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ACUTE SEVERE NECROTIZING PANCREATITIS: A GENESIS IN SURGICAL PRACTICE

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ABSTRACT

Necrotic pancreatitis is a severe form of acute pancreatitis where morbidity and mortality associated with this type of acute pancreatitis are comparatively higher especially when it is also infected. It is estimated to be around 10-24% whereas less than 1% is if in mild form. Despite relative less study, there has been a significant change in the management of acute necrotising pancreatitis over the past two decades. Although 75% to 80% of cases of acute pancreatitis is a mild disease without associate mortality it is important to identify the 20% to 25% of patients who are likely to develop severe disease associated with major complications and who would benefit from early intensive care monitoring and treatment. In recent years the treatment of acute necrotising pancreatitis has shifted away from early surgical debridement (Necrosectomy) to aggressive intensive medical care of multiple organ systems with specific criteria for operative and non-operative management. This review presents the current concepts with regards to diagnosis and management of acute necrotising pancreatitis including the variation of opinion in most critical aspects. Some of the issues addressed include the management of these patients in an intensive care/ therapy unit, the role of prophylactic antibiotics, requirement of nutrition, enteral and/or parenteral and pre-surgical resuscitative management, the role of CT scan and FNAC in diagnosing infection and finally the role of surgery.

KEYWORDS: Acute pancreatitis, Pancreatic necrosis, Hemorrhagic necrotising pancreatitis, Infected necrosis, Sterile necrosis, Intensive care unit, Necrosectomy.

Definition

The Atlanta conference,[1] in 1992 defined pancreatic necrosis as diffuse or focal area(s) of non-viable pancreatic parenchyma typically associated with peripancreatic fat necrosis. The necrosis is either sterile or infected depending on the presence of infection. The morbidity and mortality associated with acute pancreatitis are substantially higher when necrosis is present, especially when the area of necrosis is also infected.[2] Almost 20%-25% of patients with acute pancreatitis develop pancreatic necrosis.[3-4] Bacterial infection of necrotic pancreatic and retroperitoneal tissue occurs in 30-70% of patients with necrotizing pancreatitis,[4,5] with an associated mortality rate as high as 80%.[6]

Pathogenesis

The clinical syndrome of acute pancreatitis and its complications have been well recognized. Although much has been known regarding the risk factors, pathology and biochemical events, the exact trigger events or pathogenesis still remains elusive. Gallstone disease and alcohol account for 90% of cases of acute pancreatitis. The various proposed aetiologies for pathogenesis include biliary reflux, pancreatic duct hypertension or obstruction, reflux of activated enzymes, hypoxemia, free radical production and vascular endothelial injuryFigure1.[7,8]

Mortality is related with severe irreversible multiorgan dysfunction and peripancreatic sepsis. Several organ dysfunction scores have been developed like- Multiple organ dysfunction score (MODS) and sequential organ failure assessment (SOFA). Morphologically, necrotizing pancreatitis is characterized by an interstitial oedematous inflammation combined with necrosis of the pancreatic exocrine and 1. Gallstone disease. 2. Alcohol. 3. Trauma. 4. ERCP. 5. Drug induced. 6. Pancreas divisum. 7. Ischaemia. 8. Hyperlipidaemia.

The above 8 factors lead to: 1. Activated proteases. 2. Activation of complement. 3. Oxygen derived free radicals.

The above three resultant give rise to final common pathway → Acute pancreatitis → Acute oedematous pancreatitis and acute necrotizing pancreatitis

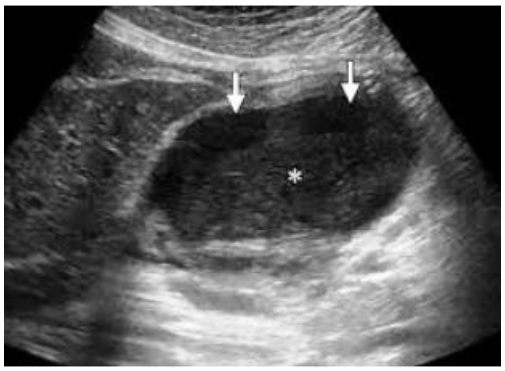

Figure-1: Endocrine parenchyma, and frequently with fatty tissue necrosis, which includes the peripancreatic tissue compartments.8 these patients usually have high concentrations of enzymes, interleukins, leukotrienes, endotoxins, and prostaglandins in the peripancreatic fluids. The necrotising process may extend to involve retroperitoneal fat, small and large bowel mesentery and the retrocolic compartment.[9] Involvement of the transverse colon can be a devastating complication.[10]

