Isolated Acute Rheumatic Pancreatitis- A Case Report

Ramachandran Muthiah

Morning Star hospital, Marthandam, Kanyakumari District, India

*Corresponding Author: Ramachandran Muthiah. Morning Star hospital, Marthandam, Kanyakumari District, India.

Abstract

To emphasize the role of antibiotics in acute pancreatitis as prophylactic and therapeutic benefits. A 32-year-old obese male was admitted with acute abdomen in the emergency room. He was supported with intravenous fluids and the blood chemistry revealed elevated amylase and lipase levels, raised ESR and a positive ASO titer test. CT abdomen suggested interstitial edematous pancreatitis (IEP) and no fluid collection. Patient was treated with IV cefotaxime and metronidaziole and his condition remarkably improved with therapy and blood parameters returned normal at the end of 4 weeks and follow up CT revealed no abnormal findings and symptom free thereafter. Acute pancreatitis is usually a sterile inflammatory process caused by chemical autodigestion of pancreas. The edematous form of acute pancreatitis needs to correct its etiological factor to avoid recurrence. It is observed as an initial manifestation of group A beta hemolytic streptococcal infection in this patient and antibiotics play a role as curative and prophylactic in selected cases.

Keywords: Acute abdomen, pancreatitis, ASO titer, elevated pancreatic enzymes, antibiotics

Introduction

Acute pancreatitis is a condition where the pancreas becomes inflamed (swollen) over a short period of time. Most people with acute pancreatitis start to feel better within about a week and have no further problems. It is sometimes associated with a systemic inflammatory response that can impair the functions of other organs, can go on to develop serious complications. Thus, there is a wide spectrum of disease from mild (80%), where patients recover within a few days, to severe (20%) with prolonged hospital stay, the need for critical care support, and 15-20% risk of death if patients have organ failure during the first few weeks of illness [1].

It occurs with an estimated incidence of 10-40 per 100,000 per year in the UK [2]. An increase in the annual incidence for acute pancreatitis has been observed worldwide varies between 4.9 and 73.4 cases per 100,000 [3],[4]. Every year, there are 275,000 hospitalisations for acute pancreatitis in the United States. In 2009, it is the most common gastroenterology discharge diagnosis with a cost of 2.6 billion dollars.

The evolving issues of antibiotics, nutrition, endoscopic, radiologic, surgical and other minimally invasive interventions will be addressed on early management to decrease morbidity and mortality.

Some studies have suggested that the administration of prophylactic antibiotics reduces the risk of pancreatic necrosis becoming infected [5]. Abdominal pain is the presenting manifestation of acute rheumatic fever [6], usually precedes the other rheumatic signs and it is the consequence of rheumatic inflammatory process affecting the pancreas in this patient and so this case had been reported.

Case Report

A 32 years old male was admitted with sudden onset of severe abdominal pain and he was found to be toxic and emaciated. His pulse rate was 114 bpm, blood pressure 90/60 mmHg and temperature 100.4·F. Physical examination revealed distended abdomen with tenderness in the epigastric region. He had a history of alcoholic drinks occasionally. He was on anticonvulsants (phenytoin sodium 100mg twice daily) for the past 4 years as he suffered 2 to 3

episodes of seizure attacks before and his CT brain revealed normal earlier. On admission, his serum amylase was 548 IU/L (normal 10 to 96 IU/L). The total leukocyte counts 7190 cells/cumm blood (normal 4000 to 10000/cumm of blood), neutrophils 65.8% (normal 40 to 75%), lymphocytes 26.3% (normal 25 to 35%), monocytes 4% (normal 3.5 to 11.5%), eosinophils 3.5% (normal 2 to 6%), basophils 0.4% (normal 0 to 1%). ESR (Erythrocyte sedimentation rate) 26 mm in one hour (normal 0 to 14 mm per hour). Serum bilirubin (total) 1.2mg/dl (normal 0.4 to 1.2mg/dl). Random blood glucose 98mg/dl (normal 60 to 125 mg/dl). Total cholesterol 180mg/dl (normal 150 to 220 mg/dl), serum triglycerides 270mg/dl (normal 50 to 150 mg/dl). Serum SGOT (AST) 88 IU/L (normal 5 to 41 IU/L, SGPT (ALT) 78 IU/L (normal 5 to 50 IU/L). The renal parameters and serum electrolytes were within normal range. Serum lipase was highly raised as 1476 IU/L (normal < 60>Figures 1 and 2, with normal pancreatic parenchyma and no significant ductal dilatation and calcification. The liver and gallbladder appear normal, no evidence of gallstones and no fluid collections. The abdominal distension subsided on 4th day and the patient was advised to resume semisolid liquid diet, tendor coconut water, fruits and smashed vegetables without chillies slowly. The milk products were avoided. His condition began to improve thereafter. After one week of treatment, the amylase level decreased to 303.1 IU/L and lipase level becoming 240.4 IU/L, AST 84 IU/L, ALT 80 IU/L. Then one week thereafter, the amylase level reduced to 151.2 IU/L, lipase level 128.4 IU/L, AST 49 IU/L and ALT remaining high as 89 IU/L. At 3rd week, AST 36 IU/L, ALT 51 IU/L, amylase 148 IU/L, lipase 115 IU/L and ASO titer 288.5 IU/ml.

The treatment continued and at the end of 4 weeks, the amylase 69 IU/L, lipase 31 IU/L and ASO titer became negative. The CT abdomen revealed no fat stranding and the pancreas appeared normal. The patient get discharged to home and advised to avoid alcohol and fatty foods thereafter. The patient was symptom free and healthy on one year follow up, advised lifelong penicillin prophylaxis with oral penicillin V 250mg twice daily to prevent recurrent attacks of pancreatitis. Since he is obese with body mass index (BMI 32%), regular exercise programmes and diet control were advised for weight reduction with periodic medical check-up.

The RT PCR for COVID 19 infection (reverse transcriptase polymerase chain reaction test) was negative at present and it was not done initially since unknown at the time of presentation.
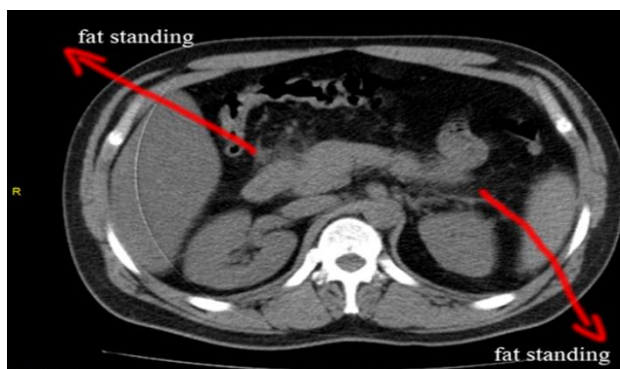

Fig 1: showing the mild increase in densities of 'fat stranding' as 'mistiness' or 'hazy streaky densities' representing the inflammatory changes in the peripancreatic fat near the uncinate process of pancreas. extending towards tail region and perinephric area suggesting "acute interstitial edematous pancreatitis (IEP)"
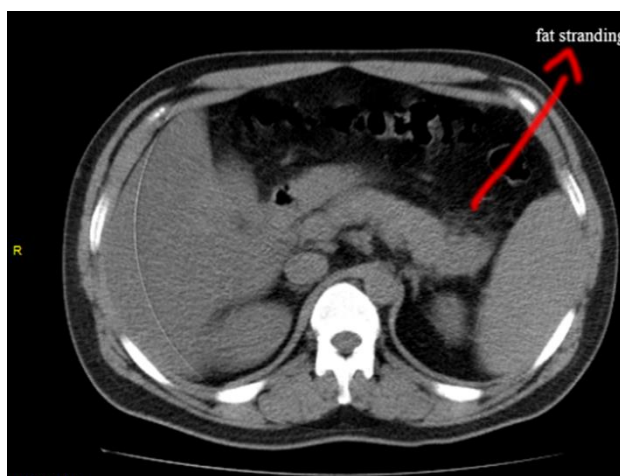

Fig 2: showing the 'mistiness' (fat stranding) in the tail region of the pancreas

Discussion

Etiopathogenesis

The pancreas is a secretory organ with both endocrine and exocrine functions and the main functional unit is the acinar cell, which comprises the parenchyma of the gland. Exocrine products from the acinar cells are secreted into a tubular system and the digestive enzymes are released via the pancreatic duct into the small intestine where they are activated to break down the fats and proteins. The digestive hormones (insulin & glucagon) produced by the pancreas are released into the blood stream where they help to regulate the blood glucose level.

