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Classification Systems for the Severity of Acute Pancreatitis

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Abstract:

The quest for a clinically relevant severity classification system for acute pancreatitis (AP) is still ongoing. Several systems have been proposed since 1889, including the Marseilles, Cambridge and Marseilles-Rome classifications. In 1993, the Atlanta Classification was published which was widely used in patient care and clinical research. Eventually, several confusions and lack of clarity were observed in this classification. At the same time, there was increasing understanding of the pathophysiology of AP and several new terminologies emerged. This resulted in the development of the Revised Atlanta Classification though a web based multiply iterative process. The Revised Atlanta Classification has introduced a three-tier severity system, with the moderately severe AP being the new group. This classification also describes necrosis, organ failure and local complications with more clarity. Concomitantly, another four-tier severity classification of AP was introduced, which categorizes severity based on the actual determinants of mortality, i.e. infected necrosis and organ failure. This classification introduces a fourth category namely critical acute pancreatitis.

In this chapter, we elaborate on the Atlanta, Revised Atlanta and the Determinant based classification systems, and discuss their relevance, utility and limitations.

1. Introduction

Several attempts have been made over decades to establish a clinically relevant classification of severity of acute pancreatitis (AP); and the quest for such a system is still ongoing. A uniform severity classification is essential for efficient therapeutic decision-making, communication with patients and relatives, and uniform research designing and data reporting. One of the earliest proposals came in the late 19th century wherein the terms pancreatic hemorrhage, hemorrhagic, suppurative and gangrenous pancreatitis, and disseminated fat necrosis were suggested. The subsequent proposal of defining severity was the Marseilles classification in 1963 (10), which was subsequently revised in 1984 (24). At the same time (1983), the Cambridge classification was also published (23), which bore several similarities with the 1984 Marseilles classification. Both the Cambridge and Marseilles 1984 classifications recognized the possibility of a variable systemic response in AP and identified complications such as necrosis, hemorrhage and pseudocysts.

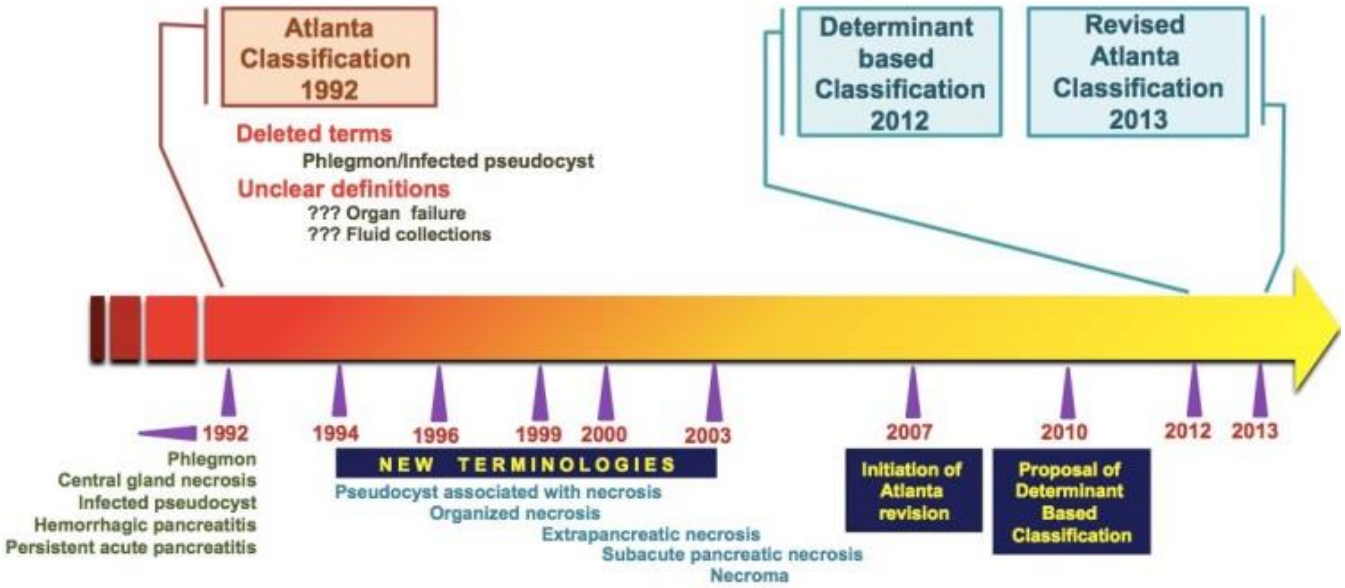

Figure 1: Timeline depicting the development of the recent classification systems for severity of acute pancreatitis.

