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Severe acute pancreatitis

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OVERVIEW

Eighty to eighty five percent of the cases of acute pancreatitis (AP) are self-limiting and resolve with conservative management. Another 10-25% of cases develop severe acute pancreatitis (SAP) and 15-20% develop a fulminant protracted course with major complications such as abscess formation and multiorgan failure. The severity of AP is a function of the extent of pancreas injured and the intensity of the inflammatory response. There are two peaks of mortality, an early peak (within the first two weeks) and a late peak. Early death is related to the systemic inflammatory response syndrome (SIRS) with cardiovascular collapse, renal failure or acute respiratory distress syndrome. This accounts for anywhere from one third to one half of the deaths in AP. Late deaths are associated with infected pancreatic necrosis, sepsis and multiorgan dysfunction syndrome (MODS).

Other complications of SAP include intestinal fistulae, pseudo-aneurysms of branches of the splenic artery or of the superior mesenteric artery and left sided portal hypertension secondary to splenic vein occlusion resulting in splenomegaly and gastric varices (left-sided or sinistral portal hypertension).

It is important to note that acute pancreatitis (AP) is a complex clinical syndrome encompassing a variety of mechanisms of pancreatic injury, activation of multiple inflammatory cascades and endangering multiple organ systems in a highly heterogeneous patient population. All of this lends to the difficulty in developing a comprehensive system of classification and outcome measures.

Although the diagnosis of acute pancreatitis is relatively straightforward, identifying those patients who will go on to fulminant severe disease is more difficult. Initial assessment is geared at identifying those patients who will need intensive monitoring and resuscitation. The classic landmark features such as Grey Turner sign (flank ecchymoses) and Cullen sign (peri umbilical ecchymoses) are late presentations.

DEFINITION OF TERMS

Phlegmon: A pancreatic/peripancreatic mass of cellular and interstitial edema with the infiltration of inflammatory cells

Necrosis: Tissue death. Pancreatic death is usually limited bit peripancreatic necrosis more extensive especially in the obese patient.

Pancreatic abscess: Infected pancreatic necrosis

Infected pancreatic pseudocyst: It is a cystic collection of fluid in the lesser sac, which becomes secondarily infected, usually after endoscopic or percutaneous aspiration.

DEFINING SEVERITY

Initially comparative studies were limited by lack of international consensus in defining and distinguishing severe disease from mild. In an attempt to standardize patient populations for comparison various classification systems were proposed. The most popular classification system currently in use is based on the

Atlanta Consensus Conference of Acute Pancreatitis held in 1992.{{96 Bradley,E.L.,3rd 1993}}

It is based on clinical, laboratory and anatomical/pathological changes of the gland.

In Atlanta SAP was defined by the presence of complications that are either systemic (e.g. organ system dysfunction) or local (e.g. peripancreatic fluid collection, pseudo cyst, abscess, pancreatic necrosis). However, local and systemic complications and their consequences reflect different mechanisms and have different outcomes.

CONTROVERSIES

Controversies still loom over the management of severe AP because of several management loopholes: -

1. Few institutions have significant experience and expertise
2. The series reported in the literature are not always comparable
3. Definition of terms is not uniform worldwide, compounding matters and making prospective randomized trials virtually impossible.

CLINICAL PREDICTORS OF SEVERITY

It is now universally agreed that there are 4 general adverse prognostic factors: obesity, chronic alcoholism, age and diabetes.{{97 Company,L. 2003; 98 Papachristou,G.I. 2006; 75 Papachristou,G.I. 2006}}{{107 Mentula,P. 2008; }}Obesity has been shown to be an independent risk factor for severe acute pancreatitis (SAP).{{76 Papachristou,G.I. 2006}} Mega analysis has also shown that a BMI >30 kg/m^2 is associated with increased risk of developing SAP. Ranson's score was also significantly higher in obese patients suggesting that obesity may amplify the immune response to injury.{{76 Papachristou,G.I. 2006}}

The presence of pleural effusion, especially left-sided or bilateral, on chest x-ray within the first 24 hours of admission likely correlates with increased mortality risk, pancreatic necrosis and maybe even pancreatic abscess. Additionally an elevated creatinine level on admission may also portend a worse outcome. {{111 Talamini,G. 1999; }}

CLINICAL ASSESSMENT

Before the 1970's clinical assessment was the only tool available in the examination of the patient. However clinical exam alone is extremely dependent on the clinician and has not been shown to reliably predict severe disease even in experienced hands.{{99 McMahon,M.J. 1980}} However, with longer follow ups clinical assessment improves and approaches multi factorial scoring systems, although the variation in patient's presentations and clinical judgment make it in general inaccurate for predicting severity.{{100 Corfield,A.P. 1985}} Although MODS is the single most important development negatively affecting the outcome of the disease, even the failure of one extra organ can have a dramatic impact on the course of the disease.

