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CRITICAL CARE MANAGEMENT OF ACUTE PANCREATITIS-AN UPDATE

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Acute pancreatitis is an acute inflammatory condition of the pancreas that may extend to local and distant extrapancreatic tissues.[1] The definitions of pancreatic inflammatory disease has been the subject of several international conferences in Marseilles 1963,[2]Cambridge 1983,[3]Marseilles 1984,[4] and Atlanta 1992.[1] The American College of Gastroenterology (ACG) practice guidelines provide acceptable terminology for the classification of acute pancreatitis and its complications.[5]

The patterns of mortality and morbidity in acute pancreatitis have changed over time. Currently about one third of patients die in the early phase of an attack from multiple organ failure,[2,3] which represents a reduction in early phase deaths when compared with reports from preceding decades.

In 1998 the British Society of Gastroenterology (BSG) published UK guidelines on the management of acute pancreatitis. A planned revision after two years was anticipated. Three further documents provide a substantial review of the evidence. An ad hoc consensus group reported in 1999 and identified some important modifications in the definition of severity and complications.

Methodology:

We searched electronic bibliographic databases: MEDLINE, PubMed, Database of Abstracts of Review of Effectiveness(DARE), Evidence Based Health Care - Latest Articles, Guideline, InfoPOEMS,Merck Manual. Using the comprehensive MEDLINE search strategy described earlier, we identified 117 citations in Annals of Internal Medicine from 1992 to June 1996 that may represent systematic reviews. In the same period, JAMA published 106 reviews, BMJ published 97, Archives of Internal Medicine published 40, and The New England Journal of Medicine published 21. we consulted with experts or workers in the field.

Inclusion criteria were English language literature from 1960 onwards, relating latest terminology allocated for acute pancreatitis and its complications, advancement of management with introduction of newer drugs and their clinical trial as well as some meta analysis, guidelines provided by British Gastroenterological society, American College of Physician with their update and recently recommended audit standard for management of acute pancreatitis.

***Terminology*[5]**

Mild acute pancreatitis is associated with minimal organ dysfunction and an uneventful recovery. The predominant pathological feature is interstitial oedema of the gland and it is also known as *Interstitial pancreatitis*. It implies preservation of pancreatic blood supply.*Severe acute pancreatitis* is associated with organ failure and/or local complications such as necrosis (with infection), pseudocyst or abscess. Most often this is an expression of the development of pancreatic necrosis, although patients with oedematous pancreatitis may manifest clinical features of a severe attack. However, organ failure present within the first week, which resolves within 48 hours should not be taken as marker for severity.*Pancreatic necrosis* is a diffuse or focal area(s) of non-viable pancreatic parenchyma, which is typically associated with peripancreatic fat necrosis. The onset of infection results in *infected necrosis*, which is associated with a trebling of the mortality risk. necrosis suggests the disruption of pancreatic blood supply with resulting ischaemia. *Acute fluid collections* occur early in the course of acute pancreatitis, are located in or near the pancreas, and always lack a wall of granulation of fibrous tissue. An *acute pseudocyst* is a collection of pancreatic juice enclosed in a wall of fibrous or granulation tissue that arises following an attack of acute pancreatitis. Formation of a pseudocyst requires

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four or more weeks from the onset of acute pancreatitis. A pancreatic abscess is a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis. When acute pancreatitis occurs on two or more occasions (evidenced by elevation of the serum pancreatic enzymes), it is classified as acute recurrent pancreatitis. In some cases, acute recurrent pancreatitis progresses to chronic pancreatitis, implying the presence of parenchymal fibrosis and loss of glandular function.

