Predicting Severity of Acute Pancreatitis

Bettina M. Rau, MD

Corresponding author
Bettina M. Rau, MD
Department of General, Visceral, and Vascular Surgery, University of the Saarland, Kirrberger Strasse, Building 57, 66421 Homburg/Saar, Germany.
E-mail: bettina.rau@uniklinikum-saarland.de

Current Gastroenterology Reports 2007, **9:**107–115
Current Medicine Group LLC ISSN 1522-8037
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Severity stratification is a critical issue in acute pancreatitis that strongly influences diagnostic and therapeutic decision making. According to the widely used Atlanta classification, "severe" disease comprises various local and systemic complications that are associated with an increased risk of mortality. However, results from recent clinical studies indicate that these complications vary in their effect on outcome, and many are not necessarily life threatening on their own. Therefore, "severe," as defined by Atlanta, must be distinguished from "prognostic," aiming at nonsurvival. In the first week after disease onset, pancreatitis-related organ failure is the preferred variable for predicting severity and prognosis because it outweighs morphologic complications. Contrast-enhanced CT and MRI allow for accurate stratification of local severity beyond the first week after symptom onset. Among the biochemical markers, C-reactive protein is still the parameter of choice to assess attack severity, although prognostic estimation is not possible. Other markers, including pancreatic protease activation peptides, interleukins-6 and -8, and polymorphonuclear elastase are useful early indicators of severity. Procalcitonin is one of the most promising single markers for assessment of major complications and prognosis throughout the disease course.

Introduction

Among the inflammatory digestive disorders, acute pancreatitis continues to challenge physicians as the least and most difficult one to predict with regard to clinical course and outcome. Although the majority of acute attacks have a "mild" course with uneventful recovery, in 25% of patients "severe" disease develops. Ever since the first classification system of acute pancreatitis was established in 1965 [1], the definition of "severe" disease has been linked to the occurrence of specific complications and an increased risk of mortality [2].

Early and reliable stratification of severity is required to select individual patients for interventions against evolving complications, for referral to specialist centers, and for comparison of patients for scientific purposes or recruitment into clinical trials. Severity assessment aims at objective quantification of the actual severity of illness, which comprises the sum of clinical course and ultimate outcome. Outcome, in turn, usually reflected by nonsurvival, forms the "gold standard" for evaluation of systems with regard to severity and prognosis.

Various approaches to severity stratification can be inferred from clinical signs and symptoms, laboratory variables, and diagnostic imaging procedures. However, the type and clinical relevance of a complication rendering acute pancreatitis "severe" have changed in the past decades. New insights into the pathomechanism and natural course of the disease, along with diagnostic improvements, have significantly influenced definitions and classification systems [2] and continue to do so. This review addresses new approaches to assessment of disease severity in acute pancreatitis.

Clinical Factors

Several single clinical variables have been found to be risk factors for complications and mortality beyond well-established parameters, such as age or comorbidity, and are described in the following sections

Obesity

Obesity is a clinical variable that is strongly associated with comorbidity in acute pancreatitis and has been controversial since it was first addressed in the literature [3]. A recent meta-analysis based on five studies in a total of 739 patients with acute pancreatitis has convincingly shown that obesity, defined by a body mass index (BMI) greater than or equal to 30 kg/m^2, is a definite risk factor for the development of severe disease [4•]. Severe acute pancreatitis was significantly more frequent in obese patients (OR of 2.9; 95% CI, 1.8–4.6), who experienced more systemic (OR of 2.3; 95% CI, 1.4–3.8) and local complications (OR of 3.8, 95% CI 2.4–6.6). In contrast to previous reports, mortality was also higher in obese patients (OR of 2.1; 95% CI, 1.0–4.8). In clinical practice, assessment of obesity is objective and easily available, and therefore it is a valuable variable to include in future scoring systems or severity classifications. However, as with other factors

