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ACUTE PANCREATITIS

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Abstract:

Introduction: *One of the most common diseases with high mortality is acute pancreatitis, which is caused by gallstone disease or excess alcohol ingestion. Elevation in serum amylase and lipase levels supports the diagnosis of acute pancreatitis. Potential valuable tests in evaluation of acute pancreatitis are ultrasound and magnetic resonance cholangiopancreatography, additionally, they're useful in identifying stones in the common bile duct and directly evaluating the pancreatic parenchyma.*

Aim of work: *In this article, we highlight the classification, treatment and prognosis of acute pancreatitis, and treatment options for complications of acute pancreatitis.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: acute pancreatitis, causes of pancreatitis, diagnosis of pancreatitis, management of pancreatitis*

Conclusions: *Acute pancreatitis remains a common reason of hospital admission necessitating a multipronged approach for the diagnosis and treatment. Management is predominantly focused toward supportive care with advanced endoscopic adjuncts (in the setting of choledocholithiasis, symptomatic pseudocysts, or walled-off pancreatic necrosis) and early surgical mediation (i.e., cholecystectomy in the setting of an index admission for gallstone pancreatitis) used when clinically needed, although its antecedents remain multifactorial, as are the number of scoring systems that define severity.*

Key words: *pancreatitis, gastroenteritis, acute care.*

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INTRODUCTION:

One of the most common diseases with high mortality is acute pancreatitis, which is caused by gallstone disease or excess alcohol ingestion. Elevation in serum amylase and lipase levels supports the diagnosis of acute pancreatitis. Elevation of amylase level occurs within hours of the development of pain and can remain elevated for 3 to 5 days. Although levels of serum lipase can be elevated in other conditions, it provides a higher specificity for pancreatic disease. Mild elevations of liver function test results, hyperglycemia, hypocalcemia, leukocytosis are laboratory abnormalities encountered in acute pancreatitis. Potential valuable tests in evaluation of acute pancreatitis are ultrasound and magnetic resonance cholangiopancreatography, additionally, they're useful in identifying stones in the common bile duct and directly evaluating the pancreatic parenchyma [1].

In this article, we highlight the classification, treatment and prognosis of acute pancreatitis, and treatment options for complications of acute pancreatitis.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: acute pancreatitis, causes of pancreatitis, diagnosis of pancreatitis, management of pancreatitis

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

PATHOPHYSIOLOGY:

Inappropriate activation of trypsinogen to trypsin is the main problem in the pathogenesis of AP. The activation of these enzymes which leads to autodigestion of pancreatic tissues is responsible for the resulting necrosis of the acini and pancreatic islets with the interstitial fat necrosis and necrotizing vasculitis [2].

The release of active pancreatic enzymes into the blood vessels and stimulation of inflammatory cytokines such as inflammatory cytokines such as interleukin-1, interleukin-6 and interleukin-8 from neutrophils, macrophages and lymphocytes, are results of pathological changes in the pancreatic gland. Once Macrophages release interleukins and tumor necrosis factor- α (TNF-α) triggering of inflammatory cascade which can lead to systemic inflammatory response syndrome (SIRS) [3]. Multiorgan dysfunction syndrome and ARDS may develop from SIRS. The natural course of SAP includes "first or early phase" which is a response to pancreatic injury from the systemic inflammation, it normally characterizes the first 14 d of the disease. There is no association with infection, however, in this phase organ failure is common. After the 14 d post onset of the disease the "second or late phase" starts, marked by infection of the gland, necrosis and septic systemic complications causing a great increase in mortality. One of the most important risk factors of necrotic pancreatitis is infection of the necrotic pancreas that happen in the 8% to 12% of the patients with AP and in 30% to 40% of patients with necrotizing pancreatitis [4].

ETIOLOGY:

To prevent recurrence of AP and in order to optimize swift management it is essential to identify the etiology. Most common causes of AP in the western world are biliary tract disease (38%) and alcoholism (36%). However, around 10% of cases remain unknown (idiopathic AP) [5].

Gallstones

When an increased serum alanine aminotransferase goes up to 3 times its normal value in patients with absent history of alcohol consumption, gallstone pancreatitis is on the top list of diagnosis.