Diagnosis

The diagnosis of severe acute pancreatitis is based on a conglomeration of clinical picture, biochemical parameters and imaging modalities. There are no pathognomonic symptoms and signs but pain is usually the early symptom. Pain is usually experienced first in the epigastrium but may be localized to either upper quadrant or felt diffusely throughout the abdomen. Other acute abdominal conditions should always be kept in mind when dealing with acute pancreatitis. Certain non-surgical conditions like myocardial infarction or sudden shock with anurias, pneumonia should also to be excluded. There is a marked elevation in serum amylase levels in acute pancreatitis. Though many other abdominal conditions are associated with hyperamylasemia, the elevations in these are much less marked than in acute pancreatitis. Serum lipase levels also raised in acute pancreatitis and it has a specificity of almost 90%.[11] Serum lipase levels remain elevated for longer periods than amylase and are usually normal in other conditions of hyperamlasemia.

Increased levels of CRP (C Reactive protein), an acute phase reactant is also associated with severe acute pancreatitis.[12] in fact a very high CRP and BMI (body mass index) >30, correlates very well with the severity and prognosis in acute pancreatitis. The morphologic severity of acute pancreatitis can be determined using a CT severity index (CTSI) that was developed by **Balthazar** and colleague which was extended to monitor organ failure by Silverman. The current gold standard for diagnosis of pancreatic necrosis is dynamic contrastenhanced computed tomography (CT).[13-14] Contrast enhanced CT scanning offers the opportunity to determine reliably both the presence and extent of pancreatic and peripancreatic fatty tissue necrosis with an accuracy of more than 90% when there is more than 30% glandular necrosis. It is based on the fact that viable pancreas has an intact blood supply and so enhances after the injection of intravascular contrast agent.[15] Non-viable tissue fails to enhance due to the abnormal microvasculature in this tissue. This test is best performed several days after acute pancreatitis has been diagnosed. The recommendation by the British Society of Gastroenterology is that the test should be performed in all severe cases of acute pancreatitis between 3 and 10 days after admission.[16] the presence of radiographically detected pancreatic necrosis markedly increases the morbidity and mortality associated with acute pancreatitis.[17]

Complications

Systemic complications include acute respiratory distress syndrome, acute renal failure, shock, coagulopathy, hyperglycaemia and hypocalcaemia.[17,18] Local complications include gastrointestinal bleeding, infected necrosis leading to multiple organ failure and adjacent bowel necrosis. late local complications that may require therapy include pancreatic abscesses and pancreatic pseudocysts.

Table 1: Complications of Acute Necrotizing Pancreatitis.

Systemic	**Local**
Multiple organ failure	Pancreatic necrosis-sterile/infected
Enceplalopathy	Pseudocyst
Coagulopathy	Abscess
Sepsis	Vascular necrosis
Hypocalcaemia	Intestinal obstruction
	CBD obstruction
	Internal pancreatic fistula
	Gastrointestinal haemorrhage
	Splenic vein thrombosis and variceal haemorrhage

The complications of severe acute pancreatitis are usually divided into three phases according to the time of occurrence. ARDS, kidney failure, encephalopathy and GI hemorrhage usually occur in the early phase, bacterial and fungal infection usually in the intermediate phase and pancreatic abscess usually in the late phase.[19] the mortality of severe acute pancreatitis ranges between 10% and 20%.

Currently infected pancreatic necrosis is still the leading cause of death. Despite advances in monitoring systems and intensive care units early and worsening multiple organ failure still accounts for almost 40-50% mortality.