Table 1: Relationship of organ failure and outcome in acute pancreatitis

Study	Patients, *n*	Positive	Mortality	Negative	Mortality
Early organ failure (ESAP)*					
Isenmann et al. [8] 2001	158	*n* = 47 ESAP +	*n* = 20 (42%)	*n* = 111 SAP only	*n* = 16 (14%)
Tao et al. [6] 2004	297	*n* = 69 ESAP +	*n* = 30 (42%)	*n* = 228 SAP only	*n* = 6 (3%)
Poves Prim et al. [11] 2004	112	*n* = 40 ESAP +	*n* = 21 (53%)	*n* = 17 SAP + late OF	*n* = 2 (12%)
		n = 57 OF +	*n* = 23 (40%)	*n* = 55 SAP, no OF	*n* = 0 (0%)
Persistent organ failure					
Buter et al. [9] 2002	121	*n* = 20 SAP + OF pers	*n* = 11 (55%)	*n* = 33 SAP + OF res	*n* = 0 (0%)
Johnson et al. [10••] 2004	290	*n* = 102 SAP + OF pers	*n* = 35 (34%)	*n* = 72 SAP + OF res	*n* = 2 (3%)
Mofidi et al. [13•] 2006	759	*n* = 89 SAP + OF pers	*n* = 37 (42%)	*n* = 120 SAP + OF res	*n* = 4 (3%)

*Early organ failure: within 72 hours after disease onset or admission.
ESAP—early severe acute pancreatitis; OF—organ failure; pers—persistent; res—resolving; SAP—severe acute pancreatitis.

of comorbidity, obesity on its own is insufficient to correctly predict major complications or death.

Abdominal compartment syndrome

Abdominal compartment syndrome, defined as intra-abdominal pressure of greater than 25 mm Hg, is currently gaining attention as a prognostic factor in patients with severe attacks, especially in those with necrotizing pancreatitis. Although data remain scarce, it can be estimated that the overall prevalence of intra-abdominal hypertension (intra-abdominal pressure >15 mm Hg) in severe acute pancreatitis is approximately 40% [5]. A limited number of studies have revealed a strong association between intra-abdominal hypertension and the development of multiple organ dysfunction, which occurred in more than 90% of patients [5,6,7•]. Multiple organ dysfunction, in turn, carries excessively high mortality rates [6,8,9,10••,11]. Clinical evidence suggests that "early" multiple organ failure may result from undiagnosed abdominal compartment syndrome arising from the extensive inflammatory process in the retroperitoneum and aggressive fluid resuscitation. Beyond its prognostic role, the diagnosis of abdominal compartment syndrome may have therapeutic consequences [7•]. Further studies on this objective and easily available clinical sign are awaited with great interest.

The role of organ failure

In searching for reliable and accurate clinical parameters to assess disease severity and outcomes, pancreatitis-associated organ failure has gained considerable headway in recent years, although acknowledgment of its prognostic importance is far from new. Clinical correlates of organ failure, such as respiratory distress, hypotension, and anuria, have been recognized as indicators of poor outcome for several decades and were objectified by Ranson and Imrie in the 1970s. However, the temporal presence of a systemic complication or a failing organ system in itself does not necessarily indicate a life-threatening illness. Specific aspects, such as onset, severity, type, and persistence of organ failure had received little attention until recently.

Early organ failure

The impact of "early-onset organ failure," defined as one or more failing organ systems within the first 3 days after onset of symptoms, was first shown by Isenmann et al. [8] in patients with necrotizing pancreatitis, among whom 47 of 158 (30%) had early organ failure. The presence of early organ failure resulted in a dramatic increase of mortality to 42%. Further progression of early multisystem organ failure was observed in 95%, and early single- to multisystem organ failure was seen in 64% of patients. Results from two studies, one from China and one from Spain, subsequently underscored the importance of early organ failure with their reports of almost identical results (Table 1) [6,11]. In addition, a very recent study by our group has shown that early multisystem organ failure (OR of 19.0; 95% CI, 4.7–77.0; $P<0.0001$) was the most important risk factor for fatal outcome in 230 patients with sterile necrosis, irrespective of whether treatment was operative or conservative and whether secondary pancreatic infections developed later [12•]. Only severe organ failure, such as mechanical ventilation (OR of 5.80; 95% CI, 1.8–19.1; $P<0.004$), hemofiltration (OR of 4.33; 95% CI, 1.5–12.2; $P<0.006$), or need for vasopressors (OR of 8.4; 95% CI, 2.8–25.6; $P=0.0002$), was found to be an independent risk factor for the development of secondary pancreatic infections, whereas extent of necrosis or treatment was not.