In addition, the Marseilles 1984 classification defined mild and severe AP based on morphological features, namely peripancreatic fat necrosis and interstitial edema that characterized mild disease and extensive peri and intrapancreatic fat necrosis, parenchymal necrosis and hemorrhage that marked severe disease. There were further modifications of the Marseilles 1984 classification in the form of Marseilles-Rome classification which was published in 1988 (21).

These classifications were followed by the Atlanta Classification in 1992 (6), which was a great improvement and became clinically useful for many years. However, several limitations of the Atlanta Classification were recognized in the following years with increasing use of imaging, and introduction of new nomenclatures (2,4). These led finally to a revision, that was made through a web-based multiply iterative process that resulted in the Revised Atlanta Classification of 2013 (3). Another system called the Determinant Based Classification (9) was also proposed in parallel, which was based on actual factors that determines mortality. **Figure 1** depicts the timeline for development of severity classification systems from the Atlanta Classification onwards.

In this chapter, we elaborate on the classification systems for severity from the Atlanta Classification onwards, and discuss their relevance, utility and limitations. **Table 1** summarizes the recent classifications of severity of AP.

2. Severity Classification Systems

Atlanta Classification

Genesis

The Atlanta Classification of 1992 was the result of an International symposium that included 40 internationally recognized experts on AP across six medical disciplines and 15 countries. The primary intent of the symposium was to develop a clinically useful classification of AP that would provide a consensus on terminologies of AP and also facilitate comparison of inter-institutional data. The development of this classification was a major step at that time since it was a clear improvement over the previously described Marseilles classification, which was primarily dependent on imaging based morphologic changes.

Table 1: Definition of severity of acute pancreatitis according to different classification systems

Atlanta Classification	Revised Atlanta Classification	Determinant based classification
Mild AP - *Minimal organ dysfunction and uneventful recovery* - *Absence of organ failure and/or local complications* **Severe AP** - *Organ failure and/or local complications*	**Mild AP** - *No organ failure* - *No local or systemic complications* **Moderately severe AP** - *Transient organ failure AND/OR local or systemic complication OR exacerbation of pre-existing co-morbidities.* **Severe AP** - *Persistent organ failure (single or multiple)*	**Mild AP** - *No organ failure* - *No (peri)pancreatic necrosis* **Moderate AP** - *Sterile (peri)pancreatic necrosis AND/OR transient organ failure* **Severe AP** - *Infected (peri)pancreatic necrosis OR persistent organ failure* **Critical AP** - *Infected (peri)pancreatic necrosis AND persistent organ failure*

The Atlanta Classification permitted a working definition of severity of AP based on clinical, biochemical and imaging data obtained within the first 1-2 days of hospitalization and can further be redefined based on new data that would be available during the hospitalization period.

Components

The Atlanta Classification defined severity based on the presence of organ failure and/or local complications and/or three or more of Ranson's criteria, or, eight or more of APACHE II criteria . Organ failure was defined as shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency (PaO2 < 60 mmHg), renal failure (serum creatinine level > 2 mg/dl after rehydration), or gastrointestinal bleeding (more than 500 ml/24h). Local complications included necrosis, abscess or (acute) pseudocyst. Presence of peripancreatic fat necrosis was considered in the definition of necrosis. Acute pseudocyst was defined as fluid collection with a definite wall in association with AP that emanates from acute fluid collections that persists for four weeks or more. Even though pancreatic abscess has been defined as a local complication of AP, it was also appreciated that mortality risk of infected pancreatic necrosis was higher than pancreatic abscess and that the modality of treatment for the two entities differ. Terms such as phlegmon and infected pseudocyst were discarded and use of terms such as hemorrhagic pancreatitis was suggested to be restricted to descriptions of operative or post-mortem appearances of the gland.