Incidence

Acute pancreatitis accounts for 3% of all cases of abdominal pain admitted to hospital in the UK.[6] The yearly incidence of acute pancreatitis in the United States is approximately 17 new cases per 100,000 populations. Some epidemiological evidence suggests that the true incidence is probably increasing,[7]partly reflecting increased alcohol intake among the young[8,9] but also due to gallstones in some areas.[10]

Mortality

Evidence from multicentre trials of various treatments[11-13] and from other multicentre reviews[7,8,14] suggests that the death rate of clearly diagnosed cases has remained unaltered at 10-15% over the past 20 years. While striving constantly to reduce mortality in acute pancreatitis it is currently accepted that some patients will die. The overall mortality should be lower than 10%, and less than 30% in those diagnosed with severe disease.[15]

Etiology[16]

Gall stone, alcoholism, post ERCP, and idiopathic are the most common causes of pancreatitis.among other causes *Traumatic*(Abdominal trauma, Penetrating duodenal ulcer), *Metabolic*(Hyperlipoproteinemia, especially types I, IV and V,Hypercalcemia,Renal failure,Acute fatty liver of pregnancy), *Viral*(Mumps,HIV,Varicella,Viral hepatitis,CMV, Epstein-Barr virus), *Parasitic*(Ascariasis), *Drug* (Diuretics, Tetracycline, Sulfonamides, Estrogens, Azathioprine ,mercaptopurine, Pentamidine, Valproic acid, Salicylates, Steroids), *Toxins (*Ethyl alcohol,Methyl alcohol,Scorpion venom, Organophosphorous insecticides,Amanita), *Miscellaneous* (Hereditary,Regional enteritis, Connective tissue disorders with vasculitis,Systemic lupus erythematosus,Polyarteritis, Thrombotic thrombocytopenic purpura,Duodenal diverticulum).

Pathophysiology[17]

Pancreatitis results from an autodigestive process. Pancreatic digestive enzymes, vasoactive materials and other toxic materials extravasate out of the pancreas into the surrounding areas, leading to a widespread chemical irritation resulting in simple edema to severe hemorrhage and necrosis. Trypsin and chymotrypsin are the initiating enzymes; their release can in turn result in the release and activation of other proenzymes (including proelastase, procollagenase and phospholipases). Trypsin damages endothelial cells and mast cells, resulting in the release of histamine. This major inflammatory mediator enhances vascular permeability, leading to edema, hemorrhage and the activation of the kallikrein system, which in turn results in the production of vasoactive peptides or kinins. The latter are thought to cause pain and further aggravate the inflammatory response. In the case of gallstones, the major theories include (1) reflux of bile into the pancreatic duct; (2) reflux of duodenal content into the pancreatic duct; and (3) distal obstruction of the pancreatic duct, with continued pancreatic secretion leading to increased ductal pressure and resulting in pancreatitis.

Although alcohol has been implicated as a major cause of acute pancreatitis, there is no evidence that an occasional bout of excessive alcohol intake can lead to an acute attack. It is suggested that chronic ingestion may lead to chronic damage and sensitization, which may result in acute pain even with small amounts of alcohol. Alcohol can cause direct damage to acinar cells in a manner similar to that in which it damages liver cells.

Clinical features

Pain from acute pancreatitis is a knife-like, steady, sharp pain that starts suddenly and reaches its zenith rapidly. It is commonly localized to the epigastric area and may radiate directly to the back. It improves on leaning forward and is frequently associated with nausea or vomiting. Depending on the location of the inflammation, the pain may be referred to either the left upper quadrant or the right upper quadrant. Frequently the pain is dyspeptic in quality and aggravated by food. This is due partially to the fact that eating stimulates secretion. Classically the pain lasts between three and four days. When the pancreatitis is severe, it may result in shock and may lead to death. Recurrent nausea and vomiting may be due to a reflex mechanism secondary to pain and occurs in over 90% of the cases. Other causes include

pseudo-obstruction secondary to ileus and distention or obstruction secondary to a pancreatic mass or pseudocyst. Jaundice may occur since the common bile duct traverses the pancreatic head before entering the duodenum, often transiently.