Pancreatic abscess and pseudocyst of pancreas are usually late complications. Percutaneous intervention is usually successful in draining the abscess, otherwise surgically drained. Mortality is in the range of 10%.[22] Life threatening hemorrhage into the GI tract, retro peritoneum, peritoneal cavity occurs in only 1-3% patients of acute pancreatitis but has a mortality of 50-80%.[23] Splenic vein thrombosis, leading to variceal bleed, usually under reported complication of acute pancreatitis accounts for a mortality of about 15%.[24] The frequency of vascular necrosis in the form of pseudoaneurysm formation is in the range of 10%.25 Common bile duct obstruction in acute pancreatitis manifests in the form of either biochemical or clinical jaundice in approximately 20% of patients. 26 Internal pancreatic fistula in the form of pancreatic ascites and pancreatic pleural effusion is being increasingly recognized as a complication of acute pancreatitis. Persistence of these fistulae beyond 3 weeks usually requires surgery. Operative mortality is usually in the range of 14%.[27] Infection of the necrotic material develops in 30 to 70% of patients with acute necrotising pancreatitis and accounts for more than 80 percent of deaths from acute pancreatitis. The risk of infected necrosis increases with the amount of pancreatic glandular necrosis and the time from the onset of acute pancreatitis, peaking at three weeks.[28]

Management

Patients of acute necrotising pancreatitis are usually very sick with single or multiple organ dysfunction. Most have a Ranson's score of more than 3 and APACHE II score of more than 8. They are usually managed in the intensive care or therapy units with majority of them requiring ventilation. As mentioned earlier, roughly 20% patients of acute pancreatitis will develop necrosis with a mortality rate exceeding 80%. Management and monitoring of this group must therefore be more intensive. • General Management. • Confirmation of diagnosis. • Prevention of infection. • Nutritional Support. • Monitoring of complications. General Support: Gallstone disease and alcohol account for almost 90% cases of acute pancreatitis. A high index of suspicion of acute pancreatitis has to be maintained by the clinician/family physician who initially sees patients with abdominal pain with the above mentioned background. This will result in early identification and severity stratification of patients with acute pancreatitis resulting in early initiation of supportive therapy.[29] The initial management involves full resuscitation and a multidisciplinary approach. These measures can reduce the proportion of early deaths relating to circulatory, respiratory and renal failure.[30,31] These patients should be managed in an intensive therapy unit (ITU) or high dependency unit (HDU). Such patients require as a minimum peripheral venous access, a central venous line (for fluid administration and CVP monitoring), a urinary catheter and nasogastric tube. Strict asepsis should be observed in the placement and care of invasive monitoring equipment such as central lines as these may serve as a source of subsequent sepsis in the presence of pancreatic necrosis. A Swan-Ganz catheter may be required for the measurement of pulmonary artery wedge pressure, cardiac output and systemic resistance. Regular arterial blood gas analysis is essential as the onset of hypoxia and acidosis may be detected late by clinical means alone. Nursing assesement as a minimum must include regular hourly pulse, blood pressure, CVP, respiratory rate, oxygen saturation, urine output and temperature. Confirmation of Diagnosis: A dynamic CT scan should be performed in all cases of severe acute pancreatitis between 3 and 10 days after admission for diagnosing acute necrotising pancreatitis.[32] Repeated CT scans may be necessary on a regular basis, usually every 2 weeks in the following circumstances.(l) indications of sepsis or other adverse clinical features, (2) planning of any surgical or drainage procedure, (3) for follow up and monitoring of established complications and (4) occasionally avert a disaster by demonstrating a pseudoaneurysm. Prevention of infection: Early studies of antibiotics in patients with acute pancreatitis failed to demonstrate a significant benefit because they included both patients with interstitial oedematous acute pancreatitis and patients with acute necrotising pancreatitis. Since the development of infected necrosis substantially increases mortality among patients with acute necrotising pancreatitis, prevention of infection is crucial. There is some evidence to support the use of prophylactic antibiotics in the prevention of local and other septic complications in acute necrotising pancreatitis.[32] The UK guidelines for the management of acute pancreatitis recommend the intravenous use of cefuroxime. Early prospective studies in a group of patients receiving imipenem-cilastin combination showed a marked reduction in incidence of pancreatic infection although a reduction in mortality was not demonstrated.[33] theoretically fluoroquinolones should offer excellent protection against infection of necrosis but trials have not shown encouraging results.[34] At the present time intravenous administration of imipenem-cilastin is recommended. Therapy should begin as soon as diagnosis of necrotising pancreatitis is made and should continue for a period of two to four weeks. Currently there has been a rethink on the use of prophylactic use of antibiotics in severe acute pancreatitis. A recent large randomized placebo controlled double blind trial has been able to demonstrate that antibiotic prophylaxis has no beneficial effect with reduction of pancreatic infection and decreased hospital mortality. The clinical data from this trial do not support antibiotic prophylaxis in all patients with necrotising pancreatitis but in subgroups of patients with pancreatic necrosis and a complicated clinical course.[35] The International Consensus conference of April 2004 also recommends against the

