iatrogenic cause of external fistulas.

The management of external pancreatic fistulas varies based on their etiology and clinical presentation. Many patients, particularly those with fistulas after pancreatic surgery, will respond to conservative management. Conservative therapy consists of nasojejunal feeding, systemic antibiotics to prevent or treat infectious complications, correction of fluid and electrolyte imbalances, and skin care. In particular, nasojejunal feeding has been shown to improve closure rates and decrease time to closure of pancreaticocutaneous fistulas as compared with TPN [99]. The use of somatostatin analogues such as octreotide in this setting has been studied extensively. Based on currently available data it appears that these agents can reduce the output of external pancreatic fistulas but do not affect the likelihood of or time to fistula closure [100]. Therefore, the use of octreotide should be limited to patients with high-output fistulas that are causing extensive electrolyte imbalance or significant skin complications.

Unfortunately, not all patients with cutaneous fistulas will respond to conservative therapy. Patients with fistulas after pancreatic surgery are likely to respond over weeks to months while patients with percutaneous drainage for DDS are highly unlikely to respond. For unresponsive patients, endoscopic therapy is usually the next option. Our group first described the use of multiple length stents for bridging ductal disruptions and short stents for tail leaks in this setting. Nine patients with cutaneous fistulas were included in the study with various etiologies for their fistulas. Three patients had stents placed that bridged the site of disruption, while the other six had stents that did not bridge the disruption. Successful closure of the fistula was achieved in eight of nine patients, including 5 within 48 h of stent placement [101].

Since our description, several other series have been published on the effectiveness of pancreatic stents for external fistulas. Costamagna et al. described the endoscopic management of 16 patients who developed fistulas after open abdominal surgery and failed conservative management. In this study patients were primarily treated with nasopancreatic drains, which were subsequently removed when the fistula closed. Drains were successfully placed in 11 of 15 patients and all patients were successfully treated except for one who was subsequently successfully treated with a pancreatic stent. Mean time to fistula closure was only 8.8 days and there was no fistula recurrence after a mean 24.7 months of follow-up [102]. Halttunen et al. also described 18 patients with cutaneous pancreatic fistulas treated endoscopically. In this series 13 patients had effective closure of the fistula. Overall published results have shown an 85 % rate of successful stent placement in the setting of cutaneous fistulas, with 92 % of those successfully stented achieving closure of the fistula [103].

DDS is commonly complicated by external pancreatic leaks but is generally not amenable to transpapillary pancreatic stenting. Fistulas from DDS are secondary to persistent fluid output from a tail segment of the pancreas that has been completely separated from the head of the pancreas by pancreatic necrosis. In this setting, placement of a transpapillary stent has no impact on the flow of pancreatic juice from this tail segment. Our group has recently described a combined endoscopic and interventional radiology technique for treatment of pancreaticocutaneous fistulas in the setting of DDS [86]. In this technique, initially a radiologist will pass a TIPS needle into the fistula tract. Using fluoroscopic and endoscopic guidance this needle is then passed through the gastric wall into the stomach lumen. The tract into the stomach is then dilated with an 8-Fr microcatheter after which two guide wires are passed into the stomach and grasped by the endoscopist using a snare and pulled up through the endoscope. Over the guidewire the transgastric tract is then further dilated with an 8-mm balloon. Subsequently, two double pigtail stents are passed over the wires to bridge the gastric wall. This technique has been used successfully in 15 patients. Three patients had recurrent fluid collections in a 25-month follow-up period secondary to stent migration, but all three

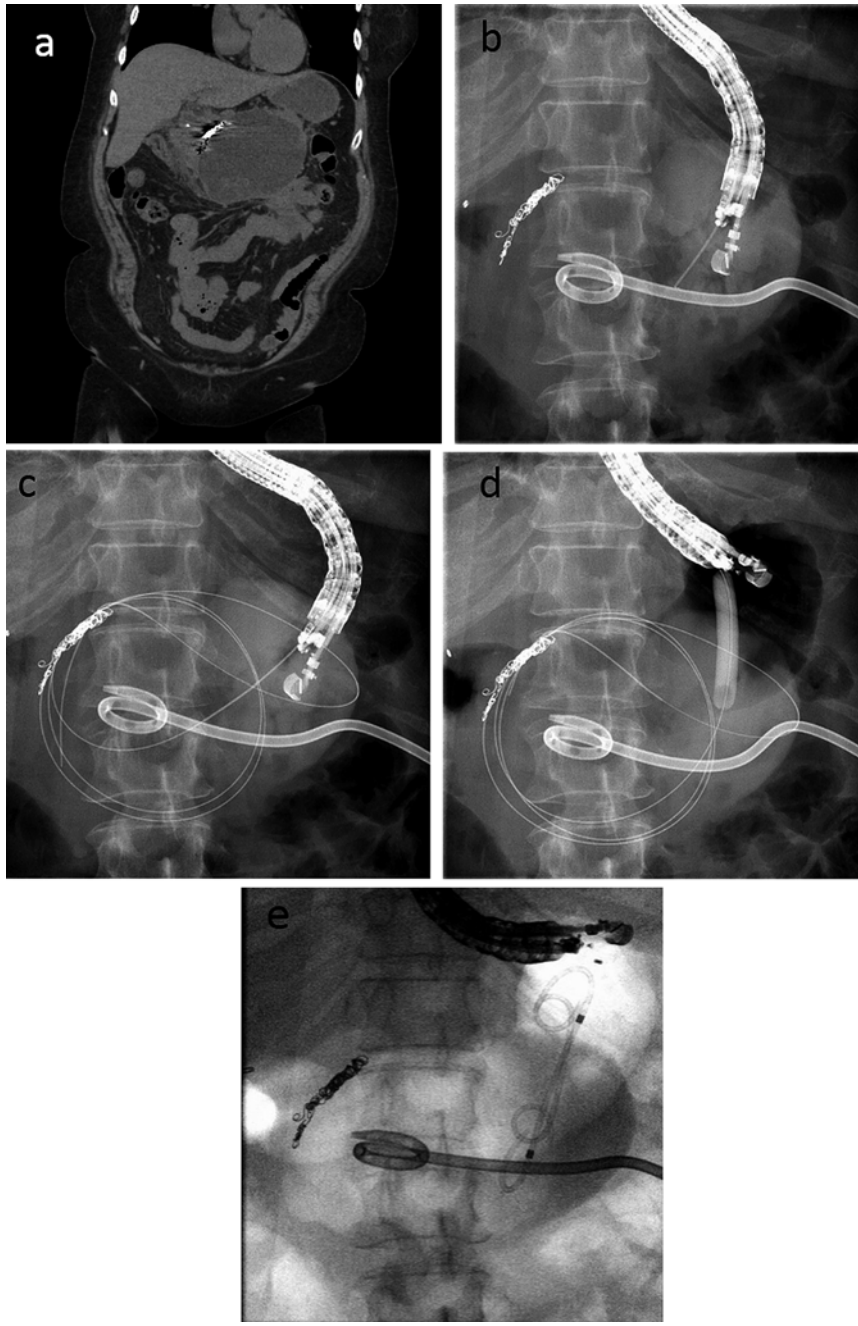

Fig. 12.3 Patient with severe acute pancreatitis with walled-off pancreatic necrosis and disconnected duct syndrome treated with percutaneous drain and transgastric stents. (**a**) CT demonstrating large WOPN. (**b**) EUS 19-gauge needle access and contrast injection of collection. (**c**) Guidewire placed within collection. (**d**) Balloon dilation of cystogastrostomy tract. (**e**) Two double pigtail transgastric stents placed across cystogastrostomy

were treated with endoscopic transmural drainage. Our current management strategy for WOPN attempts to prevent cutaneous fistulas in the setting of DDS by placing both percutaneous and transgastric drains at the onset of treatment [85] (Fig. 12.3).

In addition to their role in our combined technique described above, interventional radiologists

also have the ability to treat external pancreatic fistulas with techniques such as cyanoacrylate injection. Effective use of percutaneous drains has also been shown to be highly effective treatment for postsurgical pancreatic fistulas [104].

Disconnected Duct Syndrome

DDS represents the most severe form of a pancreatic leak as the pancreatic duct is effectively transected. This generally occurs as a result of severe acute pancreatitis with pancreatic necrosis. It occurs in up to 50 % of patients with necrotizing pancreatitis [105]. This occurs when any portion of the head, genu, or body of the pancreas is necrosed with autodigestion of the main pancreatic duct. This results in the entire upstream portion of the pancreas being isolated and not in communication with the papilla. Given that this isolated segment of the pancreas will continue to produce its exocrine pancreatic juices, they may be secreted into the abdominal cavity, resulting in a significant fistula. This type of fistula is not amenable to transpapillary stenting because the isolated portion of the pancreas cannot be reached from the papilla and, therefore, the leak cannot be bridged.

Historically DDS has required surgical excision of the isolated tail segment of the pancreas. However, endoscopic and interventional treatments have been introduced with varying success [106].

Endoscopic management of DDS has been described in several series [2, 73, 86, 105, 107] (Fig. 12.4). The treatment involves transmural drainage of fluid collections followed by leaving

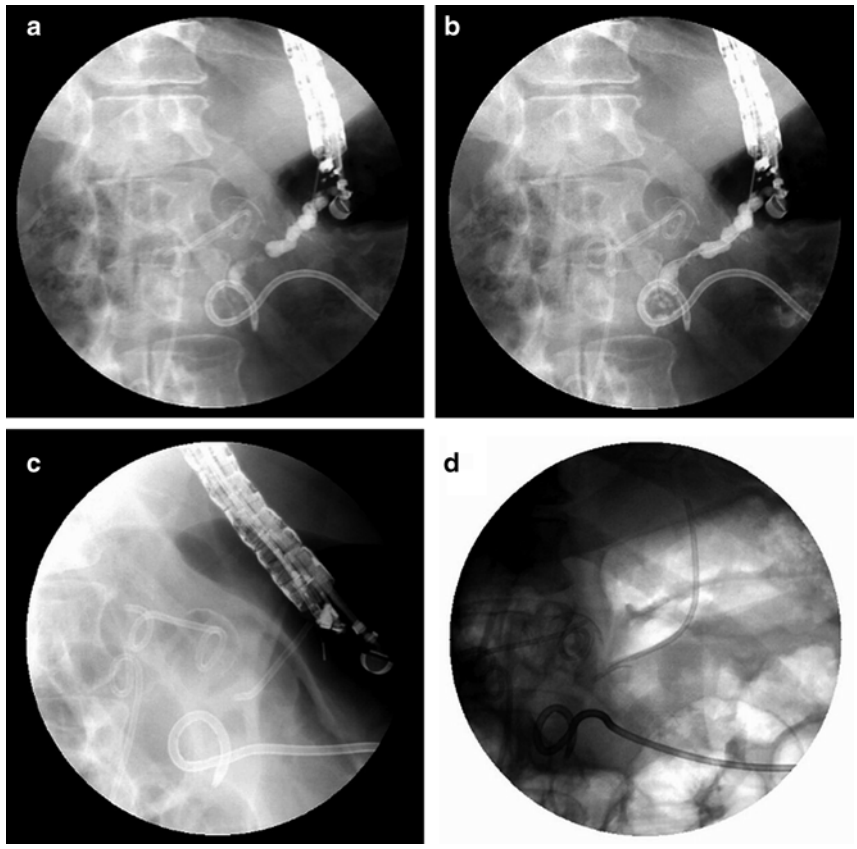

Fig. 12.4 Patient with disconnected duct syndrome with external pancreatic fistula. EUS-guided pancreatogram demonstrates disconnected tail segment's duct. Treated with transgastric stenting. (**a**) Initial transgastric EUS-guided pancreatogram demonstrates disconnected segment of dilated pancreatic duct. (**b**) Guidewire placed within the pancreatic duct. (**c**–**d**) Stent placed into disconnected duct

transmural stents in place indefinitely. Leaving transmural stents in place indefinitely creates an outlet for the pancreatic juice from the isolated tail, therefore preventing the development of fluid collections and symptoms.

Deviere et al. were the first to describe their experience with transmural drainage for DDS. They demonstrated successful endoscopic treatment in 12 of 13 patients with DDS [73]. Pelaez-Luna et al. published the Mayo clinic experience with DDS. Over a 7-year period they treated 31 patients with DDS, with 5 patients going straight to surgery and 26 undergoing endoscopic treatment. Of the patients undergoing endoscopic treatment, 19 had good long-term success while 7 eventually required surgery [2]. Varadarajulu et al. also described their experience with 33 patients with DDS. In their series 8 patients underwent surgery while 22 were successfully treated with transmural drainage with prolonged stenting. No patients experienced recurrent fluid collections despite three having spontaneous passage of stents after more than 100 days of follow-up [105]. Other small series have also demonstrated some success with endoscopic drainage.

Our group recently described a combined endoscopic and percutaneous treatment for WOPN and DDS with excellent results [85] (see Fig. 12.3). In our prior experience treating WOPN with percutaneous drains alone, many patients developed external fistulas secondary to DDS with the inability to subsequently remove the drains. Therefore, we now place transmural stents in addition to percutaneous drains for the treatment of WOPN. Transmural stents are left in place indefinitely for patients with DDS and pulled if the duct is intact once the fluid collections resolve. With this new technique we have avoided both cutaneous fistulas and greatly reduced the need for surgery for DDS. We have now treated more than 100 patients with WOPN with this technique with <1 % death related to pancreatitis and <5 % requiring surgery.

In addition to endoscopic treatments for DDS, interventional radiologists can offer other minimally invasive, surgery-sparing treatments. Our group has recently described a combined IR and endoscopic treatment for DDS and external pancreatic fistulas [86]. Further details regarding this technique are described in the section on external fistulas above. Interventional radiology administered cyanoacrylate or other glues has also been described as a treatment for DDS with an external pancreatic fistula [108, 109]. In this technique a guidewire is advanced into the main pancreatic duct within the isolated segment of the pancreas. Subsequently, a microcatheter is advanced over the wire and glue is then injected to completely fill the pancreatic duct and all of its side branches within this section of the pancreas. This works best with a small, 3- to 4-cm segment of pancreas and is associated with mild procedural pancreatitis in 50 % of patients.

Adverse Events

The most common adverse events when using endoscopy to treat pancreatic duct leaks are procedural-related pancreatitis and iatrogenic fistulas. However, other complications including drug reaction, aspiration, cardiopulmonary events, cholangitis, bleeding, and perforation can occur [110]. Pancreatitis flares approximate 10 % but may approach 50 % if pancreatic duct stenting is unsuccessful after multiple accessories are advanced into the pancreatic duct. The placement of a transpapillary stent does lower the risk of pancreatitis and attenuates the disease course if pancreatitis does occur [111]. Similarly, the administration of PR indomethacin has been shown to reduce the risk of post-ERCP pancreatitis in high-risk individuals [112]. Stent characteristics can also affect the risk of pancreatitis. Stent diameter should be adjusted to the size of the duct. For instance, a 7-Fr stent should not be used for a duct that is only 4 Fr in diameter. Similarly, a 1-cm long stent should not be used to bridge a ductal leak that is only 4 cm from the papilla.

Subacute adverse events can occur from introduction of bacteria into fluid collections or

necrotic debris at the time of ERCP. As such, all patients with internal fistula should get prophylactic antibiotics prior to ERCP, particularly in the case of WOPN. Contaminated collections should be considered for percutaneous or transmural drainage or a course of post-ERCP antibiotics.

Pancreatic stent occlusion can be associated with pancreatic sepsis and obstructive pancreatitis [113]. Also, long-term transpapillary stent placement can cause iatrogenic ductitis with focal strictures and side branch ectasis [114]. Therefore, stents should be removed or exchanged 4–6 weeks after placement. Stents placed for treatment of external fistulas should be removed 1 week after the fistula closes.

Conclusion

Over the past 30 years, the management of patients with pancreatic duct leaks and their multiple consequences and manifestations has evolved. Rather than surgeons managing all leak patients who do not respond to conservative therapy, patients are now best served by a multidisciplinary team including gastroenterologists, interventional radiologists, and pancreatic surgeons. Many leak patients can be managed by endoscopic or radiologic-guided interventions and therefore avoid surgery. ERCP with transpapillary stenting remains the cornerstone of therapy for leaks that do not have DDS. Stenting will likely result in resolution of the leak, particularly if the stent is able to bridge the disruption. Peripancreatic fluid collections such as pseudocysts and WOPN can be treated with endoscopic transmural drainage, percutaneous drainage, or a combination of the two techniques. DDS is no longer a condition treated only with surgery as many patients will respond to long-term transmural stenting and some may respond to IR-directed therapies. Pancreatic leaks remain a challenging and highly morbid complication of pancreatitis, but endoscopic techniques have evolved and likely will continue to evolve to improve outcomes for these patients.

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Endoscopic Management of Severe Gallstone Pancreatitis

13

Takao Itoi and Peter V. Draganov

Introduction

Acute gallstone pancreatitis is thought to be a consequence of a transient or persistent ampullary obstruction by gallstones or sludge resulting in compromised outflow of bile and pancreatic juice. This obstruction of flow can trigger cholangitis or inflammation of the pancreas [1, 2]. Although most attacks of gallstone pancreatitis are mild and recover with conservative treatment, approximately 25 % of the patients will develop severe disease, which still carries high morbidity and mortality [3–5]. In general, as a first step in the diagnostic evaluation of patients with gallstone pancreatitis, consideration is given to noninvasive diagnostic modalities such as blood chemistries, transabdominal ultrasonography (AUS), computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP) [5–9]. In our discussion we will focus on the role of endoscopy for the management of patients with acute gallstone pancreatitis and will specifically address the following questions which are of direct practical importance: (1) What is the role of endoscopic evaluation by endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) for the detection of retained bile duct stones [10–15]?; (2) What is the role of early ERCP with endoscopic sphincterotomy (ES)? (3) What is the optimal timing of early ERCP? (4) Are there any regional geographic differences that may affect our management strategies? (5) How does one incorporate the available data into a comprehensive patient management algorithm [16–23]? Some authors make the distinction between gallstone pancreatitis (i.e., the migrating stone originates from the gallbladder) and biliary pancreatitis (i.e., the migrating stone may originate in the gallbladder or the bile duct), but in this review we will use the two terms interchangeably. Furthermore, the terms common bile duct (CBD) stones, bile duct stones, and choledocholithiasis will all refer to stones in the extrahepatic bile duct.

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Endoscopic Diagnosis of Bile Duct Stones

EUS

EUS allows for high-resolution imaging of the bile duct which provides high sensitivity and specificity of more than 90 % for detection of CBD stones [10–14] (Fig. 13.1). EUS accuracy is far superior

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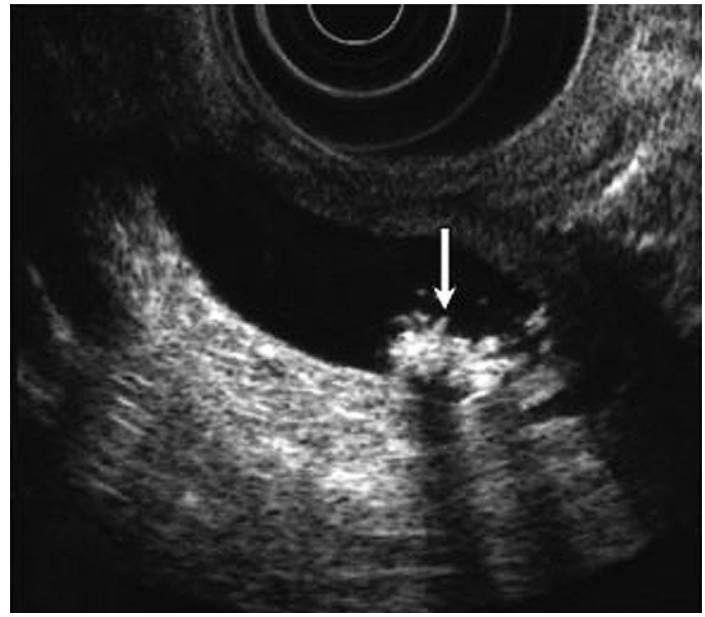

Fig. 13.1 Endoscopic ultrasound image of hyperechoic bile duct stone (*arrow*) with hypoechoic acoustic shadow

to AUS, CT, and even ERCP [10, 14]. In fact, in cases in which AUS had failed to identify abnormality, CBD stones were detected in 59–78 % of cases by performing EUS [10, 12]. Importantly, EUS accuracy is not affected by the stone size [11]. In contrast, it is recognized that MRI/MRCP may not be able to detect small CBD stones (i.e., <5 mm) [24]. Thus, since impacted gallstones may pass spontaneously [1], EUS may be a very helpful test to both rule-in or rule-out bile duct stones and provide guidance for the patient who would benefit from ERCP. Indeed, one prospective randomized study showed that EUS could safely replace diagnostic ERCP in selected patients with acute biliary pancreatitis [14]. Furthermore, one meta-analysis concluded that EUS has an excellent overall sensitivity and specificity for diagnosing choledocholithiasis and it should be used to select patients for a therapeutic ERCP in order to minimize the risk of complications associated with unnecessary diagnostic ERCP [25].

There are two types of EUS equipment, namely, radial and curved linear (convex). Radial EUS has been used in prior studies evaluating its role for detection of CBD stones [10–14]. Although there was no comparative study between radial and curved linear array EUS for the detection of CBD stones, most likely the two types of equipment can be used interchangeably depending on operator experience and availability. Indeed, the curved linear EUS has been shown to be useful for the diagnosis of CBD stones [26] and for the staging of pancreatic head cancer and can provide excellent imaging of the distal bile duct [27]. Although EUS has been shown to be superior for the detection of CBD stones compared to AUS, CT, or MRCP [10–14], it is still not currently a worldwide standard procedure performed early in the course of acute biliary pancreatitis because it tends to be time-consuming and it requires an experienced operator.

In summary, EUS has excellent sensitivity and specificity for detection of CBD stones and one can consider using it as a first-line test in institutions with available expertise.

Endoscopic Retrograde Cholangiopancreatography

ERCP has three strengths for diagnosis of gallstone pancreatitis: (1) endoscopic imaging of the ampulla, (2) direct cholangiography, and (3) intraductal ultrasonography (IDUS) and cholangioscopy.

