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Definition of Complications and Severity of Acute Pancreatitis for Clinical Practice

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Background

The clinical severity and complications of acute pancreatitis (AP) can be highly variable. While the majority of patients develop a mild course, 5–15% develop severe disease, with mortality approaching 50% in some cases [1–8]. This clinical variability led to a need for accepted definitions of severity and complications to aid study and guide management.

The Atlanta Classification 1992

The 1992 Atlanta Classification (AC) offered the first universally accepted set of definitions for AP (Table 3.1) [9]. AP was defined as an acute inflammatory process of the pancreas that may also involve regional tissue or remote organ systems. Severe AP was broadly defined as the presence of (i) organ failure (shock, pulmonary insufficiency, renal failure, gastrointestinal bleeding) and/or (ii) local complications (especially pancreatic necrosis, but also abscess or pseudocyst). Early predictors of severity included three or more of Ranson's criteria or an Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II score of 8 or more. Additional terms, including mild AP, acute fluid collections, pancreatic necrosis, acute pseudocyst, and pancreatic abscess, were defined.

The AC served as the first clinically based classification system and provided the framework for how AP is defined today. However, some of the definitions proved ambiguous and were used inconsistently, for example (i) a uniform serum lipase and/or amylase threshold for diagnosis was not established; (ii) transient and persistent organ failure were not differentiated; and (iii) a heterogeneous group of patients with varying severity and mortality were combined into a single severe AP category [10]. These limitations led to large variability in the interpretation of organ failure and local complications [10,11].

With better understanding of the pathophysiology of organ failure and pancreatic necrosis, two widely adopted classification systems were subsequently derived: the Revised Atlanta Classification (RAC) and Determinant-Based Classification (DBC) [12,13].

The Revised Atlanta Classification 2012

The RAC was derived through an iterative consultation process, ultimately generating consensus recommendations from the members of 11 international pancreatic societies [12]. The RAC provides a comprehensive classification of AP, including definitions of diagnosis, type (interstitial edematous versus necrotizing pancreatitis), clinical phase (early versus late), complications (local and systemic), and severity (mild, moderately severe, or severe). The scope of this chapter focuses on individual complications and definitions of severity.

Definition of Organ Failure and Complications in Acute Pancreatitis

Organ Failure

Persistent organ failure is the primary determinant of outcomes and accounts for nearly all the mortality in AP [14–16]. Established risk factors include older age, comorbid conditions, obesity, elevated triglyceride levels, and certain etiologies (alcohol) [17–20]. Organ failure according to RAC is defined as a score of 2 or above for at least one of three organ systems using the modified Marshall scoring system (Table 3.2) [21]. Persistent organ failure is

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Table 3.1 Comparison of Atlanta Classification, Revised Atlanta Classification, and Determinant-Based Classification.

Atlanta Classification	Mild	No organ failure and no local complications
	Severe	Organ failure and/or local complications
Revised Atlanta Classification	Mild	No organ failure and no local or systemic complications
	Moderately severe	Transient organ failure and/or local and/or systemic complications
	Severe	Persistent organ failure
Determinant-Based Classification	Mild	No organ failure and no necrosis
	Moderate	Transient organ failure and/or sterile necrosis
	Severe	Persistent organ failure or infected necrosis
	Critical	Persistent organ failure and infected necrosis

Source: adapted from Bradley [9].

defined as organ failure which lasts more than 48 hours while transient organ failure lasts less than 48 hours.

Local Complications

Local complications typically refer to a variety of pancreatic and peripancreatic fluid collections that differ in both composition and time to development. Other local complications include gastric outlet dysfunction, splanchnic vein thrombosis, and colonic necrosis. Local complications should be suspected when there is persistence or recurrence of pain, organ dysfunction, fever, or leukocytosis. High-resolution contrast-enhanced computed tomography (CECT) is often the diagnostic test of choice. In the RAC, local complications do not by themselves constitute severe AP.

Among the types of (peri)pancreatic fluid collections, an important distinction is made between collections composed of fluid alone (acute peripancreatic fluid collection and pancreatic pseudocyst) and those that arise from necrosis and contain a solid component (acute necrotic collection and walled-off necrosis). There is good interobserver agreement for the types of (peri)pancreatic fluid collections as defined by the RAC, particularly among experienced radiologists [22].