Between 50 and 90 percent of patients have signs of abdominal distension or muscle spasms with epigastric pain and left upper-quadrant tenderness.[18,19] Other signs are fever, tachycardia and jaundice. Often the patient is restless and dehydrated on presentation.[18,20]Depending on the severity of pancreatitis, the patient may appear in distress or be in shock. Bluish discoloration of the flanks (Grey Turner's sign) or of the periumbilical area (Cullen's sign) indicates that blood from hemorrhagic pancreatitis has entered the fascial planes. The signs are not specific and may occur in any condition that causes retroperitoneal hemorrhage. Tender red and painful nodules that mimic erythema nodosum may appear over the extremities. These are often due to circulating lipases.

Complications

Local complication

Local involvement of pancreatitis includes phlegmon (18%), pancreatic abscess (3%), pancreatic pseudocyst (10%) and thrombosis of the central portal system.[21] *Phlegmon* is an area of edema, inflammation and necrosis without a definite structure (unlike an abscess). A phlegmon results from acute intrapancreatic inflammation with fat necrosis and pancreatic parenchymal and peripancreatic necrosis. This arises from the ischaemic insult caused by decreased tissue perfusion and release of the digestive enzymes. The Atlanta Meeting[5] discouraged the term phlegmon and replaced it with *pancreatic necrosis*. When this damage is not cleared, further inflammation ensues, declaring itself by increased pain, fever and tenderness. In severe cases a secondary infection ensues, a process termed *infected necrosis of the pancreas,* which occurs within the first one to two weeks of the illness. Most clinical studies in adults cite pancreatic infection as the most common cause of death, accounting for 70-80% of deaths.[1,22] In 3% of acute pancreatitis an *abscess* develops, usually several weeks into the illness. An abscess is a well-defined collection of pus occurring after the acute inflammation has subsided.A *pseudocyst* develops as a result of pancreatic necrosis and the escape of activated pancreatic secretions through pancreatic ducts. It contains blood and debris. This fluid coalesces and becomes encapsulated by an inflammatory reaction and fibrosis. These patients usually have pain and hyperamylasemia, but may be asymptomatic. They may present with an abdominal mass, causing compressive symptoms.

Systemic complications[1]

Table-II

Metabolic
Hypocalcemia, hyperglycemia, hypertriglyceridemia, acidosis
Respiratory
Hypoxemia, atelectasis, effusion, pneumonitis
Acute respiratory distress syndrome (ARDS)
Renal
Renal artery or vein thrombosis
Renal failure
Circulatory
Arrhythmias
Hypovolemia and shock; myocardial infarct
Pericardial effusion, vascular thrombosis
Gastrointestinal
Ileus
Gastrointestinal hemorrhage from stress ulceration; gastric varices (secondary to splenic vein thrombosis)
Gastrointestinal obstruction
Hepatobiliary
Jaundice
Portal vein thrombosis
Neurologic
Psychosis or encephalopathy (confusion, delusion and coma)
Cerebral emboli
Blindness (angiopathic retinopathy with hemorrhage)
Hematologic
Anemia
DIC (disseminated intravascular coagulopathy)
Leucocytosis
Dermatologic
Painful subcutaneous fat necrosis

Investigation

Diagnosis of Pancreatitis

According to the the American College Of Gastroenterology(ACG) guidelines, the diagnosis of Acute Pancreatis is supported by an elevation of the serum amylase and lipase in excess of three times the upper limit of normal.

Enzyme	Onset	Peak	Duration	Sensitivity	Specificity
Amylase[23,24]	2-12 hrs	12-72 hrs	7days	75-92%	20-60%
Lipase[25]	4-8 hrs	24 hrs	8-14 days	86-100%	50-99%

The advantages of amylase testing are that it is quickly performed, easily obtained and inexpensive.[25]Lipase measurements are better than those of amylase measurement, particularly in detecting alcoholic pancreatitis.[25]The specificity of lipase measurement, as well as amylase measurement, may be improved by raising the threshold to at least three times the upper limit of the normal reference values.[26]The severity of pancreatitis does not correlate well with the magnitude of elevation of serum amylase and lipase.[27]There is no value in following daily trends of serum amylase and lipase as they do not correlate with recovery or prognosis.