Persistent organ failure

The dynamics of organ failure, in terms of response and resolution or nonresponse and persistence with supportive treatment, have been identified as another major determinant of complications and death. In two prospective studies from the UK, resolution of organ failure within the first week of disease onset resulted in mortality rates close to zero, whereas mortality rates rose to 55% if organ failure persisted beyond the first week [9,10••]. Almost

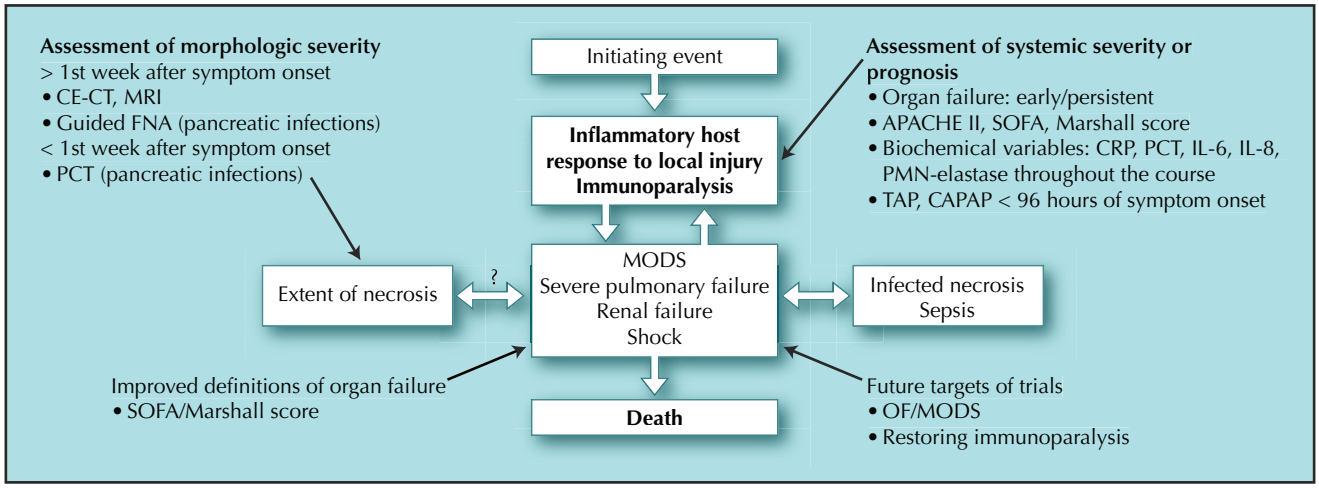

Figure 1. The pathomechanism of severe acute pancreatitis and related complications is depicted. Unlike earlier research, recent clinical observations emphasize that early/persisting organ failure is a major determinant of subsequent local complications and nonsurvival in acute pancreatitis. Proposed approaches to stratify severity and prognosis during the course of the disease and future directions concerning definitions and therapeutic targets are illustrated. APACHE—Acute Physiology and Chronic Health Evaluation; CAPAP—carboxypeptidase B activation peptide; CE-CT—contrast-enhanced computed tomography; CRP—C-reactive protein; FNA—fine-needle aspiration; IL—interleukin; MODS—multiorgan dysfunction syndrome; OF—organ failure; PCT—procalcitonin; PMN—polymorphonuclear; SOFA—Sequential Organ Failure Assessment; TAP—trypsinogen activation peptide.

identical results were reported in another recent retrospective study from the UK [13•] (Table 1). In addition, two studies, one from France [14] and one from New Zealand [15], reported that organ failure that was unresponsive to intensive-care unit (ICU) treatment was closely related to pancreatic infections [14] and death [14,15].

Despite differences in definitions and methods to assess organ failure, there is little doubt that organ failure is one of the most important determinants of mortality in acute pancreatitis and may even be a key factor for evolving local complications. These results emphasize the need for a profound revision of clinical and morphologic factors thought to indicate "severe" disease and a reevaluation of their temporal relationship in terms of cause and consequence (Fig. 1). In addition, comparison of results from the studies previously described in this review suggests that uniform definitions are needed for type and severity of organ failure and what is necessary to distinguish true organ failure from systemic complications (eg, calcium derangements, systemic inflammatory response syndrome [SIRS], neurologic disturbance, coagulation disorders).

