**Prognosis in Acute Pancreatitis**

The degree of severity should be determined promptly upon diagnosis of acute pancreatitis. Under the 1992 Atlanta Classification, mild acute pancreatitis consists of patients with interstitial pancreatitis who have minimal to no extrapancreatic organ dysfunction, and is associated with low morbidity and mortality. Severe pancreatitis manifests as organ failure and/or local complications that include fluid collections and necrosis, with high morbidity and differing mortality rates amongst these components. Early severity stratification can result in aggressive treatment and prevent the development of persistent organ damage and multiple organ dysfunction, which are the two primary causes of mortality in patients with acute pancreatitis. Due to the limited accuracy of early clinical severity assessment on admission, there has been a rise in the development of biochemical markers and early prognostic systems composed of imaging, laboratory and clinical criteria. Among the biochemical markers proposed thus far, C-reactive protein remains the parameter of choice, although other markers such as interleukins-6 and 8, trypsinogen-2 and procalcitonin allow for earlier severity assessment. In this review, we will discuss in detail the various severity scoring systems and individual prognostic markers currently in existence and assess their utility in patients with acute pancreatitis.

**INTRODUCTION**

Overall hospitalization for acute pancreatitis (AP) has increased 100% during the past two decades in USA.1 Although the clinical course of AP is generally mild and often resolves without sequelae, a severe AP attack may be seen in approximately 20% of patients. Significant morbidity and mortality due to numerous local and systemic complications, an intense inflammatory response that may progress to multiorgan failure and/or pancreatic necrosis, can result from a severe episode of AP.2, 3 In the first 24-48 hours (hrs) of symptom onset aggressive treatment may alter the course of severe acute pancreatitis; a > 24 hour (hr) delay in transferring a patient to the intensive care unit is associated with a four-fold increase in mortality.4 Unfortunately, the initial 24 hrs is when mild and severe acute pancreatitis (MAP and SAP) are the most difficult to distinguish. Accordingly, identifying patients with MAP and SAP early on in the course of the disease is very important and can guide patient management.

The most widely used criteria in literature for defining
AP severity is the 1992 Atlanta Classification, which is based on a combination of clinical manifestations, Ranson and APACHE II scores, as well as the presence/absence of organ failure and intrapancreatic pathology. Recently, the Acute Pancreatitis Classification Working Group has proposed several revisions to the Atlanta Classification aimed at improving its current drawbacks and incorporating new medical knowledge (see Table 1). The new Working Group Classification takes into account the two phases of SAP progression. Phase one generally occurs within the first week of symptom onset and is characterized by the presence of diffuse interstitial pancreatic inflammation and severe inflammatory response syndrome (SIRS), which in turn, may lead to multiple organ dysfunction syndrome (see Figure 1). If successful intervention is not timely performed, the second phase usually ensues by week 2 at which point morphologic changes, such as infected or extending necrosis, can be seen and acute peripancreatic or postnecrotic pancreatic fluid collections may form and become infected.

Although the Atlanta Classification and Working Group revision defined AP severity by the development of organ failure and/or anatomic complications, neither was intended to be used for prognosis. Given the importance of early severity stratification, several tools, mainly biochemical markers and complex scoring systems, have been developed to help the physician assess severity with great emphasis placed on early recognition of pancreatic necrosis and persistent organ failure. A number of established general severity systems have been proven useful in determining severity, there are also numerous other scores created specifically for acute pancreatitis (see Table 2). While multi-factorial scoring systems such as the Ranson and modified Glasgow scores are accurate when all laboratory parameters are available, they can only be used 48 hrs after admission. By contrast, the APACHE II score is evaluable on admission, but its cumbersome calculation limits clinical use. For these reasons, significant interest has developed in studying biochemical markers that can be routinely used for

### Table 1: Assessment of Severity in Acute Pancreatitis

<table>
<thead>
<tr>
<th><strong>Atlanta Classification (1992)</strong>&lt;sup&gt;5&lt;/sup&gt;</th>
<th><strong>Working Group (2007)</strong>&lt;sup&gt;6-8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mild (minimal organ dysfunction, uneven recovery)</td>
<td>(a) Non-severe (no organ failure or organ failure ≤ 48 hours in duration)</td>
</tr>
<tr>
<td>(b) Severe (organ failure and/or local complications)</td>
<td>(b) Severe (organ failure &gt; 48 hours in duration)</td>
</tr>
<tr>
<td>(c) Assessment of Severity</td>
<td>(c) Assessment of Severity</td>
</tr>
<tr>
<td>° Organ Failure and Systemic Complications</td>
<td>° phase #1: early (within the 1st week of AP onset) = based on clinical parameters</td>
</tr>
<tr>
<td>° Prognostic signs</td>
<td>° phase #2: late (after the first week of AP onset) = based on morphologic parameters</td>
</tr>
<tr>
<td>• Ranson’s score</td>
<td></td>
</tr>
<tr>
<td>• APACHE II points</td>
<td></td>
</tr>
<tr>
<td>• serum levels of C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>• morphologic imaging based studies</td>
<td></td>
</tr>
<tr>
<td>° Presence of local complications</td>
<td></td>
</tr>
<tr>
<td>• Acute fluid collection</td>
<td></td>
</tr>
<tr>
<td>• Necrosis</td>
<td></td>
</tr>
<tr>
<td>• Abscess</td>
<td></td>
</tr>
<tr>
<td>• Pseudocyst</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Systemic Inflammatory Response Syndrome (SIRS) Criteria