Trypsin / Elastase. Based on median sensitivities and specificities, an elevated trypsin level has a better likelihood ratio for detecting pancreatitis than the amylase level and is probably the most accurate serum indicator for acute pancreatitis.[28] The elastase level has not proved to be better than trypsin or lipase levels in assisting the diagnosis of acute pancreatitis. However, a serum trypsin assay is not widely available and therefore is not routinely used.

Hepatic Function Studies. Hepatic transaminase levels may be elevated in patients with pancreatitis caused by alcohol abuse or cholelithiasis with obstruction. Elevation of the serum alanine aminotransferase greater than 80 U/mL is highly specific but poorly sensitive for gallstone pancreatitis.[29]

Experimental biochemical markers that may hold promise for assessing severity of disease include trypsinogen activation peptide, interleukin-6, interleukin-10, and C-reactive protein.[30]

Radiologic Studies:

Abdominal radiograph shows Gas-filled duodenum (sentinel loop) secondary to obstruction is the most specific for pancreatitis.[20] The abdominal radiograph is frequently normal, but an abdominal radiograph is helpful for excluding other causes of acute abdominal pain.Chest radiograph reveals pleural effusions (most commonly left-sided), atelectasis, infiltrates suggestive of ARDS.

Ultrasonography. The sensitivity of this study in detecting pancreatitis is 62 to 95 percent.[31,32] However, in 35 percent of cases, the pancreas is obscured secondary to bowel gas.[25] It detects gallstones as a potential cause,it rules out and acute cholecystitis as a differential cause of pain and hyperamylasemia.It detects biliary dilatation suggestive of the need for early endoscopic retrograde cholangiopancreatography (ERCP).

*Computed Tomography (CT).*The American College of Gastroenterology (ACG) practice guidelines state that "a dynamic contrast-enhanced CT is recommended at some point beyond the first 3 days in severe acute pancreatitis (on the basis of a high APACHE score or organ failure) to distinguish interstitial from necrotizing pancreatitis."[22] A CT should also be considered for those in whom a localized pancreatic complication is suspected (e.g., pseudocyst, splenic vein thrombosis, splenic artery aneurysm). CT evidence of necrosis correlates well with the risk of other local and systemic complications.[33] The decision to perform CT will usually be taken after approximately one week of hospital admission with persisting organ failure, signs of sepsis, or deterioration in clinical status 6–10 days after admission.[34] Severity index can be calculated from CT scan.[35]CT grade(Normal pancreas 0/ Oedematous pancreatitis 1/Oedematous plus mild extrapancreatic changes 2/ Severe extrapancreatic changes including one fluid collection 3/ Multiple or extensive extrapancreatic collections 4). Necrosis score(None 0/ One third 2/ One third to one half 4/ Half 6).

CT severity index = CT grade+necrosis score

CT Severity Index	Complication	Death
0-3	8%	3%
4-6	35%	6%
7-10	92%	17%

Follow up CT

In patients with a CT severity index of 3–10, additional follow up scans are recommended only if the patient's clinical status deteriorates or fails to show continued improvement.[36] However, some would advise a single further scan in patients who make an apparently uncomplicated recovery, before the patient is

discharged from hospital, to detect the presence of asymptomatic complications such as pseudocyst or arterial pseudoaneurysm.[36]

Magnetic resonance imaging is similar or superior to contrast CT in its ability to stage Acute Pancreatitis and detect necrosis and complications, and it does not require intravenous contrast.ERCP has a limited role in management of acute pancreatitis. It is primarily indicated in patients with severe disease who are suspected of having biliary obstruction.[37] This procedure is sometimes done to enable endoscopic sphincterotomy and remove impacted stones.