Acute Peripancreatic Fluid Collection Acute peripancreatic fluid collections (APFCs) are fluid collections that develop in the early phase (less than four weeks) of interstitial edematous pancreatitis. On CECT (Figure 3.1), APFCs are homogeneous collections that lack a defined wall and are confined by normal fascial planes in the retroperitoneum. Most APFCs resolve spontaneously, although rarely APFCs may evolve into pancreatic pseudocysts if persistent beyond four weeks. The majority of APFCs, which spontaneously resolve and remain asymptomatic, do not require treatment.

Pancreatic Pseudocyst APFCs that persist for more than four weeks may organize into homogeneous fluid collections surrounded by a well-defined wall (Figure 3.2). These pseudocysts are thought to arise from leakage of amylase-rich pancreatic juice from the main pancreatic duct or its side branches. Pancreatic pseudocyst formation after an episode of AP is a rare event. Most well-defined collections are composed not just of pancreatic fluid, but rather a mixture of necrotic solid/liquid tissue and should be termed "walled-off necrosis" (defined in a subsequent section). Pseudocysts that remain sterile and asymptomatic do not require treatment.

Table 3.2 Modified Marshall scoring system.

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

A score ≥ 2 in any organ system defines the presence of organ failure in AP. *Source:* Banks et al. [12]. © 2013 BMJ. Reproduced with permission of BMJ Publishing Group.

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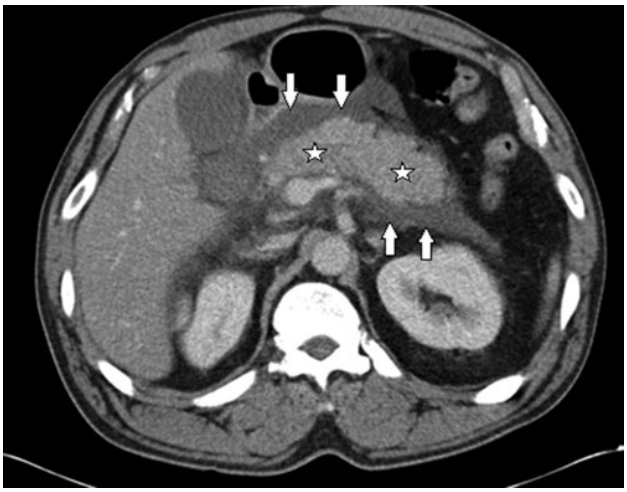

Figure 3.1 CECT showing acute interstitial edematous pancreatitis with acute peripancreatic fluid collection (APFC) in the lesser sac and the left anterior pararenal space (arrows indicate borders of APFC). The pancreatic parenchyma (stars) enhances completely, indicating absence of parenchymal necrosis. *Source:* courtesy of Peter A. Banks.

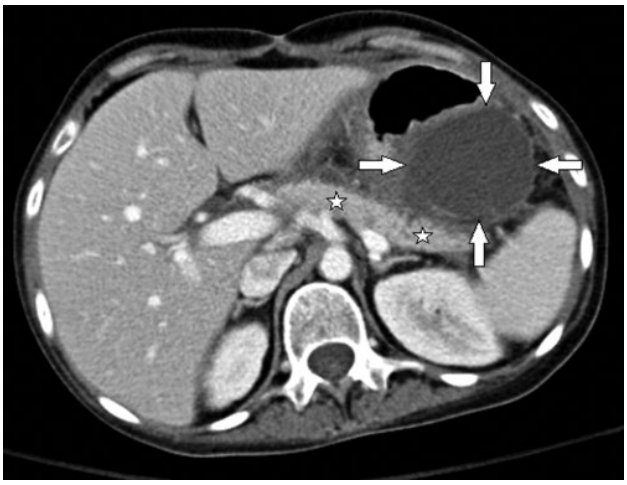

Figure 3.2 CECT showing a pancreatic pseudocyst more than four weeks after an episode of acute interstitial edematous pancreatitis. Note the round homogeneous fluid collection surrounded by a well-defined wall (arrows indicate border of pseudocyst). The pancreatic parenchyma (stars) enhances completely, indicating absence of parenchymal necrosis. *Source:* courtesy of Peter A. Banks.

