

REVIEW

Biochemical markers of acute pancreatitis

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J Clin Pathol 2006;59:340–344. doi: 10.1136/jcp.2002.002923

Serum amylase remains the most commonly used biochemical marker for the diagnosis of acute pancreatitis, but its sensitivity can be reduced by late presentation, hypertriglyceridaemia, and chronic alcoholism. Urinary trypsinogen-2 is convenient, of comparable diagnostic accuracy, and provides greater (99%) negative predictive value. Early prediction of the severity of acute pancreatitis can be made by well validated scoring systems at 48 hours, but the novel serum markers procalcitonin and interleukin 6 allow earlier prediction (12 to 24 hours after admission). Serum alanine transaminase >150 IU/l and jaundice suggest a gallstone aetiology, requiring endoscopic retrograde cholangiopancreatography. For obscure aetiologies, serum calcium and triglycerides should be measured. Genetic polymorphisms may play an important role in "idiopathic" acute recurrent pancreatitis.

ESTABLISHING THE DIAGNOSIS

Acute pancreatitis typically presents with severe, constant upper abdominal pain which may radiate through to the back and be associated with nausea and vomiting. As atypical presentations are frequent and there is a wide differential diagnosis, confirmatory tests are required to confirm the diagnosis of acute pancreatitis.⁴ Three enzymes derived from pancreatic acinar cells—amylase, lipase, and the proenzyme trypsinogen—have been tested as biochemical markers of acute pancreatitis; serum amylase is the most commonly used of these in clinical practice.

Amylase

A raised level of serum amylase activity, at least three times the upper limit of normal, supports the diagnosis of acute pancreatitis. Its activity rises quickly within the first 12 hours after the onset of symptoms and returns to normal within three to five days.⁵ Serum amylase activities may be normal in 19–32% of cases at the time of hospital admission, as a result of delayed presentation or exocrine pancreatic insufficiency—for example, secondary to chronic alcohol abuse.^{6,7} Hypertriglyceridaemia competitively interferes with the amylase assay and can produce falsely low results,⁸ although this is variable and can be modulated by the use of lipid clearing agents. Conversely, serum amylase activities can be increased in other intra-abdominal inflammatory conditions and salivary gland pathologies, and also where there is decreased renal clearance because of renal impairment or macroamylasaemia (where amylase is bound to immunoglobulins or polysaccharides to form large molecular weight complexes⁸).

The sensitivity and specificity of amylase as a diagnostic test for acute pancreatitis depends on the chosen threshold value. By raising the cut off level to 1000 IU/l (more than three times the upper limit of normal), amylase has a specificity approaching 95%, but a sensitivity as low as 61% in some studies.⁸

Lipase

Compared with serum amylase, serum lipase activity remains increased for longer (up to 8 to 14 days), thereby giving greater sensitivity in patients with a delayed presentation. Pancreatic lipase activities are more than four times that of amylase and as such are less likely to be affected

The incidence of acute pancreatitis in the United Kingdom has been estimated at 100 to 250 per million population per year.^{1,2} Men and women are affected at a similar rate, although the aetiology differs between the sexes, with gallstones and biliary sludge (echogenic, gravitating material composed of cholesterol crystals, calcium bilirubinate granules, and muco-glycoproteins) being more frequent in women, and alcohol more common in men. Iatrogenic causes include endoscopic retrograde cholangiopancreatography (ERCP) and drugs (for example, azathioprine, frusemide (furosemide), and salicylates). Hypertriglyceridaemia, hypercalcaemia, hypothermia, and pancreatic neoplasia are less common causes, as are viral infections and hereditary acute pancreatitis. In more than 80% of patients, acute pancreatitis is mild and resolves without serious morbidity, but in up to 20% it can be severe and complicated by major morbidity and mortality.³ A systemic inflammatory response syndrome (SIRS), secondary to cytokine release from the initial pancreatic parenchymal injury, is the main cause of early complications within the first two weeks, while superimposed infections of pancreatic necrosis or acute fluid collections are later events. Overall mortality is as high as 10%.¹

This review discusses the role of biochemical tests in establishing the diagnosis of acute pancreatitis, predicting its severity, and determining its cause.

