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Management of severe acute pancreatitis – How far have we come

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ABSTRACT

Background: The management of severe acute pancreatitis has undergone considerable changes.

Methods: This review presents our single centre experience in patients with SAP. Stratification of morphological severity was based on CECT. Patients with clinically suspected IPN routinely underwent image-guide FNA. Indications for operative treatment were FNA proven infection of pancreatic and extrapancreatic necrosis, persisting or deteriorating organ failure and/or abdominal complications. Careful necrosectomy of pancreatic and extrapancreatic necrosis in combination with continuous, postoperative closed lesser sac lavage was performed. We sampled necrotic pancreatic tissue (following necrosectomy), and blood for cytokines such as interleukin (IL-2, 6, 10, 12), tumour necrosis factor (TNF∝), and reactive nitrogen intermediates.

Results: Our principal findings from necrotic pancreas were that stimulated T cells had fewer IL-2 and IL-4 producing cells than controls. Production of IL-2 is less in alcoholic and biliary pancreatitis and may indicate the impaired cellular immunity and increased susceptibility to infection seen in AP. We measured and correlated the percentages of peripheral blood mononuclear cells that contain IL-6 and IL-12 and compared these with APACHE scores. Patients with severe pancreatitis had higher IL-6 values and a correlation was seen between IL-6 value and APACHE III score and based on our results it seems logical to use both APACHE III and IL-6 percentages to assess severity. Monocyte function is affected in AP as shown by reduced HLA-DR numbers and lowered TNF-∝ producing cells. We also studied the role of nitric oxide and showed significantly higher levels of RNI as compared to controls. RNI levels were higher in patients who developed sepsis (199.5 vs. 134.7 n mol/ml) and in nonsurvivors as compared with those of survivors (216.0 vs. 140.1 n mol/ml). Patients with higher serum nitric oxide levels are at a significantly higher risk of sepsis and mortality. Fifty eight patients underwent pancre-

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atic necrosectomy after a median period of 28 days after the onset of illness. Preoperative image-guided aspiration and/or drainage was carried out in 41 patients. The overall mortality was 29%.

Conclusions: The review highlights the challenges posed by SAP. Rapid advances are taking place in the assessment of severity, markers of immune activation, understanding the pathophysiology of the disease and development of anti-inflammatory therapy through targeting of tumor necrosis factor, cytokines, interleukins and other inflammatory mediators. Fine needle aspiration of the necrosis is used to detect microorganisms and IPN is an indication for surgical intervention. Enteral nutrition via the nasojejunal tube or through a feeding jejunostomy tube placed at the time of necrosectomy has become the preferred route of feeding and is feasible, well tolerated and does not exacerbate the disease. Prophylactic antibiotics with good penetration in pancreatic tissue are recommended in SAP. Surgical necrosectomy is combined with continuous closed lesser sac lavage to continuously remove necrosis and debris. There is variability in both the nature and timing of surgical necrosectomy. The role of percutaneous, radiological, endoscopic, and laparoscopic drainage techniques are being defined and show promising results.

Key Words: Severe acute pancreatitis, acute necrotizing pancreatitis, cytokines, organ failure, infective pancreatic necrosis, inflammatory mediators, computed tomography, enteral nutrition, necrosectomy, closed lesser sac lavage.

INTRODUCTION

Acute pancreatitis (AP) is a relatively common inflammatory disease of the pancreas, predominantly caused by symptomatic gallstone disease and excessive alcohol intake and is a lethal disease (1). The mortality of severe acute pancreatitis (SAP) is as high as 30-40%. Its pathogenesis is poorly understood. One of the key questions concerning the pathogenesis is why some patients develop only a limited local inflammatory response whereas others progress to systemic inflammatory response syndrome (SIRS) and multisystem organ failure (MSOF) (2,3). Pulmonary complications have long been recognized to account for a significant number of deaths occurring within the first week of AP (4). The profiles for AP depend upon the degree of pancreatic necrosis (PN) and the intensity of MSOF (5). Several inflammatory mediators have been documented to be present at increased concentrations in the plasma of patients with SAP(6). Interruption of these mediators has the potential to improve outcome in these patients (3). The value of giving antibiotics to patients with SAP remains unresolved (7). Infected pancreatic necrosis (IPN) is a serious complication of AP occurring in 20-40% of patients and one half