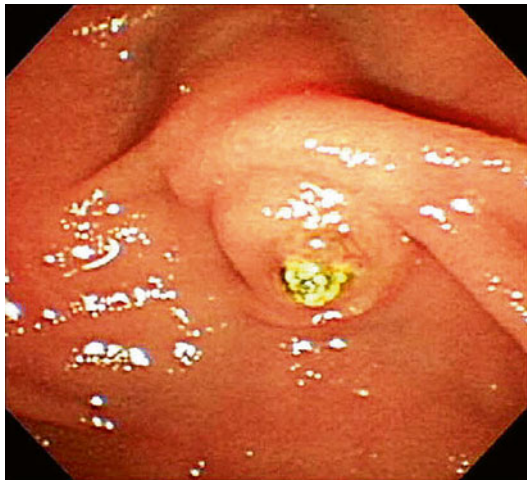

Fig. 13.2 Gallstone impacted at the ampullary orifice

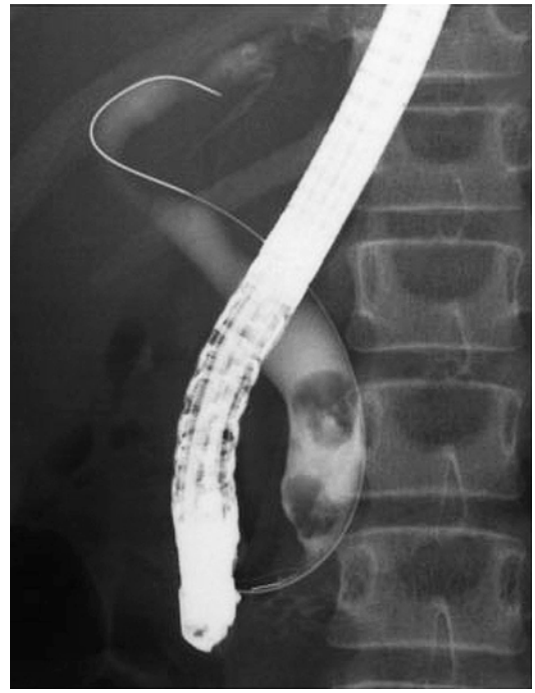

Fig. 13.3 Cholangiogram showing two distal bile duct stones

Endoscopic Imaging

A side-view duodenoscope can easily detect an impacted stone per se (Fig. 13.2) or an enlarged papilla suggesting an intrapapillary impacted stone.

Direct Cholangiography

Cholangiography using contrast medium allows delineation of bile duct stones under fluoroscopic imaging (Fig. 13.3) and it is traditionally considered the "gold standard" for detection of choledocholithiasis. In general, since the size of gallstones tends to be relatively small in patients with gallstone pancreatitis, the detection rate of cholangiography by ERCP appears higher than by MRCP [15]. However, one should consider that biliary cannulation is not always successful though EUS can provide detailed bile duct imaging in almost all cases [14].

Intraductal Ultrasonography and Direct Cholangioscopy

IDUS, which provides high resolution (20 MHz) cross-sectional images, allows the delineation of gallstones during ERCP (Fig. 13.4). IDUS in combination with direct cholangiography by ERCP is superior to ERCP alone in terms of gallstone detection rate (95 % vs. 90 %) [15]. In particular, the detection rate of gallstones less than 3 mm in size was superior to that of cholangiography (100 % vs. 0 %) [15]. Similarly, cholangioscopy provides an improved detection rate over standard cholangiograms for small bile duct stones (Fig. 13.5) [28, 29]. However, since ES and balloon sweep of the bile duct is typically carried out at the time that ERCP is performed for evaluation of a patient with acute gallstone pancreatitis, one can question the clinical value of detecting very small stones by IDUS or cholangioscopy because these stones will be easily removed, or spontaneously pass, after ES. Furthermore, ERCP-related procedures have obvious deficiencies because biliary cannulation is not always successful, though it is achieved in more than 90 % of the cases [30].

In summary, purely diagnostic ERCP with standard cholangiogram should be avoided in patients with gallstone pancreatitis. At present, there is no established role for IDUS and cholangioscopy in these patients. ERCP should be performed only when therapeutic intervention is planned.

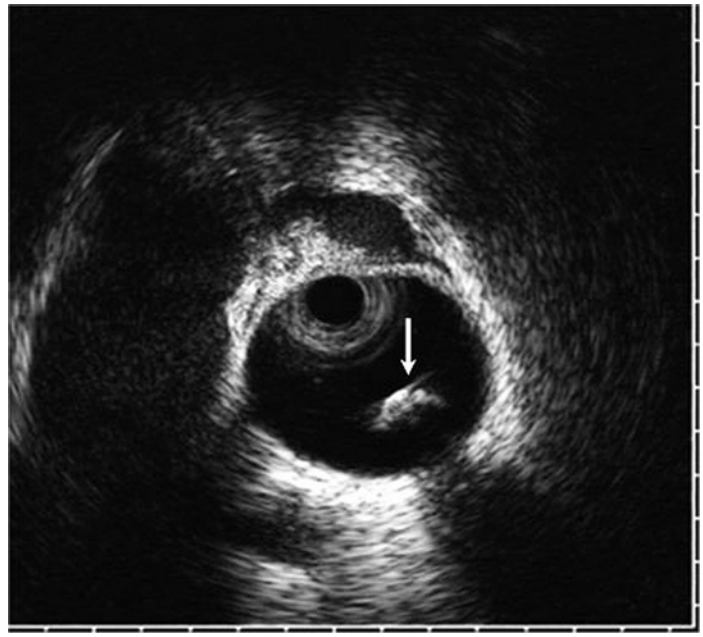

Fig. 13.4 Intraductal ultrasound image of hyperechoic bile duct stone (*arrow*) with hypoechoic acoustic shadow

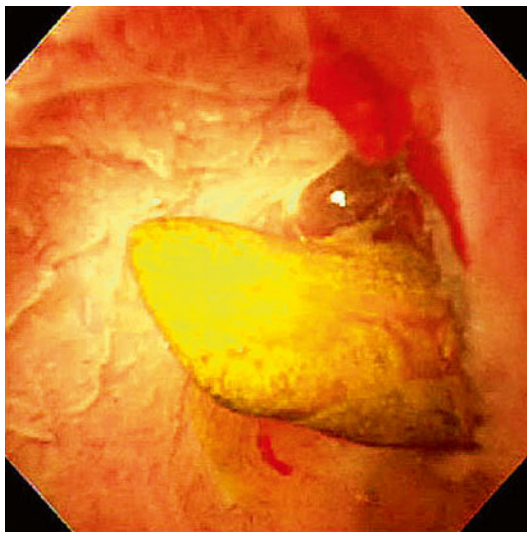

Fig. 13.5 Cholangioscopy providing direct visualization of a bile duct stone

The Role of Endoscopic Treatment with ERCP

Gallstone pancreatitis is triggered by obstruction of the flow of bile and pancreatic juice at the level of the ampulla. Therefore, it is logical to consider that relieving the obstruction by performing early ERCP with biliary ES and extracting any remaining CBD stones would be of benefit. In 1988 Neoptolemos et al. published the first randomized controlled study comparing early ERCP with ES vs. conservative management alone in patients with gallstone pancreatitis [17]. Since then six more randomized controlled studies have been published, followed by a number of meta-analyses and guidelines; but despite this significant effort controversy still remains regarding the necessity and timing of ERCP with ES [7, 8, 17–23, 31–55]. When managing patients with gallstone pancreatitis the two main questions related to the role of ERCP are the following: (1) Which patients would benefit from early ERCP with ES? (2) Which patients are likely to have retained CBD stones and would benefit from ERCP with stone extraction prior to laparoscopic cholecystectomy?

The Role of Early ERCP with ES in Patients with Acute Gallstone Pancreatitis

The meta-analyses [31–38, 42] and guidelines [7, 8, 44–55] do not recommend the routine use of

early ERCP with or without ES for all patients with acute gallstone pancreatitis. A notable exception is one meta-analysis [31] that showed benefit from early ERCP in all patients. The results of this meta-analysis were significantly influenced by the inclusion of data from one randomized controlled trial [19] that was reported in abstract form only close to 20 years ago and still has not been published as a full manuscript through the peer review process. Therefore, the present consensus is that ERCP with ES should not be performed routinely in patients with acute gallstone pancreatitis. Could early ERCP/ES be of benefit in selected patients?

Subgroups of Patients Who May Benefit from Early ERCP?

The use of early routine ERCP is controversial in patients with predicted severe gallstone pancreatitis. Several meta-analyses have shown benefit from early ERCP [32–36] while in others no statistical significance was detected [38, 41, 42] between early ERCP and a conservative management approach. These conflicting findings stem from several differences: (1) selection of studies included in the meta-analyses, (2) criteria for predicting the severity of pancreatitis, (3) methodology of diagnosis of gallstone pancreatitis, (4) strategy and timing of ERCP. Interestingly, the latest meta-analysis by Tse and Yuan, which assessed the clinical effectiveness and safety of early routine ERCP compared to conservative management based on all important, clinically relevant, and systemic complications as defined by the Atlanta Classification [56], stated that they found no statistically significant difference in mortality, local (pancreatic pseudocysts, necrosis, or abscess) and systemic complications (organ failure including shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding; disseminated intravascular coagulation or severe metabolic disturbances) between the two strategies in patients with predicted severe gallstone pancreatitis [42]. As a result, there is no consensus in the guidelines in terms of the superiority of early routine ERCP with or without ES in patients with predicted severe gallstone pancreatitis compared to routine conservative management [7, 8, 44–55]. Despite this lack of full consensus, the general practice across the world is to avoid routine early ERCP in these patients.

Subgroups likely to benefit from early ERCP with ES are patients with coexistent active cholangitis or biliary obstruction. Indeed, five of seven meta-analyses found early ERCP to be superior to conservative management in patients with acute gallstone pancreatitis and coexistent cholangitis [32–37, 42]. The latest meta-analysis found that routine early ERCP with or without ES significantly reduced the mortality and the local and systemic complications in this group of patients [43]. On the other hand, regarding coexistent biliary obstruction in the absence of cholangitis, only two meta-analyses have evaluated the use of routine early ERCP for this subgroup [32, 42]. The later study found that routine early ERCP with or without ES did not significantly reduce the mortality and local and systemic complications [42] though an earlier meta-analysis found statistically significant improvement in outcomes with the use of early ERCP [32]. Despite these inconsistencies, all guidelines recommended the use of early ERCP in patients with acute gallstone pancreatitis and coexisting cholangitis or biliary obstruction [7, 8, 44–55].

Timing of Early ERCP with ES in Acute Gallstone Pancreatitis

The definition of early ERCP used in each of the randomized controlled studies [17–23] was different, and as a result the practice guidelines that endorse early ERCP offer various time frames for patients with acute gallstone pancreatitis [36–38, 40]. They were often divided into two categories, namely, "within 24 h of admission" [38, 40] vs. "within 72 h of admission or of symptom onset" [36, 37]. The latest meta-analysis concluded that there was no significant difference in mortality between early routine ERCP and early conservative management regardless of time to early ERCP [42]. Thus, the timing of ERCP ("urgent" within 24 h vs. "early" within 72 h) should depend on the level of suspicion for the presence of cholangitis or biliary obstruction, the condition of the patient, and response to initial conservative

management [42]. Patients with a high level of suspicion for cholangitis or biliary obstruction should proceed directly to ERCP, as delaying ERCP in these critically ill patients to obtain further diagnostic imaging can be detrimental.

Is There Any Geographically Relevant Difference Between Asian and Non-Asian Patients?

Tse and Yuan [42] performed a post-hoc subgroup analysis by pooling the Asian trials [18, 21, 40, 41] separately from the non-Asian ones [17, 20, 23]. In Asian trials, the early routine ERCP strategy was associated with a significant reduction in mortality compared to the early conservative management strategy, but in non-Asian trials, there was no difference in mortality between the two management strategies [42]. Although the results of this analysis suggest that Asian populations might benefit from early routine ERCP, the results should be interpreted with caution given that the findings of the sensitivity analyses were not robust and were likely confounded by inclusion of high-risk or unclear-risk patients in the different trials [42]. Therefore, at present no clear recommendation can be made for tailored approaches in the management of patients with acute gallstone pancreatitis based on ethnicity or geographic location.

Putting It All Together

The number of meta-analyses on the role of early ERCP in gallstone pancreatitis exceeds the number of the randomized controlled studies on the subject, which highlights the fact that uncertainty remains. Our interpretation of the available data on the role of early ERCP can be summarized as follows:

1. We will perform early ERCP with ES in patients with active cholangitis, patients with documented CBD stones by imaging modality, and patients with high likelihood for CBD stones defined as bilirubin levels >4 mg/dL or when both CBD dilation and bilirubin levels between 1.8 and 4 mg/dL are present.
2. We will consider early ERCP with ES in patients with predicted severe gallstone pancreatitis. Furthermore, we will consider ERCP with ES at some point during the index hospital admission in patients who are deemed not to be candidates for laparoscopic cholecystectomy for whatever reason (e.g., cardiopulmonary comorbidities, liver cirrhosis, advanced age, multiple prior abdominal surgeries).
3. We will perform EUS or MRCP in patients with intermediate likelihood for CBD stones and on a case-by-case basis in patients with low likelihood for CBD stones in order to "clear the duct" and reassure the surgeon.

Which Patients with Improving Gallstone Pancreatitis Are Likely to Have Retained CBD Stones?

Cholecystectomy is routinely recommended in all patients after resolution of the gallstone pancreatitis. In some patients, stones exist in both the CBD and the gallbladder and in the past these patients had been managed with open cholecystectomy and bile duct exploration. The introduction of laparoscopic cholecystectomy (LC), the very high success rate for CBD stone extraction during ERCP, and improving techniques for laparoscopic bile duct exploration have given rise to multiple options for the treatment of CBD stones [55], as follows: (1) ERCP is conducted prior to surgery, while LC is performed after the CBD stones have been removed. (2) LC is performed along with an intraoperative cholangiogram (IOC). When CBD stones are detected, LC is converted to open cholecystectomy. (3) When CBD stones are detected by IOC, LC is continued until its completion and ERCP with stone extraction is conducted intraoperatively or postoperatively. (4) When CBD stones are detected by IOC, laparoscopic exploration of the bile duct with stone removal is performed.

These different strategies have not been extensively compared, but some information does exist. A randomized trial compared routine preoperative ERCP in patients considered at high risk for retained CBD stones (CBD size > 8 mm on admission ultrasound, total bilirubin level > 1.7 mg/dL, or amylase level > 150 U/L on hospital day 4) with selective postoperative ERCP only if a CBD stone was present on IOC [57]. The selective postoperative ERCP and CBD

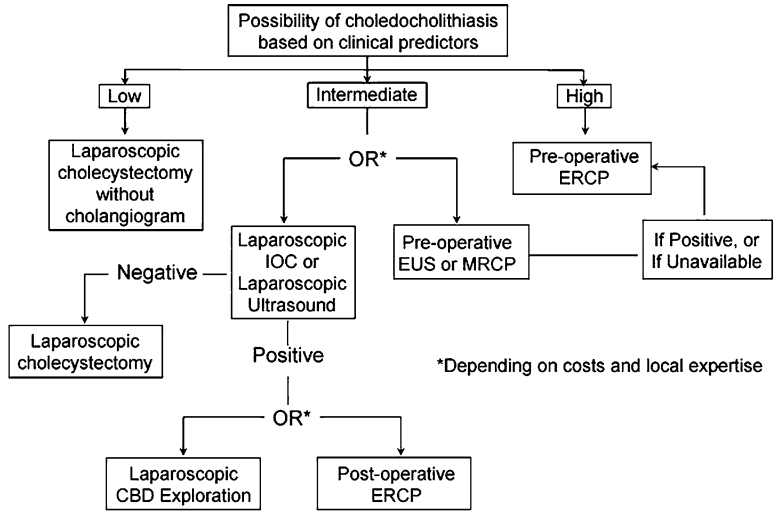

Fig. 13.6 Management algorithm of patients with suspected choledocholithiasis

stone extraction was associated with a shorter hospital stay, less cost, no increase in combined treatment failure rate, and significant reduction in ERCP use compared with routine preoperative ERCP [57]. One of the concerns raised regarding this study is that the parameters used to label a patient as "high-risk" for retained CBD stone were not sufficiently stringent. As a consequence a number of patients with no retained stone were included in the study resulting in a lot of "unnecessary" ERCPs in the preoperative ERCP group. Since then the American Society of Gastrointestinal Endoscopy (ASGE) has published more stringent criteria to delineate and stratify patient risk for retained CBD stone [58].

According to ASGE guidelines the clinical predictors for choledocholithiasis can be divided into three categories, as follows:

1. Very strong
   a. CBD stone on AUS
   b. clinical ascending cholangitis
   c. bilirubin level >4 mg/dL
2. Strong
   a. dilated CBD on US (>6 mm with gallbladder in situ)
   b. bilirubin level 1.8–4 mg/dL
3. Moderate
   a. abnormal liver biochemical test other than bilirubin
   b. age older than 55 years
   c. clinical gallstone pancreatitis

Based on this criteria the likelihood of CBD stone can be assigned as

1. High: when any one very strong predictor or two strong predictors are present
2. Low: when no predictors are present
3. Intermediate: all other patients

The likelihood of CBD stones for a particular patient then dictates management strategy (Fig. 13.6).

The ASGE guidelines provide a reasonably straightforward framework for patient evaluation, but it is worth noting that clinical predictors for CBD stones have limitations. Recently, a prospective cohort study revealed that commonly used biochemical and radiological predictors of the presence of gallstones in the CBD during ERCP in the earliest stages of acute gallstone pancreatitis can be unreliable [59]. The study, however, did not use the strict risk stratification as outlined per the ASGE guidelines, but rather used individual parameters.

Conclusion

EUS is a highly accurate tool for detection of bile duct stones in patients with gallstone pancreatitis. In institutions with available expertise, it can be used as a first-line test early in the course of pancreatitis to provide information on the presence of choledocholithiasis and cholecystolithiasis. The role of early ERCP with ES still remains controversial. Nevertheless, at this moment, current data support the use of early ERCP with ES in patients with acute gallstone pancreatitis and coexistent cholangitis or biliary obstruction, patients with high probability of retained bile duct stones, and possibly in patients with predicted severe pancreatitis. However, there are three important issues that remain to be explored in order to optimize our management of patients with gallstone pancreatitis, as follows: (1) standardized diagnostic criteria for acute gallstone pancreatitis, cholangitis, and biliary obstruction, (2) more accurate modalities in addition to MRCP and EUS to diagnose suspected bile duct stones, and (3) novel prognostic biomarkers to accurately predict the severity of acute gallstone pancreatitis.

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Direct Endoscopic Necrosectomy

14

Todd H. Baron

Introduction

Clinically severe acute pancreatitis is almost always associated with necrotizing pancreatitis and/or necrosis of surrounding peripancreatic fat [1]. With early recognition and improvements in critical care, most patients survive the early phase of systemic inflammatory response syndrome (SIRS) and multisystem organ failure. Often these patients have a prolonged course of sterile necrosis while others develop delayed infection. Several weeks after onset of pancreatitis a defined entity referred to as walled-off necrosis (WON) develops (see Chap. 2) [2]. When indicated the approaches to drainage/debridement for WON can be surgical, percutaneous, endoscopic or a combination [3]. Early, open surgical necrosectomy has largely been supplanted by delayed minimally invasive approaches to WON [4–6] using flexible endoscopic, rigid endoscopic [7], percutaneous and laparoscopic approaches, alone or in combination [8]. Unfortunately, there is no definite consensus on optimal timing and type of intervention. Several endoscopic approaches are available to manage WON [9] (Table 14.1). One approach using flexible endoscopes is termed direct endoscopic necrosectomy (DEN), whereby the necrotic cavity is entered transmurally (via the stomach or duodenum, or both [10, 11]), or through percutaneously created tracts. In this chapter the use of DEN will be discussed.

Brief History

The passage of peroral flexible endoscopes into WON (at that time termed organized pancreatic necrosis) was described in 1999 [12]. However, it was not until Siefert [13] and subsequently Seewald [14] introduced DEN as a method to remove necrotic tissue using mechanical methods that this technique was adopted in some centers. This led to studies showing that DEN may be superior to peroral endoscopic irrigation methods [15, 16].

Timing and Indications for DEN

The timing of and indications for intervention in patients with WON will be detailed in other chapters. Additionally, the types of interventions will be discussed in Chaps. 16, 17, and 18. Briefly, however, it is accepted that for patients with sterile necrosis any intervention should be delayed as long as possible and at a minimum 4 weeks after the onset of acute pancreatitis. Most patients with pancreatic necrosis can be managed with medical therapy until resolution. Endoscopic management using DEN cannot be undertaken

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Table 14.1 Flexible endoscopic approaches to organized (walled-off) pancreatic necrosis

Endoscopic approach	Advantages	Disadvantages
Single or multiple entry transmural entry with nasocystic irrigation	Technically easy	Discomfort of nasal tube
Single entry transmural with PEG-PEJ for irrigation	Avoids nasal tube	– Technically more difficult than nasocystic irrigation – External tube
Transmural entry with direct endoscopic necrosectomy (DEN)	Avoidance of external drains	– Technically difficult – Time-consuming – Labor intensive
Hybrid percutaneous irrigation-endoscopic transmural approach	Minimal endoscopic procedures	– Requires both interventional radiologist and gastroenterologist – External tube
Hybrid percutaneous-endoscopic direct necrosectomy using external/internal large diameter stents	Allows endoscopic access to areas not accessible translumenally	– Requires both interventional radiologist and gastroenterologist – External stent – Abdominal wall pain – Stent cost

until the necrotic process has become walled-off. This may occur as early as 2–3 weeks but often requires 4 weeks. For those with WON, intervention can be considered for patients who remain systemically ill and unable to resume normal life activities 4–6 weeks after the onset of pancreatitis, those with symptoms of gastric outlet obstruction, intractable pain, and inability to eat, especially when CT or MRI shows progressive enlargement. Less common indications include inability to wean from mechanical ventilation due to increased intra-abdominal pressure and documented large, high amylase level pleural effusions or ascites. Our approach is to offer DEN to patients with WON who have had a prolonged course of sterile necrosis, intractable pain, gastric outlet obstruction, inability to eat, or rapidly enlarging collections present at 4 or more weeks after onset of pancreatitis. It is believed that DEN will return the patient to a normal health status more rapidly than "watchful-waiting" (supportive care), though without clear-cut evidence.

The decision to intervene is easier in patients in whom there is a high suspicion for or known infected necrosis, and we have intervened as early as 3 weeks after the onset of acute pancreatitis and in septic patients with acute pancreatitis and WON (as determined by CT). DEN is often undertaken when patients have clinical deterioration unresponsive to medical therapy.

DEN Methods

Preprocedural Planning/Sedation

It is imperative that a cross-sectional imaging procedure (CT or MRI) be obtained within several days prior to planned intervention to best determine degree of demarcation and anticipated access points, and for evaluation for major vessels either within the cavity or between the cavity and gastric or duodenal wall. In addition, imaging can determine the degree of paracolic extension and any communication between multiple cavities. Such connections can often be appreciated on coronal CT images. One should be suspicious of a fistula between the lumen and collection when spontaneous air is present. This tract can be conveniently used for entry as described below.