Normally, digestive enzymes released by the pancreas are not activated to break down fats and proteins until they reach the small intestine. Trypsin is a digestive enzyme produced in the pancreas in an inactive form and ethanol molecules affect the pancreatic cells, triggering them to activate trypsin prematurely. When the digestive enzymes are activated in the pancreas, inflammation and local damage as 'acinar cell destruction' histologically occurs, leading to pancreatitis. Neutrophil

polymorphs and macrophages infiltrate the pancreas and release their own proteases, free radicals, and cytokines which compound the vicious cycle of tissue damage and inflammation, inducing an 'acute systemic inflammatory response syndrome (SIRS)' and organ damage. The patient may become dehydrated and then heart, lungs, kidney fail. In very severe cases, pancreatitis can result in bleeding into the gland, leading to shock, serious tissue damage, infection, fluid collections and sometimes death.

There are many causes of pancreatitis as obstruction of the secretory tree or direct parenchymal cell damage. The gallstones, infection and alcoholism are the most common causes of acute pancreatitis. In recurrent acute pancreatitis, Oddi sphincter manometry is performed and a basal sphincteric pressure > 40 mmHg [7] is the most common abnormal finding described in 30-40% of cases. DIP (drug induced pancreatitis), which is an overlooked diagnosis in the clinical setting, must be rigorously considered whenever patients are on a set of new drugs and presenting with even, minimal symptoms and signs of acute pancreatitis.

Drugs are responsible for 0.1% - 2% of acute pancreatitis incidents. The majority of drug-induced pancreatitis cases are mild to moderate in severity; however, severe and even fatal cases can occur. The newly emerged drugs like propofol infusion, antidiabetics (GLP1- Glucagon-like Peptide-1 Receptor) agonists and DDP4 (Dipeptidyl Peptase IV) inhibitors and SGLT2 (Sodium-glucose Cotransporter-2) inhibitors, particularly, canagliflozin), antibiotics (minocycline), antihypertensive agents (enalapril, lisinopril, captopril, ramipril, perindopril, and less frequently angiotensin receptor blockers), proton pump inhibitors (omeprazole, pantoprazole, and lansoprazole), anticancer drugs (nivolumab, pembrolizumab, ipilimumab), the newer TKIs (Tyrosine kinase inhibitors- vemurafenib and ponatinib), proteasome inhibitors (bortezomib), and non-selective TACE (Trans arterial chemoembolization**)**, and direct-acting antiviral therapies (DAAs) of hepatitis C virus along with ribavirin and currently, more than 500 drugs have been reported in the World Health Organization database as offenders of acute pancreatitis. The onset of drug-induced pancreatitis after initiation of medications ranges from a few months to several years, with a median of 5 weeks; onset after rechallenge can occur within hours. The latency between initiation of the offending drug and developing acute pancreatitis can be short (less than 24 h), intermediate (1-30 days), and long (more than 30 days). According to Badalov classification system of drug induced pancreatitis, the latency is described as consistent with the drug-related pancreatitis when 75% of cases were related to any of the previously mentioned groups. Potential mechanisms for drug-induced acute pancreatitis include pancreatic duct constriction, immune-mediated inflammatory response, direct cellular toxicity, arteriolar thrombosis, metabolic effects, hypersensitivity (Idiosyncratic) reactions, localized angioedema effect in the pancreas and Influence of medication on the bile flow.

The onset of acute pancreatitis induced by statins has been observed from hours to years after treatment. Because of the variance in the latency period, the mechanism may be related to a direct toxic effect to the pancreas and the accumulation of a toxic metabolite. Other mechanisms of action of statin-induced acute pancreatitis are speculated to be associated with rhabdomyolysis, myalgia, and/or metabolism or drug interactions through cytochrome P-450 3A4 (CYP3A4) In several case reports, either myalgia or rhabdomyolysis occurred before development of acute pancreatitis and pravastatin does not metabolize CYP3A4, it may have fewer case reports of drug-induced acute pancreatitis than other statins. A possible mechanism of action for angiotensin converting enzyme (ACE) inhibitor–induced acute pancreatitis is proposed to follow the mechanism of local angioedema of the pancreatic duct as they decrease the degradation of bradykinin which causes increased vascular permeability in the pancreas and can result in pancreatic edema. In addition, angiotensin II receptors may be important in regulating secretion and microcirculation within the pancreas.

The onset of acute pancreatitis is sudden. The patient presents with epigastric abdominal pain, vomiting and collapse. The pain is steady, boring and severe and often made worse by walking and lying supine and better by sitting and leaning forward. Patients are restless and bringing their knees to their chest in an effort to alleviate the pain. The pain usually radiates to back, but may radiate to the right or left. Marked epigastric or diffuse tenderness on palpation with rebound tenderness and guarding is present in severe cases. The abdomen is often distended and tympanic, with bowel sounds decreased or absent in severe disease. The vital signs may be normal, but hypotension, tachypnea, tachycardia and low grade fever are often observed, especially with widespread pancreatic inflammation and necrosis. Jaundice is a

common finding. In 3% of patients with severe acute pancreatitis, flank ecchymosis (Grey Turner sign) or periumbilical ecchymosis (Cullen sign) develops and is suggestive of retroperitoneal hemorrhage. Some patients display alterations in mental status, more common in drug-induced acute pancreatitis and reflects exposure to drugs or to ethanol but may also result from hypotension, hypoxemia, or the massive release of toxic agents from the inflamed pancreas. The condition has to be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, acute cholecystitis and infarction of intestine following sudden occlusion of the mesenteric vessels.

Acute pancreatitis is associated with multiple infections as shown in Table 1. In most reports, bacteria are considered important only in late stage of pancreatitis and not as a primary etiological agent. Pancreatic ischemia is rare due to its rich perfusion from superior and inferior pancreaticoduodenal arteries and ischemia may results from vasculitis due to rheumatic inflammation and alcohol induced 'microcirculatory impairment' potentiated by smoking.

When pancreatic ischemia occurs, its tissues begin to die as necrosis and when it happens, the pancreas can become infected and it's spread into the blood causes 'sepsis syndrome' mimicking SIRS in its early course of acute severe pancreatitis. The risk of infection is associated with degree of pancreatic necrosis. Patients with < 30> 50% have 46.5% of risk of infection [8]. Infection of necrotic tissue by bacteria carries high morbidity and mortality [9].

Infections can result from a variety of sources

1. Bacterial translocation- from small bowel and colon through transmural colonic migration is a major source of infection in necrotizing pancreatitis [10]. Endotoxemia resulting from the release of components of gram-negative bacteria from the gut is common in patients with acute pancreatitis. The bacterial translocation from the gut lumen to mesenteric lymph nodes and subsequent hematogenous dissemination could be a possible mechanism of the development of pancreatitis. Impaired body defences predispose to translocation of gastrointestinal organisms and toxins with subsequent secondary bacterial infection.

2. Hematogenous spread

3. Biliary sources- bile duct stone or gall bladder infection ascending from duodenum via the main pancreatic duct can lead to infected pancreatic necrosis.

Most pathogens in pancreatic necrosis are gastrointestinal gram-negative bacteria (*Escherichia coli*, Proteus, *Klebsiella pneumonia*), occur via disruption of intestinal flora and damage to bowel mucosa. However, gram positive bacteria (*Staphylococcus aureus*, *Streptococcus faecalis*, *enterococcus*), anaerobes, occasionally fungi have also been found and 25% are polymicrobial infection [11].