of all deaths in AP are attributed to IPN (7,8). Early recognition of IPN by image-guided fine needle aspiration (FNA) or radiological evidence of gas followed by prompt surgical management is the best way to reduce morbidity and mortality (9,10). The main unresolved issues in SAP include who require surgery, what is the optimal time to intervene and what technique should be employed (11-13). In a recent survey, no consensus was reached on optimum timing of surgery, and only 53% would operate on a patient with positive results from FNA (14). A recent study has suggested that patients with IPN and severe disease can generally be managed nonsurgically without compromising prognosis and outcome (15).

Do we know more about the pathogenesis?

The pathogenesis of AP in many ways presents the same dilemmas that have confronted the clinicians since 1889(16). Fitz's (17) contributions was based in large part on the principles of cellular pathology and presented analysis of 53 patients distinguishing between haemorrhagic, suppurative and gangrenous forms of the disease. He proclaimed that an operation in the early stage of the disease is extremely hazardous. He laid the foundation of our present knowledge of the pathology, symptomatology and treatment of this so frequently and suddenly fatal disease. Chiari (18) postulated that the underlying pathophysiological mechanism of the disease was pancreatic autodigestion- the pancreas succumbs to its own digestive properties. Opie (19) proposed that a gallstone lodged in ampulla might occlude both the common bile duct and the pancreatic duct forming a common channel that would allow reflux of bile into the pancreatic duct with activation of pancreatic enzymes and pancreatitis. Mayo (20) described acute fulminating pancreatitis and referred to this as haemorrhagic pancreatitis occurring in fleshy alcoholic males. He recommended that if a patient is seen during the first 48 hours, the abdomen should be opened and free drainage should be furnished. He noted better outcome in patients with subacute pancreatitis and localized septic accumulations that can be opened and drained.

Fitz described the initial injury in AP as one of oedema, white cell infiltration, and microvascular disruption (17). It has recently become clear that the initiating events need to be evaluated at the level of acinar cell (1). The key to mortality in the disease is related not to histological or morphological changes but to distant manifestations in organs such as lung, kidney and cardiovascular system. Patients may develop MSOF within first week of illness, 40% develop it later (21,22). Despite the differences in the initiating triggering factor, the pathophysiological events in the pancreas and systemically follow a common pathway (2). Enormous efforts have been made to unravel the complexities and intricacies surrounding the pathogenesis of pancreatitis and SIRS (5,23). The pathway between the initial pancreatic injury, the systemic response, and organ failure is mediated by a variety of inflammatory mediators in response to local tissue damage (6). It is generally believed that proinflammatory mediators released play an important role in pathogenesis (24).

We have tried to examine possible mediators in patients with SAP. We have tried to define the cytokine phenotype of individual T cells and macrophages obtained from the necrotic pancreas. This has the advantage of avoiding the pitfalls of serum cytokine measurements such as the presence of circulating cytokine inhibitors. The macrophages isolated from the necrotic tissue were examined for intracellular cytokines to scrutinize the recruitment of macrophages at the affected site. In both alcoholic and biliary pancreatitis CD4+T cell subsets produced reduced amount of IL-2. There were significantly fewer CD4+ T cells in alcoholic disease than in controls, but were significantly more in biliary cases. Alcoholic patients had more IL-4 producing cells than the biliary group. There was a significant difference between the number of CD4+ T cells that expressed IL-10 in controls and the alcoholic group. No significant differences were found in the number of cells that expressed IFN-γ in the control and biliary groups, but these were significantly more in the alcoholic group. There were fewer IL-2 producing CD8 +T cells in alcoholic disease. There was a significant reduction of IL-4 positive cells in alcohol group and a pronounced reduction in biliary group. Cells from alcoholic group produced more IFN. Our results indicate that production of IL-2 is less in alcoholic and biliary pancreatitis. This reduction may indicate the impaired cellular immunity and increased susceptibility to infection that is seen in AP. We also detected reduced amounts of IL-4 in alcoholic disease and a pronounced reduction in biliary disease. It is conceivable that during the inflammatory process the expression of IL-4 is down regulated (25). There was increased release of proinflammatory cytokines together with reduced IL-10 activity in alcoholic disease, while those with biliary disease had a pronounced downregulation of their anti-inflammatory response. The variable development of local and systemic complications could be a result of such activities.