Most cases of gallstone pancreatitis are caused by gallstones passing into the bile duct and temporarily lodging at the sphincter of Oddi. However, obstruction of duct can also be localized in the pancreatic duct. Activation of digestive enzymes which is due to a duct obstruction leading to increased pancreatic duct pressure resulting injury to acinar cells, this mechanism is not completely proven. Diameter of up to 5 mm can migrate distally into the biliary duct whilst gallstones of a diameter more than 8 mm remain in the gallbladder [6].

However, when liver function tests are normal since 15%-20% of patients with biliary AP can have normal concentrations of hepatic enzymes an etiology of biliary origin should not be excluded. The initial line of investigation should be a trans-abdominal ultrasound (T-A US) when cases of biliary etiology is suspected. Ultrasound has a great value in demonstrating gallbladder stones and dilation of the CBD in addition to other pathology which can be unrelated to the pancreases. Sometimes T-A US can

be normal although the case can be a high clinical suspicion of biliary cause of AP, magnetic resonance cholangiopancreatography or endoscopic US should be performed to be able to visualize the presence of microlithiasis or other causes of duct obstruction [7].

Alcohol

Second cause of AP is alcohol consumption. Main target of injury by ethanol is the acinar cell, despite that, there is not an accepted explanation to why some patients are more predisposed to developing AP than others who consume similar quantities of alcohol. A combination of environmental and genetic factors can be the explanation to the pathogenesis of alcohol pancreatitis. Mutation of the cationic trypsinogen gene and serine peptidase inhibitor, Kazal type 1 (SPINK1) genes, are suggestions in genetic studies explaining the cause in hereditary pancreatitis [8].

Post-ERCP acute pancreatitis

5% is the risk rate of developing AP after endoscopic retrograde cholangiopancreatography (ERCP) **[9]**. Post-ERCP main risk factors consist of female gender, presence of periampullary diverticulum, and procedure-related factors such as cannulation time of over 10min and major papilla sphincterotomy. However, there seems to be a link between procedure-related factors and the risk of developing asymptomatic hyper-amylasemia, which appears in 35%-70% of patients [10].

Trauma

Elevation in amylase and lipase in 17% of cases and clinical AP in 5% are due to abdominal trauma. An injury to the pancreas occurs more commonly in penetrating injuries (e.g. from knives, bullets) than in blunt abdominal trauma (e.g. from steering wheels, horses, bicycles). Ductal injury across the spine can be because of a blunt injury that crushes the gland [11].

Drug-induced pancreatitis

A pancreatitis which is due to a drug is considered uncommon (0.1%-2%) and is usually mild and self-limiting. In the literature, the actual incidence of drug-induced AP is unknown since the evidence is derived mainly from the case reports and the diagnosis is always difficult due to the inability to distinguish the effects of drugs from other causes of AP. The following medications has great correlation with AP these medications include azathioprine, sulfonamides, sulindac, tetracycline, valproic acid, didanosine, methyldopa, estrogens, furosemide, 6-mercaptopurine, pentamidine, 5-aminosalicylic acid compounds, corticosteroids, and octreotide [12].

Infections

Less than 1% of all AP are due to infections and tend to be milder than biliary and alcohol-induced AP. Most common list of viral infections causing AP especially in children include Epstein-Barr, coxsackie virus, echovirus, varicella-zoster and measles. Infections caused by bacteria include *Mycoplasma pneumoniae*, *Salmonella typhosa*, *Leptospira*, *Campylobacter* and *Mycobacter ium tuberculosis.*

Globally, migration of worms in and out of the duodena papillae are features of ascariasis which also can cause AP [13].

Hereditary pancreatitis

An autosomal dominant gain-of-function disorder related to mutations of the cationic trypsinogen gene (*PRSS1*) is the hallmark cause in hereditary pancreatitis, which has an 80% penetrance. Pancreatic autodigestion can be due to the mutations in PRSS1 gene causing premature conversion of trypsinogen to active trypsin. Due to this mutation or genetic syndrome patients are at high risk of developing chronic pancreatitis at young age and developing pancreatic cancer [14].