A pre-procedural INR and platelet count should be obtained and corrected, as necessary.

Pre-procedural antibiotics should be administered in patients not already receiving them. Extended intravenous penicillin agents

(piperacillin/tazobactam), quinolone agents (levofloxacin), or a carbapenem (meropenem) are recommended agents.

Sedation using anesthesia support is recommended as these patients are often ill, procedures are prolonged, aspiration risk is high, and intraprocedural adverse events (AEs) (bleeding, pneumoperitoneum) can occur.

Puncture and Access

DEN is performed using flexible endoscopes. One or more transmural access points are targeted for drainage depending on imaging, most often CT. For WON collections located in the mid-body and tail a transgastric route is usually undertaken. A transgastric approach is often a more direct approach to subsequently pass an endoscope directly into the cavity and into paracolic gutter extensions, if needed for DEN. A transduodenal approach is usually the only and best option for collections confined to the pancreatic head.

The initial transmural puncture can be performed in a variety of ways, with or without EUS guidance. Non-EUS-guided punctures can be performed using a side-viewing endoscope (therapeutic duodenoscope, ERCP endoscope) (Fig. 14.1). Advantages to using the duodenoscope are the ability to puncture at a perpendicular angle to the collection, the use of an elevator, and ability to enter collections in the cardia or fundus in a retroflexed position. The disadvantages are lack of dedicated large-caliber needles that allow passage of 0.035″ guidewires and lack of ultrasound guidance to detect underlying vessels. Using a duodenoscope the puncture is performed "blindly" using electrocautery with a biliary needle knife or Cystotome (Cook Endoscopy, Winston-Salem, NC). Alternatively, a sclerotherapy needle can be used that accepts a 0.018″ guidewire (Marcon-Haber, Cook Endoscopy). The needle, however, is short and not designed for guidewire passage; the wire often does not pass through the sheath after it is angled. Exchanges are difficult, and the small-diameter wire is not sufficiently robust to allow accessories to pass through the thicker gastric wall. In these cases, a triple-lumen needle knife or other cautery device is passed over the wire and into the cavity to allow entry and subsequent upsizing to a 0.035″ guidewire. Standard EUS needles are not long enough to pass through duodenoscopes.

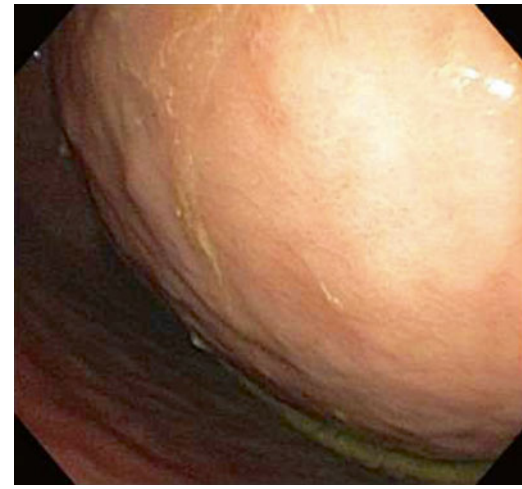

Fig. 14.1 Endoscopic image taken immediately prior to puncture of a large WON using a standard therapeutic duodenoscope

Standard upper endoscopes can also be used to create the puncture, but a perpendicular approach to the posterior gastric wall may not be possible unless the collection is massively bulging into the gastric lumen so that an end-on view of the collection is feasible. However, a standard 19-gauge EUS needle will pass through a forward endoscope and obviates the need for changing endoscopes for subsequent DEN.

Most commonly, EUS-guided puncture is performed using an oblique endoscope. The advantages to EUS guidance are the ability to target the lesion, avoid large blood vessels, and assess the degree of underlying necrosis [17]. The disadvantages are the relative inflexibility, need to have a straight access due to stiffness of the needle, tangential nature of the puncture, and the tendency of the punctures to be more proximal both because of the access angle as well as the proximal location of the exit site relative to the transducer. While there are no data to show the more proximal locations are less effective, this author believes the angle into the cavity for DEN

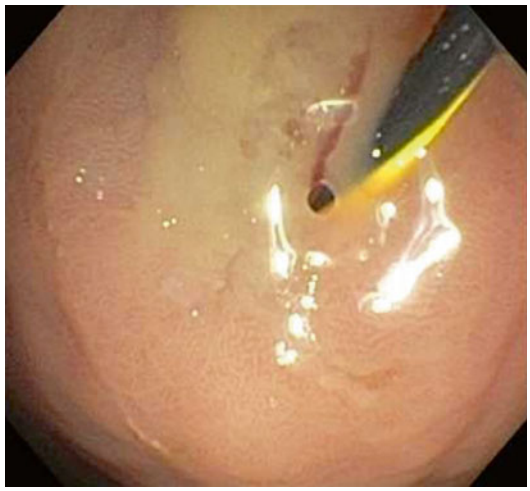

Fig. 14.2 Endoscopic image taken of gastric entry site immediately after puncture and guidewire placement into the cavity

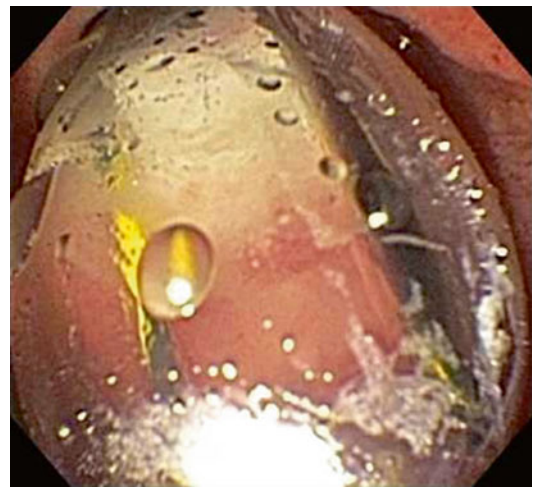

Fig. 14.3 Endoscopic image taken during large-bore balloon dilation over the guidewire

may promote separation of the collection from the thinner, more proximal stomach when entered at a tangential angle and following large-diameter balloon dilation. Finally, the echoendoscope mechanics and optics are less favorable than ERCP endoscopes.

Recently, a forward-viewing echoendoscope has been used for the puncture and to perform DEN [18]. However, the forward view poses similar difficulties in entering 90° to the posterior gastric wall.

Another option for access is to use a spontaneous fistula tract in the stomach or duodenum [19]. A fistulous connection should be suspected in any patient with spontaneous air inside the cavity as this usually represents the fistula and not simply gas-producing organisms. These tracts are usually safe to dilate as lack of antecedent clinical bleeding suggests a vessel is not present along the tract.

Management of the Tract

Once the cavity has been successfully accessed (Fig. 14.2) the transmural tract is balloon-dilated (Fig. 14.3) to allow passage of a forward-viewing endoscope into the cavity. A minimum diameter of 15 mm is required. In some cases 20-mm dilation is performed at the time of initial puncture, though may be associated with higher risks of bleeding and perforation due to tearing of vessels and separation of the wall of the collection. At this point, some prefer to place one or more double pigtail stents prior to performing DEN. This is particularly useful when transgastric DEN is performed as it may be surprisingly difficult to identify the large puncture tract in the midst of gastric folds. It is less important to place plastic stents through the duodenum prior to DEN as it is usually not difficult to identify the dilated entry site.

Another option is to dilate the transmural site to a small diameter followed by placement of large bore (16–23 mm mid-body diameter) self-expandable metal stents (SEMS) across the gastric or duodenal wall for maintaining access for DEN (Fig. 14.4) [20–24]. In the U.S. the only large-diameter fully covered SEMS are esophageal with the shortest lengths being 6–7 cm. This is still relatively long compared to the distance between the lumenal site and the inside of the cavity and results in an excessive stent length inside the lumen or the cavity. Shorter-length devices (2 cm) with larger flanges are available outside of the U.S. and at least one is expected to receive FDA approval in the near future.

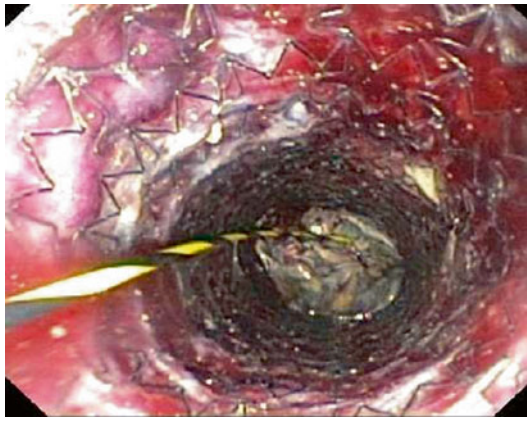

Fig. 14.4 Endoscopic image taken immediately after transgastric placement of a large-diameter fully covered self-expandable metal stent

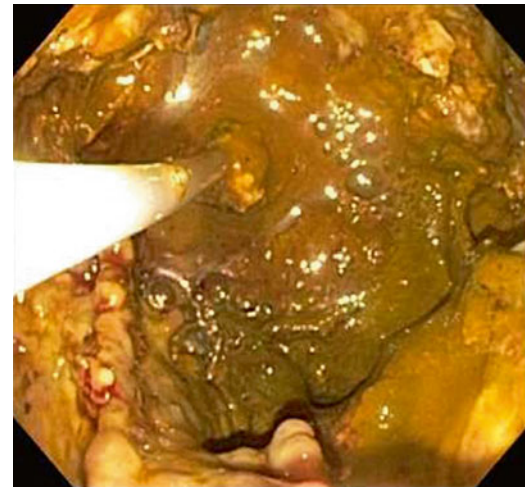

Fig. 14.5 Endoscopic image taken during DEN using a therapeutic upper endoscope. A snare can be seen grasping necrotic tissue

Necrosectomy

Once the access site is secured DEN is usually performed with a forward-viewing upper endoscope. Diagnostic channel scopes have the advantage of flexibility but the small working channel makes suctioning thick secretions difficult and also becomes filled with debris making it difficult to pass accessories for debridement. A therapeutic channel endoscope also has water jet capabilities to aid in loosening adherent necrosis. A jumbo channel endoscope with a 6-mm channel and dual suction designed for removal of clots during gastrointestinal bleeding can be used. This endoscope is rather inflexible but large fragments of necrotic debris can be suction once loosened into smaller fragments.

The endoscope is passed into the cavity (Fig. 14.5) and necrotic material is removed using mechanical measures. Accessories used include standard polypectomy snares, polyp retrieval nets, and grasping forceps. The most effective forceps have large, long prongs (Pelican-alligator forceps) rather than shorter, traditional rat-toothed forceps, which tear small pieces of tissue. I prefer to use spiral snares (Olympus Corporation, Center Valley, PA) to grasp and remove tissue. Unfortunately, these snares deform after many uses and it is not uncommon to use several during the course of one procedure. Once the tissue is grasped, it is withdrawn from the cavity and deposited in the lumen.

It is important to realize that not all necrotic contents have the same consistency. Some are large adherent, smooth, solid pieces that can be difficult to grasp with any device, whereas others are looser and more easily grasped. High flow through the scope irrigation is helpful for breaking up some types of necrotic tissue. Hydrogen peroxide irrigation has been used and may be useful in breaking down necrotic tissue during DEN [25], though comparative trials are lacking.

DEN can be a time-consuming, labor-intensive process. Many passages of the endoscope into and out of the WON are necessary. However, there does appear to be a learning curve that allows more material to be removed in a shorter period of time as experience is gained. Nonetheless, one should allow at least 90 min for the first access/debridement and 60 min for subsequent debridement procedures. The amount of time is dependent on many factors, which I often refer to as patients, patience and patients. These include patient and physician tolerance to the procedure (patients and patience) and number of cases yet to be done (patients). The goal is to remove as much necrotic tissue as possible in one session. A complete necrosectomy in one session is usually not possible, particularly when there is a large necrotic burden.

If stents were not placed prior to DEN, they are placed at the end of the procedure. Commonly two or more 7- to 10-Fr double pigtail stents are placed. Placement of a nasocystic irrigation tube is sometimes performed between DEN sessions, though the necessity of their use is not clear when DEN is used [26].

Subsequent DEN Procedures

The timing of subsequent DEN procedures has not been standardized. One approach is to perform scheduled, protocolized repeat necrosectomies [27]. The duration between procedures can be as short as 24 h or as long as several weeks. Inpatients who are debilitated and who may not be discharged soon after their first intervention can return frequently. In contrast, outpatients who are relatively well may return as outpatients on a weekly or biweekly basis. Additional considerations include the residual amount of necrotic material as determined by prior endoscopy or imaging (CT, MRI). One should consider limiting the number of CT scans in younger patients so as to minimize radiation exposure. Some patients improve dramatically after removal of the fluid component and can tolerate a moderate amount of residual necrotic debris, while others remain symptomatic. If patients develop infectious symptoms, they should return for urgent repeat necrosectomy and/or cross-sectional imaging.

Post-procedural Care

Outpatients who undergo necrosectomy can be managed as outpatients as long as the procedure was performed uneventfully and the patient meets discharge criteria. Antibiotics are continued perorally for at least several weeks and in most cases until the necrosis completely resolves. The patient may resume (or initiate) oral intake the day of the procedure, assuming no AEs occurred and there is no nausea, vomiting, or pain. Acid secretory agents should be withheld, if possible (absence of severe reflux esophagitis), as the presence of acid may reduce infection due to bacteriostatic properties and acid entry into the necrotic cavity could break down necrotic debris.

Repeat cross-sectional imaging is done on a case-by-case basis. Antithrombotic medications can be re-initiated approximately 24–48 h later, based upon risk of bleeding and thrombosis.

Management of Paracolic Gutter Extensions

Paracolic gutter extensions can be difficult to treat, particularly when extending well into the pelvis. The central areas of necrosis in the pancreatic bed are accessible and communicate with the paracolic extensions and are thus potentially amenable to necrosectomy.

Percutaneous DEN

Navarrete [28] and others [29, 30] have placed large-bore fully covered SEMS through percutaneous tracts to allow access for DEN using flexible endoscopes. This latter approach is similar to video-assisted retroperitoneal debridement (VARD) as performed by surgeons who pass rigid endoscopes through percutaneous drain tracts after dilation and/or incision of the tract [7]. This method is useful to treat paracolic gutter extensions, areas that have already been accessed with percutaneous drains but with inadequate drainage, and those collections that cannot be accessed translumenally. The timing varies between percutaneous drain placement and SEMS placement, depending on local practice. The SEMS remains in place with an ostomy bag over the stent between procedures. The SEMS is removed when the WON is completely evacuated and the space has collapsed.

Adverse Events

AEs can occur intra-procedurally or post-procedurally. Intra-procedural events include sedation, bleeding, and perforation.

Bleeding most often occurs at the entry site. Fortunately, it is usually self-limited and ceases by the end of the procedure. Uncontrolled or persistent bleeding can be managed by dilute epinephrine injection, balloon tamponade, clips, or electrocautery. Refractory or massive bleeding can be managed by placement of a large-diameter fully covered esophageal SEMS [31, 32]. Intracavitary bleeding is also usually self-limited. Severe intra-cavitary bleeding can be the most life-threatening and angst-producing for the physician. Hemostatic measures are similar to those for other bleeding including cautery and clip placement. If the bleeding is arterial, emergent embolization can be undertaken. Venous bleeding cannot be treated with interventional embolization techniques and may require surgery.

Perforation can also be at the entry site or at an intra-cavitary site. Intra-procedural perforation can result in tension pneumoperitoneum, a life-threatening emergency that requires prompt needle catheter decompression [33]. Similar to bleeding, perforation may occur at the entry site and may be managed with clips, diversion (in addition to internal pigtail stent placement), and placement of a large caliber SEMS [34]. Large intra-cavity perforations often require surgical or percutaneous management.

Air embolism can be silent, but often produces significant morbidity (stroke or spinal cord infarction) and can even result in procedural-related death [35]. It is believed to be preventable by the use of carbon dioxide for insufflation rather air, which should be utilized in all centers performing this procedure.

Introduction of organisms (bacteria and fungi) inevitably occurs during endoscopic intervention and may result in infectious complications. Thus, the need for removal of fluid and solid debris and administration of antibiotics are essential.

Outcomes

There are now many series demonstrating the efficacy of DEN [14–16, 36, 37]. However, one must be careful in interpreting the literature. For example, successful resolution can be defined as complete nonsurgical resolution, including the use of adjuvant percutaneous therapy or successful when only flexible endoscopic measures are used [15]. In addition, patients with WON are a heterogeneous group of patients based upon size of collection, total necrotic burden, paracolic gutter extension, nutritional status, comorbid medical illnesses, and time from onset of necrosis to intervention. This makes comparison of outcomes between centers and between disciplines difficult.

In a systematic review of more than 1,100 endoscopic necrosectomies in 260 patients the overall mortality was 5 % with a procedure-related morbidity of 27 %. Complete resolution of pancreatic necrosis using endoscopy alone was 76 %. However, these studies include all types of endoscopic interventions. Two large series of DEN [15, 16] showed successful resolution in approximately 90 % of patients with an adverse event rate of approximately 14 %. The median number of DEN procedures was 3.

Future Directions

Unanswered questions remain. Where does DEN fit into the management strategy of pancreatic necrosis? Is it the optimal type of endoscopic therapy? Where should DEN be performed—only in tertiary care centers or in high-level community care centers [38]? Should DEN be offered for otherwise healthy patients with sterile pancreatic necrosis who meet criteria for intervention and, if so, what is the optimal timing? Finally, can we predict which patients will fail endoscopic drainage? Unfortunately, an evidence-based approach to answer these questions is not possible at the present time.

DEN is a time-consuming, labor-intensive process not for the uncommitted [39] or faint of heart, since AEs occur more commonly than in any other pancreaticobiliary intervention and have the potential to be fatal [35]. Therefore, even more important, perhaps, is the need for support from a team of intensivists, endoscopists, surgeons, and interventional radiologists to manage these complicated patients (see Chap. 18).

Evidence in favor of endotherapy is evolving with work done by the Dutch Pancreatitis Group [8, 40] and others [26, 35, 41]. However, patients with pancreatic necrosis remain a heterogeneous group with regard to severity of illness and comorbid medical conditions at the time of intervention, because of surrounding inflammatory changes, location and extent of necrosis, and degree of underlying solid debris (necrotic tissue burden). These factors, coupled with variability in inter-center expertise of the various disciplines, means that the approach to these patients will never be standardized. Perhaps all we can hope for is the ability to tailor the best approach to the individual patient. We do believe, however, there will be unforeseen breakthroughs in endoscopic intervention as technology continues to evolve. The latter include new methods and devices to facilitate debridement, keep tracts into the necrotic cavity open to allow reintervention, and to preclude the long-term consequences of necrosis and a disconnected pancreatic duct to include recurrent fluid collections or attacks of relapsing pancreatitis.

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Retroperitoneoscopic Approaches for Infected Necrotizing Pancreatitis

15

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Background

Acute pancreatitis is usually a self-limiting disease of which patients recover without serious complications. About 20 % of patients develop severe acute pancreatitis with (extra) pancreatic necrosis or collections [1]. When these collections become organized, usually around 3–4 weeks after onset of disease, they are called walled-off necrosis (WON). In general, necrotizing pancreatitis is associated with a mortality of 15 % [2]. In two-thirds of patients the disease can be treated conservatively, when necrosis remains sterile [3, 4]. Invasive intervention for sterile necrosis carries a serious risk of introducing infection, which necessitates additional interventions and increases mortality [5, 6].

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In about one-third of patients with necrotizing pancreatitis, secondary infection of necrosis occurs [7]. Infected necrosis is one of the most severe complications of acute pancreatitis. It drives clinical deterioration and organ failure in the second phase of the disease, as it usually occurs in the second to the third week after disease onset [7]. It is generally accepted that infected necrosis is an indication for invasive intervention.

Management strategies for invasive intervention in infected necrotizing pancreatitis have evolved over the last decade. The preferred treatment used to be primary open necrosectomy with early and complete debridement of infected necrosis. The current standard is a minimally invasive step-up approach involving percutaneous (or endoscopic) catheter drainage as the first step [8, 9]. When catheter drainage does not lead to clinical improvement, necrosectomy should follow. In a Dutch randomized controlled trial, a step-up approach starting with catheter drainage, followed when needed by retroperitoneoscopic debridement, was superior to open necrosectomy in terms of major early and late complications [8]. This step-up approach is gaining widespread popularity.

There are several forms of minimally invasive necrosectomy, e.g., endoscopic transluminal necrosectomy (ETN), laparoscopic transperitoneal necrosectomy, sinus tract endoscopy (STE), and video-assisted retroperitoneal debridement (VARD). This chapter provides an overview of techniques and outcomes of different minimally invasive retroperitoneoscopic (surgical) approaches.

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Transition to Minimally Invasive Techniques

In recent years, there has been an increased interest in the development of minimally invasive techniques to treat gastrointestinal disorders in general. The treatment of infected necrotizing pancreatitis is also shifting toward minimally invasive laparoscopic (transperitoneal), radiological (retro- and transperitoneal), endoscopic (transgastric), and retroperitoneoscopic techniques [10]. Traditionally, open necrosectomy was the procedure of choice. Published mortality rates for open necrosectomy range from 6 [11] to 50 % [12].

Minimally invasive techniques have several potential advantages in comparison with open necrosectomy. These include a reduced inflammatory response to intervention with a lower risk of inducing organ failure in these already critically ill patients, reduced extent of bacteremia, reduced rate of wound complications, shorter hospital and ICU stay, and faster convalescence [2]. Several minimally invasive necrosectomy techniques have been developed, all to facilitate the removal of solid debris. In 1996 Gagner et al. [13] described a laparoscopic debridement, which theoretically holds the risk of spreading the infection into the abdominal cavity and an enhanced risk of intestinal tract erosions. This is why a retroperitoneal approach appears to be a better alternative for open necrosectomy. The peritoneum is left intact and contamination of the peritoneal cavity is prevented.

Retroperitoneoscopic Techniques

Historically, an open retroperitoneal approach with lumbotomy was performed. Three observational cohort studies have reported mortality rates of 20–33 % with a complication rate of 20–50 % [14–16]. Enteric fistulas were noted in 40 % of cases, hemorrhage in 45 %, and colonic necrosis in 15 %. These complications of the open retroperitoneal approach could be the result of the narrow surgical entrance with a largely blind necrosectomy. To overcome these disadvantages different groups have developed alternative retroperitoneal interventions under direct endoscopic vision or video-assisted.