A. GENERAL SEVERITY SCORES

1. Acute Physiology and Chronic Health Evaluation Scores: APACHE II, III and O

Since its development in 1985, Acute Physiology and Chronic Health Evaluation Score (APACHE) II has become the most commonly used prognostic score for grading AP severity and other critical medical conditions. It is made up of 12 parameters and a score of 8 is considered the threshold for identification of SAP. One major advantage of APACHE II is that it can be used on admission without potential delay in life-saving treatment. In addition, the clinician can use this scoring system to reassess severity and disease progression at variable intervals throughout the disease course. At 24 hrs, sensitivity, specificity, positive and negative predictive values (PPV, NPV) of APACHE II range between 65-70.3%, 71.9-81%, 20-67% and 80-93%, respectively. Sensitivity and specificity values increase above 80% on days two and three of admission, confirming the score’s ability to track disease course. Consequently, the system is best at predicting mild disease. There are, however, several disadvantages inherent in the APACHE II score, most importantly its complexity, low sensitivity on admission and performance that fares no better than other available scoring systems at 48 hrs.

In addition to the components that make up the APACHE II score, five new variables were introduced in 1991 as part of the APACHE III prognostic system, namely serum albumin, urea nitrogen, bilirubin, glucose, and urine output, while potassium and bicarbonate were removed from consideration. Accordingly, APACHE III consists of 16 physiologic variables and a composite numerical score ranging from 0-299. A head to head comparison of APACHE II versus APACHE III for AP severity assessment in the first 24 hrs of admission showed their respective areas under the receiver operating characteristics curve (AUC) to be 0.618 and 0.676. With similar results, and a greater number of parameters that make up the APACHE III scoring system, it offers little, if any, advantage over APACHE-II and is not routinely used in clinical practice.

By adding obesity as a factor for consideration, APACHE O was another variation on the APACHE II
score aimed at attaining greater accuracy in light of new evidence suggesting that obesity increases inflammatory response and AP severity (see Part II, Section G below for a detailed discussion). At a cutoff score of 8, APACHE O proved to be a good predictor of severity during the first 24 hrs of hospital admission with an 82% sensitivity, specificity of 86%, PPV equal to 74%, and NPV of 91%. Papachristou et al., published a prospective study assessing the predictive value of APACHE O for SAP in patients with a body mass index (BMI) > 30, which showed similar results between APACHE O and APACHE II (AUC 0.895 and 0.893, respectively). With such close results, APACHE II remains the most commonly used prognostic system in the APACHE family.

2. Organ Failure Based Scoring Systems

The sequential Organ Failure Assessment (SOFA), Logistic Organ Dysfunction (LOD) and Multiple Organ Dysfunction (MODS) scores were created to objectively and quantitatively describe organ dysfunction and to evaluate patient mortality. All three scores take into account the number of systems involved and the degree of severity within each. They differ in terms of the parameters graded, the organs involved and the scoring scale used.

SOFA is composed of six defining parameters that can be measured daily and includes the following organ systems: pulmonary (PaO2/FIO2), hematologic (platelet count), gastrointestinal (serum bilirubin level), cardiovascular (hypotension), neurologic (Glasgow coma scale), and renal (creatinine or urine output). Each organ is graded from 0 (normal) to 4 (most abnormal) based on arbitrary values, resulting in a possible daily score of 0-24 points. LOD also involves 6 organs, namely neurologic, cardiovascular, renal, pulmonary, hematologic, and hepatic, with a maximum score of 22. By contrast, there are five parameters that make up MODS: respiratory (PO2/FIO2 ratio), renal (serum creatinine), hepatic (serum bilirubin), hematologic (platelet count), and neurologic (Glasgow coma scale). Respiratory dysfunction is commonly the initial sign of multiorgan failure, followed by renal impairment, hepatic dysfunction, cardiovascular dysfunction and hematologic derangements.

Mortality generally depends on the severity and duration of the disease, as well as the number, type and combination of organs involved. Within the first 72 hrs of hospital admission sensitivity and specificity values of MODS for predicting mortality in patients with SAP were comparable to APACHE II. The AUC values for predicting mortality among patients with SAP were found to be similar amongst SOFA, MODS and LOD scores on days one (0.750, 0.775, 0.776) and three (0.738, 0.726, 0.736) of ICU stay. Moreover, at 24 hrs of admission Mason et al., found that MODS (AUC 0.80) performed similarly to SOFA (AUC 0.80), APACHE II (AUC 0.82), and LOD (AUC 0.82) in severity assessment. However, unlike both MODS and LOD, SOFA includes parameters in which the use of vasopressors and mechanical ventilation is acceptable, creating for a setting limited to those patients who are admitted to the ICU. While MODS was originally developed in the ICU setting, unlike SOFA, its parameters are more applicable to the general hospital population and the same holds true for LOD. With fewer parameters, organ system based scores are simpler models for predicting severity in comparison to the APACHE II.