Other mutation blocking the active binding site of trypsin (SPINK1 gene) renders the site inactive, associated with acute and chronic pancreatitis. In severe cases of SPINK1 mutations development of chronic pancreatitis can occur in childhood. In cases with mild gene mutations of CFTR gene, in comparison to the general population an increased risk of developing chronic and acute pancreatitis has been seen [15].

Hypercalcemia

Diseases such as primary hyperparathyroidism and hypercalcemia can cause AP. Excessive doses of vitamin D, familial hypocalciuric hypercalcemia and total parenteral nutrition are common causes of hypercalcemia in less than 1% of all cases of pancreatitis.

Hypertriglyceridemia

Once triglyceride levels reach 1000mg/dL AP commonly appears. type I, Type II and Type V hyperlipidemias are associated with hypertriglyceridemia and causes about 2% of AP. Measurement of triglyceride levels should be immediately done once clinical presentation of AP appears due to the fact that this level tends to decline during hospitalization because of fasting and IV fluid resuscitation. Alcoholism, obesity and poorly controlled diabetes mellitus are the main causes in acquired hypertriglyceridemia in adults. Low-fat diet,

a regular exercise regimen, and tight control of diabetes, with use of lipid-lowering drugs such as statins can prevent recurrent attacks of AP.

Tumor

In about 14% of patients suffering from pancreatic tumors, obstruction of the pancreatic ductal system can increase the intraduct pressure and cause AP. Other causes of AP include Pancreatic ductal carcinoma, ampullary carcinoma, islet cell tumor, solid pseudotumor of the pancreas, sarcoma, lymphoma, cholangiocarcinoma, or metastatic tumor. Additionally, other causes include a pancreatic cystic neoplasm, such as intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenoma, or serous cystadenoma [16].

Postoperative

Various surgical procedures can cause AP in the postoperative period. Intraoperative manipulation causing pancreatic trauma or transient intraoperative hypotension are the main mechanism causing pancreatitis. Compared to pancreatitis associated with other etiologies, postoperative AP is usually hard to diagnose and confirm.

Autoimmune pancreatitis

Extreme rare cause of AP includes this relatively new described entity. Confirmation of AP is done by specific radiological and histological findings to reach the diagnosis of autoimmune pancreatitis. Radiologically, on ERCP irregular narrowing of the proximal pancreatic duct and a focal mass in the pancreatic head on computed tomography is seen. Usually patients present with an elevated Ig G4 level in the serum and infiltration of IgG4-containing plasma cells in the pancreas. inflammatory bowel disease, primary sclerosing cholangitis, primary biliary cirrhosis and Sjogren's syndrome are associated with as well in young people suffering these elevated IgG4 levels. Treatment choice is based on steroids.

DIAGNOSIS:

Conditions must be met in diagnosing acute pancreatitis according to The Revised Atlanta Criteria of 2012 (updated from 1992) requiring two of three: (1) abdominal pain consistent with acute pancreatitis (i.e., epigastric abdominal pain with possible radiation to the back), (2) lipase or amylase ≥ 3 times the upper limit of normal, and or (3) characteristic imaging features of acute pancreatitis as noted on CT, MRI, or ultrasound [17]. However, recommendations in imaging of pancreas is recommended only in patients whom diagnosis is not clear, for those who have failed to improve within the initial 48-72 hours [18]. The onset is referred to the time when pain in the abdomen began, and not during hospital admission.

interstitial edematous and necrotizing are the subclassification of acute pancreatitis. Where necrotizing pancreatitis happens in around 5–10% of patients of acute pancreatitis. Sterile or infected pancreatitis are the subdivision of necrotizing pancreatitis [17].

Treatment

Treatment of acute pancreatitis is dependent on the severity of disease and the complications associated with it that may rise.

Fluid Resuscitation

Microvascular permeability, interstitial edema, vasoconstriction, and eventual decreased capillary perfusion in animal models are the consequences of proinflammatory cytokine cascade which arises from the disease process that led to acinar cell injury. Additionally, pancreatitis causes hypovolemia by inducing poor oral intake, insensible losses, third-spacing of fluids, and emesis. Thus, the cornerstone of conservative treatment is fluid resuscitation. In different recommendations on the initial fluid resuscitation regimen have varied from 250–500 cc/hr with or without bolus to achieve hemodynamic stability, with a target of mean arterial pressure > 60 or simply targeting a urine output > 0.5 cc/kg/hr that is in the absence of cardiac, pulmonary, or renal contraindications. Although there are no specific targets currently recommended, reduced uremia (indicating adequate kidney perfusion), hemodilution (decreased hematocrit), and normalization or maintenance of normal creatinine have been proposed. An approach to fluid resuscitation which is practical, evidence-based is needed [19].

