Determinant-Based Classification of Acute Pancreatitis Severity

An International Multidisciplinary Consultation

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Objective: To develop a new international classification of acute pancreatitis severity on the basis of a sound conceptual framework, comprehensive review of published evidence, and worldwide consultation.

Background: The Atlanta definitions of acute pancreatitis severity are ingrained in the lexicon of pancreatologists but suboptimal because these definitions are based on empiric description of occurrences that are merely associated with severity.

Methods: A personal invitation to contribute to the development of a new international classification of acute pancreatitis severity was sent to all surgeons, gastroenterologists, internists, intensivists, and radiologists who are currently active in clinical research on acute pancreatitis. The invitation was not limited to members of certain associations or residents of certain countries. A global Web-based survey was conducted and a dedicated international symposium was organized to bring contributors from different disciplines together and discuss the concept and definitions.

Result: The new international classification is based on the actual local and systemic determinants of severity, rather than description of events that are correlated with severity. The local determinant relates to whether there is (peri)pancreatic necrosis or not, and if present, whether it is sterile or infected. The systemic determinant relates to whether there is organ failure or not, and if present, whether it is transient or persistent. The presence of one determinant can modify the effect of another such that the presence of both infected (peri)pancreatic necrosis and persistent organ failure have a greater effect on severity than either determinant alone. The derivation of a classification based on the above principles results in 4 categories of severity—mild, moderate, severe, and critical.

Conclusions: This classification is the result of a consultative process amongst pancreatologists from 49 countries spanning North America, South America, Europe, Asia, Oceania, and Africa. It provides a set of concise up-to-date definitions of all the main entities pertinent to classifying the severity of acute pancreatitis in clinical practice and research. This ensures that the determinant-based classification can be used in a uniform manner throughout the world.

Keywords: acute pancreatitis, classification, severity, organ failure, pancreatic necrosis, peripancreatic necrosis, pancreatic infectious complications

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Accurate classification of the severity of acute pancreatitis is important in clinical practice and for research. In clinical practice, it is valuable to define severity, to monitor disease course and to support clinical decision-making. In clinical research, it is valuable to distinguish clinically meaningful patient groups for accurate recruitment into clinical trials and valid comparison between groups. For more than a century, the severity of acute pancreatitis has been classified as either "mild" or "severe" and these have been defined variably.[1–5] Over the years, the limitations of this dichotomy have become apparent as patients labeled as having "severe" disease comprise subgroups with very different outcomes. These subgroups include patients at higher risk of mortality due to persistent rather than transient organ failure, those without organ failure who are at higher risk of morbidity due to necrotizing rather than interstitial pancreatitis, and those with prohibitive mortality when infected pancreatic necrosis and persistent organ failure both are present.[6–10]

There is a need to develop a better classification system that accurately discriminates between these patient subgroups with different outcomes. Such a classification system should be based on the best available data and be comprised of clear, robust, and uniform definitions. It is also important that the classification of severity be based on key factors that are causally associated with severity (ie, actual causes of death), rather than on descriptions of events that may correlate with severity but are not causal (eg, prolonged hospitalization, exacerbation of co-morbid disease, need for endoscopic intervention).[11,12] Given that acute pancreatitis evolves over time and that, at the individual patient level, clinical events can occur in any order on any day, such a classification of severity should capture key events whenever they occur and irrespective of the sequence in which they happen.[13,14] This means being able to classify the severity accurately at any time point during the disease course, and not just at the end or such an arbitrary time point as 1 week after onset of symptoms.

The development of a new classification of severity of acute pancreatitis has involved 3 stages. The first stage started with recognizing the limitations of previous classifications, including the Atlanta classification, and a comprehensive reviewing of the best available evidence.[15–20] Then there has been the introduction of new categories of severity, including "moderate" severity[9,21] and "critical" severity,[10,22,23] and the publication of the new classification proposal.[24]

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The second stage was a global Web-based survey of pancreatologists to obtain expert opinion regarding the controversial issues related to classifying severity and those not addressed in the literature or remained inconclusive despite publications.[25] The list of pancreatologists was generated by identifying in MEDLINE the corresponding authors of all articles pertinent to clinical aspects of acute pancreatitis, which were published during the most recent 5-year period (2006 to 2010). This approach was taken to make the development of new classification maximally open and transparent: the pancreatologists currently active in the field were invited to participate regardless of affiliation with a professional body, country of residence, language of publication, etc. E-mail invitations were delivered to 528 pancreatologists from 55 countries. A total of 240 pancreatologists from 49 countries representing all the inhabited continents participated in the survey. The results of the survey were used in the development of this document.