Immunoparalysis

Aside from SIRS, recent clinical observations suggest that an impaired immune response is a detrimental early feature of severe acute pancreatitis. Depending on the presence and severity of early organ failure, "immunoparalysis," as reflected by an immediate and sustained decrease of HLA-DR expression on circulating monocytes, was observed in patients who developed septic complications or died in the further course of disease [16–18]. These results are of specific interest in that they provide a potential cellular mechanism as a link between early severe and persistent organ failure and subsequent pancreatic infections, a cause-consequence relationship that is quite the opposite of our current understanding. This insight would not only substantially change our current pathogenetic concept of pancreatic infections, but more interestingly, it would also offer potential new therapeutic approaches. By either restoring immunoparalysis [19•] or targeting organ failure, the incidence of pancreatic infections or even mortality might be more effectively decreased than with previous treatments, such as antibiotics.

Pancreatic Necrosis and Infection

During the early 1980s, intraoperative findings revealed the presence, extent [20–22], and infection necrosis [22] as the most important determinants of severity and outcome in acute pancreatitis. The introduction of contrast-enhanced computed tomography (CE-CT) and guided fine-needle-aspiration (FNA) allowed nonoperative assessment of these complications and further substantiated the era of morphology-based severity stratification. Hence, radiologic imaging and guided FNA have become indispensable for severity stratification and are integral parts of current classification systems [2] and treatment algorithms alike [23,24]. Although there is no further doubt that the presence and extent of necrosis enhance severity, an increasing number of recent reports have shown that none of these complications on their own are life threatening unless organ failure develops [12•,25–27]. Moreover, even the role of infected necrosis as a predominant risk factor for death is increasingly questioned as long as organ failure is absent or only transient [12•,27–29]. Because morphologic complications usually develop several days to weeks after onset of symptoms, neither CE-CT nor FNA are appropriate tools

to assess severity very early, whereas their role remains essential beyond the first week of acute pancreatitis and with regard to therapeutic decision making [23,24]. Further technical advances have made MRI an interesting new tool to stage severity of acute pancreatitis because MRI has fewer contraindications than CT [30]. However, the limited availability and the very high cost still preclude large-scale use of MRI for the assessment of local complications in acute pancreatitis.

Dynamic Multiple Parameter Scoring Systems

The Acute Physiology and Chronic Health Evaluation (APACHE) II system was the first dynamic multiparameter assessment measure to stratify patients at risk to develop severe acute pancreatitis [31]. This scoring system has been applied widely and was incorporated into the Atlanta classification, with a score of 8 or higher denoting a severe attack [2]. Driven by recognition of the effect of organ failure on outcome, new multiparameter ICU systems, such as the Marshall [32] and Sequential Organ Failure Assessment (SOFA) [33] scores, are increasingly used for a more flexible and practical assessment in acute pancreatitis.

Marshall score

A modification of the Marshall score that excludes hepatic function has been applied in two large prospective studies [9,10••] and one retrospective study [13•] from the UK to quantify organ failure. The components for pulmonary, cardiocirculatory, and renal function match well with the definitions of the Atlanta classification, but neurologic (Glasgow Coma Scale) and coagulation parameters (platelet function) may further increase total scores, even if true organ failure is absent. However, specific validation studies of the Marshall score are still scarce. Among five different scoring systems tested within the first 72 hours after hospital admission, Marshall scores (sensitivity, 59%; specificity, 91%; positive predictive value [PPV] and negative predictive value [NPV] not reported) were comparable with the APACHE II system (sensitivity, 65%; specificity, 91%; PPV and NPV not reported) in predicting mortality in a Finnish series of 60 patients with severe acute pancreatitis [34]. In a retrospective study by the same group in 113 patients with severe acute attacks admitted to the ICU, both admission and peak Marshall scores were as accurate as SOFA scores to assess the risk of hospital mortality [28].