Early resuscitation has proven to decrease the risk of SIRS, ICU admission, organ failure, and length of stay, with respect to timing. The initial 24 hours appear to be paramount, even though the precise duration of aggressive hydration remains unclear. Additionally, fluid type can prove to make a difference as well. In a case of randomized controlled study performed by Wu and colleagues compared the effectiveness of normal saline and ringer lactate in acute pancreatitis, they discovered a superior reduction in SIRS and CRP levels in those who received ringer lactate. These results, in combination with possible nonanion gap metabolic acidosis with normal saline renders lactated Ringer's solution preferable. therefore, we use a total infusion of 2500–4000 mL in the initial 24 hours while reevaluating

noninvasive clinical targets and biochemical targets every 6–8 hours [20].

Nutrition

Available data supports early resumption of diet with low-fat solidity accompanying mild acute pancreatitis. Although it does not lead to a lesser length of stay in the hospital nor decreased 30-day readmission rate, a trial of randomized study assessing the tolerance of low fat sold meal vs a liquid diet demonstrated no increased adverse events (pain/nausea necessitating cessation) and led to increased caloric intake. Additionally, initiation of oral intake in mild acute pancreatitis on admission appeared to be safe and that one does not have to wait for the pancreas to "cool down" per se. Incidence of pancreatic infectious complications such as infected necrosis, abscess, and multiorgan failure has shown to be decreased in a randomized controlled trial data of enteral versus parenteral nutrition in severe pancreatitis. By maintaining intestinal barrier enteral nutrition prevents microbial translocation. The usefulness of starting enteral nutrition does not prove to extend beyond 48 hours of admission, as no reduction in mortality, infectious complications, or multiorgan failure was found when initiated beyond that point [21].

In a randomized trial of 78 cases which assessed the benefit of nasogastric versus nasojejunal feeds showed that nasogastric feeding was not inferior to nasojejunal feeding with no difference in secondary endpoints such as pain, intestinal permeability (measured by lactulose/mannitol excretion), and endotoxemia (as measured by immunoglobulin core G and M endotoxins). Therefore, we use nasojejunal feeds in patients who are unable to tolerate oral feeding [22].

Role of Endoscopic Retrograde Cholangiopancreatography (ERCP)

Acute Biliary pancreatitis secondary to choledocholithiasis is specifically targeted by ERCP in patients with AP. Although countless scoring systems and algorithms were developed, the recommended strategy to assign risk of choledocholithiasis recommended by the American society for gastrointestinal endoscopy is commonly used. very strong (observed on US, cholangitis or total bilirubin > 4 mg/dL), strong (CBD > 6 mm with gallbladder in situ or total bilirubin between 1.8 and 4 mg/dL), and moderate (abnormal AST/ALT or alkaline phosphatase, clinical gallstone pancreatitis, or age > 55) are the stratified predictors of choledocholithiasis. The risk of choledocholithiasis is high when an individual has one very strong predictor or two strong predictors. The rest are considered intermediate and no qualifying predictors is considered low risk [23].

It can be harmful and of limited value in patients with mild biliary pancreatitis with signs and symptoms of improvement to use ERCP preceding cholecystectomy. In related cases, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) can be utilized for purposes of diagnosis [18].

To reduce the risk of postprocedural pancreatitis and the severity of pancreatitis in those who subsequently developed symptoms a multicenter, randomized, placebo controlled, double-blind clinical trial of 602 high risk patients was conducted with a rectal administration of indomethacin. However, in another study of 449 predominantly moderate risk individuals undergoing ERCP, no clinical benefit was seen, and the trial was discontinued due to futility. therefore, since it is easy to utilize, inexpensive, and safe, rectally administration of indomethacin could be done in high risk patients prior to ERCP [24].