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Accepted for publication
31 October 2005

by chronic pancreatic insufficiency.⁹ The recent UK guidelines for the management of pancreatitis state: "Where lipase is available it is preferred for the diagnosis of acute pancreatitis."¹⁰ Lipase is not specific to the pancreas, and serum activities may also be raised in other intra-abdominal pathologies or in renal insufficiency. Hypertriglyceridaemia does not interfere with laboratory measurement, but drugs such as frusemide can increase serum activity. The diagnostic accuracy of lipase appears to be better than that of amylase. At a cut off activity of 600 IU/l, most studies have reported specificities above 95%, with sensitivities ranging between 55% and 100%.^{8–11}

Trypsinogen

The pro-enzyme trypsinogen is cleaved by duodenal enterokinase (or trypsin itself as part of a positive feedback loop) to form the active 24 kDa protease trypsin and trypsinogen activation peptide (TAP). Trypsinogen exists as two major isoenzymes, trypsinogen-1 (cationic) and trypsinogen-2 (anionic), the latter at considerably higher serum concentrations in acute pancreatitis.¹² In families with hereditary pancreatitis, mutations in the cationic trypsinogen gene (PRSS-1) on the long arm of chromosome 7 (7q35) have been described; most of these are "gain of function" mutations that probably interfere with autolysis of trypsin or cause its premature activation.¹³ High serum calcium concentrations protect trypsin from autolysis and may also predispose some patients to pancreatitis.¹⁴

In acute pancreatitis, both serum and urinary trypsinogen-2 levels rise to high levels within a few hours and generally decline within three days. In ERCP-induced pancreatitis, serum trypsinogen-2 concentrations may rise within an hour of the insult.¹⁵ In a prospective study of 500 consecutive patients with acute abdominal pain presenting to two emergency departments in Helsinki, a urinary trypsinogen-2 dipstick test was positive in 50 of the 53 patients with a final diagnosis of acute pancreatitis (sensitivity 94%, specificity 95%), including all seven patients with severe acute pancreatitis.¹⁶ The sensitivity and specificity of the urinary trypsinogen-2 dipstick test (at a detection level of 50 µg/l) were higher than those of serum amylase (cut off 300 U/l; 85% and 91%, respectively) and urinary amylase (cut off 2000 U/l; 83% and 88%, respectively). The negative predictive value (NPV) of urinary trypsinogen was 99%, enabling the diagnosis of acute pancreatitis to be ruled out with a high degree of confidence. In a more recent study of 237 consecutive patients with abdominal pain, of whom 29 had acute pancreatitis (six severe), the sensitivity and specificity of the urinary trypsinogen-2 dipstick test on admission was 93% (27/29) and 92% (192/208), and of serum lipase 79% and 88%, respectively.¹¹ Urinary trypsinogen-2 again had a NPV of 99% and was the best means of ruling out acute pancreatitis.

PREDICTING PROGNOSIS

The severity of acute pancreatitis can be classified by clinical criteria, which take into account extension of the inflammatory process to local and distant extrapancreatic tissues, with associated complications. Severe acute pancreatitis implies the presence of organ failure, local complications, or pancreatic necrosis and associated disruption of the pancreatic blood supply.^{17–18} Early prediction of severity is an important goal in acute pancreatitis, in order to identify the 20% of patients who are likely to have a severe course. Such patients have an expected mortality of 15–20%¹⁰ and may benefit from early admission to high dependency or intensive care units, "pancreatic rest" with parenteral or nasojejunal feeding, and prophylactic antibiotics.¹⁹ In severe acute pancreatitis, multiorgan dysfunction accounts for the

majority of early deaths,²⁰ whereas pancreatic infection is a major risk factor for late mortality.¹⁷