Diagnostic Peritoneal Lavage (DPL) was advocated in the 1980s. Severity of disease was related to the volume and color of peritoneal fluid obtained shortly after presentation. It was found to be superior to clinical assessment and similar to Ranson and Glasgow criteria at 8 hours. However, it is too invasive and has fallen out of favor.

BIOCHEMICAL MARKERS

Serum Amylase and Lipase are the most frequently used diagnostic tests markers. They have little role in determining severity, and are typically reduced in late presentations, and may be falsely lowered in hypertriglyceridemia due to laboratory interference. Elevated C-reactive protein (CRP) and elevated white blood cell count (WBC) together may play a role in predicting infected necrosis.{{86 Dambrauskas,Z. 2007}}

Procalcitonin and IL-6 are playing an increasing role

in prognostic evaluation. {{88 Matull,W.R. 2006}} The measurement of inflammatory markers such as CRP, IL-6, MCP-1 etc., has not been helpful in our experience despite their increasing popularity.

MULTIFACTORIAL SCORING SYSTEMS

Pancreatitis-Specific Scoring systems

Ranson et al. initially evaluated 43 objective clinical and laboratory variables in 1000 consecutive patients with AP, the majority of cases were due to alcohol. Of these, 11 factors were identified as prognostically significant. Five are measured at admission and the remaining six during the following 48 hours. (Fig. 1) Mortality was shown to correlate with the number of positive signs, for a mortality of 0.9% in patients with less than three positive signs to a mortality of 100% with six or more signs.{{94 Ranson,J.H. 1976; 101

Ranson's Criteria {{94 Ranson,J.H. 1976}}

	Non biliary pancreatitis
ADMISSION	
Age	>55
WBC (mm^3)	>16,000
Glucose (mg/dl)	>200
LDH (iu/l)	>350
AST (iu/l)	>250
Within 48 hours	
BUN rise (mg/dl)	>5
Pao_2 (mm Hg)	<60
Serum calcium (mg/dl)	<8
Hematocrit decrease (points)	>10
Base deficit	>4
Fluid sequestration (liter)	>6

Fig 1 – **AST, Aspartatate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cells. One point is assigned to each positive finding. Scores over 4 are associated with increased morbidity and mortality.**

Modified Glasgow criteria

During Initial 48 hours
WBC > 15,000/mm^3
Glucose >10 mmol/L
PaO_2 <60mm Hg
Serum calcium <2.0 mmol/L
LDH >600U/L
AST/ALT >200 µm/L
Albumin <3.2 g/dL

Fig 2 – {{**104 Osborne,D.H. 1981**}}

Ranson,J.H. 1982}} Inherent problems with the system are the bulkiness and tardiness of the predictive model in addition to the "snap shot" one-time predictive value, as a result the model is rarely used and of limited clinical value at best.

To improve upon Ranson's criteria, Imrie proposed a modification (Fig 2). Replace hematocrit, base deficit and fluid sequestration, with albumin levels and alter the cutoff values of some of the variables. Eventually it encompassed only eight variables instead of the previous 11.{{103 Blamey,S.L. 1984; 104 Osborne,D.H. 1981}} {{112 Imrie,C.W. 1978; }}

The modified Glasgow criteria were applicable to all causes of AP not just alcohol like Ranson's but, they were no more predictive than Ranson's criteria and they still required a 48-hour delay. In general, these systems are difficult to remember and take greater than 48 hours to be realized limiting their clinical utility.