use of prophylactic antibiotics in all cases of necrotising pancreatitis in view of inconclusive evidence and divided expert opinion.[36] However it is still agreed that the benefits of prophylactic antimicrobial therapy needs to be further addressed in the form of well-designed clinical trials and further research in this area. It has also been-demonstrated in recent prospective trials that selective bowel decontamination in addition to intravenous use of antibiotics, substantially lowers the incidence of gram-negative pancreatic infection and late mortality (deaths more than two weeks after onset of acute pancreatitis) in patients of necrotising pancreatitis.[36,37] However the current thinking is that further investigation of this promising strategy in severe acute pancreatitis is warranted. A high prevalence of intra-abdominal candida infection during acute necrotising pancreatitis has been reported. Incidence has varied from 20-30% and has been associated with a four-fold greater mortality rate compared to intra-abdominal bacterial infection alone.[38-39] given the impact of Candida infection on mortality due to acute necrotising pancreatitis and apparent benefit from antimycotic therapy, data argue for an early fungicide chemotherapeutic intervention. However the data available in this regard is very limited and the recommendation by the International Consensus Conference 2004 is that the available evidence is insufficient to support the routine use of antifungal agents in necrotising pancreatitis. In fact the current view is that the routine use of prophylactic antibiotics in necrotising pancreatitis results in the emergence of antibiotic resistant organisms and fungal pancreatic infections.[40] Nutritional Support: Conventionally, management of patients with acute pancreatitis includes a nil by mouth regimen and intravenous fluid therapy from the time of admission to hospital. However patients with acute necrotising pancreatitis are in a hyper catabolic state and have increased metabolic needs. These patients may deteriorate rapidly.[41] Total parenteral nutrition (TPN) has been the standard nutritional management for many years.[42,43,44,45] Central line feeding is safe and enhances the anabolic response, which prevents muscle wasting.[46-47] Critics of TPN though argue that in addition to cost and catheter related sepsis it may lead to electrolyte and metabolic disturbances, gut barrier alteration and increased intestinal permeability.[48-49] the importance of enteral nutrition in severe acute pancreatitis has recently been emphasized. Contrary to popular belief enteral feeding delivered through nasogastric or nasojejunal tube has been shown to be safe and is preferable in patients with acute necrotising pancreatitis in absence of substantial ileus or duodenal obstruction.[50-51] Randomized clinical trials comparing enteral with parenteral therapy have confirmed that the former is less expensive, is associated with fewer septic complications and is well tolerated by the patient.[52,53,54] Nutrition per se has no effect on the disease process as such and does not hasten the resolution of acute necrotising pancreatitis, but maintains the well-being of the patient in spite of the catabolic phase. Monitoring of Complications: These very sick patients with either single or multiple organ failures require close monitoring of their respiratory, cardiovascular and renal functions.[55] Most of these patients in the intensive care units are on ventilators and regular arterial blood gas analysis should be done and the parameters monitored accordingly. Deterioration in the renal parameters may nessecitate haemodialysis. Some may need vasopressor support. Good nursing care in the management of patient posture, prevention of pressure sores, cleaning of endotracheal secretions and good aseptic measures in managing the various cannulas and tubes inserted are very essential. Any improvement or deterioration in the condition of the patient is noted. Early diagnosis of infection in the necrotic pancreas at this stage is important as it significantly increases the mortality rate. Clinically, infected necrosis is suspected when there is increased abdominal pain, fever, leucocytosis and/or organ failure. Specific signs and symptoms to differentiate between sterile and infected necrosis do not exist. Once infected necrosis is suspected surgical options should be considered.[56] Indications for Surgery: The only absolute indication for surgery in necrotising pancreatitis is the confirmation of infection in the necrotic pancreas and peripancreatic tissues,[57,58,59,60] and aspiration of necrotic material and fluid collections around the pancreas.[61,62,63] This is a reliably safe and accurate method.[64] Presence of gas bubbles in the peripancreatic areas on CT also signifies infection.