Many of the potential markers for predicting the severity of acute pancreatitis are part of the systemic inflammatory response to initial injury (for example, interleukin 6 (IL6), C reactive protein, and procalcitonin). In theory, early anti-cytokine treatment might reduce SIRS and the risk of multiorgan dysfunction. To date, attempts to intervene pharmacologically with antiseptics such as somatostatin or protease inhibitors like gabexate mesilate and aprotinin have been largely disappointing.^{17–21}

Initial clinical assessment alone identifies fewer than half the patients with severe acute pancreatitis.²² Scoring systems incorporating clinical, biochemical, or radiological criteria for severity assessment have been in use for some decades (table 1). These include the 11 criteria described by Ranson in the 1970s,²³ the Glasgow score (eight criteria),²⁴ and the acute physiology and chronic health evaluation (APACHE II) score (14 criteria).²⁵ The sensitivity and specificity of these scoring systems for predicting severe acute pancreatitis range between 55% and 90%, depending on the cut off number and the timing of scoring.^[26, 27] The predictive value of these scoring systems is improved by the addition of information provided by abdominal computed tomography (CT). Balthazar *et al*²⁸ developed a CT severity index (table 2), with an index of ≥ 7 having a 92% positive predictive value for a severe course of acute pancreatitis. If done on day 4 following symptom onset, the sensitivity for detecting pancreatic necrosis was 100%. Recently published UK guidelines recommend contrast enhanced CT in patients with persistent organ failure, signs of sepsis, or deterioration in clinical status 6–10 days after admission.²⁹ Figure 1 shows a representative example of abdominal CT in acute pancreatitis.

Limitations of these scoring systems have been either the inability to obtain a complete score until at least 48 hours into the illness (Ranson and Glasgow scores) or the complexity of the scoring system itself (APACHE II).

Several single laboratory markers for predicting the severity of acute pancreatitis have been investigated, but promising initial results have not always been confirmed in later studies. For example, a cohort study of 128 patients with acute pancreatitis reported that a packed cell volume (PCV) above 44% at 24 hours after admission had an NPV of 96% and a sensitivity of 94% for the detection of organ failure.³⁰ However, in a logistic regression analysis of 316 patients with acute pancreatitis, Lankisch *et al*³¹ confirmed an adequate NPV value of a PCV above 44% on admission (85%), but the sensitivity and specificity were only 56% and 62%, respectively.

Serum amylase and lipase, the standard tests for acute pancreatitis diagnosis, are poor predictors of severity.³ Novel markers for the early prediction of acute pancreatitis severity include the pancreatic proenzyme trypsinogen-2 and its subunit TAP, as well as early inflammatory response markers such as serum IL6, procalcitonin, polymorphonuclear elastase, and serum amyloid A. The more established marker C reactive protein has been shown to be an accurate severity predictor (sensitivity and specificity above 80%) at 48 hours post-symptom onset if a cut off level of 150 mg/l is used.⁴

Interleukin 6

The pro-inflammatory cytokine IL6 is one of the main inducers of C reactive protein synthesis in the liver, and peaks earlier than C reactive protein. In a single centre Italian study of 38 patients with acute pancreatitis (15 with severe disease), IL6, IL8, β_2 -microglobulin, and C reactive protein values were compared on admission and daily thereafter for five days. At 24 hours after admission, the sensitivity of IL6 for detecting severe acute pancreatitis was 100%, with a

specificity of 86% at a cut off concentration of 2.7 ng/l.³² The same investigators later studied 80 patients with acute abdominal pain, of whom 40 had acute pancreatitis (15 severe), using lipase for diagnosis and IL6 as a prognostic marker of acute pancreatitis. Using a different cut off value of 3.7 µg/l, the sensitivity of IL6 was again 100% and the specificity 83% for detecting severe acute pancreatitis.³³ In 50 patients with acute pancreatitis (18 severe), a Taiwanese group reported an NPV of 93% for IL6 on the day of admission.³⁴ However, serum concentrations of IL6 decrease swiftly and its use in clinical practice has also been limited by the complexity of the assay.