Revised Atlanta Classification

Genesis

The Revised Atlanta Classification was initiated as an international, web-based process that began in a clinical symposium in 2007 at the Digestive Diseases Week (32). The process was initiated with a meeting of 40 selected pancreatologists and pancreatic surgeons to decide on the process and areas of revision. Following this, a working group with 2 pancreatic surgeons, 2 pancreatologists and 1 pancreatic radiologist was constituted which prepared an initial draft. This was the first working document that was circulated among the 40

participants. After suggested revisions, the working draft was e-mailed to all members of 11 national and international organizations interested in AP. A second working draft was prepared based on the modifications suggested in the first draft and resent to the members. The process was repeated and a third draft was generated, which contained minor modifications. After this, the final revision was made wherein the three-tier classification of severity was incorporated (27, 33).

Revision of the Atlanta classification was made with an intent to address areas of confusion in the original Atlanta Classification, incorporate modern concepts of the disease, improve clinical assessment of severity, enable standardized data reporting, assist objective evaluation of new treatments, and facilitate communication among treating physicians and different institutions.

Components

The Revised Atlanta Classification dealt primarily with two broad areas, namely, a) discrete definitions of organ failure and local complications (including necrosis); and b) classification of severity of the disease.

The revised classification categorizes AP into interstitial edematous (IEP) and necrotizing pancreatitis based on contrast enhanced computed tomography (CECT) imaging. IEP constitutes 80-90% of AP, in which the pancreas appears relatively homogenously enhanced on CECT with or without mild peripancreatic stranding or peripancreatic fluid collection. Necrotizing pancreatitis on the other hand is characterized by lack of enhancement of the pancreas and/or (peri)pancreatic tissues on CECT. Both the pancreatic parenchyma and peripancreatic tissues together are involved more frequently than involvement of either alone. Recognition of the degree of necrosis (pancreatic alone, peripancreatic alone, or both) is important since the prognosis varies. For instance, peripancreatic necrosis alone results in a less severe disease course compared to pancreatic parenchymal and peri-pancreatic necrosis, but higher morbidity compared to interstitial edematous. Pure pancreatic necrosis is a rare event. Pancreatic and peripancreatic necrosis usually evolves over the first week of the disease and might not be mature enough to be detected early on (< 72 hours) by imaging. Necrotizing AP is detectable on CECT after 72 h and more definitely by 7 days, when the low attenuation of necrosis on CECT becomes more apparent. (Peri)pancreatic necrosis is prone to develop infections, which is usually seen after the first week onwards. Infected necrosis should be strongly suspected in the presence of signs of sepsis in a patient with necrotizing pancreatitis. Even though gram stain and culture of fine needle aspiration (FNA) has been recommended in earlier guidelines, it may be falsely negative. Therefore, FNA is not routinely recommended in the diagnosis of infected (peri) pancreatic necrosis, but may become necessary in patients who are not responding to antibiotics to guide the therapy based on susceptibility information. Presence of extraluminal gas bubbles on CECT strongly suggests the presence of infected necrosis.

According to the Revised Atlanta Classification, complications of AP can be organ failure, local and systemic complications. Organ failure, which needs to be evaluated by the Modified Marshall Scoring System (17), is considered to be present if the Marshall Score is 2 or higher. Organ failure may be transient (resolves within 48 h of onset) or persistent (persists for 48 h and more). Local complications include fluid collections, gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis. Four discrete types of collections have been described, namely, acute peripancreatic fluid collection (APFC), pancreatic pseudocyst (PP), acute necrotic collection (ANC) and walled off necrosis (WON). **Table 2** presents the definition and characteristics of the different types of fluid collections. Severity of AP has been categorized into mild, moderately severe and severe AP.