The third stage was convening an international symposium during the 2011 Meeting of the International Association of Pancreatology (Kochi, India) to further discuss the proposed classification and seek accord on the definitions. Around 100 participants attended the meeting and contributed to the discussion. After the meeting, a draft of this document was prepared and circulated.

DETERMINANTS OF SEVERITY

The classification is principally based on the factors that are causally associated with severity of acute pancreatitis.[11,12] These factors are called "determinants" and they are both local and systemic.

Local Determinant

The local determinant of severity is necrosis of the pancreas and/or peripancreatic tissue. This is covered by the term *(peri)pancreatic necrosis*.

Definitions

- *(Peri)pancreatic necrosis* is nonviable tissue located in the pancreas alone, or in the pancreas and peripancreatic tissues, or in peripancreatic tissues alone. It can be solid or semisolid (partially liquefied) and is without a radiologically defined wall.
- *Sterile (peri)pancreatic necrosis* is the absence of proven infection in necrosis.
- *Infected (peri)pancreatic necrosis* is defined when at least one of the following is present:
  - Gas bubbles within (peri)pancreatic necrosis on computed tomography
  - A positive culture of (peri)pancreatic necrosis obtained by image-guided fine-needle aspiration
  - A positive culture of (peri)pancreatic necrosis obtained during the first drainage and/or necrosectomy.

Discussion

There is strong agreement in the literature that pancreatic necrosis, with or without peripancreatic necrosis, is a key determinant of severity.[26–34] There is also a growing body of evidence that peripancreatic necrosis alone contributes to severity.[35–38] The global survey indicated that there is no agreement about the relative importance of pancreatic necrosis and peripancreatic necrosis as determinants of severity.[25] Although some patients develop pancreatic necrosis alone or peripancreatic necrosis alone, the majority of patients with necrotizing pancreatitis develop both of them together.[15,35,37] For these reasons, it is recommended that it is better to have one entity in the classification of severity (ie, [peri]pancreatic necrosis) which covers pancreatic necrosis alone, pancreatic necrosis with peripancreatic necrosis, and peripancreatic necrosis alone. It is also worth noting that a set of radiological terms have been proposed on the basis of a reasonably good agreement between radiologists and clinicians with regard to the interpretation of computed tomography scans.[17,20] However, given that the prognostic importance of all the proposed radiological terms has not been demonstrated yet,[20,25] occurrences other than (peri)pancreatic necrosis (as defined above) should not be used to classify the severity of acute pancreatitis. This is an area that may need to be modified with new evidence.

There is a lack of quality data regarding the optimal criteria for diagnosis of pancreatic necrosis and peripancreatic necrosis.[15,18] The global survey indicated that there was little agreement as to the extent of nonenhancement required to diagnose pancreatic necrosis on contrast-enhanced computed tomography. More than a third (35%) of the survey respondents considered that the diagnosis of pancreatic necrosis on computed tomography required the detection of any amount of nonenhancement, and another third (31%) considered there needed to be more than 30% of the pancreas to not enhance.[25] Given that "30%" is an arbitrary figure and the lack of convincing evidence in the literature regarding its use as a cutoff, the recommendation is that the diagnosis of pancreatic necrosis requires the detection of any area of nonenhancement on contrast-enhanced computed tomography. The diagnosis of peripancreatic necrosis may not be always done on computed tomography, especially early in the course of acute pancreatitis.[15,39,40] The practical consideration is to recommend that every heterogeneous peripancreatic collection on computed tomography has to be regarded as peripancreatic necrosis until proven otherwise.[41] In the global survey, 80% of the respondents considered that peripancreatic collections that did not contain necrosis were not determinants of severity.[25]