In 1998 Gambiez et al. [17] were first to describe this retroperitoneoscopic approach in the management of infected necrotizing pancreatitis. They treated 20 patients with a short left or right lumbotomy (6 cm in length) centered on the 12th rib. Under direct vision of an endoscope (23-cm mediastinoscope) the peripancreatic necrosis was removed by blunt dissection with a suction metal tube. Afterwards a continuous irrigation tube drain was left in the retroperitoneal space. Later Castellanos et al. [18] used a flexible endoscope for visualization and manual necrosectomy of the necrotic cavity, with a left or right translumbar incision of approximately 15 cm in length. In these two studies, success rate was respectively 75 % and 73 % and mortality 10 % and 27 %.

Hereafter, several derivative retroperitoneoscopic techniques have been described in larger cohorts. Two of these techniques have gained widespread acceptance: STE and VARD. These techniques and their reported results are described in more detail below.

Sinus Tract Endoscopy

Carter et al. [19] in 2000 first described 4 patients undergoing STE after placement of a percutaneous drain. Under CT guidance an 8F pigtail nephrostomy catheter is placed in the infected cavity. The selected route on the left side, that will allow subsequent dilatation, is between the lower pole of the spleen and the splenic flexure. For right-sided necrosis, the route through the gastrocolic omentum anterior to the duodenum, is taken. Under general anesthesia on the operating room, this catheter tract is dilated up to 30F with graduated dilatators under radiologic guidance. A nephroscope is inserted through this dilated drain path under intermittent irrigation and suction and the solid debris is removed using

grasping forceps. A continuous postoperative lavage system is placed, and continued until lavage fluid clears or until the next procedure. If an ongoing sepsis is suspected a second procedure may be performed, after additional CT-imaging. Both a flexible or rigid endoscopic system can be used for STE. Since only small fragments of necrosis can be removed piecemeal with a flexible endoscope, an operating nephroscope may be preferred for primary explorations.

Others have reported STE results using different terminology. Conner et al. [20] described their experience with "minimally invasive retroperitoneal pancreatic necrosectomy (or MIRPN)." They reported the results of 88 procedures in 24 patients; in 21 patients 36 complications occurred (88 %), 6 patients died (25 %), and 5 patients (21 %) required open surgery for or subsequent distant collections or bleeding.

The same group later described an updated cohort of patients undergoing "minimal access retroperitoneal pancreatic necrosectomy (or MARPN)" [11]. They compared MARPN with open necrosectomy in a retrospective analysis of prospective data in 189 patients. Mortality was 19 % compared to 38 % in the open group; 31 % and 56 % of patients, respectively, had postoperative organ failure, 43 % versus 77 % required postoperative ICU support and 55 % versus 81 % had complications. Thus, this study showed significant benefits for this retroperitoneoscopic approach compared to open necrosectomy.

Video-Assisted Retroperitoneal Debridement

VARD is another retroperitoneoscopic technique, and has proven to be safe and efficient [8, 21–23]. VARD is, in essence, a minimally invasive hybrid between the classic lumbotomy and STE, both mentioned above. STE obviates the need for an incision. VARD includes an incision of 5 cm in length, but can also be considered as minimally invasive, opposed to the 15 cm incision in a open translumbar approach. Therefore, larger pieces of necrosis can be removed and VARD seems to be easier to perform than STE, particularly in centers where interventions in this relatively rare condition are not performed routinely [23]. In 2001 Horvath et al. [21] first described the VARD procedure.

In the Dutch PANTER trial [8] VARD was part of a minimally invasive step-up approach as was compared to primary open necrosectomy. In the surgical step-up group, first, a percutaneous catheter drainage (PCD) was placed and the clinical effect was assessed for 72 h. In the case of no clinical improvement, and no possibilities for additional drainage on contrast-enhanced computed tomography (CECT), VARD was performed. In more than 65 % of patients with infected necrosis PCD through the left retroperitoneum was feasible [24].

The VARD procedure [25] is performed under general anesthesia and the patient is in supine position and 30° tilted towards the contralateral side. A VARD can be performed via a left-sided or right-sided approach, the latter being more challenging. The ipsilateral arm is positioned over the patient's head and the following landmarks can be marked; xiphoid, costal margin, anterior superior iliac spine, and mid-axillary line (Fig. 15.1). A preoperatively placed retroperitoneal percutaneous drain is needed as a guideline for safe entry into the left-sided window between spleen, kidney, and colon. From the right side, a safe entry ventral to the inferior caval vein and dorsal to the colon is needed. Near the percutaneous drain, about two fingers below the left costal margin over the mid-axillary line, the planned incision site is also marked. Now the entire abdomen and flank are prepared and draped, to enable conversion to laparotomy. A subcostal 4–5 cm incision is performed over the previously marked site and the muscles are divided sequentially. With the palpating finger the drain is located and followed into the infected collection. The collection wall can be fibrotic. A clamp over the drain may facilitate opening the collection. Care has to be taken to stay close on the drain as from the left side the colon and spleen are nearby. Once the collection is opened, pus will drain spontaneously. The first necrosis can be removed blindly

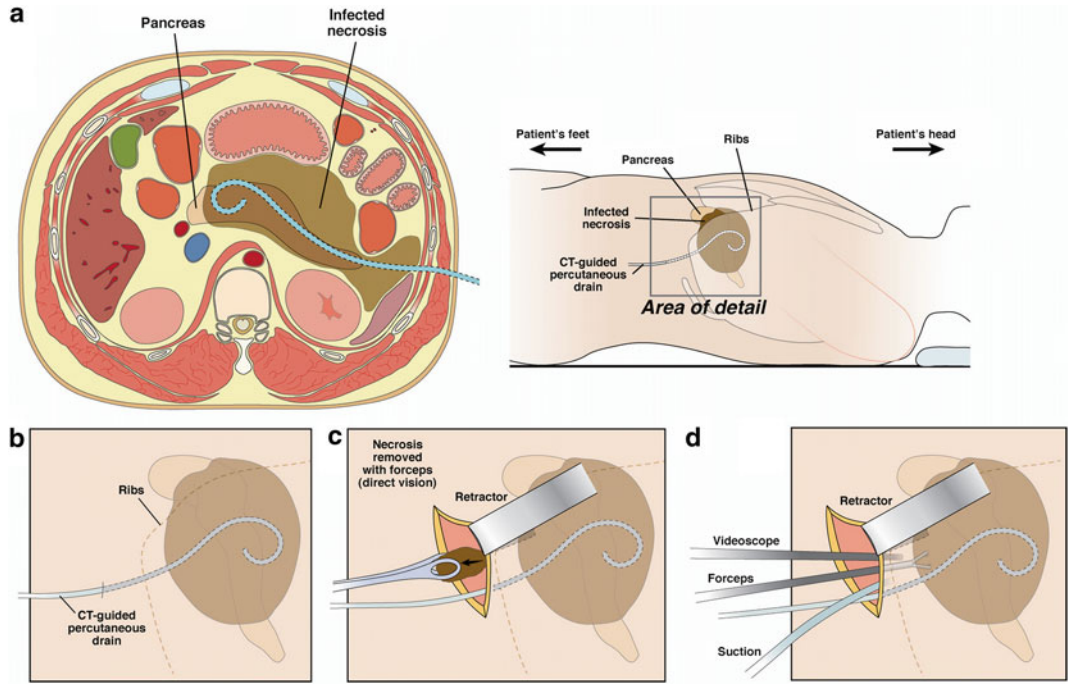

Fig. 15.1 Video-assisted retroperitoneal debridement (VARD). Reprinted from Clin Gastroenterol Hepatol, 10/11, van Brunschot S, Bakker OJ, Besselink MG, Bollen TL, Fockens P, Gooszen HG, et al., Treatment of necrotizing pancreatitis, 1190-1201, Copyright 2012, with permission from Elsevier [35]

using finger fracture, suction, and an extended ring forceps. Subsequently, a 0° laparoscope is introduced and a forceps is used parallel to the video scope in order to remove the necrosis under direct vision. Extended collections, not approachable through one incision, are quite rare but sometimes require another incision in the left groin or right flank. Only loose necrosis should be removed to minimize the risk of bleeding. If there is an arterial bleeding that cannot be easily controlled surgically, the cavity should be packed with gauzes and the intervention radiologist is asked to perform an embolization. In case of venous bleeding, packing should suffice to stop the bleeding, followed by repeat necrosectomy after 24–48 h. In case of severe hemodynamic instability, not improving by packing, the procedure should be converted to laparotomy with opening of the omental sac. In general, the more complete the collection's encapsulation, the easier the necrosectomy can be performed. After completion of the procedure, two large bore surgical drains are placed, one deep in the collection and one more superficial. The fascia is closed over the drains and the skin can be closed or left open for healing by secondary intention. Postoperatively, the drains are continuously lavaged with increasing amounts of saline or peritoneal dialysis fluid, building up from 100 mL per hour to 10 L per 24 h in the first 3 days.

In 2010 a prospective multicenter study [26] reported outcomes on 40 patients with infected necrosis treated in six university medical centers in the USA and Canada. Percutaneous drain placement was the first intervention in all patients. Nine patients (23 %) were treated with drains only. In 60 % of the other 31 patients a successful VARD was performed. The most common reason for crossover from VARD to open surgery was a central collection extending into the mesenteric root and could not be accessed via the flank. Mortality was 5 % and most common complications were pancreatic fistulae and bleeding requiring intervention in respectively 18 % and

8 % of patients. In most patients (81 %) one VARD was sufficient, and no patient required more than two VARD procedures. The overall mortality of VARD reported in literature is 13 %, with a range of 0–33 % [25].

Current Insights into Perspective for the Future

The treatment of necrotizing pancreatitis has changed considerably in the last decades. Management of patients with pancreatic necrosis should be individualized, requiring consideration of all available data (clinical, radiological, laboratory) and available expertise [27]. Intervention is now performed exclusively in case of infected (peri)pancreatic necrosis. Invasive intervention for sterile necrosis is highly controversial. Most experts believe that intervention for sterile necrosis should only be performed if a patient has persistent gastric outlet obstruction with intractable pain and is unable to eat 4–6 weeks after disease onset.

Catheter drainage (e.g., radiologic or endoscopic) is technically feasible in more than 95 % of patients, often via the preferred left-sided retroperitoneal route [8]. The rationale of PCD is to treat infected necrosis as an abscess and drain infected fluid under pressure, without actually removing necrosis. Drainage of the infected fluid may temporize sepsis, improve the patient's clinical condition, and allow for further encapsulation. The preferred route for PCD is through the left retroperitoneum so that the drain can be used as a guide wire for VARD procedure (if necessary) and the peritoneal cavity is not contaminated. Several studies have showed that, in 35–64 % of cases, patients can be successfully treated with PCD alone and do not need to undergo an additional necrosectomy [2, 8, 28, 29].

Every form of intervention, whether open necrosectomy or a minimally invasive retroperitoneoscopic approach, is usually delayed. Based on current literature [9, 30], postponing intervention, preferably until 4 weeks after onset of disease, is widely accepted as the strategy of choice. Since the surgical step-up approach is superior to open necrosectomy and it is known that, catheter drainage can be used to control sepsis and delay or even avoid an additional necrosectomy. But with implementation of the step-up approach, the best timing of catheter drainage is not yet determined. Further prospective (preferably randomized) studies should answer this question and others such as: is it better to postpone catheter drainage until there is walled-off necrosis? Should it be performed immediately after infected necrosis is diagnosed and thereby maximize its clinical effect?

In addition to retroperitoneoscopic approaches ETN is gaining popularity [31, 32]. Theoretically this approach has several advantages in comparison with surgical techniques. Endoscopic treatment of infected necrosis can be performed under deep sedation, thereby avoiding general anesthesia. Also, there is no need for any abdominal wall incision, thereby inducing less surgical stress and potentially reducing complications such as incisional hernia, pancreatic fistula, and wound infections. Until now only one small randomized controlled trial compared ETN with VARD [33]. Twenty patients with infected necrotizing pancreatitis were randomized between ETN and VARD. One-third of patients who underwent an intervention had organ failure and 95 % had proven infected necrosis. ETN significantly reduced the pro-inflammatory response measured by interleukin-6 levels, as well as the composite clinical endpoint consisting of complications and mortality. ETN seems a safe and successful alternative treatment. However, larger randomized controlled trials are needed to confirm these favorable results. In the Netherlands a nationwide multicenter randomized trial is currently being performed comparing an endoscopic with a surgical step-up approach [34]. Results are expected in 2015.

Open necrosectomy seems to be inferior to minimally invasive techniques, although randomized studies directly comparing different surgical techniques for necrosectomy are lacking. These types of studies are difficult to perform. A study powered to detect a difference in mortality is probably not feasible due to the complexity of disease and relatively low incidence of infected necrotizing pancreatitis. Alternative study designs are

needed to evaluate the role of minimally invasive surgical techniques with the other. To this end, an individual patient data meta-analysis (IPDMA) of major international cohorts with patients who underwent a pancreatic necrosectomy is currently underway. In this collaborative project several major international cohorts from seven countries will be pooled to explore risk factors for mortality and compare different methods of necrosectomy and may serve to answer this question.

In conclusion, over the last years the management of patients with necrotizing pancreatitis has changed significantly. Current evidence is clear on the fact that catheter drainage should be the initial treatment step for infected necrosis. There are no randomized studies comparing specifically which surgical technique for necrosectomy is superior in patients who failed to have an effect from catheter drainage. Both STE and VARD are safe and effective in patients with (infected) necrotizing pancreatitis. These and other retroperitoneoscopic techniques are still evolving and need further evaluation in subsequent studies.

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Surgical Approaches

16

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Definitions of Pancreatitis

Pancreatitis as a diagnosis encompasses a wide breadth of clinical presentations, ranging from mild abdominal pain that resolves without complication, to a severe, life-threatening illness with devastating long-term complications. See also Chaps. 1 and 2. Given the diversity of this disease, accurate and precise language is necessary to define it. Numerous attempts to define pancreatitis have been made over the years. In 1992, under the leadership of Edward Bradley [1], the Atlanta Classification was developed. This system attempted to unify the vocabulary describing the pancreatic disease process using clinical criteria; however, it was criticized as too vague, unobjective, and confusing. This classification system was revised in 2012, with a goal to provide more objective, clear terms to better classify and define the severity of pancreatitis and its local complications [2]. This modern classification scheme is summarized below.

The *clinical diagnosis of acute pancreatitis* can be made based on the presence of two of the three following criteria: (1) symptoms of central upper abdominal pain of acute onset, radiating to the back; (2) serum pancreatic enzyme (amylase or lipase) levels greater than three times normal; or (3) characteristic features on cross-sectional abdominal imaging consistent with acute pancreatitis [1, 3–5]. The onset of acute pancreatitis is established with time zero, defined as the time of onset of abdominal pain. Hospital admission times should not be used as time zero as there is often a delay of presentation to the hospital and commonly a need for transfer between hospitals for higher level of care considerations. Following the disease progression from time zero, to time of presentation, through the initial 24–48 h and first weeks of illness is important in stratification of the disease severity. The improvement, worsening, or stagnation of the patient's condition at these time points have important implications in the patient's prognosis and can point to increased severity of disease or the development of complications.

Two distinct types of acute pancreatitis are defined in the original and revised Atlanta Classifications [1, 2]: ***Interstitial edematous pancreatitis*** (**EP**), which can be thought of essentially as non-necrotizing pancreatitis, and ***necrotizing pancreatitis*** (**NP**). With EP there is homogeneous enhancement of the pancreas gland and inflammatory changes in the surrounding fat. The defining feature of EP is that there is no evidence of necrosis within the pancreatic parenchyma or surrounding the pancreas on imaging. Fluid collections surrounding the pancreas may or may not be present and are not indicative of necrosis. EP represents 90–95 % of clinical pancreatitis and is often managed outside the ICU,

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as most such pancreatitis episodes resolve within the first week. Meanwhile, NP constitutes the remaining 5–10 % of acute pancreatitis patients, which usually require ICU management, and often progress to multi-organ system failure with or without sepsis. The defining characteristic of NP is the presence of necrosis either within pancreatic parenchyma or of surrounding tissues. Most commonly, necrosis of both the pancreatic gland and peripancreatic tissues will occur, although either can occur alone. The most rarely seen manifestation is isolated pancreatic parenchymal necrosis. Involvement of the pancreatic parenchyma portends a more ominous clinical journey [1]. Contrast-enhanced CT (CECT) findings of necrosis include non-enhancement of pancreatic parenchyma as well as inflammatory and solid component features of surrounding tissues; however, it is important to recognize that compromise of pancreatic perfusion from necrosis and CT signs of peripancreatic necrosis can evolve over days. Therefore, early CECT imaging (i.e., within the first 7 days) is likely to underestimate the extent of tissue necrosis.

Necrotizing pancreatitis can be further classified as infected or sterile necrosis; EP does not become infected. Infection of necrotic tissue continues to be associated with a high mortality; therefore, it is essential to recognize its presence. Ongoing sepsis or acute clinical deterioration should raise the suspicion of infected necrosis; however, its presence can be proven by imaging or culture. The pathognomonic radiographic feature is the presence of gas within areas of necrosis on CECT imaging. Diagnosis and management of infected necrosis is further discussed later in the chapter.

Phases of Acute Pancreatitis

Acute pancreatitis is divided into two disease phases, each with individual risks and associated mortality [1, 2, 6]. During the **early phase of acute pancreatitis**, which usually lasts the first 1–2 weeks, the pancreatic damage and any systemic complications are a result of the autodigestion of the pancreas as well as the associated cytokine cascade that this elicits and is characterized by the systemic inflammatory response syndrome (SIRS) [7] (Table 16.1). As SIRS persists, the chance of organ failure increases. This early phase can resolve without sequelae, as in mild acute pancreatitis (MAP); however, in the more severe cases, the inflammation continues and leads to further disease processes. This continued systemic inflammation defines the **late phase of acute pancreatitis**. This phase can last for weeks to months after the initial presentation with pancreatitis, consisting of continued SIRS and/or local or systemic complications, including persistent organ failure.

Table 16.1 Criteria for systemic inflammatory response syndrome (SIRS)

General variables
Fever (core temp >38.3 °C)
Hypothermia (core temp <36 °C)
Heart rate >90 bpm
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC >12,000)
Leukopenia (WBC <4,000)
Bandemia (>10 % band forms)
Plasma C-reactive protein >2 s.d. above normal value
Plasma procalcitonin >2 s.d. above normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70, or SBP decrease >40 mmHg)
Organ dysfunction variables
Arterial hypoxemia
Acute oliguria
Creatinine increase
Coagulation abnormalities
Ileus
Thrombocytopenia
Hyperbilirubinemia
Tissue perfusion variables
Hyperlactatemia
Decreased capillary filling

Created with data from [7]
bpm beats per minute, *MAP* mean arterial pressure, *SBP* systolic blood pressure, *s.d.* standard deviations, SvO_2 venous oxygen saturation, *WBC* white blood cell count

Stratification of Severity

Stratification of the severity of acute pancreatitis is important, because as stated above, this is a dynamic disease that can manifest with a broad range of physiologic derangements and varying survivability. See also Chap. 2. Early stratification helps to determine patient risk, targets resuscitation, and can help identify patients that require transfer to higher levels of care. Precise and consistent language aids in clear communication between teams and focuses attention to the medical issues that need to be addressed in the treatment plan. The Revised Atlanta Classification of Acute Pancreatitis provides clear clinical characteristics that help to define the degree of pancreatitis that is present [2]. The presence or absence of organ failure, local complications, and/or systemic complications defines three distinct classes of acute pancreatitis: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) (Table 16.2).

Mild Acute Pancreatitis

MAP is defined as pancreatitis without the presence of organ failure and no local or systemic complications. Diagnosis is clinical and imaging is usually not required. Enteral feeding is recommended once tolerated, patients are usually discharged within a week of hospitalization, and mortality is rare [2].

Moderately Severe Acute Pancreatitis

MSAP is defined as pancreatitis with transient organ failure (less than 48 h duration) or the existence of local or systemic complications in the absence of persistent organ failure. Examples of local complication include peripancreatic fluid collections, acute necrotic collections, pancreatic pseudocyst, infected necrosis, gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis. These local complications and their management will be further discussed later in the chapter. Given the breadth of possible associated complications, it follows that the clinical course of MSAP is variable. Transient organ failure and acute fluid collections may resolve without further intervention, whereas other local complications may require debridement or drainage. Mortality in this class of pancreatitis is higher than in acute pancreatitis; however its mortality remains much lower than that of SAP, with rates reported as <8 % [8].

Severe Acute Pancreatitis

SAP is characterized by persistent organ failure (organ failure that does not resolve after 48 h). Persistent organ failure can involve one or multiple organs. While the presence of local complications is not explicitly contained in the diagnosis of SAP, the vast majority of patients with persistent organ failure have local complications as well. Those who develop persistent organ failure during the early phase of pancreatitis have a higher rate of death, with mortality rates reported to range between 36 and 50 % [2].

Table 16.2 Definitions of severity in acute pancreatitis, modified from the Revised Atlanta Classification System

	Mild acute pancreatitis	Moderately severe acute pancreatitis	Severe acute pancreatitis
Transient organ failure (<48 h duration)	No	Yes	Yes
Persistent organ failure (>48 h duration)	No	No	Yes
Local complications	Rare, can develop acute fluid collections which usually resolve without intervention	Can be present	Usually present
Mortality risk	Rare	<8 %	30–50 %

Created with data from [2]

Development of infected necrosis, in the presence of SAP, is associated with a high mortality rate and should be aggressively managed [2].

Defining Pancreatic Collections

CT or MRI imaging is helpful in identifying and classifying local complications which typically present as peripancreatic collections; however, the term "peripancreatic collections" encompasses a heterogeneous group of entities. Therefore, the Revised Atlanta Classification divides these into four distinct groups, defined by their contents and architecture. Correct diagnosis is important, as management and potential complications of these collections can differ significantly. Collections containing only fluid are defined as either acute *peripancreatic fluid collections or pancreatic pseudocysts*, whereas *acute necrotic collections* or *walled-off necrosis* are collections of necrotic tissue with or without a fluid component.

Acute peripancreatic fluid collections are fluid collections that develop during the early phase of edematous pancreatitis in the fascial planes of the retroperitoneum. They do not have any defining wall, are homogenous-appearing on imaging, and are sterile. They may be single or multiple and tend to resolve without intervention.

Pancreatic pseudocysts are peripancreatic collections composed solely of fluid, with no solid components, that have a well-defined, circumscribing wall. The fluid is usually high in amylase and results from disruption of a pancreatic duct with persistent leakage. Pseudocysts can also develop following parenchymal necrosis of the pancreatic gland that isolates a viable, functioning distal pancreas, leading to localized leakage from the separated duct. These pseudocysts often develop after necrosectomy, as fluid accumulates within the necrosectomy space.