Table 2: Definition and characteristics of local collections in acute pancreatitis according to the Revised Atlanta Classification

Terminology	Definitions and characteristics
APFC (acute peripancreatic fluid collection)	• Associated with interstitial edematous pancreatitis • Appear as peripancreatic fluid seen within the first 4 weeks after disease onset. • Does not have a definable wall. • Confined to normal peripancreatic fascial planes. • Does not have intrapancreatic extensions.
Pancreatic pseudocyst	• An encapsulated collection of fluid with a well-defined wall. • Usually located outside the pancreas. • Usually requires more than 4 weeks after onset to mature. • Does not contain non-liquid component.
ANC (acute necrotic collection)	• Contains variable amounts of both fluid and necrosis. • Associated with necrotizing pancreatitis. • Appear as heterogeneous and non-liquid density of varying degrees in different locations. • Does not have a definable wall. • Necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
WON (walled-off necrosis)	• Heterogeneous with liquid and non-liquid density with varying degrees of loculations • Usually occurs 4 weeks after onset of necrotizing pancreatitis. • Appear as an encapsulated collection in pancreatic and/or peripancreatic areas of necrosis. • Contains a well-defined inflammatory wall.

This is based on the presence or absence of local complications and organ failure. Mild AP is defined as AP without organ failure and local/systemic complications. This usually resolves within the first week after onset and has minimal morbidity and rare mortality. Patients will usually be discharged within a week. Moderately severe AP is defined as AP with transient organ failure and/or local complications and/or systemic complications. Systemic complication is defined as exacerbation of pre-existing conditions like coronary artery disease, congestive cardiac failure, chronic obstructive pulmonary disease, diabetes, and chronic liver disease, as a result of AP. Patients with moderately severe AP may run a protracted course and may develop further complications such as infected necrosis and bleeding from pseudoaneurysms. The management of moderately severe AP is guided by the type of local complications, presence of symptoms and development of issues related to the defining local complications. Mortality is significantly less compared to that of severe AP. Severe AP is defined by the presence of persistent organ failure, irrespective of the time of development in relation to disease onset.

Determinant based classification

Genesis

The primary highlight of the Determinant Based Classification was the introduction of the group called critical AP. This category and thereby the Determinant Based Classification stemmed from the results of a meta-analysis of 14 studies involving 1478 patients that evaluated the pooled effect of organ failure and infected pancreatic necrosis on mortality (20). The meta-analysis demonstrated that mortality rate among patients who had both organ failure and infected pancreatic necrosis was 43%. This was significantly higher than that of patients with organ failure alone (22%) and infected pancreatic necrosis alone (11%). The mortality rates between patients with either organ failure or infected necrosis alone were not statistically different. However, the authors did acknowledge few limitations in their study. Most notably, the individual studies in the meta-analysis were observational; definitions used for organ failure varied across different studies; and the dynamic nature of organ failure was not addressed in most of the individual studies. Nevertheless, based on these results, patients with both organ failure and infected necrosis were categorized into the new group of critical AP and the four-tier classification of severity was proposed. Once the proposal was published (19), 525 pancreatologists from 55 countries were invited by e-mail for a web-based survey, of which 240 pancreatologists from 49 countries agreed to participate. The result of the web-based global consultation led to publication of the Determinant Based Classification in English language, which was eventually published in German, Italian, Spanish and Chinese languages (14-16,31). Few issues regarding the classification and the conduct of the web-based survey and the development of the classification were observed by several authors that were highlighted in letters to editors (28, 30).

Components

The Determinant Based Classification primarily centers on causally associated factors (or determinants) for mortality. The determinants could be local, i.e. (peri)pancreatic necrosis or systemic, i.e. organ failure. (Peri)pancreatic necrosis is defined as nonviable tissue located in the pancreas alone, or in the pancreas and peripancreatic tissues, or in the peripancreatic tissues alone. (Peri)pancreatic necrosis could be sterile or infected. Infected (peri)pancreatic necrosis is defined by the presences of either gas bubbles within necrotic areas on computed tomography, a positive culture of (peri)pancreatic necrosis obtained by image guided fine-needle aspiration, or positive culture of (peri)pancreatic necrosis obtained during the first drainage and/or necrosetomy. Organ failure is defined as a score of 2 or more according the Sequential Organ Failure Assessment (SOFA) system (34); or if there is a need for inotropic support and/or serum creatinine of > 2 mg/dl, and/or PaO2/FiO2 < 300 mm Hg. Organ failure for 48 h or more is defined as persistent, while it is defined as transient if less than 48 h. This is similar to the definitions proposed in the Revised Atlanta Classification.