Streptococcus pyogenes (Lancifield group A β hemolytic streptococci, a gram positive, non-motile, non-spore forming coccus is the causative organism of Rheumatic fever which is a systemic disease affecting the periarteriolar connective tissue. Acute pancreatitis is an abrupt inflammation of the pancreas and a potential pathway of inflammatory response induced by the cytokines TNF-α and IL-6 (Interleukin 6) is responsible for the development of inflammation. During bacterial invasion, the M1 protein (Matrix protein) is shed from the surface of streptococcus pyogenes into the blood stream causing widespread activation of host innate immune cells. The 'superantigens' (streptococcal pyrogenic exotoxin (Spe) mediate a non-antigen specific binding between T cell receptors and major histocompatibility complex class II molecule on antigen presenting cells. Consequently, the monoclonal cells are activated to produce large amounts of cytokines, and expression of TNF-α (*tumor necrosis factor alpha)* in the pancreatic islets may induce an inflammatory response in the pancreas and also cause dilatation and altered permeability of blood vessels, leading to acute lung damage, hypoalbuminemia, ascites and shock in susceptible individuals [12].

Among immunocompetent individuals, mumps and coxsackie B virus are the most common cause of pancreatitis. Recently, gastrointestinal manifestations of COVID 19 (corona virus disease 2019), caused by SARS-Cov-2 (severe acute respiratory syndrome corona virus 2), a family of single-stranded RNA virus are increasingly being recognized and its pathogenesis is thought to be mediated by angiotensin converting enzyme (ACE2) receptor on the host cells, which are highly expressed in pancreatic islets [13]. Acute pancreatitis can occur due to direct cytopathic effects of local SARS-Cov-2 replication or indirectly by immune mediated inflammatory response induced by the virus [14]. It has been reported that there is 17% incidence of pancreatic damage occurred in COVID 19 patients [15],[16] and CT revealed the changes of interstitial edematous pancreatitis in majority of cases rather than necrotizing pancreatitis [17].

Table 1. Infectious agents causing pancreatitis

Mumps
E. coli
Coxsackie B virus
Candida
Hepatitis B
HIV
Varicella-zoster virus
Leptospirosis
Cytomegalo virus (CMV)
Covid 19 virus
Legionella (*L. pneomophila* found in plumbing, Shower heads, water storage tanks)
Shigella
Salmonella
Parasites
Toxoplasma
Ascariasis
Clonorchis sinensis

In 1992, the Atlanta classification for acute pancreatitis was introduced to classify its various manifestations [18]. The Atlanta classification divides acute pancreatitis into two groups: interstitial edematous acute pancreatitis and necrotizing acute pancreatitis. The first category is characterized by pancreatic parenchymal and peripancreatic inflammation without necrosis, while the latter category involves inflammation and some degree of necrosis. Relatively little necrosis or organ failure is seen in mild acute pancreatitis, but severe acute pancreatitis is characterized by extensive necrosis complicated by intrapancreatic thrombosis and vascular disruption. The revised classification described two distinct phases of acute pancreatitis, a first or early phase that occurs within the first week of onset of disease and a second or late phase that takes place after the first week of onset [19] and introduced a new terminology of fluid collections as acute peripancreatic fluid collection (APFC) and acute necrotic collections (ANC).

During the first week of acute pancreatitis, the pathologic condition in and around the pancreas progress from early inflammation with variable degrees of peripancreatic edema and ischemia to resolution or to necrosis of pancreas or surrounding fatty tissue. Over the course of first week, organ failure either resolves or become more severe. The organ failure that resolves in 48 hours are considered to have mild pancreatitis without complications [20]. Severe acute pancreatitis in the first phase is defined as organ failure that lasts more than 48 hours or

death. Expansion of systemic inflammatory response syndrome and ensuing multiorgan failure is responsible for many deaths during this phase. The late phase begins after the first week, may extend for weeks to months and is characterized by increasing necrosis, infection, and persistent multiorgan failure [21]. Local complications may manifest systemically with bacteremia and sepsis when necrotic tissue becomes infected.

Laboratory Parameters

The pancreas produces elevated levels of enzymes, the amylase, lipase and trypsinogen, all derived from pancreatic acinar cells during acute pancreatitis. Serum pancreatic enzyme measurement is the 'gold standard' for the diagnosis of acute pancreatitis (AP) [22]. Serum amylase usually rises within 6 to 24 hours, peaks at 48 hours, and return to normal within 3 to 7 days [23] and lipase rises within 4-8 hours, peaks at 24 hours and decreases to normal in 8 to 14 days [24]. In this patient, both serum amylase and lipase persistently elevated up to 4 weeks with an early peak at 24 hours of onset of symptoms. The biochemical criteria are usually sensitive for detecting acute pancreatitis (55 to 100%) and its specificity is very high (93 to 99%). Amylase or lipase levels more than three times of the upper limits of normal (300 IU / litre^{-1} for amylase and 600 IU litre^{-1} for lipase are diagnostic of acute pancreatitis and serum lipase has been recommended as assay of choice [25] since its concentrations are increased for up to 14 days after the onset of pancreatitis, and appears to be more sensitive and specific than amylase.

Trypsinogen is the zymogen of the pancreatic enzyme trypsin and in acute pancreatitis, its concentration in serum and urine rises to high levels within a few hours and decrease in 3 days. Urinary trypsinogen 2 dipstick test is a rapid and noninvasive bedside test with a reasonable sensitivity 82% and specificity 94% for acute pancreatitis [26] if positive (> 50 ng/ml).

Many clinicians consider the C reactive protein (CRP) as the gold standard for disease severity assessment [27], but its peak levels are reached only after 48 to 72 hours. The CRP at 24 hours ≥ 21 mg/dl (≥ 210 mg/l) indicates severe disease and its level on 3rd day ≥ 150 mg/l can be used as a prognostic factor for severe acute pancreatitis. Resistin is a newly identified peptide hormone, secreted by adipocytes that can cause obesity and hypertrigiceridemia, due to its association with insulin resistance. It is an important cytokine in inflammatory reactions, in the regulation of other cytokines [28] and it is better to

predict severe acute pancreatitis on day 3 and for the development of pancreatic necrosis than CRP or WBC levels. It has similar accuracy with Acute Physiology and chronic health evaluation II (APACHE II) score in predicting persistent organ failure (POF) and leptin has a weak correlation with POF [29].

PCT (procalcitonin) may be valuable in predicting the risk of developing infected pancreatic necrosis. It is an inactive 116 amino acid propeptide of the biologically active hormone calcitonin, which was first described to have significantly increased concentrations in bacterial and fungal infections [30]. Procalcitonin is the most sensitive laboratory test for detection of pancreatic infections and low serum values appear to be strong negative predictor of infected necrosis. A procalcitonin value of 3.8 ng/ml or higher within 96 hours after the onset of symptoms indicated an infected pancreatic necrosis with sensitivity of 93% and a specificity 79% [31].

A laboratory "acute pancreatic screen" to determine the etiology also include the detection of viral antibodies, especially for corona virus. Streptococcus pyogenes produces various exotoxins such as streptolysin O that can act as antigens and the affected individuals produce specific antibodies against streptolysin O (antistreptolysin O (ASO)). Determination of these antibodies is very useful for the diagnosis of streptococcal infection and their relative effects. An elevated ASO titer > 200 IU/ml may indicate an acute streptococcal infection and, in this patient, the ASO titer was raised up to 440 IU/ml at the time of admission.