Blood glucose level to detect hyperglycaemia and *hypocalcaemia* should be identified at early diagnosis.

Investigations to diagnose etiology[34]

- Fasting plasma lipids
- Fasting plasma calcium
- Viral antibody titres
- Repeat biliary ultrasound
- MRCP
- CT (helical or multislice with pancreas protocol)

Further investigations (usually appropriate for recurrent idiopathic acute pancreatitis)

- Further ultrasound
- Endoscopic ultrasound
- Autoimmune markers
- ERCP—bile for crystals-bile and pancreatic cytology
- ERCP—bile and pancreatic cytology
- Sphincter of Oddi manometry
- Pancreatic function tests to exclude chronic pancreatitis

Genetic analysis is only indicated in the presence of a family history of one or more of the following: acute pancreatitis, recurrent undiagnosed abdominal pain, pancreatic carcinoma, or type 1 diabetes mellitus.

Prediction of Severity

About 20 to 30 percent of patients with acute pancreatitis develop complications of necrosis, organ failure, or both [38-40].Unfortunately, the serum amylase level and the lipase level are not specific enough measures of disease activity to be used prognostically. Clinical monitoring is inadequate for determining severity and predicting the course of pancreatitis because it only detects about 39 percent of severe cases.[41] Several systems have been developed in an attempt to provide reliable prognostic classification for patients with acute pancreatitis. However, two systems, the APACHE II scale [42] and the multiple organ system failure (MOSF) scale [43] have some advantages over the Ranson criteria[5] and Glasgow criteria[34].

World Health Association has provided a composite guideline.[44]Features that may predict a severe attack present within 48 hours of admission to hospital.

Initial assessment Clinical impression of severity
Body mass index .30
Pleural effusion on chest radiograph
APACHE II score .8

24 h after admission Clinical impression of severity
APACHE II score .8
Glasgow score 3 or more
Persisting organ failure, especially if multiple
C reactive protein .150 mg/l

48 h after admission Clinical impression of severity
Glasgow score 3 or more
C reactive protein .150 mg/l
Persisting organ failure for 48 h
Multiple or progressive organ failure

Subsequent monitoring of progress depends on repeated clinical evaluation, regular estimation of C reactive protein levels (twice weekly) and CT when indicated. There is no evidence to support the use of repeated APACHE II scores for monitoring progress.

Management

CRITICAL CARE MANAGEMENT

Oxygen

Saturation should be measured continuously and supplemental oxygen should be administered to maintain an arterial saturation greater than 95%.[34]

Intravenous fluid

Early oxygen supplementation and fluid resuscitation may be associated with resolution of organ failure,[45] and early resolution of organ failure is associated with

very low mortality,[46,47] It is wise to treat every patient aggressively until disease severity has been established.[36]

Fluids are given intravenously (crystalloid or colloid as required) to maintain urine output .0.5 ml/kg body weight.[34] In addition to maintenance fluid requirements, the amount sequestered should be monitored and replaced with isotonic fluids such as normal saline, with a goal of evolution and hemodilution. Some patients may require as much as 250 to 350 mL/hr, particularly in the early phases of Acute Pancreatitis. Of course, the aggressiveness of fluid replacement must be tempered in the presence of underlying cardiac or renal disease. The rate of fluid replacement should be monitored by frequent measurement of central venous pressure in appropriate patients.