Acute Necrotic Collection Acute necrotic collections (ANCs) are collections containing a variable amount of liquid and solid tissue that arise during the initial four weeks of necrotizing pancreatitis. Necrosis involves only peripancreatic tissue in up to 50% of cases, which has more favorable outcomes compared to necrosis involving both the pancreatic parenchyma and peripancreatic tissue [23]. ANCs may appear poorly organized or loculated, disrupt fascial planes, and become infected. On CECT (Figure 3.3),

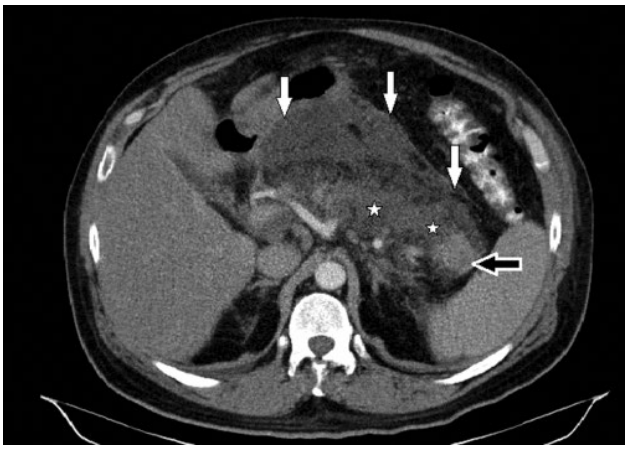

Figure 3.3 CECT showing acute necrotizing pancreatitis with an acute necrotic collection (ANC) involving both the pancreatic parenchyma and peripancreatic tissue (white arrows point to border of ANC). Note the heterogeneous appearance of liquid and solid contents within the ANC. There is extensive pancreatic necrosis (stars) with a small amount of normally enhancing tissue in the pancreatic tail (black arrow). *Source:* courtesy of Peter A. Banks.

ANCs contain varying amounts of solid necrotic tissue, though this may not be readily apparent until five to seven days after AP onset. The presence of gas is highly suggestive of infected necrosis. When in doubt, magnetic resonance imaging (MRI) may help confirm the presence of solid content. After more than four weeks, ANCs typically mature into walled-off necrotic collections.

Walled-off Necrosis Walled-off necrosis are mature collections of (peri)pancreatic necrosis encapsulated by an inflammatory wall that forms more than four weeks following onset of necrotizing pancreatitis. On CECT (Figure 3.4), walled-off necrosis appears as a heterogeneous collection of liquid and solid necrotic tissue surrounded by a well-defined rim. Like other local fluid collections, walled-off necrosis may become infected.

Systemic Complications

The RAC defines systemic complications of AP as an exacerbation of preexisting comorbid conditions, such as coronary artery disease, congestive heart failure, or chronic lung disease.

Definition of Severity in Acute Pancreatitis

The RAC defines three degrees of AP severity: mild, moderately severe, and severe (see Table 3.1). Stratification of AP severity plays an important part in clinical management, as it may aid in the identification of patients who require early aggressive treatment, who need to monitored in an intensive care setting, or who need to be transferred

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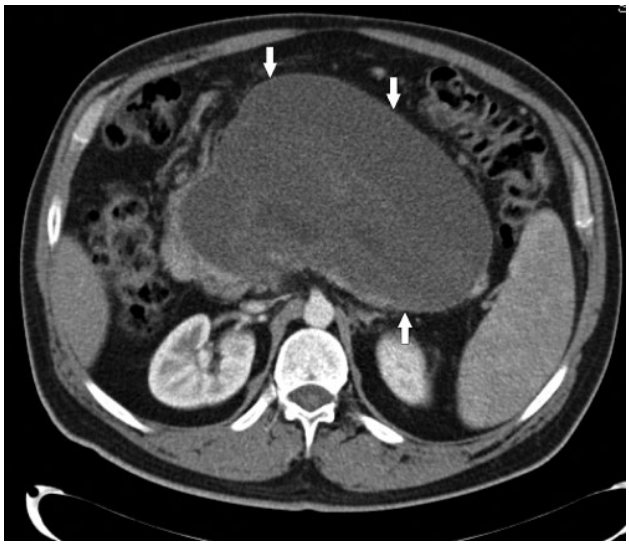

Figure 3.4 CECT showing walled-off necrosis (WON) more than four weeks after an episode of necrotizing pancreatitis. The heterogeneous collection has replaced most of the pancreatic parenchyma and has a thin, well-defined, encapsulating wall (white arrows point to border of WON). *Source:* courtesy of Peter A. Banks.

for specialist care.

Mild Acute Pancreatitis

Mild AP is characterized by absence of both organ failure and local/systemic complications. Approximately 60–70% of AP patients develop a mild disease course and recover within one week, with minimal morbidity and mortality (<1%).