Advanced laboratory analysis for patients < 40 years of age includes the detection of α-1-antitrypsin phenotype, CFTR (cystic fibrosis transmembrane conductance regulator) gene analysis, a sweat chloride test, trypsin gene studies, and duodenal aspiration for microcrystals, The best indicator of bile duct stones is a serum total bilirubin > 1.35 mg/dl on the second day of admission [32]. The level of tumor marker, CA (cancer antigen) 19-9, should be measured in patients > 40 years of age. An elevation on serum Immunoglobulin G subclass 4 level (IgG4 > 135 mg/dl) is typical of autoimmune pancreatitis (AIP), however, mild (< 2 fold) elevations are seen up to 10% of subjects without AIP including pancreatic cancer.

Predictors of Severity

It is unable to predict which patients with acute pancreatitis will develop severe disease and different scoring systems showed similar predictive accuracy for the severity of acute pancreatitis, but the

APACHE-II score demonstrated the highest accuracy [33].

It was able to identify patients at increased risk of mortality prior to the onset of organ failure [34]. The BISAP score of 2 was a statistically significant cutoff value for the diagnosis of severe acute pancreatitis, organ failure, and mortality as shown in Table 2.

Table 2: Showing the Bedside index of severity of acute pancreatitis (BISAP) [35].

Blood urea nitrogen level > 25mg/dl (89 mmol/l)
Impaired mental status (Glasgow coma score < 15)
Systemic inflammatory response syndrome
Age > 60 years
Pleural effusion

(A score of 3 points is associated with 5.3% rate of hospital death, 4 points with 12.7%, and 5 points with 22.5% of deaths)

The systemic inflammatory response syndrome (SIRS), originally adopted to predict the development of organ failure with sepsis, currently the most important predictor of prognosis [36] and it requires at least two of the following criteria as shown in Table 3. It identifies the risk very early in the course of disease and can be assessed quickly in the emergency department.

Table 3: Showing the criteria of SIRS (systemic inflammatory response syndrome) [36]

Heart rate   > 90 bpm
Core temperature < 36°C or > 38°C
White blood cells < 4000 or >12000/mm³
Respirations   >20/mm

The emerging biomarkers to distinguish septic and non-septic etiology of SIRS include TREM 1 (Triggering receptor expression on myeloid cells 1), DcR3 ('Decoy receptor 3' belongs to tumor necrosis factor family) and suPAR (Soluble urokinase type plasminogen activator receptor) [37].

CT (Computed Tomography) Imaging

The peripancreatic inflammatory changes are the most common CT findings in 88% of cases of acute pancreatitis, seen in mysentry, greater omentum and transverse mesocolon as shown in **Figures 1 & 2** and the second most common finding is 'pancreatic contour irregularity', seen in 80% of cases. Pancreatic parenchymal necrosis alone is seen in < 5>

The pancreatic parenchyma and peripancreatic fat begin to liquefy slowly and the extent of necrosis is divided with 3 categories as >30%, 30 to 50%, >50% of gland involved [39]. The modified CT grading system described only two categories as < 30>30%

[40]. Areas of no or poor attenuation indicates edema rather than necrosis and estimate to be < 30>

Ultrasound Imaging (USG)

It can be used to look for gallstones and abnormalities of biliary system and it does not emit radiation. It may difficult to visualize pancreas in presence of clear and free peritoneal fluid. A combination of endoscopy and high frequency ultrasound (EUS) may be useful if CT fails to detect the CBD (common bile duct) stones and it is highly sensitive for the diagnosis of PD (pancreatic divisum) than CT [42] [43]. It is highly specific to diagnose pancreatic cancer and able to identify pancreatic masses as small as 2 to 3 cm [44].

MR (Magnetic Resonance) Imaging

It is helpful to visualize the distal common bile duct stones and also useful in patients with renal insufficiency to avoid contrast enhanced CT [45]. MR imaging or ultrasound may be used to determine the presence of nonliquefied material.

ERCP (Endoscopic Retrograde Cholangiopancreatography)

The endoscope, a thin flexible tube with a camera at the end can help to determine the exact location of gallstone. ERCP is recommended in the setting of acute pancreatitis with cholangitis, presence of jaundice and common bile duct obstruction. Autoimmune pancreatitis can be difficult to distinguish from pancreatic cancer on CT, but typically features 'diffuse irregular narrowing of the main pancreatic duct' on ERCP. The diagnosis of choledochocele is usually confirmed by ERCP. Endoscopically, the papilla has a "bulging" appearance and feels soft (pillow sign) when pressure is applied with the catheter tip [46]. Routine ERCP is advised for all patients with acute gallstone pancreatitis. ERCP should be considered in presence of persistently abnormal liver function tests (serum ALT > 150 IU/litre-1) and it cannot be recommended without cholangitis or common bile duct obstruction due to procedure related complications including acute pancreatitis, hemorrhage, perforation, sepsis, stricture, bile leakage with mortality in 6% of cases. It does not allow the evaluation of pancreatic parenchyma and less sensitive to detect masses, chronic pancreatitis and microlithiasis [47]. Because of these reasons, ERCP is not advised in this patient.

MRCP (Magnetic Resonance Cholangiopancreatography)

It gives detailed information about the hepatobiliary and pancreatic systems [48], recommended for patients with recurrent acute pancreatitis of unknown cause to assess for pancreatic divism, choledochocele, anomalous pancreatobiliary junction or annular pancreas.

Secretin Stimulated MRCP (sMRCP)

Secretin is injected intravenously, causing the main pancreatic duct to secrete fluid, which improves the visualization of pancreatic ducts [49] and should be preferred for diagnosing pancreatic divism.

Therapeutic Aspects

The treatment planning is based on severity of pancreatitis. IEP (interstitial edematous pancreatitis) is usually self-limited and supportive measures alone suffice. Mild acute pancreatitis is moderately or severely painful. The first line treatment includes bowel rest, IV fluids to prevent dehydration and pain medications.

Pain relieving agents

All patients with acute pancreatitis must receive some form of analgesics in the first 24hrs and dilaudid (hydromorphone hydrochloride) is preferred over morphine or fentanyl in the non-intubated patient. Epidural analgesia may be considered in severe and acute critical care patients who require high doses of opioids for an extended period. Excessive sedation may worsen gut dysfunction with subsequent increase in intraabdominal pressure and intractable pain may necessitates EUS-guided celiac plexes block.

NSAIDs (non-steroidal antiinflammatory drugs) are the most promising group to attenuate the inflammatory response in acute pancreatitis. Rectal suppositories of 100 mg diclofenac or 100 mg indomethacin can reduce the incidence of post ERCP pancreatitis.

Chronic use of opioids causes spasm and dryness of pancreatic ducts, which in turn increases the inflammation and producing more pain. The "nonvalidated" medical therapies such as smooth muscle relaxers (calcium channel blockers or nitrates) may abort an attack if taken at the onset of symptoms. Oral pancreatic enzyme supplements which inhibit pancreatic enzyme secretion may be beneficial for pain control, especially in idiopathic chronic pancreatitis.

Bowel rest

Bowel rest is needed for a few days, so that not to take any food or drinks by mouth until their condition improves, resolution of pain, awaiting normalization of pancreatic enzymes and even imaging evidence of resolution of inflammation before resuming oral

feeding [50]. Several studies have shown that early oral feeding decreases the morbidity, mortality and infectious complications and it may begin as low-residue, low fat, soft diet when the patient appears to be improving as no tummy (abdominal) pain and found to be safe in mild acute pancreatitis [51].

Intravenous hydration

The microangiopathic effects and edema of inflamed pancreas worsens the pancreatic hypoperfusion and decreases the blood flow, causes increased release of pancreatic enzymes, activating numerous cascades, leading to increased parenchymal necrosis and cell death [52]. Necrotizing pancreatitis is an ischemic event and the goal of volume resuscitation is to maintain pancreatic and intestinal microcirculation to prevent intestinal ischemia and subsequent bacterial translocation [53], to prevent severe complications such as pancreatic necrosis [54] and to minimize SIRS (systemic inflammatory response syndrome) to reduce the rate of organ failure, morbidity and death. So, early intravenous hydration during the first 12 to 24 hours with close monitoring is of paramount importance.

