



Prediction of severe acute pancreatitis: Current knowledge and novel insights

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Abstract

Acute pancreatitis (AP) is a common and potentially lethal acute inflammatory process with a highly variable clinical course. It is still unclear why some patients progress to organ failure and others do not. Ability to predict which patients will develop severe disease is limited. Routine clinical and laboratory data and multi-factorial clinical scores measured on admission and during the first 48 h of hospitalization are currently the standards of care used to estimate the magnitude of the inflammatory response to injury. Current literature highlights several common environmental, metabolic and genetic factors that increase the risk of AP development and subsequent adverse sequelae. Several cytokines have been found to play a critical role in the pathogenesis of AP by driving the subsequent inflammatory response, to include tumor necrosis factor- α (TNF- α), Interleukin-1 (IL-1), IL-6 and monocyte chemoattractant protein-1 (MCP-1). Large, prospective studies are still needed to address these questions by identifying AP risk factors and serum biomarkers of severe disease.

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INTRODUCTION

Acute pancreatitis (AP) is a common and potentially lethal acute inflammatory process with a highly variable clinical course. It accounts for greater than 300 000 emergency room visits annually in the US, which is steadily increasing, with a mean length of hospital stay of 7 d^[1].

Approximately 20% of affected individuals will develop a severe clinical course in association with the development of a systemic inflammatory response syndrome (SIRS), multiple organ failure (MOF), and on occasion death. Despite substantial animal model research^[2], it is still unclear as to why some patients progress to organ failure and others do not, or at what step in the inflammatory cascade will an intervention have an impact upon disease progression. Predictive disease severity scoring systems are widely used in clinical practice; but in reality they reflect the inflammatory response rather than the severity of the insult experienced by the pancreatic parenchyma.

Several clinical and molecular pre-AP susceptibility and severity factors have been identified which may modify an individual's predisposition to AP, and the associated risk of severity. Obesity is one such important factor. An elevated BMI (≥ 30 kg/m²) significantly increases the extent of AP severity (OR, 2.6; 95% CI, 1.5-4.6) and is implicated in both local and systemic complications^[3]. The severity risk increases at an OR of 1.2 per 5 units of BMI. Severe AP is associated with android fat distribution, increased waist-hip ratio (> 1.0) and appears to correlate with an "overactive" immune response.

Alcohol consumption is another risk factor associated with severe AP as it lowers the threshold for intrapancreatic trypsin activation and shifts pancreatic acinar cell death from apoptosis to necrosis as demonstrated in alcohol-fed animals^[4]. Our group reaffirmed this finding in human subjects consuming two or more alcoholic drinks per day^[5]. Furthermore, active tobacco smoking has been suggested as a susceptibility

factor for AP (RR, 2.14; 95% CI, 1.48-3.09)^[6].

In preliminary genetic susceptibility factor studies, the presence of a single nucleotide polymorphism in the gene of a potent chemokine, named monocyte chemoattractant protein-1 (MCP-1), at position -2518 A/G predicted that the inflammatory response to AP would be systemic and associated with death^[7]. The G allele was present in 86% of severe pancreatitis cases, 46% of mild pancreatitis cases and 43% of controls. The presence of the G allele increased the risk of developing severe AP seven fold (OR, 7.7; 95% CI, 1.6-100).

Routine clinical and laboratory data and multi-factorial clinical scores measured on admission and during the first 48 h of hospitalization are currently the standards of care used to estimate the magnitude of the inflammatory response to injury, and to predict whether or not intensive care support is needed to address inflammation-associated complications. Admission hematocrit, C-reactive protein (CRP) at 48 h, Ranson's criteria and the Acute Physiology and Chronic Health Evaluation (APACHE-II) scores are the most popular. In addition, a variety of cytokines, chemokines, and other markers of the inflammatory response have been evaluated as predictors of severe AP, as well as markers of development of specific organ-system failure.

Collectively, the literature highlights several common environmental, metabolic and genetic factors that are predisposing factors increasing the risk of AP development and subsequent adverse sequelae. The mechanisms by which such factors increase the risk of severe disease, and whether or not they directly interact with or potentiate one another remains speculative. Knowledge of the inflammatory cascade is important in recognizing when the peak response occurs for various cytokines and inflammatory mediators.

Several reports have evaluated patients with endoscopic retrograde cholangiopancreatography (ERCP) induced pancreatitis, and studied post-ERCP cytokine profiles. Cytokines play a critical role in the pathogenesis of AP by driving the subsequent inflammatory response. Patients with post-ERCP AP have an amylase and lipase increase within the first hour reaching a maximum value between 4 h and 12 h following ERCP^[8]. Interleukin-6 (IL-6) increases to a maximal concentration at 24-48 h, and the highest CRP concentrations are established 72 h following an ERCP. In another study, in patients who developed post-ERCP pancreatitis, the serum levels of these cytokines including tumor necrosis factor- α (TNF- α), IL-1, IL-6, IL-8, and IL-10 rose significantly at 8 and 24 h but not at 1 h and 4 h when compared to patients without pancreatitis^[9]. These data suggest that serum markers (amylase/lipase) are detected early, but that the acute inflammatory response does not fully develop until at least 8-12 h after the initial pancreatic insult. These data may be useful for determining the extent of pancreatic injury, the timing of the acute inflammatory response and for assessing such inflammatory markers in equation-based models.