Antibiotics

It is not advised to use prophylactic antibiotic in the absence of suspected or confirmed infection. Aside from imipenem, decrease in pancreatic infection risk or mortality has not been observed with prophylactic use of antibiotic. Further trials which were randomized using prophylactic antibiotics have not shown benefits. Prompt usage of regimens which are known to penetrate pancreatic necrosis are recommended (quinolones and metronidazole, or carbapenems) when confirmed or suspected pancreatic infection (infected pseudocyst or necrosis) occurs [25].

Management of Persistent Fluid Collections or Infected Necrosis

persistent abdominal pain, gastric outlet obstruction, fluid leakage due to disconnected pancreatic duct, and infection are significant symptoms which present that requires intervention upon pancreatic fluid collection or infected necrosis ensue. It is imperative to classify fluid collections into pseudocyst or walled-off pancreatic necrosis due to the differences in prognosis and treatment. MRI and endoscopic ultrasound (EUS) are better for assessment than CT imaging since CT scan can underestimate the existence of necrotic debris. Change in management has been conducted from when it was a surgical intervention to now less invasive approaches [26].

Open Surgical Drainage

The treatment with open necrosectomy is done through laparotomy via a subcostal incision, where the removal of all necrotic tissue is made bluntly. It is better to intervene early with conservative management with late surgical intervention than to manage early with necrosectomy. It is preferred to delay the surgery for up to four weeks after the onset of disease, as this is thought to let some time for the acute collection of necrotic tissue to mature and demarcate, hereby facilitating necrosectomy. High complications or death (69%) can ensue in open necrosectomy discovered in a recent randomized control trial. In addition, higher rate of long-term complications including incisional hernias (24%), new onset diabetes (38%), and use of pancreatic enzymes (33%) can happen in patients undergoing open necrosectomy. Thus, a "step-up" approach therapy has been preferred. The approach starts with more conservative ways (percutaneous, laparoscopic, and endoscopic) first and then keeping surgery for cases of salvage therapy [27].

Minimally Invasive Techniques

There are a few unique types of noninvasive techniques to deplete and debride persistent fluid accumulations or infected pancreatic necrosis, consisting of image-guided percutaneous drainage, laparoscopy, and retroperitoneoscopy [28].

Utilizing ultrasound or CT guidance, percutaneous drain placement lets external access to the zone of necrosis to be taken. A significant number of patients can be managed with percutaneous drain (PCD) alone without the requirement for surgical necrosectomy. The PANTER trial discovered that 35% of their patient population experiencing drainage did not require further surgery. A systematic audit by van Baal et al. [29] demonstrated that percutaneous drainage by its own was helpful in 56% of cases. In the patients who needed surgery, drain placement delayed surgical management for few weeks, by allowing for sepsis control. Pancreaticocutaneous and pancreaticoenteric fistulas (most common), as well as procedure-related complications (i.e., bleeding, colonic perforation, abdominal pain, pneumothorax, or catheter dislodgment) are well known complications of percutaneous drain placement [29]. Due to the risk of contamination of peritoneal cavity, transperitoneal laparoscopy is not well supported [28].

Video-assisted retroperitoneal debridement (VARD) is an endoscopic necrosectomy done on a dilated percutaneous drain tract. Subcostal incision of 5 cm is made in the left flank, the necrosis is initially moved with handling forceps, and the videoscope is embedded. Lingering necrosis is taken out with laparoscopic grasping forceps. When required minimally invasive retroperitoneal necrosectomy is followed when initially PCD drain is placed, assignment of patients from the PANTER trial with pancreatic necrosis to either primary open necrosectomy or a step-up approach. It demonstrated that an insignificantly invasive step-up approach was related with lower rate of major complications and death when contrasted with open necrosectomy [27].

CONCLUSION:

Acute pancreatitis remains a common reason of hospital admission necessitating a multipronged approach for the diagnosis and treatment. Management is predominantly focused toward supportive care with advanced endoscopic adjuncts (in the setting of choledocholithiasis, symptomatic pseudocysts, or walled-off pancreatic necrosis) and early surgical mediation (i.e., cholecystectomy in the setting of an index admission for gallstone pancreatitis) used when clinically needed, although its antecedents remain multifactorial, as are the number of scoring systems that define severity.

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