Hydration with isotonic crystalloid solutions are advisable and the lactated Ringer's solution (20ml/kg bolus, followed by 3 ml/kg/hour improve outcome within 36 hours) appears to be more beneficial with antiinflammatory effect, resulting less SIRS compared to normal (0.9%) saline [55] and a better electrolyte balance, improved outcomes and more pH balanced since low pH activates the trypsinogen, makes the acinar cells more susceptible to injury. The use of normal saline in large volumes may lead to non-anion gap, hyperchloremic metabolic acidosis.

Continuous use of aggressive hydration over 48 hours seems to be associated with increased morbidity and mortality [56],[57] and caution to avoid excessive resuscitation (> 4 liters in 24 hours) due to complications such as volume overload, pulmonary edema (due to increased systemic permeability) and abdominal compartment syndrome [58]. Movement of fluid into the intracellular space ("third spacing") occurs in acute pancreatitis and fluid resuscitation exacerbates it. The intraabdominal hypertension (sustained intraabdominal pressure > 12 mmHg) is associated with poor outcome. It should be monitored with transvescicular bladder measurements in those patients on mechanical ventilation and managed with ultrafiltration.

Enteral feeding

Enteral nutrition is recommended to prevent gut failure and infectious complications. It is better to avoid solid foods for few days or longer since trying to digest solid foods could put too much strain on pancreas. When the solid foods need to be avoided, it may be given a special liquid food mixture through a tube as 'enteral feeding'. The enteral feeding is cheaper, safer, and associated with fewer infective complications and a better overall outcome [59] with a decrease in organ failure and mortality [60].

Enteral feeding maintains the gut mucosal barrier and prevents its disruption and translocation of bacteria that seed pancreatic necrosis. Jejunal feeding is advocated if gastric feeding fails [61] as a result of duodenal ileus or obstruction from inflammatory masses and there is some evidence of superiority of 'distal jejunal feeding' in acute pancreatitis.

Total parenteral nutrition (TPN) should be considered only for patients who do not tolerate enteral feeding because of severe ileus since it is associated with infection and line-related complications.

Antibiotics

Prophylaxis refers to the administration of antibiotics in patients when no clinical infection is present with the intent to prevent pancreatic infection. Earlier trials suggested that prophylactic antibiotics might prevent infective complications in sterile necrosis [62], but subsequent trials failed to confirm this advantage and recent trials showed no decrease in mortality [63] and thus routine prophylactic antibiotics in acute pancreatitis may increase the incidence of infection with resistant bacteria or fungi and is no longer recommended [64].

CT rarely demonstrates gas in pancreas, lesser sac or retroperitoneum and it is only present in limited number of patients [65]. CT guided FNA (fine needle aspiration) for gram stain and cultures can guide to choose appropriate antibiotic regimen [66], but many centers abandoned the routine use of FNA because of high rate of false negative results. A more rational approach is to consider antibiotics if there is evidence of systemic sepsis or organ failure while recognizing the many signs of SIRS, especially with marked leukocytosis.

Since most infections in severe acute pancreatitis are caused by gram negative organisms, translocated from the gut, the carbapenems (imipenem and meropenem) have a good broad-spectrum coverage, excellent pancreatic penetrance [67] and it should be used only in critically ill patients due to the spread of carbapenem resistant Klebsiella pneumonia. Aminoglycosides are poor penetrance to pancreas and are of little use [68].

Acylureidopenicillins (azlocillin, mezlocillin, piperacillin, and furazlocillin) have an intermediate penetrance into the pancreas and are effective against gram negative organisms [69]. Among these antibiotics, only Piperacillin/tazobactam is effective against gram positive bacteria and anaerobes. Quinolones (ciprofloxacin and moxifloxacin) have good tissue penetration into pancreas with an excellent anaerobic coverage [70], but discouraged due to high rate of resistance worldwide. Metronidazole with its bactericidal spectrum focused almost exclusively against anaerobes, also shown good penetration into pancreas.

Fungal infection is a serious complication of acute pancreatitis and is associated with an increase in morbidity and mortality. When there is no clinical response to antibiotics, fungal infection can be suspected. Candida albicans is most frequent, followed by candida tropicalis and candida krusei. Fluconazole must be given if fungal isolates are identified.

Specific medical therapy

Insulin infusion (0.1 units/kg/hour in 24 hours until triglyceride level became < 500>

In certain cases, a successful method of treatment relies on apheresis for lowering of triglyceride levels. Plasmapheresis (PEX) improves the outcome not only by lowering triglyceride but also by removing proinflammatory markers and cytokines to downregulate the inflammatory process [72].

CBPT (combined blood purification therapy) is a two-step approach for the management of acute severe pancreatitis involving plasmapheresis and continuous venovenous hemofiltration (CVVH) and shown to improve mortality and lowering of inflammatory markers in severe acute pancreatitis irrespective of its etiology [73].

HVHF (high volume hemofiltration) and hemoperfusion (HP) is considered when plasmapheresis is not available and it removes the proinflammatory cytokines in addition to lowering triglyceride level.

Purified apoC-II infusion has yielded transient normalization of triglyceride levels and clinical improvement in pancreatitis patients with apoC-II deficiency. Medium-chain triglycerides have also been used to prevent acute hyperlipidemic pancreatitis during pregnancy as their absorption doesn't require chylomicron formation. Anti-oxidant therapy (selenium, beta-carotene, vitamin C and α-tocopherol) has been used with success in the reduction of recurrent pancreatitis episodes in patients with familial lipoprotein lipase deficiency who remained markedly hypertriglyceridemic after medical therapy. It is postulated that the antioxidants might protect the pancreatic acinar cells from free radical damage brought on by the ischemia of chylomicron-induced changes in pancreatic capillary circulation.

Steroids (prednisolone 0.6 mg/kg/day and maintenance dose over 3 to 6 months) are indicated in autoimmune pancreatitis (AIP), characterized by infiltration of IgG4-positive plasma cells [74]. It is important to differentiate pancreatic cancer from AIP before starting steroid treatment and periodic analysis to be done to avoid steroid - induced pancreatic damage such as obstruction of small pancreatic ductules due to increased viscosity of pancreatic secretions.

The benefits of other agents such as antisecretory drugs (somatostatin, octreotide, lanreotide), N-acetyl cysteine and anti-inflammatory agent (lefipixant) are disappointing.

Surgical therapy

Surgical intervention is associated with high risk of death than medical therapy especially in sterile pancreatitis. Documented infection has been considered as a definite indication for debridement and infected necrosis may also be treated successfully with antibiotics alone.

A single- stage surgical transgastric necrosectomy is a good option in patients with disconnected pancreatic duct syndrome since it results peripancreatic collections in symptomatic patients with lack of improvement [75] and a postoperative mortality of 2% [76]. Routine intraoperative cholangiography is unnecessary in mild gallstone pancreatitis with normalizing bilirubin levels [77].

Interventional therapy

A catheter directed balloon tamponade, coil embolization or covered stent is preferable to control the massive hemorrhage occurring in 1 to 3% of cases of severe acute pancreatitis and late hemorrhage due to rupture of pseudoaneurysm of splenic artery. Pancreatic duct stent placement may decrease the post ERCP pancreatitis in those patients undergoing endoscopic procedures such as ampullectomy.

Outcome

The disease takes a mild course in most patients and the severe form carries a hospital mortality rate of 15%. Infection occurs in 20-40% of cases, contribute to 80% of deaths in acute pancreatitis [78] and it is associated with worsening organ dysfunction in < 5>

Case analysis

This 32 years old male was presented with acute abdomen as an initial manifestation of rheumatic fever due to Lancifield group A beta hemolytic streptococci [82] as evidenced by raised ASO titer and ESR. Elevated amylase and lipase with CT features of peripancreatic inflammatory changes as 'mistiness' (fat strandings) suggesting acute interstitial edematous pancreatitis (IEP) as in **Figures 1 & 2** and these inflammatory changes are responded to antibiotic therapy. The patient improved dramatically within few days and resumed oral intake without any further complications. Cefotaxime showed good penetration into the pancreas to eradicate the infective process [83].