B. PANCREATITIS SPECIFIC SCORES

1. Ranson Criteria

Ranson criteria was originally established in 1974 in an effort to identify, at an early stage, patients with AP who are at the highest risk for developing severe complications and death. The original Ranson criteria was validated for alcohol-related AP, but in 1979 it was revised and made applicable to patients with gallstone pancreatitis as well. However, the modified version of the Ranson criteria for biliary pancreatitis is less frequently used in clinical practice because the underlying cause of AP is often unknown at the time of admission. The Ranson score is composed of eleven factors, five of which are measured on admission and the remaining six taken after 48 hrs. On this scale, a 100% mortality rate was found at grade 6, with SAP defined by a score of ≥ 3. Ranson criteria has been shown to be a good predictor of severity in AP with sensitivity, specificity, PPV and NPV ranging from 67-84%, 76-90%, 49-70% and 89-95%, respectively. Although, the Ranson score is relatively accurate in determining AP prognosis, several concerns do exist. First of all, some laboratory data included in the Ranson score, such as lactate dehydrogenase, base excess, and fluid sequestration, may not be routinely gathered, thereby decreasing the overall validity of the scoring
system and the true mortality rate of individuals with AP. Secondly, assessment can only be done after 48 hrs, which poses a delay in administering potential therapy. The modified Glasgow score is a variation of the Ranson criteria consisting of only 8 variables and suffers from similar drawbacks.16

2. The Pancreatic Outcome Prediction Score

Another score recently examined in the ICU setting is the Pancreatic Outcome Prediction score (POP). This prognostic system was tested in 2007 by Harrison et al., in 2,462 ICU patients in the United Kingdom using arterial pH, age, serum urea nitrogen, mean arterial pressure, PaO2/FIO2 ratio, and total serum calcium (in order of decreasing impact) as the variables in the first 24 hrs of admission with a 0-40 POP score range.13 Results were favorable with an AUC of 0.853 for POP, compared with 0.804 for APACHE II.13 While this data suggests that POP may be a more accurate predictor of severity further studies, particularly in populations outside the United Kingdom, are necessary in order to validate these results.

3. Bedside Index for Severity in Acute Pancreatitis

The Bedside Index for Severity in Acute Pancreatitis (BISAP) utilizes five points to determine mortality: blood urea nitrogen > 25mg/dL, impaired mental status, presence of SIRS, age > 60 years, and pleural effusions.14 Each variable constitutes one point towards a 5-point maximum score.14 A cutoff value of ≥ 3 can predict the development of organ failure (odds ratio = 7.4), persistent organ failure (odds ratio = 12.7), and pancreatic necrosis (odds ratio = 3.8).15 In terms of its prognostic value, in the first 24 hrs of admission mortality prediction was similar between BISAP (AUC 0.82) and APACHE II (AUC 0.83).14 Moreover, when SAP was defined by persistent organ failure over 48 hrs, results of a retrospective cohort study showed AUC values for severity assessment of 0.81, 0.94, 0.78 and

Table 2: Prognostic Scoring Systems

<table>
<thead>
<tr>
<th>Prognostic Score</th>
<th>Timeframe (≥ 48 hours)*</th>
<th>Pancreas Specific</th>
<th>Severity (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranson</td>
<td>+</td>
<td>+</td>
<td>0.9410</td>
</tr>
<tr>
<td>CTSI</td>
<td>+</td>
<td>+</td>
<td>0.8410</td>
</tr>
<tr>
<td>APACHE II</td>
<td>–</td>
<td>–</td>
<td>0.618–0.90411-13</td>
</tr>
<tr>
<td>BISAP</td>
<td>–</td>
<td>+</td>
<td>0.8214</td>
</tr>
<tr>
<td>POP</td>
<td>–</td>
<td>+</td>
<td>0.85313</td>
</tr>
<tr>
<td>SOFA</td>
<td>–</td>
<td>–</td>
<td>0.8034</td>
</tr>
<tr>
<td>MODS</td>
<td>–</td>
<td>–</td>
<td>0.8034</td>
</tr>
<tr>
<td>LOD</td>
<td>–</td>
<td>–</td>
<td>0.8234</td>
</tr>
<tr>
<td>EPIC</td>
<td>–</td>
<td>+</td>
<td>0.9115</td>
</tr>
</tbody>
</table>

*At or over 48 hours of disease onset

Abbreviations: Ranson = Ranson criteria; CTSI = Computed tomography severity index; APACHE II = Acute physiology and chronic health evaluation score; BISAP = Bedside index for severity in acute pancreatitis; POP = Pancreatic outcome prediction score; SOFA = Sequential organ failure assessment score; MODS = Multiple organ dysfunction score; LOD = Logistic organ dysfunction score; EPIC = Extrapancreatic inflammation of CT score; AUC= area under the receiver operating characteristics curve.
0.84 using BISAP, Ranson, APACHE II and Computed Tomography Severity Index (CTSI), respectively.\textsuperscript{10} The simplicity of a scoring system is one of the most important factors when deciding what system to utilize in a clinical setting. A major advantage of the BISAP score is its availability on admission.

4. Harmless Acute Pancreatitis Score

Lankisch and colleagues are credited with developing the Harmless Acute Pancreatitis Score (HAPS) in their 2009 prospective study of 394 patients, which showed that normal hematocrit and serum creatinine levels, and a lack of rebound tenderness and/or guarding were the three parameters demonstrating the highest correlation with MAP.\textsuperscript{52} The authors found that HAPS identified patients with MAP on admission with a 98% accuracy (P < 0.0001).\textsuperscript{52} In a follow-up 2011 validation study by a different group, HAPS was applied to 353 AP patients, predicting a non-severe course with 96.3% specificity and a PPV of 98.7%.\textsuperscript{53} To date, there have been no prospective studies addressing the prognostic accuracy of HAPS compared to Ranson, APACHE II, or CTSI, however, HAPS appears to be a simple and relatively easy approach for triaging patients with AP. In comparison to the 11 parameters of APACHE II, HAPS allows for a quick evaluation with only 3 variables that do not require difficult to obtain tests (i.e. arterial blood gas) to prognosticate severity, thus, ensuring greater time for clinical assessment of the patient.