NON-SPECIFIC SCORING SYSTEMS

The acute physiology and chronic health evaluation (APACHE) scoring system was developed in 1981 as a physiologically based group classification for the severity of a broad range of diseases and consisted of the acute physiology score and a preadmission health score.{{105 Knaus,W.A. 1981}} This system although validated was too bulky for regular use and was even-

tually modified leading to the APACHE II system. {{106 Knaus,W.A. 1985}} The new system was found to correlate with hospital mortality and it was soon being used for a variety of diseases. It was not long before it was tested on AP. The immediate advantage was its ability to reduce the 48-hour waiting period of the direct predictive scoring systems for AP previously proposed. It could be calculated on admission and daily thereafter. However, it is better suited for populations than for the individual patient and is too time consuming and bulky for daily use.

The recently proposed APACHE-O score with the addition of obesity appears to offer no benefit in improving the predictive accuracy of the APACHE-II on admission, as all obese patients appear to be at higher risk regardless of a small change in their BMI.{{80 Johnson,C.D. 2004}} However time will tell the usefulness of the model. The most commonly used predictive multifactorial scoring system are the Ranson's score (Fig.1) and the Acute Physiology and Chronic Health Evaluation (APACHE) II. Components of both systems measure the end organ's failure to respond to inflammatory challenge (SIRS) and thus are indirect markers of the inflammatory response. (i.e. arteriolar pO2<60,mm Hg, rise in BUN >5mg/dl, fluid sequestration >6 liters in Ranson's score). The overall accuracy of these two systems does not exceed 80%.{{77 Papachristou,G.I. 2004}}

A newer scoring system, The Panc 3 Score has recently been proposed. {{91 Brown,A. 2007}} It uses only 3 variables, hematocrit (HCT>44 mg/dL), BMI>30kg/m^2 and a pleural effusion on chest x-ray. Hemoconcentration was shown to be the most predictive risk factor for development of SAP. The scoring system was developed at a single center using retrospective data as compared to the Atlanta criteria for SAP. It must undergo prospective analysis and many questions remain such as for how long do these criteria remain valid especially with aggressive rehydration and hemoconcentration and the timing of the detection of a pleural effusion on chest x-ray. Nonetheless due to its simplicity it is intriguing.

ANATOMIC OR RADIOGRAPHIC GRADING:

A contrast enhanced computed tomography scan has a sensitivity and PPV close to 100% for detecting pancreatic necrosis between 4 and 10 days after initial onset of symptoms. To improve upon this Balthazar and Ranson {{81 Balthazar,E.J. 1985}} developed a grading system for severity based on initial CT findings. Fig 1 No patient with grade A or B pancreatitis developed an abscess or died whereas five of the study's six deaths and 89% of all abscesses occurred in patients initially classified as grade D or E. Combining the CT grade with the Ranson criteria further improved the categorization of severity. The investigators also found large pleural effusions associated with more severe disease. Bilateral effusion was seen primarily in grade E scans lending importance to the findings of pleural effusions and severe disease.

A significant limitation of the CT findings was the inability to predict the more than 50% of patients with grade D and E scans who spontaneously resolved their fluid collections rather than progress to abscess formation. The CT Severity Index (CTSI) was developed to address these issues. Improvements in the contrast bolus technique now allow more accurate imaging of the perfusion of the pancreatic parenchyma.

These finding were incorporated with the earlier work on CT grading to provide the CT severity index.{{82 Balthazar,E.J. 1990}} The new data on necrosis is combined with the prior A to E CT score with additional points given for the percentage of necrosis. The CTSI has an even stronger correlation with morbidity and mortality. For extended necrosis (greater than 50%) the sensitivity and specificity approach 100%. {{84 Balthazar,E.J. 2002}} A contrast enhanced CT scan taken between the first 24 hours and 48 hours is standard to the evaluation of AP. To improve the detection of pancreatic necrosis it is advisable to delay the CT scan as necrosis may not be immediately apparent and the delay also serves to re-hydrate the patient reducing the risk of contrast enhanced nephropathy.