Procalcitonin

Procalcitonin, a 116 amino acid propeptide of calcitonin, is an acute phase reactant that has been investigated extensively as an early marker of severity in SIRS and sepsis.³⁵ Kylänpää-Bäck *et al*³⁶ employed a semiquantitative serum strip test in 162 patients with acute pancreatitis (38 severe). At 24 hours after admission, the test had a 97% NPV for identifying those patients who later developed organ failure (cut off 0.5 pg/l), with a sensitivity of 92% and a specificity of 84%. A Slovakian study of 101 patients with acute pancreatitis reported an NPV of 83% for severity when procalcitonin was measured within 12 hours of admission.³⁷ The results of further prospective trials using this uncomplicated, affordable method are awaited.

Polymorphonuclear elastase

Activated polymorphonuclear leucocytes, the first line of defensive cells following tissue injury, release an enzyme that degrades the extracellular matrix—polymorphonuclear elastase. In a study of 182 patients with acute pancreatitis (28 severe), serum polymorphonuclear elastase activities at 24 hours postadmission differentiated between a mild and severe course, with an NPV of 98% and a sensitivity of 93%, using a cut off value of 300 µg/l.³⁸ However, more recent studies by Japanese and Swiss groups have yielded conflicting results.^{39 40}

Serum amyloid A

Serum amyloid A, a family of apolipoproteins synthesised in the liver in response to tissue trauma and inflammation, has



Figure 1 Axial computed tomogram of the abdomen through the pancreas, scanned in the portal venous phase. The pancreas (black arrows) is enhancing uniformly. This means it is being perfused throughout and there is no evidence of necrosis. Surrounding the pancreas there is loss of clarity of the intraperitoneal fat and some peripancreatic fluid. These are radiographic signs of acute pancreatitis.

been investigated as a prognostic marker in a multicentre European trial of 172 patients with acute pancreatitis (35 severe).⁴¹ Using a plasma enzyme linked immunosorbent assay at a cut off concentration of 418 mg/l, the reported NPV of serum amyloid A was 89% on admission, with a sensitivity of 67% in predicting a severe course. However, the results of a German single centre study, using a different immunoassay in a population that also included healthy subjects and patients with chronic pancreatitis and malignancy, did not support these findings.⁴²

Trypsinogen-2 and trypsinogen activated protein

A simple urinary dipstick method based on immunochromatography has been developed for the detection of the pancreatic proenzyme trypsinogen-2 and its subunit TAP. As described earlier, urinary trypsinogen-2 has been shown to be highly diagnostic of acute pancreatitis at a cut off value of 50 µg/l.¹¹ In an attempt to improve specificity, the same group investigated 150 consecutive patients using a higher detection limit of 2 mg/l. The specificity of trypsinogen-2 remained unchanged at 87%, but the sensitivity fell to 62%, with approximately one third of severe cases of acute pancreatitis being missed.⁴³ Overall, trypsinogen-2 appears to be more useful as a diagnostic marker for acute pancreatitis than as a predictor of severity.⁴⁴