C. IMAGING SCORES

1. Computed Tomography Severity Index

Computed Tomography Severity Index has shown a strong positive correlation with the development of complications and mortality in patients with AP.\textsuperscript{54, 55} It was developed by Balthazar et al. to evaluate the degree of pancreatic edema, necrosis and the presence of peripancreatic fluid collections. CTSI is graded on a 10 point scale and is composed of 2 radiologic categories with pancreatic inflammation and the presence of fluid collections as the first, and the extent of pancreatic necrosis the second. Category number one carries a maximum of 4 points and is divided into five grades from A-E where each grade correlates with the degree of pancreatic and peripancreatic inflammation, as well as fluid accumulation. The remaining 6 points are derived from the CT necrosis score, which signifies the percentage of pancreatic necrosis.

In the CTSI pilot study, a score of 7-10 was able to predict a 92% morbidity and 17% mortality rate in patients with AP, compared to the low morbidity (2%) and mortality (0%) associated with a CTSI score of 0-1.\textsuperscript{56} One shortcoming of this study is the fact that it was performed 7 days after admission, at which time the necrosis had already fully developed, but these favorable results were later confirmed at 48\textsuperscript{56-58} and 72 hrs\textsuperscript{59-63} of admission as well. Conflicting evidence regarding the correlation between pancreatic necrosis and organ failure has undermined the validity of CTSI as a prognostic tool of severity; while two studies found no significant correlation,\textsuperscript{60, 61} a strong association was evident in the third.\textsuperscript{62} This is particularly important since it is ultimately organ failure that determines mortality in AP.\textsuperscript{66-70}

A modified CTSI score emerged in 2004 to simplify the scoring of pancreatic necrosis and inflammation in and around the pancreas, and to include considerations of extrapancreatic complications (pleural effusion, ascites, vascular, parenchymal, or gastrointestinal) into the original 10-point CTSI scale. When compared to classic CTSI in a study by Mortelé et al., the modified score showed a stronger association with length of hospital stay and better interobserver agreement.\textsuperscript{71} While the results of both scores were similar for the presence of infection, a significant correlation was found between the modified CTSI and organ dysfunction (\textit{p} = 0.0024), compared to only a trend for classic CTSI (\textit{p} = 0.0513).\textsuperscript{71} However, these results must be interpreted with caution since the study evaluated only those patients who had a CT scan performed one week of symptom onset without assessment at 48 or 72 hrs.

2. The Extrapancreatic Inflammation on Computed Tomography Score

The Extrapancreatic Inflammation on Computed Tomography Score (EPIC) is based exclusively on extrapancreatic radiologic manifestations of AP, which include pleural effusions, ascites, retroperitoneal inflammation, and mesenteric ischemia. The focus on extrapancreatic manifestations allows for the estimation of severity within the first 24 hrs of admission, at a time when pancreatic necrosis is very unlikely to be detected. EPIC fared well when measured against CTSI for prediction of mortality (AUC of 0.85 vs. 0.59) and severity (AUC of 0.91 vs. 0.71) at 24 hrs after admission, with 100% sensitivity and 70.8% specificity.

\textit{(continued on page 28)}
for severe disease at an EPIC score ≥ 4.15 Besides the scores’ ability for early severity stratification, another major benefit of EPIC is that it does not require the use of intravenous contrast, which may potentially lead to renal toxicity and further deterioration of AP.72-74

PART II: SINGLE MARKERS OF SEVERITY

A. HEMATOCRIT

Hemoconcentration reflects a decrease in plasma volume and is demonstrated by elevated hematocrit levels. Consensus holds that low hemoconcentration at the time of admission indicates a low risk of pancreatic necrosis, however, uncertainty exists as to the predictive value of elevated hematocrit. Although a 2001 trial found no correlation between hemoconcentration and organ failure at a hematocrit cut-off level of 43% for male and 39.6% for female patients,53 other studies suggest that hematocrit of at least 44% on admission and/or one that fails to decrease 24 hrs after rehydration is an important early predictor of pancreatic necrosis and, therefore, a marker of severe disease.76-78 At a hematocrit level greater than 44%, one study found sensitivity in detecting organ failure of 72% on admission and 94% after 24 hrs have elapsed.76 All in all, these studies suggest that hematocrit is important in patient management and should be noted on admission, used to monitor disease progression, and utilized as a tool to guide the rate of intravenous hydration.

B. BLOOD UREA NITROGEN

Like hematocrit, blood urea nitrogen (BUN) is a laboratory test that may be used to monitor changes in intravascular volume status and fluid resuscitation response. Multiple studies have found that the accuracy of serial BUN measurements for evaluating mortality risk is comparable to the APACHE II score in the same population.79, 80 In two large cohort studies, Wu and colleagues found that the adjusted odds ratio grew by 2.2 for every 5 mg/dL BUN increase within the first 24 hrs of admission80 and any rise in BUN beyond the 24 hr period was associated with an increased risk of death; risk of death was also higher when BUN was ≥ 20 mg/dL at admission.80 In both studies, superior predictive values and accuracy of BUN led to the conclusion that BUN measurements were one of most reliable routine laboratory practices for predicting mortality in AP, a conclusion which is supported by the incorporation of BUN for the prediction of mortality in several prognostic scoring systems, including the Ranson criteria and BISAP. Accordingly, BUN is a useful routine laboratory test for predicting survival and duration of ICU stay81 that is cheap, easy to perform, and can be used to target fluid resuscitation. In light of the fact that the highest accuracy of BUN was at 24 and 48 hrs, BUN measurements should be trended and closely monitored.79, 80