The current recommendation is that in patients with documented acute necrotising pancreatitis who show signs of sepsis or multiorgan failure with deterioration in clinical status, CT or ultrasonographically guided aspiration of fluid should be performed for examination and bacteriological culture to confirm infected necrosis.[65] If infected necrosis is confirmed, surgical debridement is recommended. Controversial Aspects of Surgery in Necrotising Pancreatitis: There has been considerable debate over the role of surgery in acute necrotising pancreatitis, including the timing and type of intervention. Standard practice in 1960s was to debride the necrotic pancreas in all cases with an associated mortality rate of 24-82%.66 The rationale for this simplistic approach was seemingly straightforward: removal of necrotic tissues was thought to be beneficial in that the mortality rate would be decreased and associated complications, such as organ failure or secondary infection, might be prevented or at least ameliorated. However in early 1990s Bradley and Alien.[67] popularized the concept of conservative management of sterile necrosis and showed improved survival in patients with necrotising pancreatitis without evidence of infection. They concluded that neither the existence nor the extent of sterile necrosis constitutes an indication for surgery. As many of their patients of sterile necrosis.[68] had associated organ failure that responded to non-operative management; they concluded that neither the presence nor duration of organ failure should be considered a surgical imperative in sterile pancreatic necrosis.[69] Several prospective trials have

been carried out which have described sterile pancreatic necrosis treated conservatively with a mortality rate of 0-10%. Foitzi.[68,69] et al in a retrospective study found no benefit from necrosectomy for sterile necrosis and suggested that surgery may convert sterile necrosis into an infected necrosis. Presently non-operative treatment of sterile necrosis is well established and guidelines have been produced by the American College of Gastroenterology,[69] Bangkok World Congress of Gastroenterology.[70] and others.[70-71] On the other hand, non-operative therapy for infected necrosis cannot be recommended.[72] Infected acute necrotising pancreatitis is considered uniformly fatal without intervention. Despite occasional anecdotal and uncontrolled reports of successful medical management of infected necrosis, the very rarity of these reports affirms the clinical reality that in the overwhelming majority of patients, infected necrosis requires surgical debridement and drainage. Early detection of infected pancreatic necrosis has a major impact on the management and outcome. Ultrasound and CT guided FNAC is a fast and reliable technique for the diagnosis of infected necrosis. As complication rates are very low, the procedure is well tolerated and can be repeated at intervals to increase the diagnostic accuracy. The overall sensitivity and specificity of these procedures is about 88% and 90%. This method however should not be applied too early in the course of the disease. This procedure is recommended for all patients with necrotising pancreatitis in whom the systemic inflammatory response syndrome persists beyond the first week after onset of symptoms.[73] Aggressive pancreatic debridement (Necrosectomy) remains the standard surgical procedure,[74,75] and may require multiple abdominal explorations. This removes the infective necrotic tissue that drives the systemic inflammatory response leading to multiple organ failure. Some authors also recommend surgery in patients who develop clinical sepsis syndrome with increasing severity of organ failure even without evidence of infected necrosis (negative aspiration cultures).[75]