Our results have shown that local response of cytokines varies with the aetiology of the disease. Biliary group had less local proinflammatory response than the alcoholic group. IL-6 and IL-12 levels were measured in peripheral blood cells on day of admission. Percentage of positive cells for IL-6 and IL-12 were significantly higher in SAP as compared to mild disease. IL-12 values were high in alcoholic acute pancreatitis as compared to patients with biliary pathology.

We monitored the cytokine concentration from the drainage fluid following closed lesser sac lavage. Increased IL 12 levels were observed in fluid from both groups. IL-6 levels were increased in alcoholic cases as compared to biliary group. Can these observations be used to stop the lavage following necrosectomy is difficult to answer at this stage.

We have made an attempt to understand the role of lymphocyte monocyte system in limiting the destructive process in AP. HLA-DR expression on monocytes was significantly reduced in SAP. Assessment of intracellular cytokines in immunocompetent cells could be a useful tool to study the relationship between the different mediators and their role in cases of dysregulation as seen in AP (26).

We correlated the percentages of peripheral blood mononuclear cells that contain IL-6 and IL-12 and compared with APACHE III score in patients with SAP IL-6 positive peripheral blood mononuclear cells reflect the severity of AP. Cutoff percentage for IL-6 and IL-12 positive peripheral blood mononuclear cells were >25% and >9% respectively. Based on our results it would seem logical to use both APACHE score and IL-6 percentages to assess severity in AP(27).

We have studied adhesion and activation molecules in order to evaluate dysregulation. ICAM_1 in the pancreas is a critical link in the development of tissue injury and organ dysfunction. The adhesion molecules showed a unanimous rise in the blood and tissue samples. Monocyte function is affected in AP as shown by reduced HLA-DR numbers and lowered TNF-∝ producing cells (28).

The role of nitric oxide in AP has been a subject of intense research and controversy. Serum nitric oxide levels represent the extent of cytokine response induced by pancreatic inflammation. We tried to correlate the blood levels of nitric oxide in patients with SAP with computed tomography severity score and APACHE II scores. Patients with high levels of nitric oxide in the blood are at a significantly higher risk of sepsis and mortality. High APACHE score and reactive nitrogen intermediates (RNI) levels on admission were associated with an increasing number of organs failed. RNI levels were higher in those who subsequently developed biliary sepsis. High RNI levels were associated with an increased risk of mortality. RNI levels were higher in nonsurvivor group as compared with the survivor group (29).

Several pathologic responses occur in AP and include oedema, inflammation, parenchymal cell injury and death including disorganization of cellular ultrastructure, necrosis, and apoptosis (1). Ischemia of tissue in the pancreas participates in the mechanism of pancreatitis. A recent study compared the angiographic abnormalities with perfusion abnormalities by contrast enhanced computed tomography (CECT). The correlation between angiography and CECT demonstrated the vasospasm in small and medium sized vessels of the pancreatic bed led to decreased downstream perfusion. These areas of decreased perfusion resulted in necrosis in upto 50% of the patients. The mortality was related directly to the severity of the vasospasm on the initial examination (30). Another experimental study has shown that endothelial nitric oxide synthase activation (e Nos) leads to increased blood flow in the pancreas and in the absence of its activation, the increased blood flow is blocked, resulting in worsening of severity of pancreatitis (31).

Even today the precise means by which diverse elements induce pancreatitis remain unclear. A significant morbidity and mortality associated with the disease reminds us that we are still chasing a destructive path rather than interrupting or controlling the events of the disease. The continuing challenge is to translate the findings into treatment strategies. Based on our results we hope that in future we will witness immune modulation therapy for arresting systemic manifestations of AP and to institute organ support early in the course of the disease.

Have advances in imaging techniques changed the evaluation or management of these patients with SAP?