The four categories in the Determinant Based Classification include mild, moderate, severe and critical AP. Mild AP is defined as the absence of both (peri)pancreatic necrosis and organ failure; moderate AP is defined as sterile (peri)pancreatic necrosis and/or transient organ failure; severe AP is defined as the presence of either infected (peri)pancreatic necrosis or persistent organ failure; and critical AP is defined as the presence of both infected (peri)pancreatic necrosis and persistent organ failure.

3. Utility and Limitations

Table 3 depicts the similarities and differences between different classifications of severity of AP.

Table 3: Similarities and differences between different classifications of severity of acute pancreatitis

	Atlanta Classification	Revised Atlanta Classification	Determinant based Classification
Description of the natural course of the disease (early and late phases)	• No	• Yes	• No
Distinction of organ failure depending on duration	• No	• Yes (Transient and persistent organ failure)	• Yes (Transient and persistent organ failure)
Definition of organ failure	• Non-uniform	• Uniform (use of Modified Marshall Scoring system).	• Uniform (use of Sequential Organ Failure Assessment system).
Definition of local complications	• No distinction of (peri)pancreatic collections with and without necrotic debris. • Local complications included necrosis, abscess and pseudocyst.	• Defines pancreatic and peripancreatic necrosis. • Discrete definitions of fluid collections [acute (peri)pancreatic fluid collections, pancreatic pseudocyst, acute necrotic collection and walled off necrosis]. • Included gastric outlet dysfunction, portal and splenic vein thrombosis, and colonic necrosis.	• Defines pancreatic and peripancreatic necrosis. • No definitions of fluid collections. • Does not consider gastric outlet dysfunction, portal and splenic vein thrombosis, and colonic necrosis as local complications.
Systemic complications	• Not considered in classification of severity.	• Defined as exacerbation of pre-existing conditions such as coronary artery disease, congestive cardiac failure, chronic obstructive pulmonary disease, diabetes, and chronic liver disease.	• Not considered in classification of severity.

Even though the 1992 Atlanta Classification came with substantial enthusiasm initially, it was observed over time that several descriptions pertaining to the disease as such definition of local complications, and definition and duration of organ failure, were either not addressed elaborately or lacked clarity (2). It was observed that over the past two decades, the terminologies from the Atlanta classification were inappropriately used, and several new terms were introduced as more data on the natural history and pathophysiology of the disease emerged (4, 5). This was complemented by the developments in cross sectional imaging techniques. Terms such as pancreatic phlegmon and infected pseudocyst found continued use and terms such as organized pancreatic necrosis,

subacute pancreatic necrosis, necroma and pseudocyst associated with necrosis came into existence **(Figure 1)**. There were even alterations in the definitions of organ failure in clinical practice and studies; and the reliance on the Atlanta Classification diminished with time. This mandated the revision of the classification system that culminated in the Revised Atlanta Classification.

The Revised Atlanta and the Determinant Based Classifications were published almost simultaneously and have since been validated and compared in several studies. The Determinant Based Classification was initially validated on a cohort of 151 patients in a 2-year prospective study (29). In this study, 13.9% patients had mild, 41.7% moderate, 39.1% severe, and 5.3% critical AP. The study outcomes were length of hospital stay, CTSI scores, occurrence of bloodstream infections, incidence of infected necrosis, requirements for percutaneous catheter drain, numbers of operations, and mortality; all of which had a step-wise increase in frequency across the groups. Another recent small study from China with 92 consecutive patients evaluated the moderate category of the Determinant Based Classification and concluded that this is a distinct group compared to the severe and critical groups (12). However, this group was not compared with the moderately severe group in the Revised Atlanta Classification. Furthermore, evaluation of the critical group according to the Determinant Based Classification would have been more meaningful in view of the emphasis on critical AP in this classification.