C. SERUM CREATININE

Although recently brought into question, evidence suggests that increased serum creatinine (Cr) within the first 48 hrs of admission is strongly associated with the development of pancreatic necrosis.78, 82 In a cohort study, a peak Cr of > 1.8 mg/dL during the first 48 hrs of admission predicted pancreatic necrosis with high PPV (93.3%), specificity of 98.9%, 41.2% sensitivity, and NPV of 82.5%, with pancreatic necrosis evident in 14 out of 15 patients.78 However, Lankisch and colleagues did not find this association in their follow-up study aimed at testing Cr as a marker of severity; while the specificity (95%) and NPV (87-89%) was still high, sensitivity and PPV showed a significant decrease to 14-23% and 41-50%, respectively.82 Although this study did cast some doubt on the predictive value of Cr, the lower prevalence of pancreatic necrosis may explain the lower positive predictive value.83

D. MARKERS OF PANCREATIC INJURY

The inflammatory process in AP leads to the release of proenzymes, activation peptides and pancreatic enzymes into circulation, each of which can be measured to evaluate disease severity. Trypsinogen activation peptide (TAP) is the amino-terminal peptide that is produced during the cleavage of trypsinogen to trypsin by the enzyme enterokinase due to premature intrapancreatic activation in AP. Trypsin, in turn, activates the conversion of proenzymes, such as trypsinogen, phospholipase A2, carboxypeptidase and precursors of elastase, to active enzymes, which then leads to pancreatic autodigestion.84 Because the degree of pancreatic necrosis and systemic inflammatory response is directly related to the pancreatic inflammation cascade, a number of markers that are involved in this process have been investigated.17, 18, 85-90 Results indicate that TAP, carboxypeptidase B activation peptide (CAPAP), and trypsinogen-2 (TRY-2) have proved to be the most promising.
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1. Trypsinogen Activation Peptide
A correlation has been shown between elevated urinary TAP (≥ 10 ng/mL, > 30 nmol/L) at admission and disease severity, with sensitivity and specificity values initially reported to be as high as 100% and 85%, respectively. While this has been reaffirmed in some subsequent trials, others have shown less favorable results with significantly lower statistical markers at 24 hrs from symptom onset (sensitivity = 52-63%, specificity = 73-92%) with a slight improvement after 48 hrs (sensitivity = 83%, specificity = 72%, PPV = 44% and NPV = 94%). Despite lower sensitivity, TAP was found to be as good as APACHE II at 24 hrs after admission and even more effective after 48 hrs in predicting severity. However, TAP should not be used to monitor disease progression because early secretion of TAP decline rapidly making it impossible to distinguish AP severity. In addition, the current enzyme-linked immunosorbent assay (ELISA) technique restricts the practical use of this test.

2. Carboxypeptidase B activation peptide
Carboxypeptidase B activation peptide is composed of an 81-amino acid polypeptide, thus, making it more stable than TAP and easier to measure with high affinity antibodies. It appears to be specific to the pancreas and can be used both for diagnosis and assessment of disease severity on admission. CAPAP is renally excreted and does not bind to other substances in the blood. Both urine and plasma levels of CAPAP can discriminate between mild and severe cases of AP. However, urinary levels have proven to be more accurate and up to 10 times higher in concentration than plasma.

Severity assessment with urinary CAPAP on admission was shown to be as good as with APACHE II at 48 hrs. Twenty four hours after symptom onset, results of urinary CAPAP revealed PPV and NPV of 72.7% and 92.9%, respectively with a sensitivity of 88.9% and specificity equal to 81.3%, but these measurements decreased significantly by 72 hrs. Like TAP, an early rise in CAPAP levels follows a rapid decline, thus preventing the test from being useful in monitoring disease progression. Because CAPAP is currently tested by a radioimmunoassay technique, it is not utilized on a routine bases.

3. Trypsinogen-2
Trypsinogen has two major isoenzymes, trypsinogen-1 (cationic) and trypsinogen-2 (anionic), both of which are secreted by acinar cells and excreted in the urine. While a rapid dipstick test can be used to detect TRY-2 in the urine and it has proven to be a very sensitive and specific marker for diagnosis and severity assessment of AP. Earlier studies using quantitative immunofluorometric assay to measure urinary trypsinogen proved that trypsinogen was at least as good as urinary TAP in predicting SAP on admission. A recent study confirmed these findings at 24 hrs after symptom onset using a rapid urinary TRY-2 test strip with the following sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios, respectively: 65.7%, 66.4%, 33.3%, 88.4%, 1.9, and 0.51 for urinary TRY-2, compared to 63.2%, 65.8%, 32.0%, 87.5%, 1.9, and 0.58 for TAP > 35 nmol/L. In addition, cost has been shown to be significantly lower when using trypsinogen-2 instead of TAP. Favorable results in predicting severity, combined with its low cost and ease of use makes the TRY-2 rapid dipstick test a promising technique that can be utilized in routine clinical practice.

E: MARKERS OF INFLAMMATION
1. Acute Phase Proteins: C-Reactive Protein and Serum Amyloid A Protein
Activation of acute phase proteins by cytokines plays an essential role in the inflammatory mechanism governing AP and has been show to reflect severity. All acute phase proteins are general markers of inflammation that are not specific to the pancreas. C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to interleukin-1, interleukin-6 and tumor necrosis factor-α and it is the most widely available, low cost and well studied marker of severity in AP. A cutoff level of 150 mg/L within the first 48 hrs of symptom onset has a sensitivity and specificity of 80-86% and 61-84%, respectively for SAP and accuracy > 80% for necrotizing pancreatitis. Because CRP reaches its peak level 48-72 hrs after symptoms begin, it is of little use in assessing severity during the initial phase of AP. However, a 2010 trial has shown that CRP levels > 170mg/L in the first 24 hrs correlate with a sevenfold increase in hospital mortality in AP patients, although albumin < 30 g/L was found to be a slightly stronger predictor.