TNF- α

TNF- α is a pleiotropic cytokine expressed in acinar cells, and is a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules which acts as a priming activator of immune cells^[10]. It is also a cell death signal through the TNF- α -related apoptosis induced ligand (TRAIL) receptor pathway, with the potential to cause severe tissue damage. TNF- α plays a pivotal role in severe AP, acting early in the disease course, and is quickly cleared. As a result of its rapid clearance, TNF- α serum levels are less useful as biomarkers of early events than downstream cytokines (e.g. IL-6). To limit the systemic effect of TNF- α , the body releases TNF- α inhibitors. The soluble TNF receptor (sTNFR) attenuates the effects of TNF- α by binding to TNF- α in the serum and thus acts as an anti-inflammatory molecule. sTNFR levels have been found to predict severity in AP with an accuracy of 96%, and also to have a high sensitivity for mortality^[11].

IL-1

IL-1 is another major pro-inflammatory cytokine that can drive the SIRS response. It has recently been shown to be the major cytokine mediating inflammation in sterile necrosis^[12], which is often problematic in severe AP. In contrast to TNF- α , IL-6 does not directly cause pancreatic damage^[13]. It has been used as a biomarker of disease severity and has similar accuracy to IL-6 in predicting severe AP on admission (82% *vs* 88%)^[11]. IL-1 receptor antagonist (IL1-RA) levels also correlate with the inflammatory response and severity in AP and may in fact be superior to IL-6 or CRP within the first 48 h.

IL-6

IL-6 is a multifunctional cytokine released by macrophages in response to tissue injury and constitutes the principal mediator in the synthesis of acute-phase proteins, in addition to transitioning the acute inflammatory response to a chronic response. It is an accurate early predictor of severity in AP, with a sensitivity range of 89% to 100% and 90% accuracy within the initial 24 h^[11]. It has also been shown to be superior to CRP and the APACHE-II score at 24 h following admission.

MCP-1

MCP-1 is a potent chemokine which is released early in the inflammatory process. MCP-1 serum concentrations have been shown to display a dramatic increase in patients with AP who develop local complications or remote organ failure. A close correlation has also been found between the incidence of remote organ failure and the degree of MCP-1 level elevation^[7,14]. As highlighted earlier, a common single nucleotide polymorphism on the MCP-1 gene is shown to predispose to severe AP. Macrophage migration inhibitory factor (MIF) is a unique chemokine; that participates in inflammation, immune response and cell growth. Serum MIF levels

have been found to be higher in patients with severe AP than patients with mild disease^[11].

Although altering the inflammatory response in animals translates into a possible benefit, the potential translational benefit to humans has not been confirmed to date. For example, the platelet activating factor (PAF) inhibitor, Lexipafant displayed early promise. However, it was not deemed to be an effective treatment in a large, multi-national study of 1500 patients^[15]. Although IL-10 decreases the severity of AP in mouse models, and could be of potential benefit in humans, sufficiently powered human studies have yet to be reported in the literature.

The discriminatory power of general prediction schemes improved considerably in the early 1990's. Indeed, Ranson's criteria and APACHE II score achieved reasonable discrimination with receiver-operating characteristic curve (ROC) area under the curve (AUC) values approaching 0.8 in most validation studies. Yet, these classification tools are designed to predict ICU mortality and not potentially preventable complications; they are, therefore, least useful in the middle prediction range where the clinician needs most support and information to direct management. Although these tools are of assistance in medical decision making at the extreme end of the prediction range, their use has been confined to a global ICU performance assessment and criteria for clinical trial enrolment.

Successful prediction of individual outcomes is undoubtedly one of the holy grails in the care of the critically ill. Remarkably, although progress has been made along all those fronts in risks and markers for severe AP, little has been achieved in translating data and quantitative tools into clinically useful and appealing predictive knowledge for physicians managing patients with AP.

Large, prospective studies are needed to address these questions by identifying AP risk factors and serum biomarkers of severe disease. Such data could be potentially used to develop patient-specific predictive algorithms of AP risk and to guide the treatment decision-making process early in the disease course. Such studies could aim to: firstly, determine the role of demographic, environmental, genetic and physiological variables on the initiation, progression, severity and clinical outcomes of AP; secondly to identify biomarkers that reflect the extent of pancreatic injury and the acute inflammatory response which are critical in the assessment of the activity of potentially pathologic cascades; thirdly to build advanced statistical models based on pre-injury risk factors and biomarkers of pancreatic injury and inflammation to accurately predict primary and secondary outcomes of AP, including organ failure, complications and death; and finally to guide the research on inflammatory cascade

blocking agents administered early in the disease course based on patient-specific predictive algorithms.

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