Presence of obesity, history of alcoholism, use of anticonvulsants and moderately raised triglyceride levels are the risk factors to trigger the pancreatic infection by streptococcus in this case. Periarteriolar connective tissue inflammation caused by the organism causes vasculitis and the resultant ischemia in the pancreas as an isolated event, may predisposes to further infection and so penicillin prophylaxis is indicated.

Preventive measures

a) A healthy lifestyle can reduce the chances of developing acute pancreatitis.

Hypertriglyceridemia causes 2 to 5 % of cases of pancreatitis and is associated with inherited disorders of lipoprotein metabolism, congenital type1, II and V without a precipitating factor in children [84]. Chylomicrons are triglyceride-rich lipoprotein particles believed to be responsible for pancreatic inflammation. They usually present in the circulation when serum triglyceride levels exceed 10 mmol/L. These largest of lipoproteins might impair circulatory flow in capillary beds; if this occurs in the pancreas, the resulting ischemia might disturb the acinar structure and expose these triglyceride-rich particles to pancreatic lipase. The pro-inflammatory non-esterified free fatty acids generated from the enzymatic degradation of chylomicron-triglycerides (ie, the release of free fatty acids by lipase) may lead to further damage of pancreatic acinar cells and microvasculature. Subsequent amplification of the release of inflammatory mediators and free radicals may ultimately lead to necrosis, edema, and inflammation. Hypertriglyceridemia was the cause of 56

Conclusion

GAS pharngitis and invasive infections are more common as seasonal trends, "a wave of airborne infection" with close 'person-to-person contacts' and predisposing to viral infections [113]. Mucosal hygiene (nasal, oral cavity and genitals) is an important measure to prevent it [114]. COVID 19 is similarly presenting and amenable to antibiotics in mild cases and vaccine development remains as a challenge for both conditions since seroconversions occurring frequently as noticed in the United Kingdom due to new outbreaks of corona virus with different strains recently. Live attenuated vaccine similar to oral polio vaccine as "drops" at the exposed mucosal surfaces of the body (mucosal vaccine) to induce immunity (both 'humoral' or serum immunity and local immune response) is a better option to control the outbreaks.

Acute abdomen, as pancreatitis and acute lung damage, as ARDS are the presenting manifestations of both of these infections. Penicillin prophylaxis is indicated in endemic areas to prevent its unexpected outbreaks and, serum ASO titer screening and PCR tests are advised to identify these infections.

References

1. Johnson, C.D., Besselink, M., G.,Carter,R.(2014) Acute Pancreatitis, British Medical Journal, 349, g 4859.

2. Goldacre, M.,J., Roberts, S.,E.,(2004) Hospital Admission For Acute Pancreatitis In An English Population, 1963-1998: Database Study of Incidence And Mortality, British Medical Journal, 328, 1466-1469.

3. Rebours, V., Vullierma, M.,P., Hentic, O., et al (2012) Smoking And The Course of Recurrent Acute And Chronic Alcoholic Pancreatitis: A Dose Dependent Relationship. Pancreas, 41, 1219-1224.

4. Whitcomb, D.,C. (2005) Genetic Polymorphisms In Alcoholic Pancreatitis, Digestive Diseases, 23, 247-254.

5. Isenmann,R.,Runzi, M., Kron,M., et al (2004) Prophylactic Antibiotic Treatment In Patients With Predicted Severe Acute Pancreatitis: A Placebo-Controlled, Double-Blind Trial, Gastroenterology, 126, 997-1004.

6. Picard,E.,Gedalia,A.,Benmeir,P.,Zucker, N.,Barki,Y.,(1992) Abdominal Pain With Free Peritoneal Fluid Detected By Ultrasonography As A Presenting Manifestation of Acute Rheumatic Fever, Annals of The Rheumatic Diseases, 51, 394-395.

7. Hogan,W.,J.,Geenen,J.,E.,Dodds,W.,J.(1987)Dy smotility Disturbances of The Biliary Tract: Classification, Diagnosis, And Treatment,

Seminars in Liver Disease, 7, 302-310.

8. Beger,H.,G., Rau, B.,M.(2007) Severe Acute Pancreatitis: Clinical Course And Management, World Journal of Gastroenterology, 13, 5043-5051.

9. Perez, A., Whang, E.,E., Brooks, D.,C., et al (2002). Is Severity of Necrotizing Pancreatitis Increased In Extended Necrosis And Infected Necrosis? Pancreas, 25, 229–233.

10. Mourad, M.,M., Evans, R.,P.,T., Kalidindi, V., Navaratnam, R., Dvorkin, L., Bramhall, S.,R..(2017) Prophylactic Antibiotics In Acute Pancreatitis: Endless Debate. Annals of the Royal College of Surgeons of England, 99, 107–112.

11. Reuken, P.,A., Albig, H., Rödel, J., Hocke, M., Will, U., Stallmach, A., et al (2018). Fungal Infections In Patients With Infected Pancreatic Necrosis And Pseudocysts: Risk Factors And Outcome. Pancreas, 47, 92–98.

12. Chiu,C.,H., Lin,T.,Y., Wu.J.,L. (1996) Acute Pancreatitis Associated With Streptococcal Toxic Shock Syndrome, Clinical Infectious Diseases, 22, 724-726.

13. Liu,F.,Long,X.,Zhang,B.,Chen,X.,Zhang,Z., (2020) ACE2 Expression In Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection, Clinical Gastroeterology And Hepatology, 18, 2128-2130.

14. Wang, F.,Wang,H.,Fan,J.,(2020)Pancreatic Injury Patterns In Patients With Corona virus Disease 19 Pneumonia, Gastroenterology, 159, 367-370.

15. Aloysius,M.,M., Thatti,A., Gupta, A., Sharma,N., Bansai,P.,Goyal.H., (2020) COVID 19 Presenting As Acute Pancreatitis, Pancreatology, 20, 1026-1027.

16. Anand, E.,R.,Major,C.,Pickering,O.,Nelson,M.(2020) Acute Pancreatitis In A COVID 19 Patient, British Journal of Surgery, 107, e182.

17. Kandasamy,S., (2020) An Unusual Presentation of COVID 19: Acute Pancreatitis, Annals of Hepato-biliary- Pancreatic Surgery, 24, 539-541.

18. Bradley 3rd, E.,L.,(1993) A Clinically Based Classification System For Acute Pancreatitis. Summary of The International Symposium On Acute Pancreatitis, Atlanta, Ga, September 11 Through 13, 1992. Archives of Surgery, 128, 586–590.

19. Besselink ,M.,G., Van Santvoort, H.,C., Witteman, B.,J., Gooszen, H.,G., (2007) Management of Severe Acute Pancreatitis: It's All About Timing. Current Opinion In Critical Care , 13, 200–206.

20. Johnson, C.,D., Abu-Hilal, M.,(2004) Persistent Organ Failure During The First Week As a Marker of Fatal Outcome In Acute Pancreatitis. Gut, 53, 1340–1344.

21. Abu-Zidan, F.,M., Bonham, M.,J., Windsor, J.,A..(2000) Severity of Acute Pancreatitis: A Multivariate Analysis of Oxidative Stress Markers And Modified Glasgow Criteria. British Journal of Surgery, 87, 1019–1023.

22. Toouli ,J., Brooke-Smith, M., Bassi, C., Carr-Locke, D., Telford, J., Freeny, P., et al.(2002) Guidelines For The Management Of Acute Pancreatitis. Journal of Gastroenterology And Hepatology, February:17(Suppl), S15–39.

23. Tenner, S., Baillie, J., DeWitt, J., Vege, S.,S..(2013) Management of Acute Pancreatitis. American Journal of Gastroenterology, 108, 1400–1416.

24. Rompianesi, G., Hann, A., Komolafe, O., Pereira, S.,P., Davidson, B.,R., Gurusamy, K.,S..(2017) Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. Cochrane Database of Systematic Reviews, 4, CD012010.