Serum amyloid A (SAA), part of a family of...
apolipoproteins, is another acute phase reactant used for severity stratification of AP. Although SAA has a wider dynamic range than CRP, its ability to predict SAP has yielded conflicting results. Studies reveal a range of 58-96% specificity and 37.9-62% sensitivity for SAA, with low PPV and high NPV values that vary depending on the cutoff value and time drawn. Using the ELISA method to measure plasma SAA levels in patients with severe and mild AP, an adequately powered prospective multicenter trial found that SAA levels were considerably higher in patients with SAP on admission and ≥ 24 hrs of symptom onset, whereas CRP did not prove to be significant until 30-36 hrs after symptom onset, suggesting that SAA can be used earlier in the disease course to predict severity. However, a trial employing an automated immunoassay technique to compare SAA and CRP found SAA to be inferior in predicting the development of necrosis, infected necrosis, multiple organ dysfunction and death. Taking it a step further, findings of a more recent study indicate that the difference in SAA levels by automated immunoassay between SAP and MAP are not statistically significant at all. With the conflicting evidence available today there is not enough justification to use SAA over the readily available and cheap CRP.

2. Interleukins
Activated leukocytes release proinflammatory cytokines that stimulate the liver to produce acute phase proteins. Since the concentration of cytokines increases before acute phase proteins, numerous clinical studies have been done to assess the usefulness of cytokines, such as interleukin (IL)-1, IL-6, IL-8, IL-10 and IL-18, in predicting severity early in the course of AP. Most trials have focused on the proinflammatory cytokines of IL-6 and IL-8. Both are significantly elevated in SAP on the day of admission and tend to peak at 72 hrs after the clinical onset of disease, which makes IL-6 and IL-8 excellent markers of early severity stratification. In addition, AUC, sensitivity, and specificity for predicting AP severity is similarly high in these two cytokines; a 2009 meta-analysis, defining severity by the Atlanta Classification, revealed that the sensitivity and specificity range for IL-6 in the first three days of admission was 81-83.6% and 75.6-85.3%, respectively (compared to 65.8-70.9% sensitivity and 66.5-91.3% specificity for IL-8), with an IL-6 AUC of 0.75 on day one and 0.88 on the second day of admission (compared to IL-8 AUCs of 0.73 and 0.91 on the same days). IL-6 and IL-8 can also be used as early surrogate markers for organ failure in AP, and when measured daily in patients with necrotizing pancreatitis, they have proved to be excellent markers for detecting AP progression to infected pancreatic necrosis. Despite the favorable results and availability of a fully automated assay for both IL-6 and IL-8, relatively high costs limit their routine use in clinical practice.

3. Procalcitonin
Procalcitonin (PCT) is a propeptide of the hormone calcitonin, which is released by hepatocytes, peripheral monocytes and G-cells of the thyroid gland. PCT level can be measured by a semiquantitative strip test for fast results or by a fully automated assay to obtain a more accurate measurement. An increased PCT level has been found to be an early predictor of severity, and organ failure. A recent meta-analysis a subgroup of 8 studies using PCT cutoff values of 0.5 ng/mL as a discriminator, found that the sensitivity and specificity of PCT for development of SAP was 73% and 87%, respectively with an overall AUC of 0.88. The accuracy of PCT as a predictor of organ failure and complications has also been reported to be high; at a cutoff value > 0.4 ng/mL 24 hrs after admission, sensitivity and specificity values for predicting organ failure were 94% and 73%, respectively (PPV = 58 %, NPV = 97%) and PCT predicted the occurrence of pancreatic infections and other severe complications of AP with a sensitivity of 79% and a specificity of 93% (PPV = 65%, NPV = 97%) at a cutoff > 3.8 ng/mL within 48-96 hrs of symptom onset. Although it is important to keep in mind that PCT is a nonspecific marker of infection, evidence from an international multicenter trial, revealed that abdominal infections caused the largest PCT increase in comparison to the chest and urinary tract. Since infected pancreatic necrosis is often diagnosed by fine needle aspiration of pancreatic tissue that may require an additional 48 hr period of incubation to yield an accurate diagnosis, a reliable prognostic marker of infected pancreatic necrosis is particularly important when deciding on the use of prophylactic antibiotics. At the present time, PCT is one of the most promising parameters because it can be employed both in emergency and routine clinical use, not only to guide early stratification, but also to monitor disease progression.
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### 4. Polymorphonuclear Leukocyte Elastase

Polymorphonuclear (PMN) elastase is one of the potent hydrolytic enzymes released by activated polymorphonuclear granulocytes, which has been shown to be a valuable marker of AP severity and organ failure. A 2006 large multicenter trial confirmed earlier findings by the same group that enhanced systemic release of PMN-elastase is an early feature of severe attacks, as defined by the Atlanta Classification, revealing a sensitivity of 92%, a 91% specificity, with PPV and NPV values of 78% and 96%, respectively for the prognostic evaluation of severe AP at a plasma concentration > 110 μg/L within 24-72 hrs of symptom onset. Compared to the more common parameters of severity, such as CRP, peak values of PMN-elastase were the first to be observed. The test utilized for polymorphonuclear quantification in this study was based on latex immunoagglutination, a turbidimetric method that is more easily automated than previous assays and applicable to urgent situations. Despite the favorable results of PMN-elastase, this test is not available in most hospitals today.