There is no consensus about the timing of surgery for acute infected necrotising pancreatitis although the current trend is towards delayed operation. Proponents of early surgery advocate the benefit of early removal of infective focus and hope of terminating the inflammatory response. However the normal tissue "lanes are lost, gland is very friable and the risk of surgical complications is more.[76] The benefits of delayed surgery are better demarcation of necrotic tissue in a resuscitated and relatively stable patient. This results in an easier separation of necrotic material with less of damage to the viable pancreatic tissue as veil as a complete removal of the necrotic material. This would obviously result in a reduction of postoperative complications as well as in the number of further re explorations required. A randomized clinical trial by Mier et al.[77] comparing early versus late, surgery in necrotising pancreatitis showed a mortality rate 58% in the early operation group as against 27% in the late operation group. Types of Surgical Procedures: The choice of procedure is determined by the duration from onset, the degree of organ dysfunction and the position of the necrotic material within the abdomen.[9] Current surgical practice in necrotising pancreatitis involves necrosectomy of the devitalized pancreatic and peripancreatic tissues.78 There are three main types of surgical debridement: i. Conventional drainage. ii. Open or semi-open procedure. iii. Closed procedure. Conventional drainage involves necrosectomy with placement of standard surgical drains and re-operation as required by clinical criteria or lack of improvement according to imaging studies. Open or semi-open (Laparostomy) management involves necrosectomy and either scheduled repeated laparotomies or open packing that leaves the abdominal wound exposed for frequent changes of dressing.[79,80,81] Closed management involves necrosectomy with extensive intraoperative lavage of the pancreatic bed. The abdomen is closed over large bore drains for continuous high volume postoperative lavage of the lesser sac.[82] Comparison of the results of conventional, open/semi open (Laparostomy) and closed techniques from published series as done by Rau et al.[82] showed collective mortality rates as 42%, 20% and 21% respectively indicating a superiority for necrosectomy followed by re-exploration or continuous lavage. Studies comparing conventional relaparotomy with laparostomy after necrosectomy for pancreatic necrosis offer no difference in terms of morbidity and mortality.[83] Complications of Necrosectomy: Necrosectomy by any of the above-mentioned techniques is always attended by postoperative complications. It is also to be understood that most of these patients will require multiple laparotomies and debridement of necrotic tissues along with drainage of intraabdominal or retroperitoneal collections.[84] The usual attendant local complications are intra-abdominal and retroperitoneal collections, bleeding from pancreatic bed, pancreatic fistulas, small bowel and colonic fistulas. Pancreatic and gastrointestinal fistulas occur in about 40% of patients following necrosectomy and often require additional surgery for closure.[85] The mortality from debridement with open or closed techniques is approximately 20%. Necrotising pancreatitis also has prominent effects on long- term pancreatic exocrine and endocrine function in about 50% of patients, but most preserve a good overall functional status. The development of pancreatic insufficiency varies with the extent of pancreatic parenchymal necrosis.[85]

CONCLUSIONS

Pancreatic necrosis is being increasingly recognized as a complication of severe acute pancreatitis. A very high index of suspicion is essential by the clinician who makes the initial assessment as early identification and severity stratification results in early institution of supportive therapy in an ICU setting the identification of pancreatic necrosis is important, since the morbidity and mortality associated with acute pancreatitis are markedly

increased in the presence of necrosis. Contrast enhanced CT scan is the gold standard for diagnosis of necrotising pancreatitis. There has been considerable debate over the decades regarding management of pancreatic necrosis. Current evidence suggests aggressive medical care in an intensive therapy unit, with/without use of antibiotics in the management of sterile necrosis. However, infected pancreatic necrosis diagnosed by gas on CT or CT/ultrasound guided positive culture, should be treated by surgical debridement (Necrosectomy). Although there is a consensus for delayed surgery, there is no consensus on the exact indication and timing of any intervention. Inspite of various techniques of surgical debridement (Necrosectomy), the mortality and morbidity in cases of infected pancreatic necrosis continues to be high. The main emphasis of this article is to stress the shift in management of necrotising pancreatitis from early surgery (in preceding decades), to late and deferred surgery in properly selected cases. This has been on account of the recognition of the concept of sterile pancreatic necrosis, the treatment for which is primarily conservative, and supportive therapy.

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