Acute necrotic collections are defined as a collection of variable amounts of necrotic tissue with or without fluid, which occurs within 4 weeks of an episode of pancreatitis. These collections may be loculated and may be difficult to differentiate from acute pancreatic fluid collections when imaging performed during the first week of the disease process; therefore, sequential imaging is often helpful to fully define the collection. MRI and ultrasound may help to better define the solid components of these collections.

Walled-off necrosis is a collection of necrotic tissue with an enhancing wall that implies maturity and encapsulation of acute necrotic collections. These usually require greater than 4 weeks to develop. These may be single or multiple, near to the gland or located at sites distant from the pancreas. These may be sterile or infected. Similarly to acute necrotic collections, these may be misdiagnosed as pancreatic pseudocysts due to CT imaging limitations, which is why additional imaging such as MRI and ultrasound techniques is useful to correctly identify these collections.

Prognostic Measures of Acute Pancreatitis

Given the wide spectrum of pancreatitis, early identification of those patients at risk for severe disease, complications, and mortality is imperative. See also Chaps. 4 and 6. Patients with obvious organ dysfunction or severe disease warrant intensive care monitoring; however, predicting patients who will develop severe disease on admission is not always straightforward. Multiple scoring systems have been proposed to attempt to identify patients at risk. One of the earliest prognostic scores was developed by Dr. JH Ranson in 1974 using clinical criteria at admission and 48 h to evaluate the severity and mortality risk of acute pancreatitis based on clinical data. Several other prognostication systems have been proposed. The CT Severity Index (CTSI), which grades pancreatitis severity based on radiographic findings of necrosis and fluid collection, has been shown to correlate with statistical significance with mortality of pancreatitis [9]. APACHE II score [10] uses physiologic variables to calculate risk. Although it can be calculated at 24 h, the score at this time has a poor predictive value for severe disease [5]; however, because it can be calculated daily, following the trend can be very useful. Increasing APACHE

II scores during the first 48 h are associated with development of severe pancreatitis, whereas decreases point toward mild, resolving disease. SIRS [7] (see Table 16.1) has also been used to predict mortality. In one study, patients with acute pancreatitis and the absence of SIRS on admission had a mortality rate of 0.7 %, patients with SIRS on admission that resolved after 48 h had a mortality rate of 8 %, whereas patients with persistent SIRS at 48 h had a mortality rate of 25 % [11]. None of these scoring systems have been conclusively proven to most accurately predict severe disease and mortality, rather they should be used to triage patients and identify those at risk for more severe disease.

Surgical Management of Severe Acute Pancreatitis

In current practice, surgical interventions in acute pancreatitis are aimed at the management of complications of SAP and the ensuing inflammatory process as well as at prevention of recurrent pancreatitis, as in cases of gallstone pancreatitis. Surgical intervention during the early phase of acute pancreatitis is extremely difficult given the severe inflammation and should be limited to life-threatening complications.

Historical Approach: Surgical Indications

Early in the twentieth century, the mainstay of treatment of SAP was early debridement. Lord Moynihan, a prominent British surgeon in the 1920s went so far as to say that "… recovery from this disease, apart from operation, is so rare that no case should be left untreated" [12]. Surgical interventions ranged from debridement with gauze drainage, marsupialization of the gland, to complete resection, with the main goal of treatment to remove all necrotic tissue early in the disease process. Surgical practice in the 1970s and 1980s, however, shifted to emphasis on conservative management, with teaching suggesting that surgical intervention was futile and associated with high mortality. Identification of patients likely to benefit from surgical intervention and surgical techniques promoting safe removal of infected, necrotic tissue were pioneered by Bradley et al. [13]. This landmark study demonstrated a significantly improved survival with pancreatic debridement in those patients with infected necrosis. The optimal timing of surgical intervention was investigated over the ensuing decade, with evidence suggesting later surgical intervention preferable to early intervention in most patients. This was proven via a randomized clinical study by Mier et al. that was ultimately stopped prior to completion given the extremely high mortality rate in patients who underwent early debridement (58 %) compared to those who underwent late debridement (27 %) [14].

Indications for Surgery: Acute Complications

During the early phase of pancreatitis, the main tenet of current therapy is conservative and supportive management. Adequate and early fluid resuscitation is critically important in the care of these patients and may help reduce the incidence of SIRS and organ failure [15]. Early enteral feeding can be accomplished in most patients, with the benefit of decreased infectious complications and mortality [16]. Enteral feeding has most often been accomplished via nasojejunal tube placement, to decrease stimulation of the pancreas; however, multiple studies have demonstrated that nasogastric or nasoduodenal feeding is safe and of similar benefit compared to jejunal feeding [17, 18]. Any abdominal interventions should be limited in this acute phase of active inflammation, with the main recommendation to only to treat severe, catastrophic conditions, such as hemorrhage, perforation of a hollow viscus organ, and abdominal compartment syndrome (ACS).

Catastrophic Abdomen

Pancreatitis is primarily a destructive inflammatory process, which not only destroys its own parenchyma, but can erode into adjacent structures

and lead to injury and compromise of surrounding structures, with devastating complications. Rare abdominal catastrophes, such as bowel ischemia, ACS, and uncontrolled hemorrhage, require emergent surgical intervention, even in the early phases of pancreatitis.

Bowel ischemia can develop due to ACS and occasionally needs to be treated emergently. ACS by itself, without bowel ischemia, is also a surgical emergency regardless of stage of pancreatitis. ACS is defined as sustained intra-abdominal pressure >20 mmHg that is associated with the onset of new organ failure. This can occur due to the massive fluid resuscitation required during the treatment of the early phase of pancreatitis. Emergent decompressive laparotomy for relief of ACS is imperative, with removal of any nonviable bowel occasionally warranted, although complications of this intervention are high.

Additionally, bowel ischemia can be due to inflammation from pancreatitis surrounding the mesenteric vessels, resulting in compromise of the small bowel and occasionally the colon. The most common presentation in this case is a patient who fails to respond appropriately to apparently adequate resuscitative measures. Diagnosis is difficult and is typically made at exploration (Fig. 16.1).

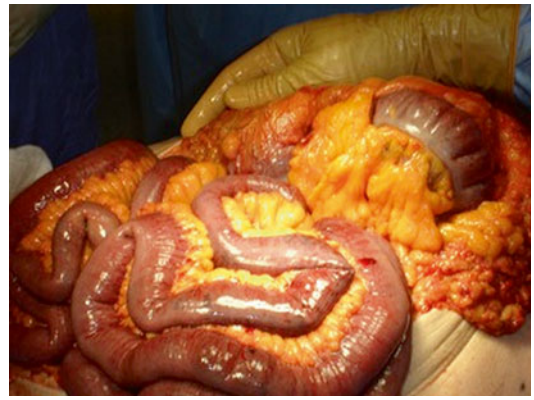

Fig. 16.1 Intraoperative findings in during exploratory laparotomy performed in a 65-year-old male who initially presented to an outside hospital with acute abdominal pain found to be due to gallstone pancreatitis. His clinical condition worsened overnight, during which time he required 6 L fluid for the treatment of oliguria and hypotension. He was transferred to our hospital and received 18 h of aggressive resuscitation, but continued to have worsening lactate and subsequent development of intra-abdominal compartment syndrome. Upon exploration he was found to have a large section of ischemic and necrotic bowel

Intra-abdominal hemorrhage associated with acute pancreatitis is most often due to bleeding from a pseudoaneurysm. Pseudoaneurysms develop due to weakening of the vessel wall after exposure to proteolytic enzymes and other inflammatory mediators of pancreatitis. Fortunately, this complication occurs with relative infrequency, affecting only 1–3 % of acute pancreatitis patients; however, it is associated with high mortality [19, 20]. Acute catastrophic hemorrhage from pseudoaneurysmal bleeding has been increasingly managed by angiographic and interventional techniques and is the preferred initial management. If noninvasive techniques fail or are unavailable, surgical intervention becomes necessary. Immediate laparotomy followed by packing to control the bleeding is the first step. If feasible, repair and exclusion of the pseudoaneurysm is performed, however, given the massive inflammation in the area surrounding the pseudoaneurysm it is often not possible. At this time, packing of the wound cavity is the next step, most often in the context of damage control surgery. Definitive repair of the pseudoaneurysm is undertaken once the patient can tolerate further surgical intervention and the early phase of pancreatitis is past.

In addition to pseudoaneurysm formation, pancreatitis can cause diffuse bleeding from tissue necrosis, and bleeding can occur from hemorrhagic pseudocysts, which can lead to uncontrolled hemorrhage in the event of pseudocyst rupture. Similarly to pseudoaneurysms, these complications present more often during the late phase of pancreatitis, but can occur during the early phase as well. Typically, selective mesenteric angiography can identify the site of bleeding [19]. Initial management remains the same, control of bleeding, hopefully via noninvasive angiography or via abdominal packing. Further management, such as removal of necrotic tissue and management of pseudocysts, is discussed later in this chapter and should be attempted once the patient can tolerate surgery and the active inflammatory phase

is over. This further management is important, as without removal of the necrotic tissue, intra-abdominal hemorrhage has a very high rate of recurrence [20].

Indications for Surgery: Later Complications

Infected Necrosis

Infection of necrotic tissue during SAP is an important determinant of mortality; therefore, it is essential to differentiate between sterile and infected necrosis. Ongoing sepsis or acute clinical deterioration should raise suspicion of infected necrosis and its presence can be proven by imaging or culture. The presence of the pathognomic finding of gas in necrotic tissue spaces on cross-sectional imaging confirms the diagnosis. In our experience, the presence of gas is frequently associated with duodenal or enteric fistulae. Without gas within the necrotic area on imaging, infected necrosis can be diagnosed via image-guided fine-needle aspiration (FNA) sent for gram stain and culture. It should be noted that current recommendations of the International and American Pancreatic Associations (APA) state that FNA should not routinely be performed, in part due to the risk of false negative results (12–25 %) [4]. Infection can develop de novo in previously sterile necrotic tissue via bacterial translocation from the gastrointestinal tract; however, it is important to recognize that secondary infection can occur after instrumentation, via FNA, endoscopy, and ERCP. These procedures should be performed only when necessary, and fever or worsening of the patient's condition following these interventions should prompt concern for infection. Clinical scenarios that should arouse suspicion of the presence of infected pancreatic necrosis include patients with severe pancreatitis whose severe SIRS now progresses to severe sepsis, or in patients with sepsis who continues to decline clinically despite targeted antibiotic therapy. In the critically ill pancreatitis patient, all other sources for infection must be thoroughly searched for and either ruled out or treated promptly, such as pneumonia, urinary tract infection, line infection, sinusitis, and cholecystitis.

Once infected necrosis is diagnosed, timely intervention must be undertaken with the goal of surgical treatment being debridement and removal of the infected tissue, thereby controlling the infection and halting the release of proinflammatory mediators. If patient condition permits, removal of the necrotic tissue should be postponed until 3–4 weeks after the onset of pancreatitis. This leads to safer operating conditions, as decreased inflammation leads to decreased operative bleeding and better delineation of necrotic tissue, which allows the surgeon to minimize the amount of viable tissue that is removed, thereby reducing the exocrine and endocrine complications with pancreatic insufficiency [20]. Surgical removal of necrotic tissue is also indicated if the necrotic tissue is, or has previously been, hemorrhagic, if the necrotic tissue leads to ongoing gastric, intestinal, or biliary obstruction continuing >4 to 8 weeks after pancreatitis, or the patient continues to have ongoing organ failure after several weeks of acute pancreatitis without improvement.

The most current recommendations from the International Association of Pancreatology (IPA) and APA state that the optimal interventional strategy for suspected or confirmed infected necrosis is initial management with image-guided percutaneous catheter drainage or endoscopic transluminal drainage, followed by endoscopic or surgical debridement only if necessary [4]. This is following the results of the PANTER trail, a randomized controlled trial comparing open surgical necrosectomy to a minimally invasive approach [21]. This study compared 88 patients randomized to either open necrosectomy or a minimally-invasive "step-up" approach involving percutaneous drainage and post-procedural irrigation of the drained space. If necessary, this was followed by definitive tissue debridement via a video-assisted retroperitoneal debridement (VARD) (Fig. 16.2) and continued postoperative irrigation and drainage. These patients were followed through 6 months after discharge. The primary endpoint was a composite of either "death" or the occurrence of "major complications" comprised of: new-onset organ failure (parameters defined for

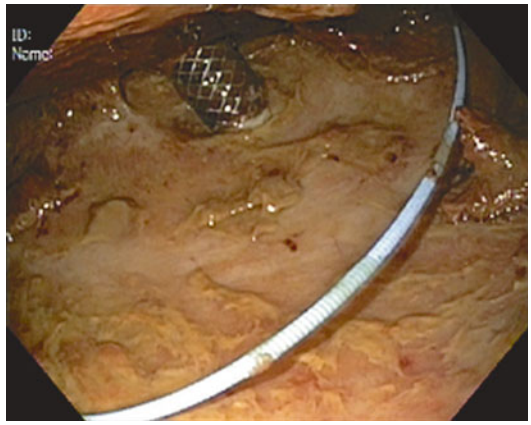

Fig. 16.2 An image from a video-assisted retroperitoneal debridement for infected necrosis of the pancreas. This is a view of the retroperitoneal approach in a patient with infected necrosis tracking down left gutter. A stent has been placed through stomach in left upper field and the guidewire from retroperitoneal approach in right camera field

pulmonary, circulatory, and renal failure), any system complications such as DIC, severe metabolic disturbances or GI bleeding, or visceral organ perforation, ECF, or intra-abdominal hemorrhage. The secondary endpoints were the individual components of the primary endpoint. This study demonstrated that there was no difference in mortality between the groups, and the minimally invasive step-up approach was associated with significantly lower rates of new-onset organ failure, as well as fewer longer-term complications such as pancreatic insufficiency. In addition, health care resource utilization and ICU readmission rates were significantly lower in the minimally invasive step-up group. The medical costs, both direct and indirect, per admission and at 6-month follow-up were shown to be lower by 12 % in the step-up group.

Endoscopic procedures have also been performed in conjunction with percutaneous or VARD procedures to remove necrotic pancreatic tissue. They can be performed via transluminal or transgastric approach. The benefit of these approaches is that pancreatic fistulas will not develop, as all pancreatic fluid produced will be drained into the stomach or intestine. However, a significant disadvantage is that multiple procedures are needed to remove sufficient necrotic tissues [22].

Open Techniques

If open necrostomy is performed, a variety of techniques have been employed. The mortality rates for the following techniques have been shown to be equivalent in experienced hands, with rates less than 15 % for any of the listed techniques [20]. Thus, surgeon preference dictates the approach, although the distinct advantages and disadvantages of each are worth mentioning. All four of these methods have in common initial debridement, which can often be completed during the initial visit, and these methods then vary by the manner in which they establish continued debridement or lavage of the necrosectomy space to facilitate continued egress of stubbornly attached necrotic tissue.

- Transperitoneal laparotomy with open packing—open midline laparotomy, surgical necrosectomy, packing the retroperitoneal space with the abdomen left open, requiring multiple re-laparotomies.
- Transperitoneal laparotomy with staged re-laparotomy—open midline laparotomy, surgical necrosectomy, no packing left within, open abdomen requiring multiple re-laparotomies.
- Closed lavage of the retroperitoneum—open laparotomy, surgical necrosectomy, drains left within the retroperitoneum, closure of lesser sac, postoperative continuous irrigation.
- Closed packing—open laparotomy, surgical necrosectomy, packing left within the retroperitoneum, return to OR for removal of packing, and closure of the abdomen.

Complications of the open procedures above include extensive bleeding in the necrosectomy space and increased cumulative blood loss, fistula formations to the GI tract, gastric outlet obstruction, and incisional hernia [20].

A few comments regarding the technical approach to the open debridement of pancreatic necrosis seem appropriate. It is the habit of this author to perform a transverse incision in the upper abdomen and to remove the gallbladder at the first operation. Typically, a surgical jejunostomy tube is placed, then the transverse colonic mesentery is divided, opening the lesser sac. At this point, pancreatic sequestrum is usually

easily entered. It is important to *gently* debride the pancreatic tissue, as bleeding may ensue with more vigorous debridement. Irrigation typically frees additional tissue. The inferior transverse colonic omentum is tacked to the peritoneum at the inferior margin of the incision, to keep purulence in the lesser sac from spreading to the lower abdomen. The lesser sac is packed with laps or kerlex gauze, and the wound is temporarily closed with a vacuum-assisted dressing, with planned reoperation every 48 h until no further necrotic tissue is encountered. At this point the fascia can be closed with drains placed in the lesser sac.

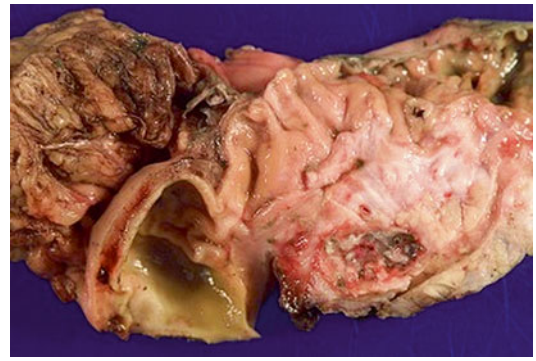

Fig. 16.3 Specimen of the duodenum and pancreatic head after Whipple procedure resection for recurrent pancreatitis in a patient with persistent pancreatic fistula. Note the enteric staining of cut surface of pancreatic head

Pancreatic Abscess

Pancreatic abscess is the most common complication of pancreatitis that mandates re-intervention after necrosectomy [20]. These generally occur after 5 weeks of the onset of pancreatitis. Pancreatic abscesses usually remain contained and are less destructive than infected pancreatic necrosis, and thus can be managed typically with percutaneous drainage. Failure of percutaneous approach would mandate operative intervention for drainage.

Pancreatic Pseudocyst

The management of pancreatic pseudocysts is a continually evolving paradigm. Previous dogma recommending drainage of pseudocysts that persisted greater than 6 weeks no longer holds true. The majority will resolve on their own, follow a benign course, and can be managed with no further intervention [20]; however, if they become symptomatic or are noted to grow during a period of observation, intervention becomes necessary. A diameter of >6 cm is often quoted as an indication for intervention; however, this remains controversial. Treatment can be performed in many ways, and the management is best decided via interdisciplinary team discussions. Percutaneous drainage is currently indicated only for emergency drainage of infected cysts, especially early in the course of pancreatitis, since recurrence and fistula development occur with high rates in this approach [23]. Endoscopic drainage, either via transpapillary or transmural approach, has a high success rate in experienced hands, and lower risk of fistula formation, as the drainage of pancreatic secretions can be directed enterally [23]. Surgical interventions that can be used to drain pseudocysts cysts enterally include cystgastrostomy or a Roux loop cystojejunostomy. Pseudocysts located in the pancreatic tail are difficult to drain enterally and may be best treated by pancreatic resection. However, the mortality and morbidity following resection are higher than after surgical drainage [20].

Pancreatic Fistula

Treatment of pancreatic fistulas due to acute pancreatitis is managed in a similar fashion to fistulas of other etiologies. Conservative management is usually attempted first (e.g., jejunal tube feeds, bowel rest, TPN, octreotide); however, if this fails, further interventions are necessary. Endoscopic transpapillary stenting has also been proposed as an intervention to treat pancreatic fistulas, as the stenting decreases the intraductal pressure and helps shunt the pancreatic secretions into the duodenum instead of the fistula [24]. Surgical management is reserved for those patients who are not responding to the above measures. In this setting, depending on the location of the fistula, the patient may undergo Whipple procedure (Fig. 16.3), Roux-en Y pancreaticojejunostomy, cystojejunostomy, or distal pancreatic resection [25].

Special Considerations with Biliary Pancreatitis

The two leading causes of acute pancreatitis in the United States are gallstones and alcohol consumption. Although it may seem intuitive to perform ERCP in patients with gallstone pancreatitis, early ERCP has not been routinely recommended for patients with mild or severe gallstone pancreatitis. The only group that has been demonstrated in prospective, randomized clinical trials to benefit from early ERCP with stone extraction and sphincterotomy has been the subset of patients with gallstone pancreatitis *who have obstructive jaundice and/or cholangitis*. Without these features, early ERCP has been shown to lead to high complication rates with no observable benefit [26, 27].

In patients with biliary pancreatitis, patients discharged after resolution of pancreatitis have a high recurrence rate if the causative factor is not controlled. One review reported that 18 % of patients who had an interval cholecystectomy performed a median of 40 days after the initial pancreatitis admission were readmitted prior to cholecystectomy for biliary-related complications [28]. Current recommendations are that patients with MAP undergo laparoscopic cholecystectomy during their index admission [4]. In elderly or unfit patients with biliary pancreatitis who are unable to tolerate same-admission cholecystectomy, an alternative or bridge to surgery is elective ERCP with sphincterotomy to lower the risk of recurrent SAP. For patients with concurrent cholecystitis, if the patient is at high risk for cholecystectomy, a cholecystostomy tube can be placed [29]. For severe biliary pancreatitis with peripancreatic collections, cholecystectomy should be delayed until the collections resolve, typically 6 weeks after the onset of pancreatitis [4]. Cholecystectomy is advised in all patients that can tolerate the procedure, as the risk of recurrent pancreatitis is decreased following ERCP with sphincterotomy, but has no effect on the risk of acute cholecystitis and other gallstone-related gallbladder disease [28]. It is important for the surgeon to recognize the fact that these procedures are frequently difficult and may require an open approach. This requires appropriate counseling of the patient and appropriate preoperative planning.

Conclusion

Acute pancreatitis and its complications make up a diverse and nuanced disease, whose management is characterized by complex issues and many subtleties. Multidisciplinary management is best for the patient and provides a greater breadth of treatment options. Surgical management continues to play an important role in the care of patients with acute pancreatitis and its sequelae.

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17 Interventions for Necrotizing Pancreatitis: A Multidisciplinary Approach

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Introduction

Acute pancreatitis (AP) is a dynamic inflammatory process involving the pancreas, peripancreatic tissues, and less commonly remote organ systems [1–6]. The most widely used definitions for acute pancreatitis are derived from the recently revised Atlanta classification, which has undergone extensive revision by an international panel of experts from multiple disciplines [7]. According to these revisions, AP is either interstitial or necrotizing. Pancreatic necrosis is typically defined by non-enhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT). Necrosis can involve either pancreatic parenchyma alone (less commonly), both the pancreatic parenchyma and the peripancreatic tissues (more commonly), or isolated peripancreatic tissue alone (least commonly). Isolated peripancreatic or extrapancreatic necrosis may be associated with improved long-term outcomes compared to pancreatic necrosis [8]. However, peri- or extrapancreatic necrosis carries a worse prognosis than acute interstitial pancreatitis. Both pancreatic and peripancreatic necrosis can be either sterile or infected. Mortality of necrotizing pancreatitis has traditionally varied from approximately 15 % in patients with sterile necrosis, to as much as 39 % in patients with infected necrosis, which occurs in approximately 40–70 % of patients.