SOFA score

Results from two detailed evaluative studies in acute pancreatitis are available. In a prospective international multicenter study in 104 patients with severe disease, SOFA scores higher than 4 were predictive of death, with a sensitivity of 86% and a specificity of 79% (PPV, 27%; NPV, 98%) 48 hours after onset of symptoms [35]; corresponding results have been reported by Finnish investigators for admission scores in an ICU population–based cohort at a cutoff level of greater than 8 [28]. A detailed analysis of the six components in the Finnish study revealed that not all types of organ failure affect nonsurvival to the same degree: only cardiocirculatory, renal, and hepatic failure were independently associated with hospital mortality. Moreover, the severity of all failing organ systems was significantly higher in nonsurvivors throughout the course of acute pancreatitis, with the cardiovascular and renal system showing the most pronounced differences [28].

Despite encouraging results, each of the critical care scoring systems still suffers from shortcomings in that they perform variably depending on the setting (ICU vs non-ICU patients). In addition, most of the studies are not completely comparable due to modifications by omitting single components, such as hepatic or neurologic function. The latter are truly problematic in acute pancreatitis because high bilirubin values or delirium tremens are frequent features of biliary or alcoholic pancreatitis that do not represent essential organ failure and thus erroneously lead to high scores. Among the critical care systems discussed, the SOFA system offers obvious advantages because it is easy to calculate, includes therapeutic requirements, and allows comparison of acute pancreatitis with other critical care diseases. Further studies are needed to define pancreatitis-specific modifications and adequate cutoff levels.

Biochemical Parameters

In the mid-1960s, the first evidence emerged indicating that acute pancreatitis is reflected by abnormalities of many serum/plasma variables [36]. Hence, much effort has been expended in the search for laboratory parameters that allow early stratification of patients at risk to develop necrosis or severe disease, as defined by Atlanta (Table 2) [37]. Unfortunately, the majority of the markers have never been investigated with regard to whether prediction of infected necrosis, septic complications, or death is possible as well. (Table 2) An ideal laboratory test should be simple to perform, readily available under routine and emergency conditions, accurate, and cost-effective. Given these attributes, biochemical severity stratification is considered an attractive alternative to imaging procedures or multiple-parameter scoring systems. However, despite an increasing array of potentially useful parameters, their large-scale clinical use is often limited by time-consuming and expensive assay procedures.

Activation peptides of pancreatic proteases

Trypsinogen activation peptide (TAP) and carboxypeptidase B activation peptide (CAPAP) are the most important activation peptides in acute pancreatitis. Measurement of activation peptides is superior to measurement of leaking proenzymes because of the high stability of the cleaved propeptide in the systemic circulation [38].

Table 2. Clinical value of relevant biochemical parameters in predicting severity, infected necrosis/septic shock, and death in patients with acute pancreatitis*

Parameter	Severity	Infection	Organ failure	Death	Assay	References
Pancreatic proteases						
TAP	Yes (<48 h)	No	NA	NA	ELISA	[39–42,43,45]
CAPAP	Yes (<48 h)	No	NA	NA	RIA	[43–45]
Leukocyte-derived proteases						
PMN-elastase	Yes (<48 h)†	No	NA	NA	Automated IA	[57–59,60•]
Cytokines/chemokines						
IL-6	Yes (<48 h)†	No	Yes (>48 h)‡	No	Automated IA	[48,50–55]
IL-8	yes (<48 h)†	Septic MODS	Septic MODS	Yes (>48 h)‡	Automated IA	[52,54–56]
Acute-phase proteins						
CRP	Yes (>48 h)‡	No		No	Automated IA	[41,42,46–49, 52,55,56,58]
SAA	Yes (<48 h)‡	No		No	Automated IA	[46,49]
Others						
PCT	No	Yes (>48 h)‡		Yes (>48 h)‡	Semi- and fully automated IA, dipstick	[56,64–66, 67••,68]

*Based on results of meta-analyses, multicenter trials, or at least two adequately powered ($n \geq 50$ patients) clinical studies.
†Within 48 hours of disease onset.
‡Beyond 48 hours from disease onset.
CAPAP—carboxypeptidase B activation peptide; CRP—C-reactive protein; ELISA—enzyme-linked immunosorbent assay; IA—immunoassay; IL—interleukin; MODS—multiorgan dysfunction syndrome; NA—not assessed; PCT—procalcitonin; PMN—polymorphonuclear; RIA—radioimmunoassay; SAA—serum amyloid A protein; TAP—trypsinogen activation peptide.