Advances in imaging techniques have changed the evaluation and management of patients with SAP (32). The imaging modality of choice currently is multidetector row computed tomography (MDCT). The role of imaging in AP is to confirm the diagnosis, to identify necrosis, their topographical location and to determine the presence of complications (fluid collection, and vascular abnormalities). Resolution can only be confirmed by repeat CT study. CT imaging should be performed in patients with SAP with persisting organ failure, signs of sepsis, or clinical deterioration after admission. The early detection of PN signified severe disease and is used as a prognostic indicator in the initial evaluation. Computed tomography severity index (CTSI) grades the severity of pancreatitis on the basis of degree of pancreatic inflammation and necrosis and is a significant advance in the assessment of patients with AP. The anatomical site of necrosis is clearly better than its crude extent in predicting the risk of complications (33). Patients with necrosis in the head of pancreas have a severe course of the disease.

CTSI does not correlate with the development of organ failure or pancreatic complications. The modified CTSI (inflammation, necrosis, extrapancreatic complications) shows improved correlation with organ failure, severity, the occurrence of infection, the need for surgical or radiological intervention, and hospital stay (34).

Other imaging modalities that have been studied include magnetic resonance cholangiopancreatography (35), tissue harmonic imaging(36), and leukocyte scintigraphy(37). Magnetic resonance severity index scores correlated with serum levels of C - reactive protein at 48 hours, duration of hospitalization, Ranson score, and morbidity from local and systemic complications (35).

In our own experience, CTSI ranged from 4-10 in 64.4% of patients. Systemic complications and culture proven infection were higher in these patients ($p<0.05$). A recent study has shown that CTSI is superior to Ranson criteria and APACHE II score in predicting acute pancreatitis outcome, the mortality, length of stay and complications were higher in patients with a CTSI >5 than that in patients with CTSI<5(38).

The extent of PN appears to be a useful determinant of prognosis. Mortality increases markedly in patients with necrosis involving >30% of the gland (39,40).

Early detection of vascular complication by CT is important (41-43). Massive haemorrhage after PN results from a ruptured pseudoaneurysm, severe capillary or venous bleeding may be seen in the immediate aftermath of PN (42).

Infected necrosis is diagnosed by CT guided FNA (9). It is recommended that FNA should be performed 7-14 days after the onset of pancreatitis in all patients with persistent symptoms and greater than 30% PN, and those with small areas of necrosis and clinical suspicion of sepsis (44). Image guided FNA may need to be repeated to detect IPN.

Innovations that have improved outcome.

The treatment of SAP continues to be largely supportive therapy and subse-

quently to treat specific complications. Management has alternated between aggressive intervention and intensive nonsurgical support (45). Treatment currently focuses on three factors of supposed pathophysiologic significance. First it is generally accepted that secondary infection of PN constitutes one of the crucial factors in the progression from SIRS to sepsis in patients with SAP. Second recent data suggest that is possible to diminish SIRS by giving specific anti-inflammatory components. Thirdly the importance of early intensive care therapy and organ support is being increasingly emphasized. The findings of a recent study suggest that these patients can be managed conservatively and surgery can be avoided without compromising prognosis and outcome. Sixteen patients (APACHE II score 18.1 (11-33), Ranson score 5.9 (4-10) were managed with medical treatment alone with a mortality of 12.5%, six patients recovered without further complications, 10 patients developed single or multiple organ failure (15).

The real challenge is the development of a more accurate predictor of severity and organ failure. The determination of the severity is difficult as all methods exhibit a significant uncertainty. Various scoring systems have been used to make the prediction. However their value in everyday clinical practice is limited as they are cumbersome, and requiring multiple measurements (45). Severity is now determined by Atlanta criteria (46), CTSI (33) and modified CTSI (34).