According to the recent revisions, there are only four kinds of collections associated with interstitial and necrotizing pancreatitis [7] (Table 17.1). Of importance is that many walled-off collections formerly referred to as pseudocysts in fact represent walled-off necrosis (WON), a distinction that has major implications for management [9]. Simple drainage is almost always effective for pseudocysts, but only for the minority of WON. In general, sterile necrosis does not require intervention, while infected necrosis usually requires evacuation. The traditional management of infected necrosis has centered on open surgical debridement, with additional percutaneous drainage and peritoneal lavage, all of which usually require multiple operative sessions and interventions. Open surgical debridement is accompanied by significant risk of perioperative stress, organ failure, and

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Table 17.1 Revised Atlanta Criteria terminology for collections in acute pancreatitis

Interstitial edematous pancreatitis
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis
CECT criteria
• Pancreatic parenchyma enhancement by intravenous contrast agent
• No findings of peripancreatic necrosis (see below)
Necrotizing pancreatitis
Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
CECT criteria
• Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
• Presence of findings of peripancreatic necrosis (see below—ANC and WON)
1. APFC (acute peripancreatic fluid collection)
Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within first 4 weeks after onset, not a pseudocyst
CECT criteria
• Occurs in the setting of interstitial edematous pancreatitis
• Homogeneous collection with fluid density
• Confined by normal peripancreatic fascial planes
• No definable wall encapsulating the collection
• Adjacent to pancreas (no intrapancreatic extension)
2. Pancreatic pseudocyst
An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset
CECT criteria
• Well circumscribed, usually round or oval
• Homogeneous fluid density
• No nonliquid component
• Well-defined wall; that is, completely encapsulated
• Maturation usually requires >4 weeks after onset of acute interstitial edematous pancreatitis
3. ANC (acute necrotic collection)
A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
CECT criteria
• Occurs only in the setting of acute necrotizing pancreatitis
• Heterogeneous and nonliquid density of varying degrees in different locations (some appear homogeneous early in their course)
• No definable wall encapsulating the collection
• Location—intrapancreatic and/or extrapancreatic
4. WON (walled-off necrosis)
A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotizing pancreatitis CECT criteria
• Heterogeneous with liquid and nonliquid density with varying degrees of loculations (some may appear homogeneous)
• Well-defined wall, that is, completely encapsulated
• Location—intrapancreatic and/or extrapancreatic
• Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

long-term complications including external fistulas, diabetes, pancreatic exocrine insufficiency, and incisional hernias [5, 10–18]. Over the past decade, the management of pancreatic necrosis has evolved substantially with introduction and refinement of a variety of minimally invasive approaches to drainage and evacuation of necrosis. The aim of the current review is to give an insight into the various minimally invasive modalities available for necrosectomy. Regardless of approach, in order to achieve optimal outcomes, emphasis is placed on the necessity for multidisciplinary management in advanced medical centers with specialized expertise in the management of severe acute pancreatitis. Such an approach involves routine coordinated involvement of dedicated interventional endoscopists, surgeons, and interventional radiologists, all with specific understanding of and experience with management of necrotizing pancreatitis. Ongoing consultation and ideally weekly conferences are essential to the systematic management of these challenging patients.

Diagnosis of Pancreatic, Peripancreatic, and Infected Necrosis

CECT remains the "gold standard" for imaging in severe acute pancreatitis [1–6] (Figs. 17.1 and 17.2). CECT aids in the diagnosis of pancreatic parenchymal necrosis, in determining the extent

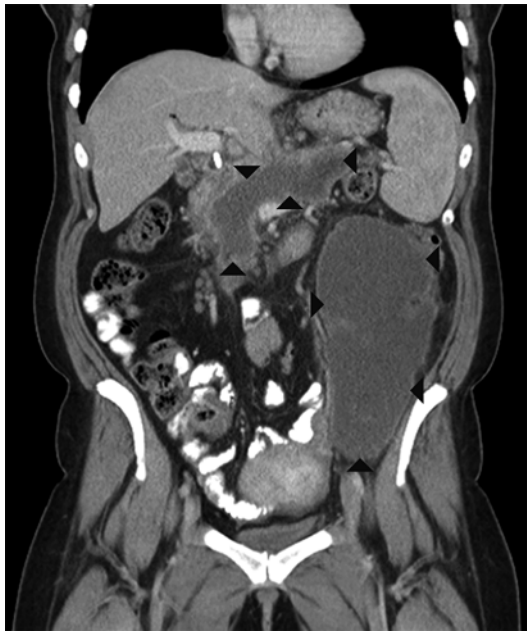

Fig. 17.1 CECT (coronal image) showing very large walled-off necrotic collections involving the pancreas itself (central collection outlined by *arrows*) and peripancreatic tissues extending deep into left pelvis (*arrows* to screen *lower right*). These types of complex WON will often fail to resolve using a single approach and require adjunctive techniques

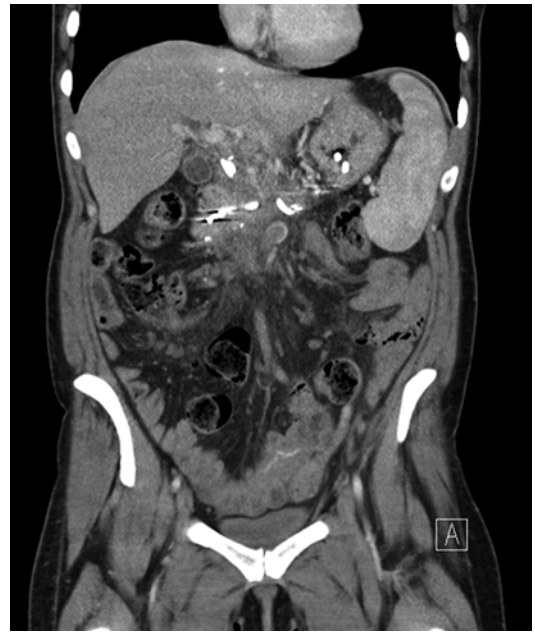

Fig. 17.2 CECT (coronal image) showing complete resolution of WON in Fig. 17.1, after combined dual entry endoscopic transmural drainage and necrosectomy, combined with left flank retroperitoneal percutaneous catheter drainage (PCD) and sinus tract endoscopic necrosectomy (see Fig. 17.7)

of necrosis, and can identify local complications including venous thrombosis and pseudoaneurysm. Complete evolution of pancreatic necrosis may take up to 5 days. Hence, CECT can underestimate or underdiagnose necrosis if performed before this interval. Disadvantages of CECT include radiation exposure, especially with repeated imaging, and contrast-induced nephropathy. MRI with MRCP is considered as an alternative for the diagnosis of necrosis. Even without the use of intravenous gadolinium, MRI can demonstrate the presence of pancreatic necrosis, based on fat-suppressed T1-weighted images, enabling its use in renal insufficiency. Avoidance of radiation exposure, enhanced detection of nonliquid material in pancreatic and peripancreatic fluid collections, and ability of MRCP to detect bile duct stones and image the pancreatic duct above and below any disruption make MR imaging attractive when compared to CT imaging. Comparative drawbacks of MR include more variable quality and interpretation, longer acquisition times, difficult patient tolerance in the setting of critical illness, toxicity of gadolinium in patients with chronic kidney disease, and contraindication of MRI in pacemakers and other metallic objects. EUS can be performed at bedside in critically ill patients, allows the most precise identification of gallbladder and bile duct stones, and, if necrosis is present, enables the combination of imaging with intervention and drainage with the same procedure. On the other hand, EUS has potential for adverse events in profoundly ill patients, especially cardiopulmonary risk in patients who are not on ventilator support, and may overestimate the necrotic debris content of pancreatic collections.

The peak incidence of infection of pancreatic or peripancreatic necrosis is between 2 and 4 weeks after presentation, but can occur at any time during the clinical course [1–6]. Clinically, infected necrosis should be suspected

when there is new onset of sepsis in a previously stable patient, or progressive clinical deterioration such as worsening renal function, rising white blood cell count, or persistent tachycardia despite maximal support, and without an alternate source for infection.

In a minority of patients, there are characteristic findings on CT including intra- or peripancreatic gas due to gas-forming organisms or fistulous communication with the stomach, small intestine, or colon (with introduction of organisms and air). The microbial spectrum in infected necrosis includes monomicrobial flora in 60–87 % of patients and polymicrobial flora in 13–40 % of patients with a predominance of gram-negative aerobic organisms [19, 20]. In the past, a positive aspirate from a diagnostic image-guided fine-needle aspiration (FNA) was considered an indication for immediate surgical intervention, and such procedures were commonly performed [21]. However, FNA has been demonstrated to have a false-negative rate of 10 % or more and with the acceptance of the "step-up" approach to intervention, diagnostic FNA has largely been deemed unnecessary. Rather, the decision to intervene is made on clinical grounds including strong suspicion of infected and symptomatic necrosis. Once minimally invasive intervention is undertaken, cultures for bacteria and fungi can be obtained to further guide antimicrobial therapy. Using a clinical strategy for management of infected necrosis in the PANTER trial, cultures obtained during minimally invasive intervention yielded a definitive evidence for infected necrosis in over 90 % of patients [16]. Currently, one of the few remaining indications for diagnostic FNA in necrotizing pancreatitis is to detect fungal superinfection when a patient remains febrile despite ongoing treatment with broad-spectrum antibiotics [1, 4].

Indications and Timing for Intervention

Indications for intervention including endoscopic, percutaneous, or surgical in necrotizing pancreatitis are shown in Table 17.2. The primary indication for intervention in necrotizing pancreatitis is presence of infected necrosis. Sterile acute necrotic collections almost never warrant intervention early in the course of the disease, i.e., in the first 4 weeks. Interventions should be considered later in the course of sterile necrotizing pancreatitis only in the presence of persistent organ failure, disabling symptoms such as persistent pain requiring narcotics or preventing oral intake, gastric outlet or biliary obstruction, or presence of disconnected pancreatic duct. In order to optimize outcomes, interventions should be delayed as much as possible until there is "walled-off" necrosis (WON), which typically takes 4 weeks or more, but may be highly variable. Asymptomatic WON does not mandate intervention, regardless of the size and extension of the collection, and may resolve spontaneously over time.

Table 17.2 Indications for intervention (endoscopic, radiologic, or surgical) in necrotizing pancreatitis

1.	Clinical suspicion or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled off
2.	In absence of documented infection, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled off
3.	In sterile necrosis: ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect
4.	In sterile necrosis: persistent symptoms (e.g., intractable pain, "persistent unwellness") in patients with walled-off necrosis
5.	Disconnected duct syndrome (i.e., transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic collection(s)

Adapted from Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis

Interventions of any kind, whether endoscopic, percutaneous, or surgical, for pancreatic or peripancreatic necrosis within the first few weeks are generally associated with adverse outcomes and are typically reserved for infected necrosis in severely deteriorating patients [4, 5]. The primary exception is in the setting of abdominal compartment syndrome, wherein surgical or image-guided decompression is potentially lifesaving, but involves primarily fasciotomy and does not include debridement or drainage of acute necrotic collections [5].

Minimally Invasive Approaches to Necrosectomy

The presence of infected necrosis has traditionally been thought to be an indication for debridement or necrosectomy [21]. Recently, several studies have suggested the possibility of treatment of infected necrosis without formal drainage or necrosectomy; several studies have described nonsurgical treatment of infected necrosis by management in an ICU setting with targeted antibiotics (third-generation cephalosporin with beta-lactamase inhibitors and carbapenems), aggressive nutritional support, and judicious percutaneous intervention in the event of infected WON [22–26]. They have suggested significantly decreased length of hospitalization, duration of external drainage, and number of radiological procedures, and a mortality that was comparable to surgery. It is, however, unclear which patients could be safely and effectively managed without any form of necrosectomy, as these studies do not consider percutaneous drainage as an intervention, or consider endoscopic methods at all.

Traditional approaches to debridement involve open surgery, either via an anterior transperitoneal approach or via retroperitoneal approach through a flank incision [5, 10–18]. Alternative techniques continue to evolve and undergo refinement, and are collectively referred to as minimally invasive necrosectomy. They can be classified based on the method of visualization (open, radiologic, endoscopic, hybrid, or other) and route (per oral, transpapillary, or transmural, percutaneous retroperitoneal, percutaneous transperitoneal, percutaneous transmural, or other) according to a taxonomy developed by Windsor and colleagues [27] (Fig. 17.3). Minimally invasive procedures are thought to induce less physiological stress as compared with open surgical debridement.

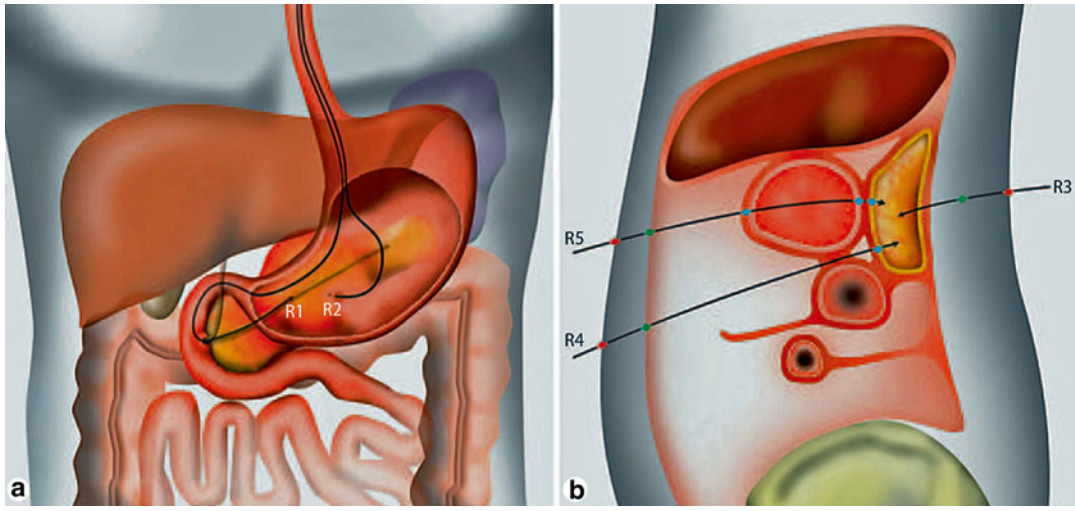

Fig. 17.3 Illustrations of a comprehensive classification of invasive procedures for treating the local complications of acute pancreatitis, as described by Loveday, Windsor, and coauthors at University of Auckland, Auckland, New Zealand. R1, Per-os transpapillary; I, internal route traversing duodenal papilla to enter pancreatic duct; R2, Per-os transmural; External orifice entry point, internal route traversing gastrointestinal wall; R3, Percutaneous retroperitoneal; Skin-external entry point, internal route traversing retroperitoneum; R4, Percutaneous transperitoneal; Skin-external entry point, internal route traversing peritoneum; R5, Percutaneous transmural; Skin-external entry point, internal route traversing gastrointestinal wall. Reprinted from Pancreatology, 11/4, Loveday BPT, Petrov MS, Connor S, Rossaak JI, Mittal A, Phillips ARJ, et al., A comprehensive classification of invasive procedures for treating the local complications of acute pancreatitis based on visualization, route, and purpose, 406–13, Copyright 2011, with permission from Elsevier

Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) of pancreatic and peripancreatic necrosis involves placement of single or multiple catheters, which are subsequently upsized, irrigated, and manipulated, sometimes along with direct percutaneous necrosectomy (Figs. 17.4 and 17.5). Freeny et al. first described a series of 34 patients with infected acute necrotizing pancreatitis who were treated primarily with imaging-guided PCD as an alternative to primary surgical necrosectomy, using PCD with active percutaneous necrosectomy by placement of multiple large-bore catheters and vigorous irrigation [28]. PCD was successful in postponing surgical intervention for a median of 4 weeks in 9 months and in obviating the need for surgical necrosectomy in 47 % of patients. Over the past two decades, PCD has been increasingly utilized to stabilize critical patients both as "a bridge to surgery" and sometimes as definitive therapy. The preferred route for PCD is via a flank approach through the retroperitoneum, because it avoids enteric leaks and dissemination of infected material into the peritoneal cavity. In addition, a retroperitoneal approach for PCD allows the tract to be used as guidance for surgical video-assisted retroperitoneal necrosectomy (VARD) or sinus tract endoscopy (Figs. 17.6 and 17.7). The Dutch Pancreatitis group recently reported a nationwide multicenter prospective study primarily of patients with infected necrosis. In that study, 63 % ($n=130$) of patients underwent PCD as a primary intervention [30]. Of this group 35 % of patients recovered without additional necrosectomy. Further a comprehensive systematic review of 11 retrospective studies involving 384 patients (both sterile and infected) showed that 56 % of patients who underwent PCD for sterile or infected necrosis did not need surgical intervention [31]. However care should be taken with interpretation of the conclusions of this systematic review, as selection bias and the design of the included studies may lead to overestimation of the proportion of patients who could be treated with PCD alone. The authors acknowledged the wide variation in techniques with drains varying from 8 to 28 Fr; only one study utilized routine stepwise dilation for upsizing the drains. Prospective studies have suggested a more realistic primary success rate of PCD of approximately 33 % [16].

PCD is a relatively simple and well-established radiologic procedure. It is beneficial especially as

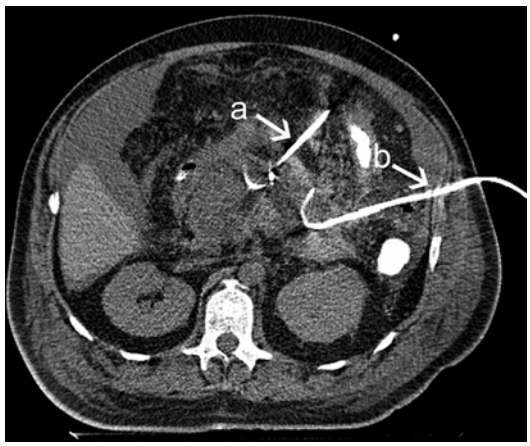

Fig. 17.4 CECT (axial image) showing dual PCD of WON; (*a*) shows anterior transperitoneal (R4) approach; (*b*) shows retroperitoneal (R3) approach

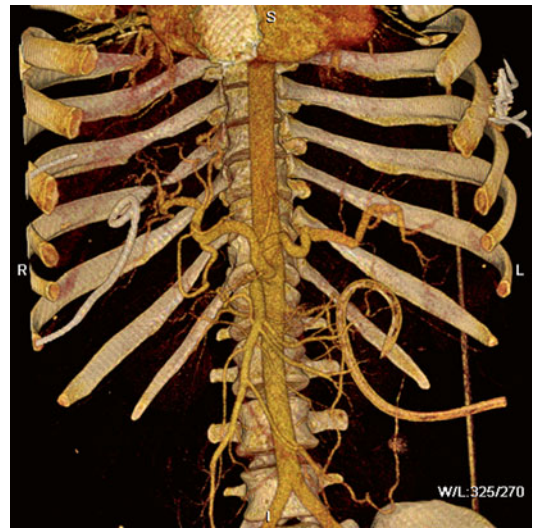

Fig. 17.5 CT angiogram showing two percutaneous catheters placed to treat patient with infected peripancreatic necrosis that was poorly encapsulated and extending deep into left retroperitoneum and intraperitoneally under liver; catheter through left flank is retroperitoneal (R3), and catheter in right upper quadrant is transperitoneal (R4)

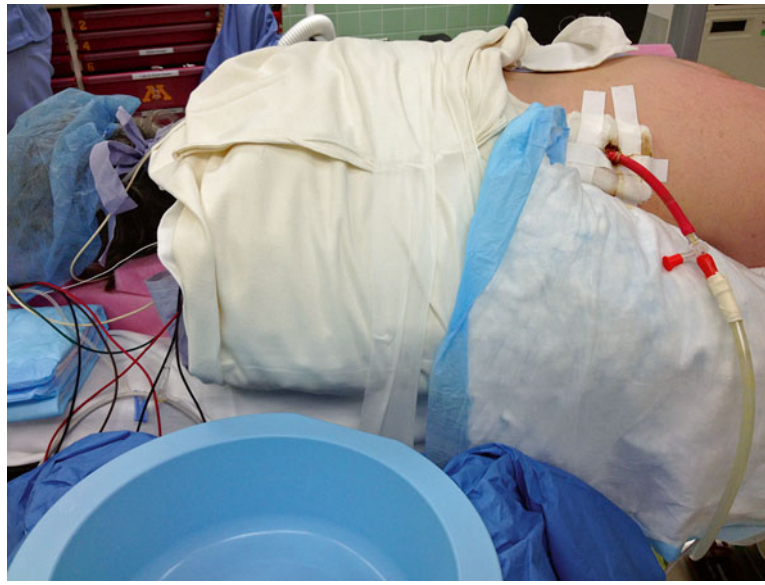

Fig. 17.6 Patient (same patient as Figs. 17.1 and 17.2) in prone position under general anesthesia showing left flank retroperitoneal percutaneous catheter (*red tube*) about to undergo minimally invasive retroperitoneal debridement via sinus tract endoscopy

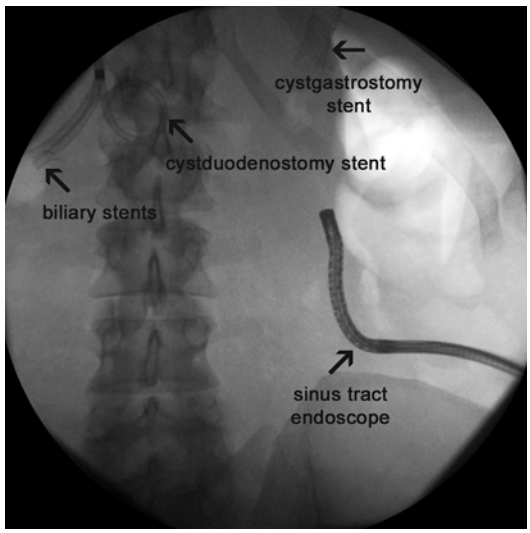

Fig. 17.7 Fluoroscopic image of patient (same patient as in Figs. 17.1, 17.2, and 17.6) showing maximal combined multimodality approaches to extensive WON including minimally invasive retroperitoneal debridement via sinus tract endoscopy, after dual endoscopic transluminal drainage and necrosectomy via cystogastrostomy and cystoduodenostomy, plus biliary stenting; *arrows* from *left* to *right*: biliary stents, cystoduodenostomy stent, endoscope passed from left flank tract through retroperitoneum into lesser sac; self-expanding metallic stent in cystogastrostomy

a prelude to definitive necrosectomy or when combined with another modality of treatment such as endoscopic drainage. It remains an adjunctive treatment in situations where the collection cannot be accessed endoscopically, such as deep retroperitoneal extension, or when the collection is poorly demarcated or walled off. Of note, percutaneous drains placed before 3 weeks are associated with a prolonged course and more frequent drain exchanges, underscoring the importance of maturation of WON before intervention. PCD is technically not adequate or feasible when retroperitoneal hemorrhage, bowel necrosis, or duodenal/biliary obstruction further complicates necrotizing pancreatitis. One of the main drawbacks of PCD is persistent external fistulae, which occur in up to 27 % of patients [5]. Other drawbacks include limited ability to remove necrotic debris. Dilatation of the percutaneous tract up to 26 Fr and use of grasping forceps to extract the debris have been described, as has the use of assist devices such as stone retrieval baskets, but these techniques are seldom performed in clinical practice [29, 32]. A dedicated team of radiologists willing to assiduously follow

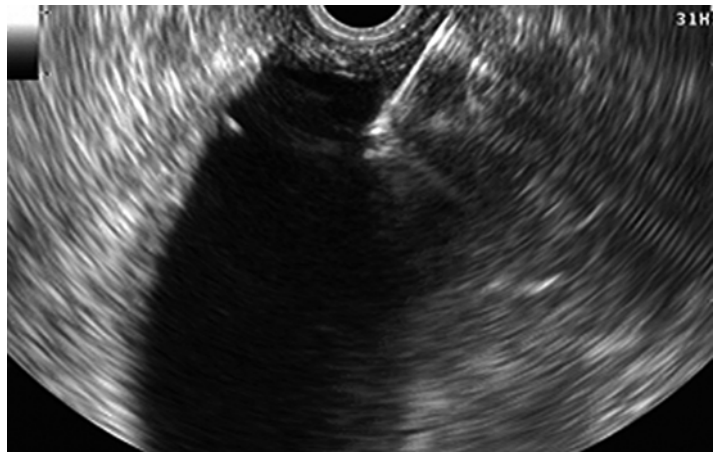

Fig. 17.8 Endoscopic ultrasound-guided transgastric puncture of WON

these patients and perform meticulous catheter care, with frequent upsizing of drainage catheters and frequent imaging to localize the loculated undrained areas is critical for successful percutaneous management of necrotizing pancreatitis as a primary strategy.