Infection of necrosis, both pancreatic and peripancreatic, can be diagnosed by noninvasive and invasive methods.[42] Gas bubbles within (peri)pancreatic necrosis on computed tomography have an almost 100% specificity in the diagnosis of pancreatic infection.[43,44] However, it is worth mentioning that on rare occasions the presence of gas can indicate the presence of a communication with the gastrointestinal tract. Procalcitonin is a promising serological marker of pancreatic infection and, especially, pancreatic infection in conjunction with organ failure.[45] However, the reported pooled specificity in meta-analyses for procalcitonin is in the range of 83% to 91%[46,47] and it cannot be used as an accurate sole diagnostic test for pancreatic infection. It is likely that the combination of procalcitonin with other markers of infection (clinical, biochemical, radiological) would increase the accuracy, but this is an area that requires further evidence.

Systemic Determinant

The systemic determinant of severity is a certain degree of distant organs dysfunction due to acute pancreatitis. This is covered by the term *organ failure*.

Definitions

- *Organ failure* is defined for 3 organ systems (cardiovascular, renal, and respiratory) on the basis of the worst measurement over a 24-hour period. In patients without preexisting organ dysfunction, organ failure is defined as either a score of 2 or more in the assessed organ system using the SOFA (Sepsis-related Organ Failure Assessment) score[48] or when the relevant threshold is breached, as shown:
  - *Cardiovascular:* need for inotropic agent
  - *Renal:* creatinine $\geq$ 171 μmol/L ($\geq$2.0 mg/dL)
  - *Respiratory:* $PaO_2/FiO_2 \leq 300$ mmHg ($\leq$40 kPa).
- *Persistent organ failure* is the evidence of organ failure in the same organ system for 48 hours or more.

- *Transient organ failure* is the evidence of organ failure in the same organ system for less than 48 hours.

Discussion

There was considerable discussion about how best to capture the different aspects of organ failure in a classification of severity. The importance of the time of onset of organ failure in relation to outcome was debated. There is evidence from some single-center studies demonstrating that "early" organ failure is associated with a higher mortality,[19,49,50] but limitations in each of these studies might confound the observed difference in mortality between the "early" and "late" groups. Early necrosectomy, now abandoned because of an overwhelming mortality, was advocated in the 2 earlier studies.[49,50] The definitions used for "organ failure" were suboptimal and included systemic inflammatory response syndrome and sepsis[49] and pancreatic bed bleeding.[15] In one study, a referral bias might influence the results.[19] Furthermore, several other studies showed that duration/reversibility of organ failure, irrespective of the time of onset of organ failure, is the most important aspect of organ failure.[7,51–53] The latter notion was also supported by recent guidelines.[15,18] There was lively debate regarding whether the fulminant and subfulminant subcategories should be included in the classification of severity.[19,54] Given the lack of accord, the issue of the timing of organ failure will require further consideration and probably further prospective evaluation from nonintervention studies.

Another aspect of organ failure that was considered was which organs are the most important to assess when diagnosing organ failure and its role as a determinant of severity. On the basis of the published clinical studies and the global survey, it is recommended that 3 (cardiovascular, renal, and respiratory) organ systems should be considered when classifying the severity of acute pancreatitis.[25,55–58] There are a number of composite scoring systems for organ dysfunction and their use is advocated in the literature.[15,59–61] However, the global survey revealed a difference of expert opinion with respect to the method used to diagnose organ failure, with 45% of the respondents opting to diagnose each organ failure separately using a threshold, rather than a composite score with a number of levels (55%).[25] Because of this lack of accord and absence of convincing evidence in the literature, both approaches to the diagnosis of organ failure are included.

CLASSIFICATION OF SEVERITY

The definitions used for the categories of severity are based on attributes of the *local determinant* (absent, sterile, or infected [peri]pancreatic necrosis) and the *systemic determinant* (absent, transient, or persistent organ failure) as well as possibility of interaction between the determinants during the same episode of acute pancreatitis (Table 1). Beyond these local and systemic determinants of severity, other occurrences should be considered complications and should not be used for the purpose of classifying the severity.