Balthazar CT Grading of Acute Pancreatitis

Grade	CT Findings
A	Normal pancreas
B	Focal or diffuse enlargement of the pancreas
C	Inflammation of pancreatic parenchyma or peripancreatic fat
D	One fluid collection
E	Two or more fluid collections

Fig. 3 – {{**82 Balthazar,E.J. 1990**}}

CT severity Index{{82 Balthazar,E.J. 1990}}

CT grade	Points	Necrosis %	Extra points	Severity Index
A (normal pancreas)	0	0	0	0
B (enlargement)	1	0	0	1
C	2	<30	2	4
D	3	30-50	4	7
E	4	>50	6	10

Fig 4 – **a severity index of 7-10 yields 17% mortality and 92% complication rate**

All the prognostic markers and severity indices are based on the physiologic systemic responses to events occurring within and around the pancreas. They are useful to compare large populations but do not help in the management of the individual patient.

A good CT scan, according to the pancreas protocol to evaluate the anatomic basis of what is happening in the lesser sac, is universally recommended. While Balthazar's CT grading is very useful it must not be taken in isolation. The CT appearance may not always correlate with the clinical picture. Thus clinical judgment is paramount and must take into account all the clinical and laboratory data together with CT findings. Lack of pancreatic perfusion can occur in phlegmon as well as necrosis.

PHYSIOLOGIC SEVERITY

Nutrition

AP creates a state of catabolic stress, encouraging SIRS and nutritional deterioration. Enteral nutrition is favored unless there is some indication for TPN for example gastric outlet or, duodenal obstruction or ileus. Enteral nutrition is associated with cost savings,

better glycemic control and likely reductions in infectious morbidity and length of hospital stay. No differences in incidence of organ failure or mortality has been documented.{{93 Heinrich,S. 2006}} However, enteral feeding should only be resumed as early as it is safe.

The role of nutritional supplementation is controversial supplemental; agrinine, glutamine, omega-3 polyunsaturated fatty acids and probiotics may however, positively affect length of stay and duration of nutritional therapy.{{87 McClave,S.A. 2006}}

Antibiotics

Several studies and several meta-analysis have failed to show conclusively the benefit of prophylactic antibiotic use. However, the early use of antibiotics in severe necrotizing pancreatitis is generally unquestioned. Given the role of infection in causing morbidity and mortality early use of a carbapenems in patients with a clinical picture consistent with infection as evidenced by leukocytosis, fever and hemodynamic instability is indicated. At our institution a 2-week course is usually started empirically on these patients and may be prolonged in cases of persistent illness. A distinction must be made based on the patient's clinical presentation not CT findings of necrosis alone.

FINE NEEDLE ASPIRATION

The presence of infection is a major predictor of outcome, increasing mortality several fold.{{95 Beger,H.G. 1997}} Since infected pancreatic necrosis necessitates surgical intervention many clinicians have advocated FNA in determining the state of infection as CT scans and laboratory tests are rarely conclusive. We do not advocate routine early FNA. It is unnecessary in most cases and clinical presentations and the patient's clinical course is the basis of our operative intervention. The clinical course of the patient will determine who will need debridement from those who will not. Furthermore FNA is not without risk, including the risk of converting sterile necrosis to infected necrosis.

THE TIMING OF SURGICAL INTERVENTION.

Sterile necrosis is best managed non-operatively. Previously early surgical intervention and debridement was advocated for infected necrosis. Recently studies have confirmed that delayed surgical intervention is associated with enhanced outcomes. {{89 Howard,T.J. 2007; 90 Mier,J. 1997}} Infection typically develops roughly 2 -3 weeks after the initial attack and is likely due to translocation of intestinal organisms. Traditionally gram negative organisms were mostly responsible but there is recent evidence that *Enterococcus* and *Staphylococcus* species are responsible for a large number of infections.

Delayed intervention allows the organization and separation of necrotic parenchyma

facilitating dissection, it also results in better outcomes even in the setting of infected necrosis. The exact timing of operative intervention is based on the observation of the clinical course of the disease over a few weeks combined with the laboratory values and CT scan appearances. The late Kenneth Warren warned that the two commonest mistakes that are made are 1) to operate too early and do too much or 2) to operate too late and do too little.