TAP

Since its first description in 1990 [39], the clinical usefulness of TAP has been investigated extensively. Three multicenter trials have been published with the common endpoint of "severe disease" according to the Atlanta classification. The initial enthusiasm following the excellent results of an American trial [40] became somewhat beclouded by two subsequent European multicenter trials that brought less favorable results. Sensitivity and specificity rates of urinary TAP at 24 hours after symptom onset did not exceed 58% and 80% (PPV <39%; NPV<90%), respectively [41,42]. Although the test performed better 48 hours after disease onset, overall accuracy rates did not exceed 75% in predicting a severe attack, which was also achieved by clinical scoring systems [41]. Whether early prediction of specific complications, such as organ failure or death, is possible remains unknown because none of the studies addressed these aspects. Unfortunately, the very early burst-like secretion of TAP with a rapid decline makes it impossible to discriminate between severe and mild pancreatitis after 72 hours. Therefore, monitoring the progression to multisystem organ failure or septic complications, which usually develop beyond 48 hours after symptom onset, is hardly possible. The current enzyme-linked immunosorbent assay (ELISA) technique prohibits analysis of this parameter in the daily laboratory routine.

CAPAP

The activation peptide CAPAP possesses diagnostic and prognostic properties in acute pancreatitis and has been found to correlate well with severe disease as defined by the Atlanta classification [43–45]. CAPAP can be measured in plasma and urine and is more stable than TAP due to its larger size. The highest diagnostic accuracy in predicting severity or necrosis is obtained by measuring urinary concentrations, with excellent accuracy rates of approximately 90% within 24 to 48 hours of symptom onset throughout all studies [43–45]. Unfortunately, CAPAP levels also rapidly decline and are thus not useful for monitoring the later course of the disease. The CAPAP assay is currently available as radioimmunoassay only, which prohibits its introduction for routine clinical analysis at present.

On the basis of the published literature, assessment of pancreatic protease activation peptides is one of the very few approaches to early severity stratification of acute pancreatitis. However, because many patients with acute pancreatitis are hospitalized or referred beyond the 48-hour diagnostic window after disease onset, the general need for very early markers of severity must be questioned. Even if an "immunostick" for a single or combined assessment of activation peptides is developed in the future, the use of these parameters will probably remain scientific rather than clinical due to their limited indication and consequent high cost.

Acute-phase proteins

The most famous member among the family of the acute-phase proteins is C-reactive protein (CRP); more recently serum amyloid A protein (SAA) has accomplished the spectrum of acute-phase reactants for the biochemical severity stratification of acute pancreatitis. The two parameters share a feature that is essential for large-scale routine application: they have become available as fully automated immunoassays.

CRP

Severity stratification of acute pancreatitis by CRP has a long tradition and still represents the gold standard with which new biochemical parameters must compete. The assay, along with its low cost and availability, have made CRP a widely established marker for severity stratification and monitoring of disease course. CRP is the parameter of choice to differentiate necrotizing from interstitial edematous acute pancreatitis [37]. However, the majority of the studies focused on the discrimination between mild and severe acute pancreatitis and obtained only moderate diagnostic accuracy, ranging between 60% and 80%, at a cutoff level higher than 150 mg/L within the first 48 hours of disease onset [41,42,46]. CRP performs better beyond the 48-hour interval with accuracy rates of more than 80% at cutoff levels greater than 200 mg/L [47]. As well documented for all acute-phase proteins, CRP is neither disease-specific nor is it useful for the prediction of infected necrosis, organ failure, or death within the first week after disease onset [48,49]. Another shortcoming of CRP is the relatively long delay of its induction, with systemic peak values at 72 to 96 hours after disease onset, making very early severity assessment impossible.