The study by Nawaz et al was the first report to compare the Revised Atlanta and the Determinant Based classifications (18). This post-hoc analysis of 256 prospectively admitted patients (49% transferred) used both the classifications to predict mortality, need for ICU admission, need for interventions, length of stay in the ICU and total hospital stay. According to the Revised Atlanta Classification, 49% patients in this study had mild disease, 25.5% moderately severe and 25.5% severe disease. On the other hand, according to the Determinant Based Classification 67% patients had mild AP, 7% moderate, 19% severe and 7% critical. The Revised Atlanta Classification appeared to predict length of hospital stay better than the Determinant Based Classification, while the latter appeared to predict need for intervention better. However, it is important to note that two classification systems are meant to categorize the disease severity once a certain criteria of severity is reached. This is different from prediction, which is performed before the severity criteria are reached. Furthermore, using different systems to predict different outcomes is unlikely to be appealing in clinical practice.

The next comparison between the two classifications came from Spain in a community based retrospective study of 459 patients who had 543 episodes of AP over five years (1). In this study, according to the Revised Atlanta Classification 66.9%, 29.5% and 3.7% patients had mild, moderately severe and severe AP respectively. On the other hand, according to the Determinant Based Classification, 71.1%, 24.1%, 4.2% and 0.6% patients has mild, moderate, severe and critical AP. Interestingly, unlike the study by Nawaz et al, this study did not observe any significant differences in frequency and outcomes between the two classifications.

A recent retrospective study of over 7 years from China evaluated 553 patients for outcomes according to the severity categories proposed in the Revised Atlanta Classification (8). The authors observed that mortality was significantly higher in patients with infected necrosis and organ failure compared to organ failure alone (32.2% vs 8%). Mortality was similar in patients who had infected necrosis without organ failure compared to patients with organ failure alone (7.1% vs 8%). Infected necrosis either preceded or developed concurrently in 45.8% of patients with persistent organ failure.

It was observed in a prospective study of 163 directly admitted consecutive patients with AP that 44.4% of patients with SAP developed persistent organ failure within the first week of disease onset;

and mortality within this group of patients was as high as 37.5% (26). This entity was not addressed in the Revised Atlanta and the Determinant Based Classifications. Previous studies have also shown that persistent organ failure in the early phase of disease can result in a mortality rate of 36-50% (7, 13). Early organ failure usually results from severe and persistent systemic inflammatory response syndrome; and the high mortality among these patients make it a discrete group, which was previously named early severe AP, but has not been considered in the two recent classifications (11, 22, 25).

4. Future Directions

It needs to be reiterated that both the Revised Atlanta and the Determinant Based classification were meant to classify severity, i.e. to categorize a patient into a predefined set of characteristics once the patient had developed those. Based on the dynamic progression of the disease, the categorization could progressively change according to the classification system utilized. Even though both the classification could guide the management of patients, none has the provision to track the progression from one severity category to the other. It is understandable that classification and prediction of severity are different aspects altogether; but incorporation of some provision of prediction would make the utility of either of the classification system more meaningful. This is particularly important for patients managed in the community setting, wherein referral to higher center early on becomes important. On the other hand, in the tertiary care setting, classification systems could guide patient management. For example, the management strategies for acute necrotic collection and walled off necrosis (as per the Revised Atlanta Classification) would be different in the presence or absence of mechanical symptoms and/or infections. Classification and guidelines in AP are based mostly on studies from tertiary care academic centers; while a substantial proportion of patients initially present to primary and community level healthcare facilities. It is the latter group of patients that need to be studied to have a better understanding on the dynamic progression of the disease and evaluate the utility of classification and predicting systems.

Even though both the recent classifications bear certain merits, there is substantial scope for improvement. Concerted efforts should be made to address the dynamics of the disease in both the classification systems and the individual categories in each classification need to be validated in large population based prospective cohorts of patients. An ideal classification system would be one that incorporates all attributes of the disease pathophysiology, tracks the disease dynamics, and has provision for prediction of transition from one category to the other. These would make the system applicable at all levels of healthcare and guide clinical decision making accurately.

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