### F: COAGULATION PARAMETERS

Coagulation disorders are a common feature of SAP and play an important role in its pathophysiology. Proteases have the enzymatic capacity to activate both inflammation and coagulation. Coagulation factors such as thrombin and tissue factor, in turn, can bind to protease activated receptors on various cells and elicit intracellular signaling, resulting in modulation of inflammatory response. Initial expression of tissue factor activates the extrinsic pathway of coagulation, which may lead to a hypercoagulative state and impaired fibrinolysis. Overwhelming activation of this cascade often results in microthrombus formation that can cause microvessel obstruction, bleeding, and ischemia of pancreatic tissue.

#### 1. Disseminated Intravascular Coagulation

A study evaluating 139 patients with AP based on the Japanese Staging System revealed a strong correlation between disseminated intravascular coagulation (DIC) parameters on admission and disease severity. Amongst the six different parameters tested, antithrombin III level < 69% was the most accurate in predicting poor outcome (sensitivity, 81%; specificity, 86%). Other useful markers included fibrin/fibrinogen degradation product-E, platelet count, D-dimer, and thrombin-antithrombin-III complex. Compared with C-reactive protein, these DIC parameters showed better area under the receiver operating characteristics curve values, which is expected since CRP peaks at 48 hrs. Because elapsed time between symptom onset and admission was not accounted for in the above-mentioned study, the clinical value of coagulation parameters for early assessment of severity and prognosis remains to be determined. The advantage of the DIC panel is its convenience, as it can be obtained quickly and easily at a relatively low cost.

#### 2. Tissue Factor

Tissue factor is a relatively new marker of AP severity. A single center study found that a cut-off value for tissue factor of 40 pg/ml has a sensitivity of 71% and specificity of 67% for prediction of SAP. At 12 hours, tissue factor proved to be a slightly better predictor of SAP in comparison to CRP, but it was inferior to IL-6 at all times. No difference in tissue factor level was observed between patients with SAP and MAP on day 1 and 3, indicating that it is a poor test to monitor disease progression. Given the availability of better parameters, we cannot recommend the use of this test at the present time.

#### 3. D-Dimer

Multiple studies have evaluated the relationship between AP severity and d-dimer, a marker of fibrinolytic activation that reflects plasmin generation. Results indicate that d-dimer is a good initial marker of severity with peak levels seen by day four. A major benefit of d-dimer is its high sensitivity, specificity, PPV and NPV for predicting the development of organ failure (90%, 89%, 75% and 96%, respectively) at a d-dimer value of 414.00 microg/L on admission.

#### 4. Protein C

Protein C is currently the only parameter of hemostasis that has been proven to act simultaneous as an anti-inflammatory, anticoagulant, and profibrinolytic factor. A low level of protein C at a cut-off value of 87% is associated with the development of multorgan failure in patients with SAP. Evidence suggests that application of recombinant activated protein C may improve outcome in these patients. Such findings demonstrate the importance of early recognition of
hemostatic disorders in the prediction of AP severity and will likely lead to further investigations in the use of therapy with recombinant forms of hemostatic factors. 

**G: OBESITY**

AP incidence and obesity have increased markedly over the past two decades. Obesity may lead to fatty infiltration in the heart, kidney, liver, and pancreas. Severity, mortality, local and systemic complications in AP are directly associated with obesity. Combining the results of seven past studies, a recent meta-analysis by Hong and colleagues showed a summary relative risk of 2.16, 2.21, 2.57, and 1.82 for SAP development, mortality, local and systemic complications, respectively at a BMI > 30 kg/m². Obesity is particularly important in AP since it creates a chronic low-grade inflammatory state characterized by high circulating levels of proinflammatory cytokines and because adipose tissue has been implicated in the pathophysiology of diseases with increased immune response, such as inflammatory bowel disease. Moreover, the risk of tissue ischemia due to changes in microcirculation is higher when there is increased volume of peripancreatic fat.

**Table 3: Markers of AP Severity**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Time* (hours)</th>
<th>Cut-off Value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
<th>AUC</th>
<th>Current Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>48</td>
<td>150 mg/L</td>
<td>80.0–86.0</td>
<td>61.0–84.0</td>
<td>37.0–71.0</td>
<td>90.0–94.0</td>
<td>0.75–0.84</td>
<td>Automated immunoassay</td>
</tr>
<tr>
<td>IL-6</td>
<td>0–24</td>
<td>31.7–118 pg/ml</td>
<td>68.7–80.0</td>
<td>67.0–69.9</td>
<td>44.0–50.0</td>
<td>83.6–91.0</td>
<td>0.84</td>
<td>Automated immunoassay</td>
</tr>
<tr>
<td>SAA</td>
<td>12–24</td>
<td>31.4–360 mg/L</td>
<td>58.0–81.8</td>
<td>37.9–62.0</td>
<td>30.0–38.4</td>
<td>83.0–98.0</td>
<td>0.65–0.75</td>
<td>Automated immunoassay</td>
</tr>
<tr>
<td>PMN</td>
<td>24</td>
<td>110 μg/L</td>
<td>92.0</td>
<td>91.0</td>
<td>78.0</td>
<td>96.0</td>
<td>0.956</td>
<td>Automated immunoassay</td>
</tr>
<tr>
<td>PCT</td>
<td>24</td>
<td>0.5 ng/ml</td>
<td>36.0–92.0</td>
<td>68.0–93.1</td>
<td>29.0–60.0</td>
<td>79.4–97.0</td>
<td>0.71</td>
<td>Automated immunoassay-Urine dipstick</td>
</tr>
<tr>
<td>TAP</td>
<td>24</td>
<td>35 nmol/L</td>
<td>52.0–64.0</td>
<td>73.0–92.0</td>
<td>39.0–68.0</td>
<td>86.0–88.0</td>
<td>0.69–0.83</td>
<td>-Urine Spot Measurement -ELISA</td>
</tr>
<tr>
<td>CAPAP</td>
<td>0–72</td>
<td>2.32–100 nmol/L</td>
<td>66.7–100.0</td>
<td>95.5–95.6</td>
<td>96.6–96.9</td>
<td>56.7–100.0</td>
<td>0.942</td>
<td>Radio immunoassay</td>
</tr>
<tr>
<td>TRY-2</td>
<td>24</td>
<td>3000 μg/L</td>
<td>72.0–82.0</td>
<td>78.0–81.0</td>
<td>55.0</td>
<td>90.0–93.0</td>
<td>0.83–0.90</td>
<td>Urine dipstick</td>
</tr>
</tbody>
</table>