A prospective European multicentre study investigated the urinary TAP immunoassay as an early predictor in 176 patients with acute pancreatitis, 35 (20%) of whom had severe disease.²⁵ At 24 hours after admission, the NPV of a urinary TAP concentration greater than 35 nmol/l was only marginally better than a serum C reactive protein level >150 mg/l in predicting a severe course (89% v 84%); both were similar to the APACHE II score (88%). The sensitivity of urinary TAP was 68%, compared with 63% for APACHE II and 47% for C reactive protein. A Finish-UK study of 190 patients with acute pancreatitis presenting within 24 hours of symptom onset, and which excluded transient organ failures in the analysis for severe acute pancreatitis prediction, reported similar receiver operator characteristic curves for urinary TAP, serum C reactive protein, and clinical APACHE II score on admission.⁴⁵ At 24 hours, urinary TAP was more accurate (area under the receiver operator characteristic curve (AUC) = 0.81 (95% confidence interval, 0.72 to 0.90)) than C reactive protein (AUC = 0.66 (0.54 to 0.78)). The combination of urinary TAP (cut off 25 nmol/l) and serum C reactive protein (cut off 100 mg/l) had the highest specificity (95%) for detecting severe acute pancreatitis at 24 hours after admission, but the sensitivity of this combination was only 35%.

Carboxypeptidase B

Carboxypeptidase B (CAPB) is an exoprotease synthesised as an inactive proenzyme procarboxypeptidase B (proCAPB) by acinar cells. CAPB from the pancreatic gland may exist in three different molecular and immunoreactive forms: the proenzyme, the active enzyme, and the activation peptide. In a study of 85 patients with acute pancreatitis (categorised as oedematous or necrotic), and 53 patients with acute abdominal pain of non-pancreatic origin, measurement of the activation peptide levels on admission correlated with an accuracy of 92% with the later development of pancreatic necrosis. Measurement of the proenzyme was useful for the diagnosis of acute pancreatitis (accuracy = 99%) but levels did not correlate with later development of pancreatic necrosis (accuracy = 56%).⁴⁶ In a comparative study of measurement of serum CAPB and urinary TAP in 52 patients with acute pancreatitis, both were excellent prognostic markers but within the first day of admission urinary TAP was superior.⁴⁷

Table 1 Scoring systems for prediction of the severity of acute pancreatitis

Variable	Ranson (at 0 and 48 hours)	Glasgow (within first 48 hours)	Apache II (*) (on admission, then daily)†
Age	>55 years	-	+
	-	-	Premorbid state
WBC count ($\times 10^9/l$)	>16 (on admission)	>15	+
Blood glucose (mmol/l)	>11.1 (on admission)	>10	-
AST (U/l)	>250 (on admission)	>200	-
LDH (U/l)	>350 (on admission)	>600	-
Serum urea (mmol/l)	>1.8 increase (at 48 h)	>16	Creatinine
Serum calcium (mmol/l)	<2 (at 48 h)	<2	-
Serum albumin (g/l)	-	<32	-
PaO ₂ (mm Hg)	<60 (at 48 h)	<60	+
Base deficit	>4 (at 48 h)	-	Arterial pH
Fluid sequestration	>6000 ml (at 48 h)	-	-
Packed cell volume (%)	≥ 10 fall (at 48 h)	-	+
Serum sodium	-	-	+
Serum potassium	-	-	+
Temperature	-	-	+
Mean arterial BP	-	-	+
Heart rate	-	-	+
Respiration rate	-	-	+
Glasgow coma scale	-	-	+
Suggested cut off number	11 criteria: <3 criteria indicate mild AP	8 criteria: ≥ 3 criteria indicate severe AP	14 criteria: ≥ 8 points (*) indicate severe AP

*Points system per variable: ranges from 0 (normal) to +4 (very abnormal); minimum total score: 0, maximum score = 71.

†+, included in test.

AP, acute pancreatitis; AST, aspartate transaminase; BP, blood pressure; LDH, lactate dehydrogenase; WBC, white blood cell.