Issue of antibiotic prophylaxis: Infection of PN can lead to local and systemic septic complications which can cause MSOF and account for a mortality of upto 30%. Its incidence tends to peak in the third week of disease. Several randomized controlled trials suggest that prophylactic antibiotics can reduce morbidity and mortality in these patients by preventing pancreatic infections (47). A recent study has concluded that prophylactic antibiotics did not reduce the incidence of IPN in patients with SAP (7). Fungal infections appear in 15 to 30% of cases [50]. In our own experience, Candida infection was observed in 17.9%, and Candida spp. were isolated from pancreatic tissue in 36.7% .There is conflicting evidence regarding association of secondary fungal infections with the widespread use of antibiotic prophylaxis (51,52). However, studies are needed to accurately quantify the incidence and risk of fungal colonization, any association with antibiotic prophylaxis, and association with a significant increase in mortality. A recent study has shown that prophylactic dosage of antifungal agents can reduce the incidence of fungal infections in patients with SAP (53). There is insufficient evidence to recommend antifungal prophylaxis in patients with SAP (10). Our practice is to use prophylactic broad spectrum antibiotics in all patients with SAP which is corroborated by current recommendations (48, 49).

Specific anti-inflammatory therapy: Recent data suggests that it is possible to diminish SIRS by giving specific antiinflammatory components. There is a therapeutic window between onset of symptoms and development of organ failure during which anticytokine therapy may be successful (10). The role of many inflammatory mediators has been investigated (54). However in large multicentre trials the role of platelet activating factor antagonist could not be confirmed (55,56). The failure of beneficial

effect may be due to the fact that patients had already developed MSOF before the beginning of the treatment (10).

Nutritional support: It seems logical to meet the calorie and protein requirement of these patients with SAP to protect intestinal barrier function reducing bacterial translocation from the gut (57). Timely institution of feeding is important to prevent malnutrition and has been demonstrated to be safe (1). Evidence has emerged from clinical trials that enteral nutrition is superior to parenteral nutrition (58,59). Parenteral nutrition is associated with an enhanced systemic inflammatory response and increased septic complications (49). Enteral nutrition by means of a nasojejunal feeding tube helps in preventing atrophy of the intestinal mucosa and loss of barrier function (10). A recent metaanalysis has shown that infection rates, rates of surgical intervention and hospital stay were significantly lower in those fed enterally (60). A recent consensus statement also recommends that enteral nutrition be used in preference to parenteral nutrition after initial resuscitation (10). Enteral nutrition modulates acute phase response, improves immune function, reduces mortality rate and reduces risk of infections (61). Our current practice is to place a nasojejunal feeding tube once the ileus has settled down. Following necrosectomy, we routinely place a feeding jejunostomy tube for enteral nutrition. Postoperative enteral nutrition has been shown to be safe and to decrease infectious complications (62).

Pancreatic necrosectomy

The main contribution to the overall management of SAP is pancreatic necrosectomy (8). Surgery is indicated when there are signs of MSOF, clinical sepsis with no improvement on intensive care treatment, and CT shows extensive areas of PN with confirmation of bacterial infection by FNA. The principles include optimal debridement with a postoperative management concept that maximizes drainage of the residual and ongoing necrosis, and evacuation of retroperitoneal exudates and debris. Necrosectomy should favour an organ preserving approach and should be delayed to permit proper demarcation of pancreatic and peripancreatic necrosis (8). A recent consensus conference recommended debridement in those with IPN or abscess confirmed by radiologic evidence of gas or results of FNA (48).

Several approaches described are open transperitoneal approach (11-13), laparoscopic (63), and the extraperitoneal translumbar approach (64,65). Another unresolved tissue is what drainage technique to use- continuous closed lesser sac lavage (CLSL) (12-13), planned staged relaparotomy(11), and the open packing technique (66). Rau *et al* (12) reported an overall mortality of 25% following necrosectomy and CLSL. In our experience of 58 patients who underwent necrosectomy and postoperative CLSL, it was possible to start irrigation in 48 patients, the overall mortality was 29% (13). In another study, planned staged reoperative necrosectomy using an abdominal zipper in the treatment of necrotizing pancreatitis reported 34% hospital mortality (11). Extraperitoneal translumbar approach (64) with periodically programmed retroperitoneal endoscopy enables to explore the retroperitoneal space under direct

visual guidance (avoids contamination of the peritoneal cavity). In a study of 11 patients, there was no technique- related morbidity and no subsequent operations needed, the mortality rate was 27% due to MSOF, and the integrity of abdominal wall was preserved (65).