25. Matull,W.,R., Pereira, S.,P., O'Donohue,J.,W.(2006) Biochemical Markers of Acute Pancreatitis, Journal of Clinical Pathology, 59, 340-344.

26. Chang, K., Lu, W., Zhang, K., Jia, S., Li, F., Wang, F., et al (2012) Rapid Urinary Trypsinogen 2 Test In The Early Diagnosis of Acute Pancreatitis: A Meta-Analysis. Clinical Biochemistry, 45, 1051–1056.

27. Staubli,S., M., Oertli, D., Nebiker, C.,A..(2015) Laboratory markers predicting severity of acute pancreatitis. Critical Reviews In Clinical Laboratory Sciences, 52, 273–283.

28. Kibar, Y.,I., Albayrak, F., Arabul, M., Dursun, H., Albayrak, Y., Ozturk, Y..(2016) Resistin: New Serum Marker For Predicting Severity Of Acute Pancreatitis. Journal of International Medical Research. 44, 328–337.

29. Yu, P., Wang, S., Qiu, Z., Bai, B., Zhao, Z., Hao, Y., et al.(2016) Efficacy Of Resistin And Leptin In Predicting Persistent Organ Failure In Patients With Acute Pancreatitis. Pancreatology, 16, 952–957.

30. Assicot, M., Gendrel, D., Carsin, H., et al.(1993) High Serum Procalcitonin Concentrations In Patients With Sepsis And Infection. Lancet. 341, 515–518.

31. Yang, C.,J., Chen, J., Phillips, A.,R.,J., Windsor, J.,A., Petrov, M.,S.(2014). Predictors Of Severe And Critical Acute Pancreatitis: A Systematic Review. Digestive And Liver Disease.46, 446–451.

32. Chang, L., Lo, S.R., Stabile, B.E., et al. (1998) Gallstone Pancreatitis: A Prospective Study on the Incidence of Cholangitis and Clinical Predictors of Retained Common Bile Duct Stones. American Journal of Gastroenterology, 93, 527-531.

33. Cho, J.,H., Kim, T.,N., Chung, H.,H., Kim, K.,H..(2015) Comparison Of Scoring Systems In Predicting The Severity Of Acute Pancreatitis. World Journal of Gastroenterology, 21, 2387–2394.

34. Wu, B.,U., Johannes, R.,S., Sun, X., Tabak, Y.,Conwell, D.,L.,Banks, P.,A..(2008)The Early Prediction Of Mortality In Acute Pancreatitis: A Large Population Based Study. Gut, 57, 1698-1703.

35. Park, J.,Y., Jeon, T.,J., Ha, T.,H., Hwang, J.,T., Sinn, D.,H., Oh, T.,H., et al.(2013) Bedside Index For Severity In Acute Pancreatitis: Comparison With Other Scoring Systems In Predicting Severity And Organ Failure. Hepatobiliary And Pancreatic Diseases International. 12, 645–650.

36. Todd Baron, (2013) Managing Severe Acute Pancreatitis,Cleveland Clinic Journal of Medicine, 80, 354-359.

37. Chakraborty, R.,K., Burns, B.(2020) Systemic Inflammatory Response Syndrome, In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, Last update, November 16.

38. Kim, Y.,K., Ko, S.,W., Kim, C.,S., Hwang, S.,B..(2006) Effectiveness of MR Imaging For Diagnosing The Mild Forms of Acute Pancreatitis: Comparison With MDCT. Journal of Magnetic Resonance Imaging, 24, 1342–1349.

39. Balthazar, E.,J., Robinson, D.,L., Megibow, A.,J., Ranson, J.,H.. (1990) Acute Pancreatitis: Value of CT In Establishing Prognosis. Radiology, 174, 331–336.

40. Bollen, T.,L., Singh, V.,K., Maurer, R., et al (2011). Comparative Evaluation of The Modified CT Severity Index And CT Severity Index In Assessing Severity of Acute Pancreatitis. AJR (American Journal of Roentgenology), 197, 386–392.

41. Balthazar, E.,J.,(2002). Acute Pancreatitis: Assessment of Severity With Clinical And CT Evaluation , Radiology, 223, 603–613.

42. Giljaca,V.,Gurusamy,K.,S.,Takwoingi,Y.,Higgie, D.,Poropat,G.,Stimac,D.,et. al (2015) Endoscopic Ultrasound Versus Magnetic Resonance Cholangiopancreatography For Common Bile Duct Stones, Cochrane Data Base Systematic Reviews, 2, CD011549.

43. Sharma,M.,Pathak,A.,RameshBabu,C.,S.,Rai,P. ,Kirnake,V.,Shoukat,A.,(2016) Imaging of Pancreas Divisum By Linear - Array Endoscopic Ultrasonography, Endoscopic Ultrasound, 5, 21-29.

44. Byme,M.,F.,Jowell,P.,S.,(2002)Gastrointestinal Imaging: Endoscopic Ultrasound, Gastroenterology, 122, 1631-1648.

45. Xiao,B.,Zhang,X.,M.,Tang,W.,Zeng,N.,L.,Zhai,Z. ,H.,(2010)Magnetic Resonance Imaging For Local Complications of Acute Pancreatitis: A Pictorial Review, World Journal of Gastroenterology, 16, 2735-2742.

46. Tse, F., Yuan, Y.,(2012) Early Routine Endoscopic Retrograde Cholangiopancreatography Strategy Versus Early Conservative Management Strategy In Acute Gallstone Pancreatitis. Cochrane Database Systematic Reviews,16, CD009779.

47. Hurter,D.,DeVries,C.,Potgieter,P.,Barry,R.,Botha ,F.,Joubert,G.,(2008) Accuracy of MRCP Compared to ERCP In The Diagnosis of Bile Duct Disorders, South African Journal of Radiology, 12, a 580.

48. Yattoo, G.,N., Waiz, G.,A., Feroze, A.,S., Showkat, Z., Gul, J.,(2014) The Efficacy of Magnetic Resonance Cholangiopancreatography In Assessing The Etiology of Acute Idiopathic Pancreatitis. International Journal of Hepatobiliary And Pancreatic Diseases. 4, 32-39.

49. Manfredi,R.,Pozzi Mucelli,R.,(2016) Secretin-Enhanced MR Imaging of The Pancreas, Radiology, 279, 29-43.

50. Banks, P., A., Freeman, M.,L.,(2006) Practice Guidelines In Acute Pancreatitis. American Journal of Gastroenterology, 101, 2379–2400.

51. Eckerwall, G.,E., Tingstedt, B.,B.,A., Bergenzaun, P.,E., et al (2007) Immediate Oral Feeding In Patients With Mild Acute Pancreatitis Is Safe And May Accelerate Recovery—A

Randomized Clinical Study, Clinical Nutrition, 26, 758–763..

52. Takeda, K., Mikami, Y., Fukuyama, S., et al.(2005) Pancreatic Ischemia Associated With Vasospasm In The Early Phase of Human Acute Necrotizing Pancreatitis. Pancreas, 30, 40–49.

53. Fisher,J.,M.,Gardner,T.,B.,(2012) The "Golden Hours " of Management In Acute Pancreatitis, American Journal of Gastroenterology, 107, 1146-1150

54. Gardner,T.,B.,Vege,S.,S.,Pearson,R.,K.,et al (2008) Fluid Resuscitation In Acute Pancreatitis, Clinical Gastroenterology And Hepatology, 10, 1070-1076.

55. Wu., B.,U., Hwang, J.,Q., Gardner, T.,H. et al (2011). Lactated Ringer's Solution Reduces Systemic Inflammation Compared With Saline In Patients With Acute Pancreatitis. Clinical Gastroenterology And Hepatology, 9, 710–717.

56. Mao, E.,Q., Fei, J., Peng, Y.,B., et al (2010). Rapid Hemodilution Is Associated With Increased Sepsis And Mortality Among Patients With Severe Acute Pancreatitis. Chinese Medical Journal (English Edition),123, 1639–1644.