Definitions

- *Mild acute pancreatitis* is characterized by the absence of both (peri)pancreatic necrosis *and* organ failure.
- *Moderate acute pancreatitis* is characterized by the presence of sterile (peri)pancreatic necrosis *and/or* transient organ failure.
- *Severe acute pancreatitis* is characterized by the presence of either infected (peri)pancreatic necrosis *or* persistent organ failure.
- *Critical acute pancreatitis* is characterized by the presence of infected (peri)pancreatic necrosis *and* persistent organ failure.

Discussion

There are 2 main principles upon which the new international multidisciplinary classification of severity is founded. First, it is based on *actual* factors of severity rather than factors that are predictive of severity. The use of multifactorial scoring systems (eg, APACHE II score, Ranson criteria) to predict severity was incorporated in the original Atlanta classification and, undoubtedly, was an important development 2 decades ago when the imaging was not sophisticated and the importance of organ failure in acute pancreatitis was not fully recognized.[62] However, these scoring systems are all plagued by a significant misclassification error which limits their utility in clinical practice and in recruitment of individual patients into clinical trials.[63–66] Notwithstanding the above, the prediction of severity is still a valuable concept but, to improve clinical usefulness, it should predict the actual factors of severity–(peri)pancreatic necrosis and/or organ failure.[67] A recent example of this is the measurement of angiopoietin-2, a marker of vascular leak syndrome, in predicting persistent organ failure.[68] Identification of early markers of persistent organ failure is important as there is a concern, especially among intensivists, that patients are often admitted to the intensive care unit too late.[69]

Second, the new international multidisciplinary classification defines severity solely on the basis of factors that have a *causal association* with severity. Based on the concept of causal inference, these factors in patients with acute pancreatitis are (peri)pancreatic necrosis and organ failure.[11] This contrasts with empirical attempts to link the severity of acute pancreatitis and such noncausal occurrences as prolonged hospitalization, exacerbation of co-morbid disease, need for an intervention, and death.[70–74] The literature is replete with countless studies that demonstrate a statistically significant association between a wide array of factors and the severity of acute pancreatitis.[75–78] While possibly statistically correct, it is worth noting that these associations are noncausal, with confounding and effect-cause relationship being most common.[11,12] As such, these associations are meaningless and may even be misleading in classifying the severity.

When the aforementioned principles were applied, 4 categories of severity resulted. Although there was strong support (by 88% respondents) for this determinant-based classification in the global survey and was considered to be useful for both clinical practice (90%) and research (91%), it might be questioned as to what particular advantage it had over other published classifications.[25] Ultimately, the answer to this will be determined as the new international multidisciplinary classification is applied to the care of patients, to the plotting of clinical course, and to the audit of clinical experience.[79,80] For now, an obvious clinical advantage is that the definitions are easy-to-use, standardized, and unambiguous and as such will be an aid in monitoring the disease course and in communication between clinicians.[24]

TABLE 1. Determinant-Based Classification of Acute Pancreatitis Severity

	Mild AP	Moderate AP	Severe AP	Critical AP
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	AND	*AND/OR*	*OR*	*AND*
Organ failure	No	Transient	Persistent	Persistent

AP indicates acute pancreatitis.

In the context of clinical research, the determinant-based classification of severity will also prove useful in selecting more homogeneous patients for clinical trials and evaluating the effect of treatment (eg, upstaging the severity as an endpoint of intervention studies).[11,13] The distribution of severity is pyramidal, which means that collaborative multicenter trials are likely to be required to study the smaller groups with severe and critical severity, whereas single-center trials will be able to study the larger groups with mild and moderate severity.[22,23]

CONCLUSIONS

This global multidisciplinary consultation was made possible because of active and constructive contribution of more than 200 surgeons, gastroenterologists, internists, intensivists, and radiologists from 49 countries representing all the inhabited continents. The classification of acute pancreatitis severity continues to evolve. Further modifications will be required in the future, driven by the systematic review of new data and a new international consultative process. But at this time, there is sufficient evidence, expert opinion, and justification to apply the new international multidisciplinary classification of acute pancreatitis in both clinical practice and research.

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