Laparoscopic technique with transperitoneal infracolic approach as an alternative is also considered in the treatment of PN. Laparoscopic necrosectomy is feasible with dislocation of the infected sequestrum and followed by closed irrigation of the lesser sac. The main difficulty is with evacuation of necrotic material due to its viscous consistency. Out of 13 patients who underwent laparoscopic pancreatic necrosectomy, 11 survived and made a full recovery (63).

Percutaneous necrosectomy has been introduced to remove debris in a minimally invasive way (67,68), and is stated to be more successful later in the course of the disease . This is indicated in patients with organized necrosis after the acute episode, after open surgery to remove residual devitalized tissue thereby avoiding multiple operations, and in patients with devitalized tissue following percutaneous drainage (68). In a study of 6 patients undergoing percutaneous video- assisted necrosectomy, sepsis control was achieved in all patients with no mortality (69).

Endoscopic necrosectomy and lavage has added a new therapeutic dimension to the management of PN and pancreatic abscess (70). The efficacy of endoscopic treatment of pancreatic necrosis and abscess has been demonstrated (71). Seifert *et al* (72) described endoscopic ultrasound directed transmural puncture into necrotizing pancreatitis or abscess followed by tract dilatation and repeated endoscopic debridement of lesser sac. Endoscopic therapy was successful in resolving the infected necrosis or the abscess in 12 of 13 patients with minor bleeding in 4 cases in a recent study (73). They state that this aggressive endoscopic approach expands the potential for endoscopic treatment in these patients. However, the effectiveness of endoscopic therapy needs further trials.

Acute gall stone pancreatitis (AGP)

It is still a matter of controversy whether there is a need for early endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy (ES) in acute gallstone pancreatitis (74). Pezelli *et al* (75) evaluated the effect of ductal decompression in patients with AGP and common bile duct stones in two groups: ES within 24 hours of admission (n=21) and conservative medical treatment (n=21). AP worsened in one patient in ES group, in contrast to seven patients in the group receiving medical treatment ($p<0.02$). In another study, early ES had no impact on the outcome or period of hospitalization (76). Uhl *et al* (77) advocate that at least 3 weeks should elapse in patients with SAP before undertaking cholecystectomy because of an increased infection risk. Fagniez and Rotman (78) have confirmed that early biliary surgery worsens the prognosis in SAP. Postponing the biliary operation until after the acute attack reduces the need for early exploration and drainage of the pancreas (79). Nealon *et al* (80) in a retrospective analysis of patients with moderate to severe gallstone associated pancreatitis advocate that

cholecystectomy be delayed. Delayed treatment is associated with lesser chances of infecting fluid collections and lesser complications of cholecystectomy. In our experience, ES was carried out in patients with jaundice or cholangitis.

Conclusions

The management of patients with SAP has changed over recent years with readily available imaging and image guided interventions and improvement in intensive care unit management. The degree of necrosis and presence of infection are the crucial determinants of the outcome in patients with PN. The primary objective in the management of patients with PN is supportive therapy and subsequently to treat specific complications. Another objective is to limit the severity of pancreatic inflammation and necrosis and the systemic effects by removing causative factors. Image guided FNA is recommended in patients with SAP, greater than 30% necrosis and those with clinical suspicion of sepsis. A positive FNA result or the presence of gas in a collection is usually an indication for intervention. Patients with SAP require repeated imaging as guidance to progress. With the advent of FNA to diagnose infection, more timely operations can be performed.

The strategy of management of patients with PN has changed dramatically. The main contribution to the overall management of SAP is necrosectomy. Necrosectomy is performed usually at around 3-4 weeks. The standard open technique followed by postoperative lavage, and / or drainage to evacuate devitalized tissue has recently been challenged by various minimally invasive approaches- percutaneous, endoscopic or laparoscopic determined by size and localization of necrotic lesions, sequestra and septa.

Given the advances in care and ongoing challenges, treatment of SAP will continue to be an

area of innovation and discovery. Treatments targeted at specific events may be able to halt development of or progression and may impact disease control.

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