TYPE OF SURGICAL INTERVENTION

Surgical intervention is indicated in a patient with necrotizing pancreatitis who fails to improve or deteriorates after 3-4 weeks of intensive management and support. We do not typically treat these patients with percutaneous drainage, as small drains are inadequate for extracting the necrotic, thickened pancreatic and peripancreatic tissue. The planning and technical details of the operation have been well described.{{115 Bouvet M, Moossa AR 2004; }} Operative interven-

tion typically takes place in two forms: Necrosectomy with blunt finger debridement followed by closed drainage, or blunt finger debridement followed by open drainage (abdominal packing with return trips to the operating room for dressing changes). The latter has fallen out of favor and may even lead to increased morbidity and possibly higher mortality.{{93 Heinrich,S. 2006}} Formal pancreatic resections should not be undertaken in the setting of SAP. Cholecystectomy should be performed in cases of gallstone pancreatitis only if it can be done safely. Creating unnecessary enterotomies such as a feeding J tube is not indicated.

INTERVENTIONAL RADIOLOGY

Plays little role in the pre-operative patient. However, the re-accumulation of fluids in the surgical bed may be drained percutaneously once all necrotic tissue has been removed. Failure to improve following surgery should be tempered with patience, repeat CT scans and aggressive percutaneous drainage if indicated. If there is evidence of ongoing necrosis, ere-operation and further debridement may be warranted.

OPEN INTERVENTION VS. SMALL INCISION FLANK DRAINAGE

Recently much enthusiasm is shown over minimal flank incision drainage. A retrospective Dutch study found mortality was only 11% for minimally invasive procedures (small flank incision necrosectomies) vs. 42% for laparotomy and primary abdominal closure.{{85 Besselink,M.G. 2006}} To confirm these findings there is currently a prospective randomized controlled multicenter study (PANTER trial) underway. {{113 Besselink,M.G. 2006; }}

COMPLICATIONS

Complications following debridement are common although overall morbidity and mortality have declined.{{89 Howard,T.J. 2007}}These include pancreatic or enterocutaneous fistula (both of which should be treated conservatively at least initially), wound infection, wound dehiscence and incisional hernias. Bleeding though rare is handled by embolization and angiography. Endocrine and exocrine insufficiency is also relatively common. Pancreatic pseudocysts may develop in those patients with sterile necrosis who were treated conservatively.

PERIPANCREATIC EFFUSIONS AND PSEUDOCYSTS

Fluid collections around the inflamed pancreas are common. Most will resolve spontaneously with time. A small percentage will persist for weeks and become encapsulated forming a pseudocyst, which may or may not communicate with the pancreatic ductal system. Early or late percutaneous aspiration is not warranted.

It is never urgent to operate on a pseudocyst. Observation by ultrasound can be done for weeks without ill effect. The indication to drain a pseudocyst is based on 1) size >7.5 cm in diameter, 2) presence of a thick wall, 3) duration longer than 6 weeks, 4) patient's symptoms, 5) suspicion of infection within the cyst. This usually follows contamination by endoscopic or percutaneous needle aspirations. In general, internal drainage of the cyst is recommended whether the cyst is infected or not.

HEMORRHAGE ASSOCIATED WITH PANCREATITIS

Erosion of the inflammatory process can lead to pseudo aneurysms of a nearby artery, which can rupture with catastrophic internal hemorrhage. Resuscitation and angiographic embolization can be life saving. Once the patient is stabilized operative intervention is dependent on the individual clinical situation.

Upper gastrointestinal hemorrhage from gastric

varices due to splenic vein occlusion and sinistral (left-sided) portal hypertension can occur acutely or in a chronic form, month or years later. Upper gastrointestinal endoscopy is essential to rule out other causes of gastroduodenal bleeding. Treatment is conservative management with blood transfusions and acid suppression using a proton pump inhibitor. In the long term, splenectomy and gastric devascularization may be needed. {{108 Little,A.G. 1981; }}{{109 Moossa, A.R. 1985; }}

LONG-TERM SEQUELAE

The convalescence of patients recovering from severe acute pancreatitis must not be underestimated, as it is often protracted and difficult. Transfer to a skilled nursing facility and rehabilitation unit is mandatory. Physical therapy and rehabilitation from alcohol and drugs are essential to restore these individuals to normal.

SUMMARY

The management and treatment of SAP depends on clinical judgment and expertise. Clinical judgment is based on some or all of the measured values available in addition to experience. There are many factors which play a role in our approach and treatment that have not been studied. It is invaluable to observe the course and tempo of the individual patient's disease.

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