SAA

SAA is another acute-phase reactant used for severity stratification of acute pancreatitis. It has been evaluated in two adequately powered studies [46,49]. A common finding of the two studies was an earlier release with a wider dynamic range of SAA than that observed for CRP. Investigators in a multicenter study found that SAA was a better early predictor of severe acute pancreatitis than was CRP by using a conventional ELISA technique [46]. The second study, conducted by our group, could not demonstrate any advantage of SAA over CRP in stratifying severity at any time point during the course of acute pancreatitis using a fully automated assay technique [49]. Further studies are needed to define a convincing clinical benefit of SAA over CRP determinations to justify the higher cost of this alternative acute-phase reactant.

Among the acute-phase proteins, CRP remains the gold standard for predicting severity beyond 48 hours after onset of acute pancreatitis. This readily available, fast, and inexpensive test is still the reference parameter among the indicators of necrosis and severe disease according to the Atlanta classification.

Cytokines and chemokines

Since the early 1990s, the first clinical reports about the role of cytokine measurements in acute pancreatitis appeared in the literature, and this topic continues to be addressed [37]. Fast and fully automated assay techniques have overcome the problems of the conventional ELISA measurements, but the majority of cytokine and chemokine family members have no role as biochemical markers for severity assessment of acute pancreatitis in the clinical setting. So far, only the cytokine interleukin (IL)-6 and the chemokine IL-8 have passed the threshold from pathophysiologic importance to limited clinical application [37].

IL-6

Systemic concentrations of IL-6 have been found to be early and excellent predictors of severity. A large number of clinical studies have uniformly shown that IL-6 is dramatically increased in complicated attacks [48,50–54]. The elevation of IL-6 concentrations generally occurs 24 to 36 hours earlier than that of CRP, with significantly elevated levels as long as complications persist [50–53]. Beyond discriminating mild from severe attacks, IL-6 closely correlates with evolving organ failure [48,50,53], whereas early prediction of death has been investigated but does not seem to be possible [51]. IL-6 has been introduced as a routine parameter in some laboratories and represents an easy and rapid means to select patients at risk to develop severe disease.

IL-8

IL-8 was initially described as an early marker of disease severity within the first day after onset of symptoms, with a rapid decease after 3 to 5 days, revealing obvious parallels to IL-6 [55]. However, beyond discriminating mild from severe attacks, a more important aspect has been reported for IL-8. In patients with necrotizing pancreatitis who developed septic multiorgan failure or died, IL-8 has proved to be an excellent but rather late marker for monitoring this life-threatening complication [53,56]. As for IL-6, a fully automated assay is available for IL-8, and the use of this chemokine for disease monitoring has become possible on a daily routine basis. However, the relatively high cost still prohibits large-scale application of both IL-6 and IL-8 in clinical practice.

Polymorphonuclear elastase

Several polymorphonuclear (PMN)-derived proteolytic enzymes have been described as valuable biochemical markers for severity stratification of acute pancreatitis. Among these enzymes, PMN-elastase brings the best results throughout the studies. Enhanced systemic release of PMN-elastase is an early feature in severe attacks, with peak values even before CRP and other parameters begin to rise [57–59]. However, despite these encouraging results, PMN-elastase has not been adopted into routine laboratory use due to assay-related problems with non-reproducible test results. Very recently, an improved, routinely applica-

ble assay was tested prospectively in a Spanish multicenter trial and confirmed the favorable results of a previous trial by the same group [59]. At a plasma concentration higher than 110 μg/L, a sensitivity of 92% and a specificity of 91% (PPV, 78%; NPV, 96%) for the prognostic evaluation of severe acute pancreatitis were obtained within 24 to 72 hours after disease onset [60•]. However, neither of the two multicenter studies provided information about the value of PMN-elastase in predicting more relevant complications, such as pancreatic infections, organ failure, or death, probably due to the overall low severity in either series. Because a number of excellent parameters are already available for early severity stratification of acute pancreatitis, the fate of PMN-elastase measurement remains to be defined.