Moderately Severe Acute Pancreatitis

Moderately severe AP is characterized by the presence of transient (<48 hours) organ failure and/or local and/or systemic complications. Approximately 20–30% of AP patients develop a moderately severe disease course. While those with transient organ failure or an acute fluid collection may experience rapid resolution of symptoms, patients who develop persistent fluid collections or necrotic collections may experience prolonged hospitalizations, difficulty with oral feeding, and long-term morbidity. Like mild AP, mortality in moderately severe AP is minimal (1–3%).

Severe Acute Pancreatitis

Severe AP is defined by persistent organ failure (>48 hours). Primary organ failure develops in the early phase of AP when cytokine cascades result in the systemic inflammatory response syndrome (SIRS). Secondary organ failure may develop later in the disease course (more than two weeks) as a result of infected pancreatic necrosis. Approximately 5–15% of AP patients develop a severe disease course, though this proportion may be as high as 40% in tertiary care referral centers [24,25]. Severe AP is associated with high morbidity and mortality (40–50%).

Limitations of the Revised Atlanta Classification

While studies have validated the RAC as being a superior classification system compared to the original AC, limitations exist [1,2,4,6]. Notably, the RAC does not differentiate between several characteristics of organ failure that have been shown to impact outcomes.

First, persistent multisystem organ failure has far greater mortality compared to persistent single-system organ failure [4,24,26]. Second, a higher grade of persistent organ failure (e.g. modified Marshall grade 3 or 4 requiring respiratory ventilation) is associated with worse outcomes [27]. Additional factors which may influence outcomes, such as timing (early versus late onset) of persistent organ failure, duration of persistent organ failure, and organ system affected (cardiovascular versus renal versus respiratory), require clarification [24,25,27,28].

Several additional factors that impact mortality in AP are not addressed by the RAC. First, compared to subsequent episodes, the initial episode of AP may follow a more severe course and accounts for nearly 100% of the mortality [29]. Second, AP patients requiring hospital transfer have higher rates of multisystem organ failure, need for intensive care, and mortality [30]. Third, mortality in necrotizing pancreatitis affecting only the peripancreatic tissue is lower compared to cases affecting both pancreatic and peripancreatic tissue (8–9% vs. 20%) [23].

The Determinant-Based Classification

The DBC was created through a consensus of international experts from 49 countries [13]. The DBC uses the local determinant (i.e. infected necrosis) and/or systemic determinant (i.e. organ failure) of mortality to categorize AP into four levels of severity: mild, moderate, severe, and critical (see Table 3.1) [31]. Mild AP is defined as no pancreatic or peripancreatic necrosis and no organ failure. Moderate AP is defined as sterile necrosis and/or transient organ failure. Severe AP is defined as either infected necrosis or persistent organ failure. A fourth category termed "critical AP" is defined by the presence of both persistent organ failure and infected necrosis.

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Organ failure is defined by a Sepsis-related Organ Failure Assessment (SOFA) score of 2 or more, or when the following thresholds are met.

1) Cardiovascular: use of inotropic agent.
2) Renal: creatinine ≥171 μmol/l (≥2.0 mg/dl).
3) Respiratory: PaO_2/FiO_2 ≤300 mmHg (≤40 kPa).

As in the RAC, persistent organ failure is defined as lasting for 48 hours or more. Transient organ failure is defined as lasting less than 48 hours.

The RAC and DBC share many similarities, and multiple independent validation studies have found no significant differences in performance between the two classification systems [1–8].

The primary distinction between the two classification systems is the emphasis the DBC places on infected necrosis as a determinant of outcomes; however, the contribution of infected necrosis to mortality may be limited. While previous studies have shown infected necrosis to be a risk factor for mortality independent of persistent organ failure, these studies were largely performed in an era when patients with infected necrosis underwent early surgical debridement [31]. More recent studies performed after the advent of direct endoscopic necrosectomy have shown that mortality of infected necrosis in the absence of organ failure is much lower (<5%) [3,4,8,24]. Conversely, in the setting of persistent organ failure, neither the presence nor absence of infected necrosis affects the overall high mortality rates [3,8,24]. If these observations are confirmed in future studies, revisions of the DBC should no longer classify infected necrosis in the absence of persistent organ failure as severe AP, nor should the presence of both infected necrosis and persistent organ failure be separated into its own "critical" category.

Conclusion

The clinical severity and complications of AP can be highly variable. Both the RAC and DBC have made major advances on the original AC, adding standardized definitions of local complications and emphasizing the role of persistent organ failure as a determinant of mortality. Both classifications require revisions based on updated information, including the significant difference in mortality among patients with persistent single-system versus persistent multisystem organ failure.

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