* Time represents the timeframe from disease onset to test use

Abbreviations: CRP = C-reactive protein; IL = Interleukin; SAA= Serum amyloid A; PMN = Polymorphonuclear elastase; PCT = Procalcitonin; TAP = Trypsinogen Activation Peptide; CAPAP = Carboxypeptidase B activation peptide; TRY-2 = Trypsinogen-2; ELISA= enzyme-linked immunosorbent assay; AUC= area under the receiver operating characteristics curve.

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Improving the outcome of AP through prognostic markers continues to be an expanding area of research. The growing list of early inflammatory markers used to predict SAP now includes macrophage migration inhibitory factor and monocyte chemotactic protein. As the pathogenesis of AP is better understood, more of its steps can be targeted for prognosis. Nitric oxide and other free radicals that take part in the oxidative stress and injury have been shown to have a positive correlation with APACHE II. Furthermore, severity markers have been combined to yield better accuracy; for example, conjunctive use of base excess and creatinine in patients with SAP was found to be superior to APACHE II and Ranson criteria for prediction of death in the first 10 days of disease onset. The activated protein C-protein C inhibitor complex in plasma, which is useful in detecting the hypercoagulative condition in SAP, has also shown some promise in differentiating severity. Additionally, in a small trial E-Cadherin, a transmembrane glycoprotein involved in calcium dependent adhesion of epithelial cells, was significantly higher in SAP than MAP within 12 hrs of symptom onset. Although promising, lack of availability, as well as difficulty in use and standardization of these markers makes it unlikely that they will be employed routinely in the near future.

**FUTURE PROSPECTS**

Since the Atlanta Classification identified the importance of organ failure in defining AP severity but did not quantify it or differentiate the time course involved, much attention has been directed towards investigating these aspects and a great deal of progress in the natural history of AP has been made. The association between mortality (34-55%) and multi-organ failure or persistent organ failure for a period longer than 48 hrs has been well demonstrated and the converse has also been shown to hold true with a low mortality of 0-3% in the absence of organ failure or resolution thereof within 48 hrs. Evidence of negligible mortality when there is no evidence of persistent or multiorgan failure suggests that organ failure is the main cause of death even in patients with necrotizing pancreatitis.

As defined by the Atlanta Classification, SAP is composed of a heterogeneous group of patients with low mortality and high morbidity, as well as those with high morbidity and mortality rates. A severity classification system stratifying patients into the following 3 groups has been proposed by various authors: (i) MAP without morbidity and mortality, (ii) moderately severe AP with high morbidity and low mortality and (iii) SAP with high morbidity and mortality. We are in full agreement that there is a need for a moderate category of SAP whose hallmarks should be threefold – the absence of persistent or multiorgan failure, coupled with the presence of local complications, such as acute fluid collections, necrosis, and a corresponding high morbidity and low mortality. Currently, the lack of uniform use of criteria for defining SAP in literature makes it difficult to assess the full potential of a severity marker. Although most studies use the Atlanta Classification to defined SAP, others have based their assessment on different definitions, such as multiple or single organ failure, Japanese criteria of severity, presence of sterile or infected necrosis, the need for intervention, development of local or systemic complications and length of hospitalization. Perhaps the Working Group’s recent revision of the current Atlanta Classification will allow for greater uniformity.

**Key Points**

1. The cornerstone in the diagnosis of acute pancreatitis is elevation in amylase and lipase, but these enzymes are not useful in assessing disease severity.

2. At 24 hours of admission organ failure scores, such as MODS, SOFA and LOD, have proven to be just as accurate as APACHE II and less cumbersome.

3. While imaging scores based on pancreatic morphology are not useful prior to 48 hrs of symptom onset, new criteria based exclusively on extrapancreatic radiologic manifestations of AP can predict severity in the first 24 hrs of disease onset.

4. Several simple and easy to obtain risk factors, including BMI, age, hematocrit, BUN, and presence of pleural effusions on a chest x-ray, should be documented to assist in severity assessment.

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5. Hemoconcentration has been shown to be an accurate predictor of necrosis and organ failure. Serial BUN measurements are a valuable routine laboratory marker for following disease progression.

6. C-reactive protein is the most heavily utilized, easy to employ, readily available, and inexpensive acute phase reactant, and it remains the gold standard for predicting severity of AP beyond 48 hrs of symptom onset.

7. Cytokines play a critical role in the pathogenesis of early inflammatory cascade in AP. Currently, cytokine IL-6 and the chemokine IL-8 can be measured by fully automated assays and are available for clinical use.

8. Increased serum levels of procalcitonin correlate closely with severity, organ failure and development of infected pancreatic necrosis.

9. Markers shown to be useful within 48 hrs of disease onset include TAP, CAPAP, PMN-elastase, IL-6, IL-8, PCT, SAA and a DIC panel.

10. The development of persistent or multiorgan failure during acute pancreatitis is associated with the highest risk of death.

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