Analgesia

In addressing the patient's pain, analgesia with meperidine (Pethidine) along with an antiemetic is preferred over the use of morphine, because morphine may cause spasm of the sphincter of Oddi, which has the potential to worsen the condition.[2]

NUTRITION

- Withholding oral intake in an attempt to reduce pancreatic stimulation by food, hydrochloric acid, cholecystokinin and secretin.[18]
- Nasogastric tube may be used when the patient has protracted vomiting or if obstruction is seen on the abdominal radiograph.[18,21,23,48]
- Nutrition support may be withheld in mild pancreatitis for several days. The ACG guidelines advise nutrition support if NPO status is maintained for longer than 5 to 7 days.[22] In patients with severe disease, oral intake is inhibited by nausea; the acute inflammatory response is associated with impaired gut mucosal barrier function. It has been suggested that nutritional support may help to preserve mucosal function and limit the stimulus to the inflammatory response. In these circumstances enteral feeding seems to be safer than parenteral feeding, with fewer septic complications.[49,50] The use of enteral feeding may be limited by ileus. If this persists for more than five days, parenteral nutrition will be required.

Prophylactic antibiotic

Combination of the numbers observed in studies suggests that there may be a significant reduction in complications and deaths in patients with predicted severe acute pancreatitis treated with prophylactic antibiotics but this ignores the major inconsistencies within and between these trials.[51-58]

There remains no consensus view on the value of antibiotic prophylaxis. If antibiotic prophylaxis is used, it seems sensible to limit the duration of prophylaxis to 7–14 days. Treatment should not be continued beyond that time without evidence of infection provided by bacterial growth on culture. When such evidence exists, appropriate antibiotic therapy should be guided by the results of sensitivity testing in accordance with critical care medicine guidelines.[58]

Trials of antibiotic prophylaxis against untreated controls in severe acute pancreatitis

Reference	Agent	Durationx	Pancreatic infection		Deaths	
		(Days)	Treated	Control	Treated	Control
Delcenserie[53]	Ceftazidime, amikacin, metronidazole	10	0/11	3/12	1/11	3/12
Isenmann[54]	Ciprofloxacin, metronidazole	14 (3–23)	7/58	5/56	3/58	4/56
Nordback[55]	Imipenem/cilastatin	Not stated	2/25	14/33	2/25	5/33
Pederzoli[56]	Imipenem	14	5/41	10/33	3/41	4/33
Sainio[57]	Cefuroxime	14	9/30	12/30	1/30	7/30
Schwarz[58]	Ofloxacin, metronidazole	10	8/13	7/13	0/13	3/13
Total	31/178		51/177	10/178	26/177	

SPECIFIC DRUG THERAPY

There is no proven therapy for the treatment of acute pancreatitis.[36,59]Despite initial encouraging results, antiproteases such as gabexate, antisecretory agents such as octreotide, and anti-inflammatory agents such as lexipafant have all proved disappointing in large randomised studies.[60-62]Anticholinergics have been used in an attempt to decrease gastric secretions and increase pH. As with the use of nasogastric tubes, anticholinergics do not decrease hospital stay or pain.

GALL STONE PANCREATITIS AND TREATMENT OF GALL STONES

- ERCP with papillotomy and stone extraction in the setting of stone impaction and cholangitis.[63]
- Severe gallstone pancreatitis in the presence of increasingly deranged liver function tests and signs of cholangitis (fever, rigors, and positive blood cultures) require an immediate and therapeutic ERCP."[44]

SURGICAL TREATMENT FOR ACUTE PANCREATITIS AND PANCREATIC NECROSIS

- Patients with persistent symptoms for more than seven days, and greater than 30% pancreatic necrosis, and those with smaller areas of necrosis and clinical suspicion of sepsis should undergo image guided fine needle aspiration (FNA) to obtain material for culture.[64]
- All patients with infected necrosis require intervention by radiological or surgical drainage.[36,59,64]
- Local complications of pancreatic necrosis, such as pseudocyst and pancreatic abscess, often require surgical, endoscopic, or radiological intervention. Reported results of surgical and endoscopic drainage are similar.[36,59]

Outcome: Overall outcome is variable. Incase of Interstitial Acute Pancreatitis it is <1%, incase of Sterile it is 10% and incase of Infected one 30%.

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