Endoscopic Transluminal Drainage and Necrosectomy

Endoscopic transluminal drainage and necrosectomy represent true natural orifice transluminal endoscopic surgical (NOTES) approaches (Figs. 17.8, 17.9, 17.10, 17.11, 17.12, 17.13, 17.14, 17.15, and 17.16). Endoscopic necrosectomy is increasingly gaining traction as primary therapy for infected pancreatic necrosis in carefully selected patients. Transmural drainage of chronic pancreatic pseudocysts is a well-established modality particularly when performed by experienced interventional endoscopists [33–35], and has been extrapolated to the management of WON [36, 37]. However, the principal difference is that unlike with pseudocysts, endoscopic necrosectomy involves direct debridement of solid debris [38]. Endoscopic approaches also offer simultaneous ability to treat biliary obstruction and also to treat disconnected pancreatic duct by performing transpapillary and/or internal cystenterostomy stenting.

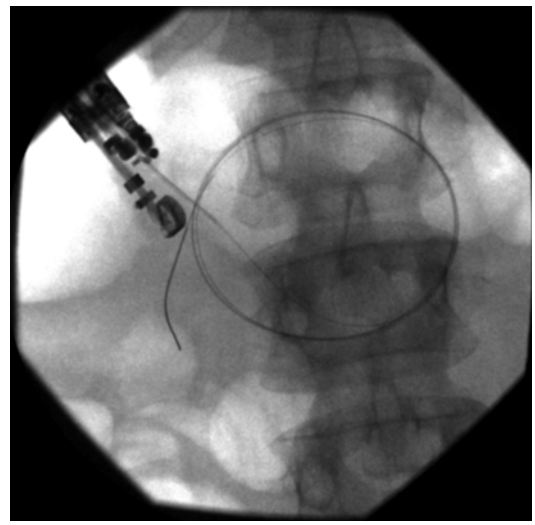

Fig. 17.9 Endoscopic ultrasound-guided transgastric puncture of WON; fluoroscopic view showing guidewire coiled in cavity

Endoscopic transmural necrosectomy (ETN) was first reported by Seifert and colleagues [39]. ETN involves creation of a cystenterostomy, followed by large-diameter (10–20 mm) balloon dilation, and direct entry into the necrotic cavity using a forward-viewing endoscope. Necrosectomy is performed under direct endoscopic vision using forceful irrigation, suction, snares, rat toothed-forceps, tripod retrieval, stone removal baskets, and a range of other endoscopic accessories. Endoscopic necrosectomy is generally repeated

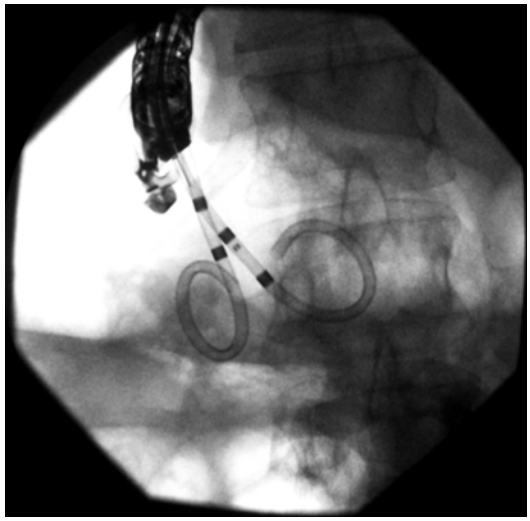

Fig. 17.10 Endoscopic ultrasound-guided transgastric puncture of WON; fluoroscopic view showing two double pigtail 10F stents placed through cystogastrostomy

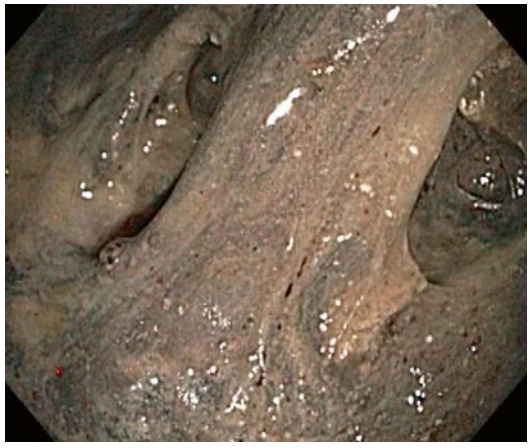

Fig. 17.11 Endoscopic transgastric view of freshly accessed infected WON, demonstrating obviously purulent partially liquefied necrosis poorly amenable to mechanical debridement, and prompting endoscopic drainage, plus minus lavage, with attempts at debriding solid necrosis best deferred

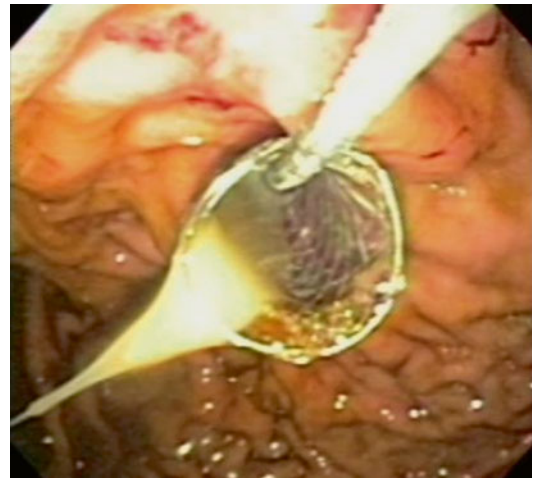

Fig. 17.12 Endoscopic view of initial placement of fully covered metallic stent into infected WON via a transgastric route, with drainage of obviously purulent contents

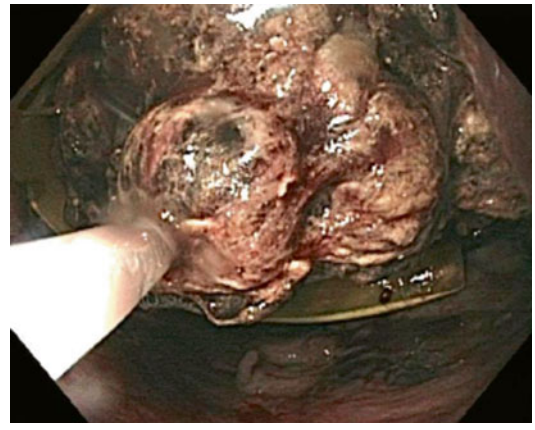

Fig. 17.13 Endoscopic view of transluminal necrosectomy using an endoscopic net. Just below the necrosis, a percutaneous large-bore drain is visible, which has flushed away the liquid component, leaving only solid debris for necrosectomy

until the necrotic cavity is thoroughly evacuated and healthy granulation tissue is evident.

Several retrospective studies of ETN have been reported [39–51]. It must be emphasized that these represent selected groups of patients with endoscopically accessible collections that were deemed feasible to treat by this route, and are thus not directly comparable to series of surgical or PCD without adjustment for other variables. Some but not all series of ETN/ETD involve selective use of adjunctive techniques such as nasocystic lavage or PCD. The GEPARD study involved 93 patients at six centers in Germany, with 6-year follow-up. Initial clinical success was reported in 80 % of patients, with an overall complication rate of 26 and a 7.5 % mortality rate at 30 days [41]. At a mean follow-up

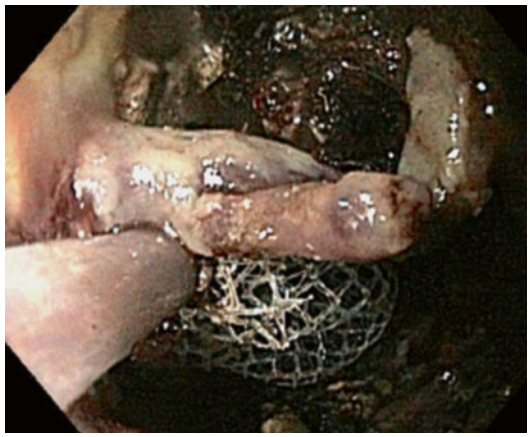

Fig. 17.14 Another view showing careful net debridement of solid necrosis just underneath a very large vessel, possibly the splenic artery

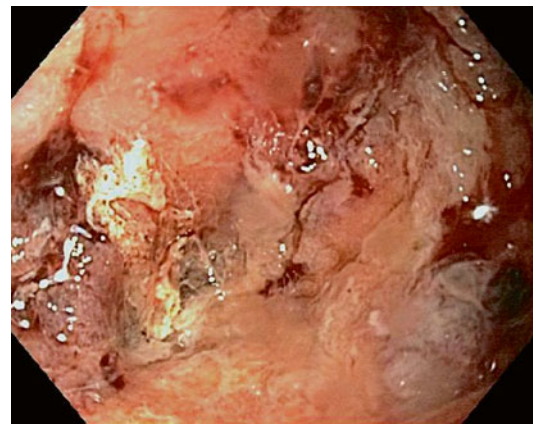

Fig. 17.15 Endoscopic view of clean cavity after successful endoscopic transluminal necrosectomy

of nearly 4 years, 84 % of initially successful patients had a sustained clinical improvement, with 10 % needing further endoscopic drainage and only 4 % needing surgery. An American multicenter study included 104 patients at six American centers undergoing endoscopic necrosectomy for symptomatic WON. A minority of patients had infected necrosis, and like other series included only patients selected as suitable for endoscopic necrosectomy, rather than as "intent-to-treat" [42]. Successful resolution was achieved in 91 % of patients, with a mean duration of treatment of 4 months. Two patients underwent operative drainage for persistent WON, one required surgery for massive bleeding on fistula tract dilation, and one died during intraprocedure presumably due to an air embolus. The study by Gardner and colleagues confirmed ETN to be an efficacious and reproducible technique with an acceptable safety profile. Overall, retrospective studies of endoscopic necrosectomy report a

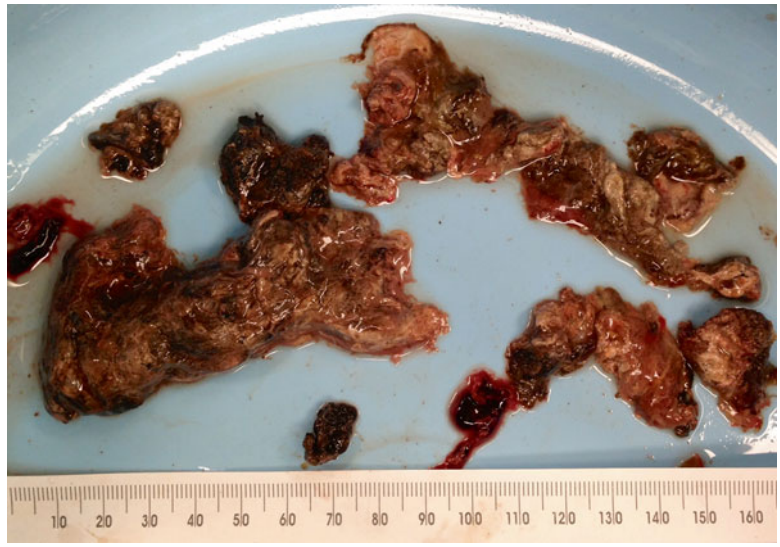

Fig. 17.16 Pan containing large amounts of solid necrotic material extracted through cystenterostomy after combined endoscopic transluminal and PCD and lavage of very large infected WON

clinical success rate of approximately 70–95 %, requiring typically three to six sessions for completion with surgery required in anywhere from 2 to 25 % of cases, a morbidity of 11–70 %, and a mortality from 0 to 15 % [52]. As with all retrospective series of a single technique, case selection may be a primary determinant of outcome.

The Dutch Pancreatitis Study Group recently reported the results of the first randomized control trial comparing endoscopic transgastric necrosectomy ($n=10$) and surgical necrosectomy (video-assisted retroperitoneal debridement or, if not feasible open necrosectomy, $n=10$) in patients with infected necrotizing pancreatitis [53]. Patients underwent PCD, via a step-up approach, and if that failed, were randomized either to endoscopic necrosectomy or VARD. In the PENGUIN trial, the investigators utilized a surrogate marker post-procedural serum interleukin as the primary outcome rather than clinical endpoints due to small sample size. Secondary outcomes included a composite clinical endpoint of death or major morbidity including new-onset multi-organ failure, intra-abdominal hemorrhage, perforation of a visceral organ needing intervention, enterocutaneous or pancreatic fistula. IL-6 rose rapidly within the first 24 h after surgical necrosectomy, but did not increase in the endoscopic group ($p=0.004$). There were also strikingly improved clinical outcomes in the endoscopic group. Major complications were significantly reduced in the endoscopic group (20 % vs. 80 %, risk difference 0.6, $p=0.03$). New-onset multi-organ failure did not occur in the endoscopic group and fewer patients developed pancreatic fistula. The authors attributed the superior outcome to the use of a natural orifice as access route to the retroperitoneal cavity as compared to surgical dissection which contributed to more physiological stress. Endoscopic interventions were performed under moderate conscious sedation, obviating the need for general anesthesia. General anesthesia is known to provoke or prolong systemic inflammation in critically ill patients, but is widely utilized for ETD/ETN in the United States. These promising results need to be replicated in larger trials before being extrapolated into routine clinical practice.

There are many variations of technique and approaches for endoscopic necrosectomy. Varadarajulu et al. described a multi-gateway approach which uses multiple transmural entry sites created under EUS guidance, to facilitate rapid drainage in large symptomatic WON (measuring >80 mm in diameter) [54] (see Fig. 17.6). Through the creation of two to three fistulous tracts from the enteric lumen to the necrotic collection, one tract may serve as a channel for irrigation while the other acts as an egress conduit for drainage of the necrotic contents and also minimizes the probability of closed-space infection. However, the authors cautioned that this technique may not be feasible in smaller sized WON and those which are not in close approximation to the lumen. The Virginia Mason group has advocated another variation consisting of combining percutaneous large-bore catheter drainage and debridement with internal transmural endoscopic drainage, in order to blend the advantages of both techniques, and in particular to avoid external fistulas [55, 56]. Lavage through the percutaneous approach with egress through the transmural fistula theoretically facilitates more rapid debridement than either technique alone. Combined modality therapy was retrospectively compared with standard PCD alone, suggesting significantly decreased hospitalization (26 vs. 55 days, $p<0.0026$), duration of external drainage (83.9 vs. 189 days, $p<0.002$), number of CECTs (8.95 vs. 14.3, $p<0.002$), drain studies (6.5 vs. 13, $p<0.0001$), and lower rate of external fistula (0 vs. 3 patients) in favor of the combined modality therapy over percutaneous catheter-based management alone [56]. The authors postulated that the decreased need for external drainage and fistula was the result of luminal exit for pancreatic secretions in those patients with disconnected pancreatic ducts, which was maintained by leaving cystogastrostomy stents in place indefinitely. A major advantage of combining PCD and endoscopic internal drainage is the ability to perform "one-way" flushing of the percutaneous catheter on the floor at regular intervals (up to once every 8 h) that washes debris out of the cystenterostomy into the bowel lumen, rather than requiring egress through sometimes limited

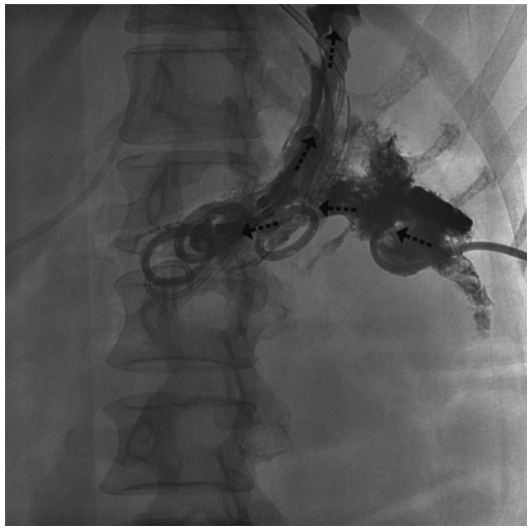

Fig. 17.17 Fluoroscopy showing "one way" flushing possible via left flank percutaneous catheter drain that communicated with endoscopic cystogastrostomy. *Arrows* show direction of flow of contrast through left flank drain, through cavity, and out into stomach

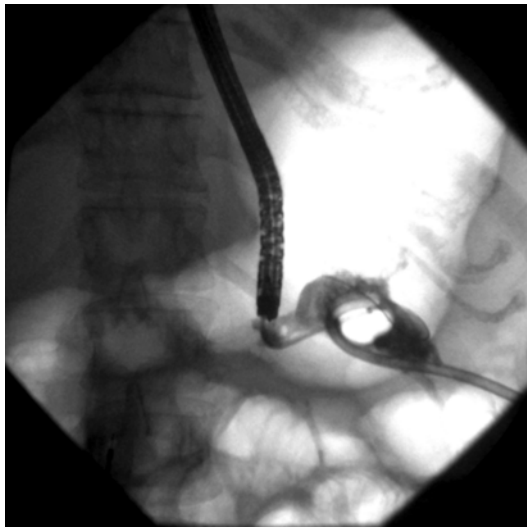

Fig. 17.18 Fluoroscopy showing "rendezvous" between endoscopic transluminal necrosectomy with endoscope passed though cystogastrostomy and meeting with percutaneous left flank retroperitoneal catheter

size of percutaneous catheters (Figs. 17.17, 17.18, 17.19, and 17.20). Limitations of any technique based primarily on PCD are difficulty reaching central collections and long duration of external drainage catheters, which may be quite

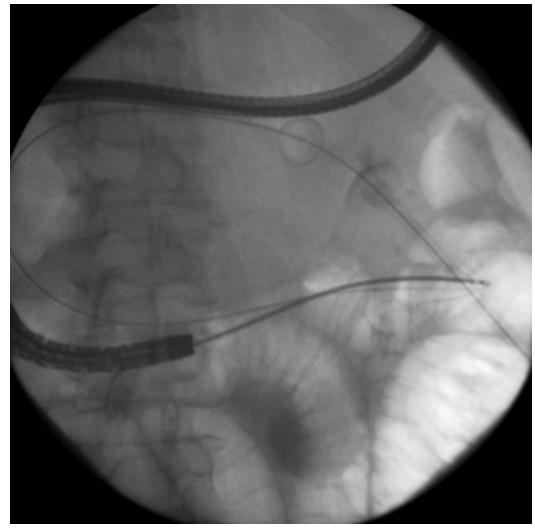

Fig. 17.19 Endoscopic placement of jejunal feeding tube to ligament of Treitz through percutaneous endoscopic gastrostomy tube that was just inserted during same procedure. Enteral feeding is a critical component of treatment of WON in ill patients and may interfere with or delay endoscopic treatments unless stomach is fixated to abdominal wall using sutures or T-tacks

limiting for ambulatory patients once discharged. However, the principle of combining endoscopic and percutaneous techniques is a sound one that deserves wider application.

Two factors render endoscopic visualization of the contact point with a collection and GI tract difficult. One is the location in the tail of the pancreas. The second is the low serum albumin which is prevalent in profoundly moribund patients and results in diffuse edema of the gastrointestinal mucosa. The use of endoscopic ultrasound-guided drainage has been shown in two randomized controlled trials involving pseudocysts to significantly increase rate of successful access to the collection, with a trend towards reduced complications, likely because of enhanced visualization and transluminal targeting of the collection, and because of ability to identify and avoid vascular structures [57, 58] (see Figs. 17.8 and 17.9).