Coagulation parameters

Coagulation disorders are a known feature of severe acute pancreatitis, but parameters of coagulation have gained increasing attention for the assessment of severity and prognosis only recently. In a Japanese study by Maeda et al. [61], six different coagulation parameters were analyzed at hospital admission in 139 patients with acute pancreatitis, 80 of whom suffered from severe disease. Among the variables tested, antithrombin-III (AT-III) was the most accurate parameter, predicting nonsurvival with a sensitivity of 81% and a specificity of 86% (PPV and NPV not reported) at a cutoff level of less than 69%. Unfortunately, the authors did not provide information about the delay between symptom onset and admission, which precludes an estimate of how early AT-III levels allow prediction of this most serious complication. Protein C and AT-III levels revealed a significant and persistent depletion in another study in 41 operatively treated patients with severe acute pancreatitis with the similar problem that all parameters were only assessed during the postoperative course beyond the first week after symptoms [62]. Further studies are needed to prove the clinical value of coagulation parameters for early prediction of complications or prognosis, with the added advantage that routine assessment is already possible.

Procalcitonin

An extensive number of reports confirm that procalcitonin (PCT) is the first biochemical variable that closely correlates with the presence of bacterial or fungal infections and sepsis [63]. In a cohort study comprising 50 patients with acute pancreatitis, our group first described a significant correlation of elevated PCT concentrations and the subsequent development of infected necrosis [56]. This observation was confirmed by a number of subsequent studies, although some authors reported different results, causing considerable controversy about the usefulness of this parameter [64]. Results from two large Finish studies showed that PCT could predict organ failure at a cutoff level greater than 0.4 ng/mL, with a sensitivity of 94% and a specificity of 73% (PPV, 58%; NPV, 97%) 24 hours after hospital admission [65]. Even with a semiquantitative PCT strip test, in a series of 162 acute attacks all patients who developed subsequent organ failure were correctly identified within 24 hours of hospital admission [66]. The first international multicenter trial on PCT showed, in 104 patients with severe acute pancreatitis, that PCT is able to predict severe complications such as pancreatic infection or death with a sensitivity of 79% and a specificity of 93% (PPV, 65%; NPV 97%) at a cutoff level greater than 3.8 ng/mL within 48 to 96 hours after onset of symptoms [67••]. This trial also confirmed that this parameter is of little value for simple stratification of patients as "mild" or "severe" according to the Atlanta classification [68]. PCT determination is available as a fully automated assay for routine use, and a semiquantitative strip test is an alternative for fast and easy quantification.

On the basis of the data available at present, PCT is one of the most promising parameters for early stratification of patients at risk to develop the most serious complications of acute pancreatitis and for monitoring the disease course. In terms of the assay technique, PCT meets all demands for clinical routine and emergency conditions.

Conclusions

A variety of clinical, radiologic, and laboratory approaches are currently available for reliable and accurate assessment of severity and prognosis in acute pancreatitis, and these approaches continue to evolve. The Atlanta system was a major step forward by providing definitions that allow comparison of patients and evaluation of new approaches with respect to diagnosis and therapy. However, the limitations of the system are becoming increasingly evident, as the complications of severe disease do not necessarily affect outcome in terms of nonsurvival. Clinical assessment has proved unreliable, and even independent risk factors, such as obesity, are not accurate predictors of severity and prognosis on their own. The presence and dynamics of organ failure in terms of onset and persistence within the early course of the disease have been shown to be the most reliable and important factors determining the course and outcome of acute pancreatitis, and they outperform morphologic complications in terms of presence, extent, and even infection of necrosis. Organ failure–related multiparameter scoring systems, such as Marshall and SOFA, allow better definition of organ failure and are at least as accurate but more practical than the widely used APACHE II system to quantify severity and estimate prognosis. CE-CT, MRI, and guided FNA are indispensable tools for reliable assessment of local severity but are still costly and carry the risk of complications. In keeping with the importance of the systemic aspects of acute pancreatitis during the early course, radiologic imaging and FNA to assess severity should be restricted to patients with early severe or persistent organ failure beyond the first week after symptom onset. Assays for a variety of biochemical markers have been developed and are an attractive alternative to cost-intensive imaging.

CRP is still the parameter of choice for fast and cost-effective assessment of severe attacks, although neither very early (<48 hours) nor prognostic assessment is possible. PCT is one of the most promising single parameters for reliable assessment of major complications and prognosis throughout the course of acute pancreatitis.

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Papers of particular interest, published recently, have been highlighted as:

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