ESTABLISHING AETIOLOGY

In the United Kingdom, the most common causes of acute pancreatitis are common bile duct stones and chronic heavy alcohol intake, each accounting for 20–50% of cases depending on the population studied.¹

In predicted severe acute pancreatitis, detecting stone disease as the cause at an early stage is important, as ERCP with biliary sphincterotomy within 24 to 72 hours of symptom onset improves morbidity and mortality.^{48–49} A serum alanine aminotransferase (ALT) activity of >150 IU/l is predictive of gallstone pancreatitis (positive predictive value 95%), but only half the patients with gallstone induced acute pancreatitis will present with high ALT values.⁵⁰ A transabdominal ultrasound scan has up to a 95% sensitivity to detect gallbladder stones,⁵¹ but its sensitivity for detecting common bile duct stones was as low as 50% in some studies⁵² and it is inferior to other imaging methods such as magnetic

resonance cholangiopancreatography and endoscopic ultrasound.²⁷

Alcohol induced acute pancreatitis is the result of an acute toxic insult on a background of a chronically damaged pancreatic organ caused by longstanding injury from alcohol. A lipase to amylase ratio of >5 has been proposed as a diagnostic test for alcohol induced pancreatitis, but has a sensitivity of less than 50%.⁵³

A laboratory “acute pancreatitis screen” to determine aetiology also includes fasting blood triglycerides (suggestive as a cause if the concentration is >11.3 mmol/l) and serum calcium concentrations. Early and convalescent viral antibodies to mumps, coxsackievirus, cytomegalovirus, varicella-zoster, herpes simplex, and hepatitis B viruses,⁵⁴ including the possibility of HIV infection, should be considered if no other cause for acute pancreatitis has been found.

Genetic polymorphisms may play a role in some of the 10–20% of cases of acute pancreatitis currently labelled as idiopathic, as well as being a co-factor in the development of chronic alcoholic pancreatitis.¹⁴ Hereditary pancreatitis is suspected if there is a history of recurrent episodes of pancreatitis often beginning in childhood, with no identifiable precipitating factors and affecting at least two other family members. Single point mutations in cationic trypsinogen (PRSS-1), pancreatic secretory trypsin inhibitor (PSTI or SPINK-1), and cystic fibrosis transmembrane conductance regulator (CFTR) have been identified in some patients with recurrent acute pancreatitis,¹⁴ but their clinical significance remains uncertain. A single nucleotide polymorphism in the promoter region of monocyte chemotactic protein 1 (MCP-1-2518 A/G), an inflammatory chemokine, has also been described. In a study of 77 patients with acute pancreatitis, development of a severe course was associated with the presence of the G allele at the MCP-1 gene.²⁴

CONCLUSIONS

For the diagnosis of acute pancreatitis, serum amylase remains the most commonly used biochemical marker, but its sensitivity can be reduced by late presentation,

Table 2 Index of severity of acute pancreatitis by computed tomographic criteria

CT severity index (time not specified)	Points
(A) Normal pancreas	0
(B) Pancreatic enlargement (oedema)	1
(C) Pancreatic inflammation and/or peripancreatic changes	2
(D) Single peripancreatic fluid collection	3
(E) Two or more fluid collections and/or retroperitoneal air	4
(A–E are exclusive)	
Plus	Add
Necrosis (% of pancreatic parenchyma)	
0%	0
<30%	2
30–50%	4
>50%	6
Total	

Minimum score: 0, maximum score: 10.

CT, computed tomography.

hypertriglyceridaemia, and chronic alcoholism. Urinary trypsinogen-2 is convenient, of comparable diagnostic accuracy, and provides greater (99%) negative predictive value. Early prediction of the severity of acute pancreatitis can be made by well validated scoring systems at 48 hours, but the novel serum markers procalcitonin and IL6 allow earlier prediction (12 to 24 hours after admission). Serum ALT >150 IU/l and jaundice suggest a gallstone aetiology requiring ERCP. For obscure aetiologies, serum calcium and triglycerides should be measured. Genetic polymorphisms may have an important role in "idiopathic" acute recurrent pancreatitis.

ACKNOWLEDGEMENTS

We thank Dr Anna Leslie, University Hospital Lewisham, London, for supplying the CT.

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