Complications are relatively common with endoscopic transluminal necrosectomy. A recent systematic review of endoscopic necrosectomy pooling the results of ten studies involving 260 patients (60 % infected necrosis) showed a

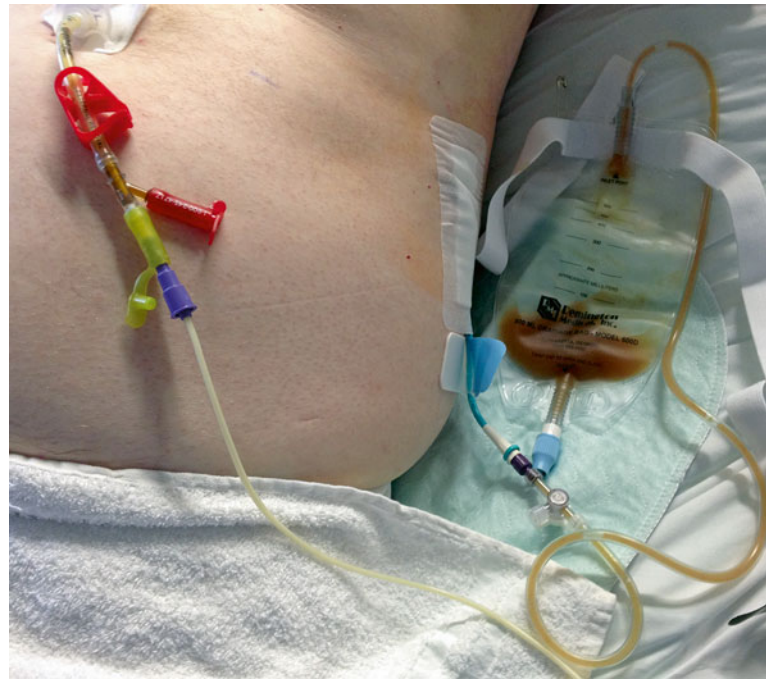

Fig. 17.20 External view of same patient in Fig. 17.19 showing gastrostomy tube (*red* clamp to screen left) with jejunal extension receiving jejunal feeds, because of inability to tolerate oral nutrition. To screen right (posterior left flank) is retroperitoneal percutaneous catheter with drainage of purulent contents placed as adjunct to endoscopic transmural drainage and necrosectomy for very large WON extending to left flank and pelvis

Fig. 17.21 Different patient than Fig. 17.20, showing bleeding through left flank percutaneous drain in very large infected WON after aggressive endoscopic transluminal necrosectomy. This proved to be herald bleeding from a pseudoaneurysm of the splenic artery requiring angiographic embolization (see Fig. 17.22)

procedure-related morbidity in 27 % of patients. The most commonly reported complication was bleeding, which may occur during access to the collection, particularly if a vessel is punctured during dilatation of the transmural tract, and during the actual debridement of the necrotic material [52] (Figs. 17.21 and 17.22). Other serious and occasionally fatal complications have been reported [39–58]. Perforation may be due to dissection of air (or preferably carbon dioxide used for insufflation during necrosectomy) (Fig. 17.23). Stents or untreated necrosis may fistulize to vessels, bowel,

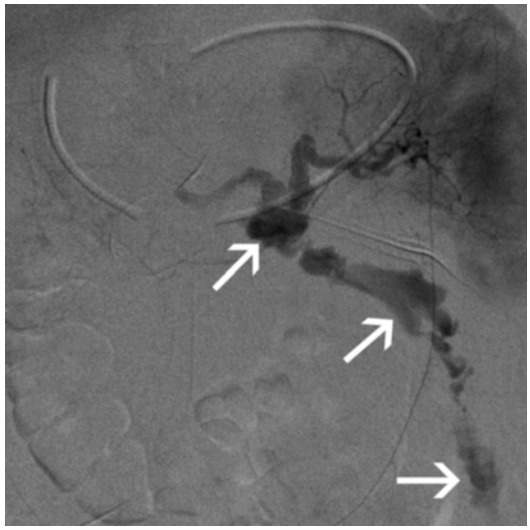

Fig. 17.22 Angiography showing very large extravasation of contrast from splenic artery due to pseudoaneurysm (same patient as Fig. 17.21)

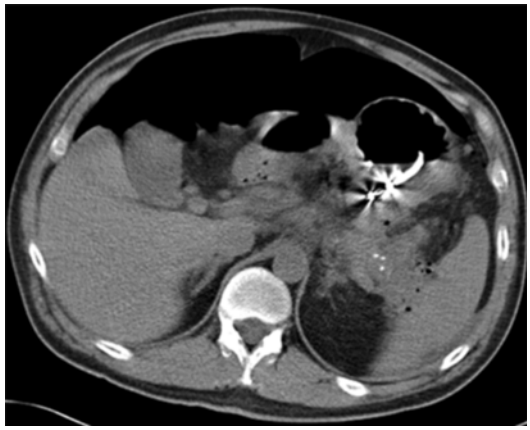

Fig. 17.23 CECT (axial image) showing extensive intraperitoneal free air after final session of endoscopic transluminal necrosectomy (cystogastrostomy stents and collapsed necrotic cavity can be seen to screen right). Patient was managed conservatively with nasogastric suction, bowel rest, and antibiotics

or even through the diaphragm (Fig. 17.24). Air embolism is a very rare but potentially fatal complication due to dissection of air through retroperitoneal veins into the systemic circulation. Carbon dioxide is increasingly used for insufflation during necrosectomy and endoscopy in general for many reasons, and is thought to reduce risk of embolism.

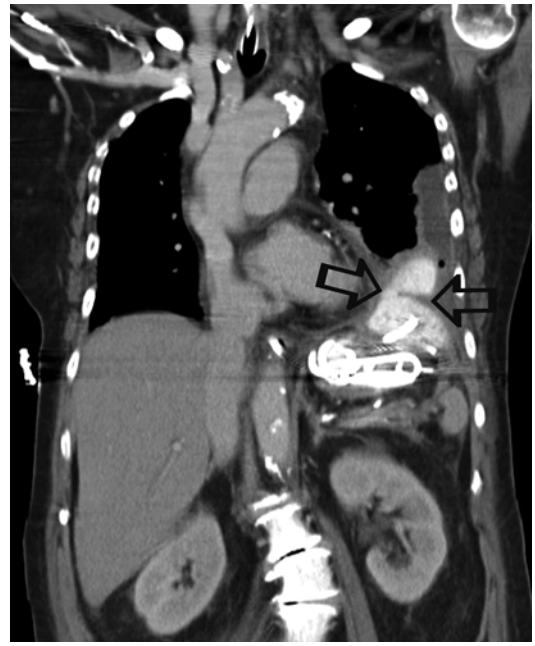

Fig. 17.24 CECT (coronal image) showing complication of endoscopic transmural drainage of infected WON just under diaphragm: a large fistula has developed (*arrows*) through the diaphragm into the left pleural space resulting in empyema. The defect was thought to be due to erosion of the stent through the diaphragm, combined with unresolved infected necrosis. The patient recovered fully after requiring two chest tubes and one session of video-assisted thoracic surgery to close the diaphragmatic defect

Not all necrotic collections are amenable for endoscopic necrosectomy; when necrosis is poorly organized, does not abut the lumen of the stomach or duodenum, or extends deeply into the retroperitoneum or other areas, use of substitute or adjuvant approaches needs to be considered. Although the balloon size utilized to dilate the cystenterostomy may be correlated with the success of the procedure [38], the ideal balloon size is yet to be determined. Probably the aspect most in flux is which type of stent to use in the cystenterostomy. While two or more 10F double pigtail stents have been utilized traditionally, increasingly large bore (10-20 mm) fully covered metallic stents, including even larger covered esophageal stents, are being used more commonly. A newly designed "spool-shaped" shallow wide bore stent specifically designed for cystenterostomy have also been developed, one of which (Axios) has recently

become available in the US [59–63]. Potential advantages of large-bore fully covered metallic stents include creation of a very large (up to 2 cm) cystenterostomy, allowing spontaneous digestion and egress of necrotic material with less need for mechanical debridement.

The optimal schedule for endoscopic debridement, the completeness of required necrosectomy required once undertaken, and need for repeat imaging remain uncertain. ETD/ETN is a time-consuming and labor-intensive process, which demands a special commitment by the patient and the entire team of physicians. It is best to undertake these procedures either in the operating room or in the endoscopic suite in close proximity to the operating room. Since the training requirement and the learning curve are unknown, this procedure is best performed by highly experienced and specialized endoscopists with the support of surgeons, interventional radiologists, and intensivists. Despite these limitations, the promising outcomes and the safety profile suggest that endoscopic necrosectomy is a central addition to the evolving techniques for the management of WON.

Laparoscopic Debridement

Laparoscopic-assisted pancreatic debridement is performed with laparoscopic visualization followed by hand-assisted or laparoscopic necrosectomy through a separate port, or alternatively by creation of a cystenterostomy via a transgastric or retrogastric approach [5, 64–69]. Laparoscopic debridement, although conceptually appealing, has gained little acceptance, especially in ill patients with infected necrosis, because it usually involves a transperitoneal route and thus risk of disseminating retroperitoneal infection into the peritoneal cavity [5].

Gagner and colleagues pioneered the treatment of pancreatic necrosis using three different minimally invasive approaches: transgastric, retrogastric retrocolic, and a full retroperitoneoscopic technique in eight patients [65]. Bucher et al. demonstrated the successful use of single-port laparoscopic necrosectomy in 8 patients with infected WON patients not responding to radiological drainage [64]. The authors reported that the use of a single large port laparoscopic trocar enabled good visualization for debridement and extraction. Only one patient needed a repeat minimally invasive necrosectomy. No perioperative complications or postoperative morbidity was reported. Parekh and colleagues reported on a series of 19 patients undergoing laparoscopic hand-assisted necrosectomy through a transperitoneal infracolic approach [66]. Only 1 of the 19 patients needed conversion to open necrosectomy. The authors demonstrated a significantly reduced local peritoneal and systemic immune response following laparoscopic approach compared to open necrosectomy, as well as no postoperative complications such as wound dehiscence or external bowel fistulae, and a shorter hospital stay. Fischer et al. described a novel laparoendoscopic rendezvous maneuver which was successful in five out of six cases of symptomatic WON [69].

Overall, laparoscopic necrosectomy has a clinical success rate of 70–95 %, morbidity of approximately 20 %, and mortality of 0–18 %. Laparoscopic debridement through a transgastric route via cystenterostomy is less likely to injure major vessels and thus may avoid the associated risk of visceral ischemia and bleeding. A transperitoneal approach enables access to areas inaccessible through endoscope to the lesser sac, right and left paracolic gutters, perinephric space, retroduodenal space, and root of the mesentery. Single large-port laparoscopic necrosectomy permits resection of a large amount of necrotic debris and may obviate the need for repeated interventions. It also permits simultaneous laparoscopic cholecystectomy in patients with biliary pancreatitis. However, it is unclear if the pneumoperitoneum created during laparoscopy has deleterious effects in hemodynamically unstable patients. The laparoscopic approach to WON should be undertaken by highly experienced minimally invasive surgeons, and the transgastric approach only in cases in which the collection closely abuts the stomach lumen. Laparoscopic debridement appears to be a valid therapeutic option which definitely warrants further

refinement and investigation. At present, it may be most widely applicable for patients with well-organized necrosis who are scheduled to undergo simultaneous cholecystectomy late in the course of the disease [5].

Minimally Invasive Retroperitoneal Approach

Once a radiological image-guided percutaneous tract is established by a retroperitoneal route, a wide array of minimally invasive techniques are available to perform necrosectomy [5, 32, 70–75]. Minimally invasive necrosectomy via a flank tract has evolved from an adjunct to open debridement through lumbar incision (as guided by the percutaneous drain) to a primarily endoscopic technique for thorough irrigation and debridement (see Figs. 17.6 and 17.7). All variants of retroperitoneoscopy are collectively known as either sinus tract endoscopy or VARD [32, 70–76]. Sinus tract endoscopy involves intraoperative dilatation of the percutaneous drain tract followed by irrigation, lavage, and suction using a nephroscope or flexible endoscope. Gambiez et al. was the first to report this technique by using a mediastinoscope in a series of 20 patients with infected necrosis, and reported a success rate of 75 % with 10 % mortality [71]. Carter et al. used a nephroscope and long grasping forceps for debridement and continuous irrigation after serial dilation to 30F tract under fluoroscopic guidance [74]. Multiple sessions were needed to adequately evacuate all of the necrotic debris. Horvath et al. subsequently described the VARD technique, which involved a small subcostal incision (5 cm or less) to access the retroperitoneal necrotic collection, followed by limited blunt dissection and then placement of a port through which a videoscope was inserted [70, 72]. Debridement was achieved with hydrodissection and a long laparoscopic spoon forceps inserted through a second port. Only loosely adherent debris was removed, thereby minimizing the risk of trauma to underlying blood vessels and other structures. Following irrigation with normal saline, the percutaneous drain was replaced by two large-bore single-lumen drains, one placed at the deepest point of the cavity, and the other positioned closer to the incision. Continuous postoperative lavage was performed with normal saline until the effluent was clear. A repeat CECT was performed to evaluate resolution of the collection.

While theoretically appealing, the benefits of a minimally invasive retroperitoneal approach were not initially apparent. The Liverpool pancreas group retrospectively compared 137 patients who underwent retroperitoneal minimally invasive techniques to a cohort of patients who underwent open necrosectomy during the same period. The reported complications and mortality rates were lower in the minimally invasive group than in the open surgically treated group (55 % vs. 81 %, and 19 % vs. 38 %, $p=0.009$, respectively) [73]. A Taiwanese group recently proposed a "delay until liquefaction" strategy wherein surgery was delayed until the retroperitoneal necrosis liquefied and reached the left flank [75]. A sump drain was placed via a small left flank incision that remained in place for an average period of 4 months. They reported success in 17 out of 19 patients without the need for multiple dilations and debridement procedures. Other case series of minimally invasive retroperitoneal approaches have estimated periprocedural complication rates to be less than 5 %, median number of interventions to be less than 3, and mortality ranging from 0 to 20 %.

VARD and sinus tract endoscopy are relatively simple and cost-effective techniques that can be performed by any gastrointestinal surgeon with basic laparoscopic or endoscopic skills. Utilizing minimal or no incisions, surgeons have been able to perform large necrosectomies, resulting in shorter operating time and lesser need for repetitive procedures. These techniques are particularly suitable for collections extending deep into the left side of the retroperitoneum that are partly liquefied. Collectively, minimally invasive retroperitoneal debridement techniques have a clinical success rate of 60–84 %, morbidity of up to 90 %, and mortality of 0–40 % [5]. As in all series, case selection and patient comorbidity are likely dominant factors in outcomes.

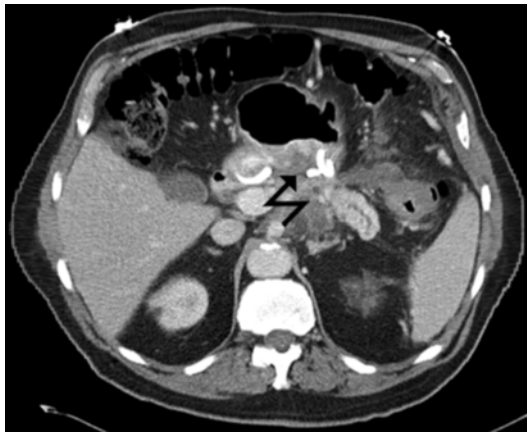

Fig. 17.25 CECT (axial image) showing disconnected pancreatic duct (*arrow*) 2 years after endoscopic transluminal necrosectomy, with dual double pigtail stents left in place indefinitely to prevent recurrent fluid collections. The patient developed inflammatory pancreatitis around the disconnected tail after the central end of the remnant pancreatic duct closed off, with subsequent ischemic colitis and requiring distal pancreatectomy and left hemicolectomy

Limitations of minimally invasive retroperitoneal approaches include limited applicability to WON of the head and the uncinate process, which may not be readily amenable for percutaneous drainage via a retroperitoneal approach. Also, any technique that involves an external percutaneous approach is associated with a substantial risk of external pancreatic fistula, especially in patients with disconnected pancreatic duct (Fig. 17.25). Sinus tract endoscopy involves the use of C-arm fluoroscopy and thereby additional risks of radiation exposure and possible increased costs. Although a reduction in morbidity has been clearly demonstrated using these techniques in comparison to open necrosectomy, a reduction in mortality or reduction in hospital stay has not been clearly demonstrated for minimally invasive retroperitoneal techniques.

Step-Up Approach

The Dutch Pancreatitis Study Group recently published the findings of a landmark trial comparing a minimally invasive "step-up" approach with traditional open necrosectomy for patients with infected necrosis [16]. The PANTER trial involved seven university and 12 major teaching hospitals across the Netherlands. Eighty-eight patients with proven or suspected infected necrosis were randomly assigned to undergo either primary open necrosectomy with continuous postoperative lavage ($n=45$) or the step-up approach ($n=43$). Step-up approach consisted of initial percutaneous (or in a few cases endoscopic) drainage, and if there was no clinical improvement within 72 h, a second drainage was performed followed by VARD; patients then underwent open necrosectomy if that strategy failed. Combined endpoints of death or major morbidity were significantly lower in the step-up approach than in the open surgery group (40 % vs. 69 %, $p=0.006$). Similarly, rates of new-onset multi-organ failure (12 % vs. 40 %), incisional hernia (7 % vs. 24 %), new-onset diabetes mellitus (16 % vs. 38 %), and pancreatic enzyme use (7 % vs. 33 %) were all significantly lower in the step-up group. The PANTER trial provides compelling evidence for a minimally invasive strategy for patients with suspected or confirmed infected necrosis. The same group has recently embarked on a nationwide randomized trial comparing the outcomes of the percutaneous and the endoscopic step-up approach, with initial drainage and debridement as needed both performed by the same route as the initial drainage, i.e., VARD or endoscopic necrosectomy (TENSION trial, registration number ISRCTN09186711) [76].

Disconnected Pancreatic Duct

Disconnected pancreatic duct represents isolation of an upstream portion of viable pancreas caused by dissolution or disruption of a central portion of the pancreas either by necrosis or by surgical or instrumental intervention. Subsequent fistulas either to internal organs or to the skin are common, as are recurrent pancreatic fluid collections after necrosis is evacuated. Management of disconnected duct represents a challenge for all disciplines involved [5]. Options include endoscopic transpapillary stenting, which often fails in the long term, leaving cystenterostomy

stents in place indefinitely, endoscopic and/or percutaneous rendezvous to reconnect the duct, percutaneous techniques for gluing or occluding fistulas, and surgery including internal drainage operations, or resection of remaining upstream isolated pancreas with or without islet cell autotransplantation [77]. As such, careful consideration of all options should be evaluated with input from all relevant specialties.

Overall Strategy for Interventions in Necrotizing Pancreatitis

As there are now so many options for interventions in necrotizing pancreatitis, in reality the strategy at any center tends to be led by the specialist or specialists with the most interest and experience, be they surgeons, interventional radiologists, or endoscopists. A center focused on necrotizing pancreatitis should have all three specialists available and collaborating in management decisions regarding all incoming patients with necrotizing pancreatitis.

Our center's approach has been to individualize the approach depending on the acuity and stability of the patient, and the size, location, extent, and maturity of the collection or collections. All decisions for intervention are made in collaboration between interventional endoscopy, critical care surgery, and interventional radiology. Ill patients are generally managed in the surgical intensive care unit. All active patients are reviewed at a weekly interdisciplinary conference specifically dedicated to acute pancreaticobiliary disease management.

One of the central challenges is providing early and adequate nutrition. Enteral nutrition has been shown consistently to be superior to parenteral nutrition, with best outcomes when started within first day or two of hospitalization for severe acute pancreatitis. Nasojejunal or nasogastric tube feeding is limited for long-term nutrition, especially once patients become ambulatory. Percutaneous endoscopic gastrostomy with jejunal tube extension is advisable for many patients. However, conventional passive gastrostomy allows risk of dehiscence or leakage, especially during repeated endoscopic interventions. As such, use of T-fasteners as commonly performed by interventional radiology, or a newly described endoscopic full-thickness suturing technique for gastrostomy is advised if the patient is to undergo endoscopic necrosectomy (Attam R, personal communication) see (Figs. 17.19 and 17.20).

For walled-off collections abutting the stomach or duodenum, and especially central collections, endoscopic approach is recommended as the primary technique. For very large collections, two separate cystenterostomies, usually transgastric and transduodenal, are recommended. However, many situations call for combining percutaneous techniques. Especially if collections require early intervention because of infection but are poorly demarcated, or extend deeply into the abdomen, typically into the pelvis, percutaneous techniques should be primarily utilized, followed by minimally invasive retroperitoneal necrosectomy if insufficient. It is always preferable for a percutaneous catheter to be placed via a retroperitoneal posterior route rather than anterior/transperitoneally, as that will allow subsequent sinus tract endoscopy or VARD without dissemination of infection throughout the peritoneal cavity. Endoscopic transluminal drainage can be performed as an adjunct to avoid external fistulae, which then provides a major advantage in that aggressive flushing of percutaneous catheter on the floor results in one-way lavage of necrotic material through the cystenterostomy, rather than requiring egress out the percutaneous catheter.

For deep collections that persist after PCD, retroperitoneal flexible endoscopic approaches through the percutaneous tract are ideal, and are essentially identical to those performed via an endoscopic transluminal route but with greater reach into the pelvis, and can be performed during the same anesthesia as the per-oral necrosectomy.

Consensus Recommendations and Future Directions

Results of a multidisciplinary consensus conference on interventions for necrotizing pancreatitis have been published recently, representing the first

contemporary consensus guidelines incorporating minimally invasive interventions for necrotizing pancreatitis. Subsequently, a consensus meeting was convened by the International Association of Pancreatology and the American Pancreatic Association regarding management of acute pancreatitis. Both consensus meetings included leading surgeons, endoscopists, radiologists, and medical pancreatologists with special interest and expertise in severe acute pancreatitis. Findings and recommendations were similar between both. When intervention was indicated, a step-up approach utilizing percutaneous or endoscopic drainage followed by minimally invasive or endoscopic necrosectomy was recommended, with traditional open necrosectomy reserved as a second-line intervention for patients who fail minimally invasive approaches. No specific recommendations were made as to combining approaches.

In the future, areas of further studies include improved ways for recognizing and predicting patients at risk for developing pancreatic necrosis, optimal early strategies to minimize risk of progression to pancreatic necrosis, and identifying factors associated with development of infection and organ failure in patients who develop necrosis. On the technical front, refinements in endoscopic and minimally invasive retroperitoneal necrosectomy will likely include larger removable covered stents for cystenterostomy, and hopefully devices allowing performance of secure large-bore stapled cystenterostomy. In addition, there will no doubt be improved devices for direct endoscopic debridement, and perhaps dissolution agents to facilitate liquefaction and evacuation of solid necrosis. Most importantly, combinations of techniques such as endoscopic transluminal and minimally invasive retroperitoneal necrosectomy may prove superior to single techniques for very extensive collections. Laparoscopic and percutaneous techniques will also progress to the point that any minimally invasive intervention will likely become definitive rather than require repeated procedures as is currently typical.

It should be emphasized that no single approach can be applied universally to all patients with necrotizing pancreatitis, so that the ideal approach for a particular patient should be determined based on the individual clinical scenario. Combinations of techniques in the same patient may prove superior to any single approach. Given the complexity associated with minimally invasive techniques for necrosectomy, patients with severe acute pancreatitis should be managed by a multidisciplinary team consisting of specialists from surgery, interventional endoscopy, interventional radiology, and critical care.

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Index

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