57. De-Madaria, E., Soler-Sala, G., Sánchez-Paya, J., et al (2011) Influence of Fluid Therapy On The Prognosis of Acute Pancreatitis: A Prospective Cohort Study. American Journal of Gastroenterology,106, 1843–1850.

58. Eckerwall, G., Olin, H., Andersson, B., et al (2006). Fluid Resuscitation And Nutritional Support During Severe Acute Pancreatitis In The Past: What Have We Learned And How Can We Do Better? Clinical Nutrition, 25, 497–504.

59. Windsor,A.,C.,Kanwar,S.,Li,A.,G., et al (1998) Compared With Parenteral Nutrition, Enteral Feeding Attenuates The Acute Phase Response And Improves Disease Severity In Acute Pancreatitis, Gut, 42, 431-435.

60. Bakker, O.,J., Van Brunschot, S., Van Santvoort, H.,C., Besselink, M.,G., Bollen, T.,L., Boermeester, M.,A., et al (2014) Early Versus On-Demand Nasoenteric Tube Feeding In Acute Pancreatitis. New England Journal of Medicine,. 371, 1983–1993.

61. Eatock,F.,C.,Chong,P.,Menezes,N.,et al (2005) A Randomized Study of Early Nasogastric Versus Nasojejunal Feeding In Severe Acute Pancreatitis, American Journal of Gastroenterology, 100, 432-439.

62. Pederzoli,P.,Bassi,C.,Vesentini,S.,et al (1993) A Randomized Multicenter Clinical Trial of Antibiotic Prophylaxis of Septic Complications In Acute Necrotizing Pancreatitis With Imipenem, Surgery, Gynecology & Obstetrics, 176, 480-483.

63. Jiang, K., Huang, W., Yang, X.,N., et al (2012). Present And Future of Prophylactic Antibiotics For Severe Acute Pancreatitis. World Journal of Gastroenterology., 18, 279–284.

64. Schmid, S., Uhl,W.,Friess, H.,et al (1999) The Role of Infection In Acute Pancreatitis, Gut, 45, 311-316.

65. De Waele, J.,J..(2011) Rational Use of Antimicrobials In Patients With Severe Acute Pancreatitis. Seminars In Respiratory And Critical Care Medicine, 32, 174–180.

66. Eloubeidi, M.,A., Tamhane, A., Varadarajulu, S., et al (2006). Frequency of Major Complications After EUS-Guided FNA of Solid Pancreatic Masses: A Prospective Evaluation, Gastrointestinal Endoscopy. 63, 622–629.

67. Nathens, A.,B.,Curtis,J.,R.,Beale,R.,J.,et al (2004) Management of The Critically ill Patient With Severe Acute Pancreatitis, Critical Care Medicine, 32, 2524-2536.

68. Buchler, M., Malfertheiner, P., et al (1992) Human Pancreatic Tissue Concentration of Bactericidal Antibiotics, Gastroenterology, 103, 1902–1908.

69. Otto, W., Komorzycki, K., Krawczyk, M..(2006) Efficacy of Antibiotic Penetration Into Pancreatic Necrosis. HPB (The Official Journal of the International Hepato Pancreato Biliary Association), 8, 43–48.

70. Schubert, S., Dalhoff, A..(2012) Activity of Moxifloxacin, Imipenem, And Ertapenem Against Escherichia Coli, Enterobacter Cloacae, Enterococcus Faecalis, And Bacteroides Fragilis In Monocultures And Mixed Cultures In An In Vitro Pharmacokinetic/Pharmacodynamic Model Simulating Concentrations In The Human Pancreas. Antimicrobial Agents and Chemotherapy, 56, 6434-6436.

71. Li, J., Chen, T.R., Gong, H.L., Wan, M.H., Chen, G.Y. and Tang, W.F.(2012) Intensive Insulin Therapy in Severe Acute Pancreatitis: A Meta Analysis and Systematic Review. West Indian Medical Journal, 61, 574-579.

72. Stefanutti, C., Labbadin, G. and Morozzi, C. (2013) Severe Hypertriglyceridemia-Related Acute Pancreatitis. Therapeutic Apheresis and Dialysis, 17, 130-137.

73. He, C., Zhang, L., Shi, W., et al. (2013) Coupled

Plasma Filtration Adsorption Combined with Continuous Veno-Venous Hemofiltration Treatment in Patients with Severe Acute Pancreatitis. Journal of Clinical Gastroenterology, 47, 62-68.

74. Pannala, R. and Chari, S.T. (2009) Corticosteroid Treatment for Autoimmune Pancreatitis. Gut, 58, 1438-1439.

75. Dua, M.,M., Jensen, C.,W., Friedland, S., Worth, P.,J., Poultsides, G.,A., Norton, J.,A., et al (2018), Isolated Pancreatic Tail Remnants After Transgastric Necrosectomy Can Be Observed. Journal of Surgical Research,. 231, 109–115.

76. Bang, J.,Y., Wilcox, C.,M., Navaneethan, U., Hasan, M.,K., Peter, S., Christein, J., et al (2018), Impact of Disconnected Pancreatic Duct Syndrome On The Endoscopic Management of Pancreatic Fluid Collections. Annals of Surgery, 267, 561–568.

77. Pham, X-B.,D., De Virgilio, C., Al-Khouja, L., Bermudez, M.,C., Schwed, A.,C., Kaji, A.,H., et al (2016) Routine Intraoperative Cholangiography Is Unnecessary In Patients With Mild Gallstone Pancreatitis And Normalizing Bilirubin Levels. American Journal of Surgery. 212, 1047–1053.

78. Delcenserie,R.,Yzet,T.,Ducroix,J.,P.,(1996) Prophylactic antibiotics In Treatment of Severe Acute Alcoholic Pancreatitis, Pancreas, 13, 198-201.

79. Mann,D.,V.,Hershman, M.,J.,Hitinger,R.,et al (1994) Multicentre Audit of Death From Acute Pancreatitis, British Journal of Surgery, 51, 890-893.

80. Working Group IAP/APA Acute Pancreatitis Guidelines (2013). IAP/APA Evidence-Based Guidelines For The Management of Acute Pancreatitis. Pancreatology. 4 (Suppl 2), e1–15.

81. Wyncoll, D.,L.,(1999) The Management of Severe Acute Necrotizing Pancreatitis: An Evidence Based Review of The Literature, Intensive Care Medicine, 25, 146-156

82. Cross, H.,D.(1965) Pancreatitis And Acute Rheumatic Fever, The Journal of The Maine Medical Association, 56 , 268.

83. Lankish,P.,G., Klesel,N.,Seeger,K.,Seidel,G.,Winckler,K.(1983) Penetration of Cefotaxime Into The Pancreas, Zeitschrift fur Gastroenterologie , 21, 601-603.

84. Murphy, M.,J.,Sheng,X., MacDonald, T.,Wei,L.,(2012) Hypertriglyceridemia And Acute Pancreatitis, Archives of Internal Medicine, 173, 1-3.

85. Ramachandran (2019) Occupational Health-Mineralization of Heart Valves, 2nd Global Summit On Occupational Health & Safety, Dubai-Deira (Crowne Plaza), October, 11-12 (You Tube).

86. You.Y.,et al (2018) Scarlet Fever Epidemic In China Caused By Streptococcus Pyogenes Serotype M12: Epidemiologic And Molecular Analysis, EBiomedicine, 28, 128-135.

87. Tse, H. et al (2012). Molecular Characterization of The 2011 Hong Kong Scarlet Fever Outbreak. Journal of Infectious. Diseases. 206, 341–351.

88. Turner, C. E. et al (2016). Scarlet Fever Upsurge In England And Molecular-Genetic Analysis In North-West London, 2014. Emerging Infectious Diseases. 22, 1075–1078.

89. Chalker, V. et al (2017). Genome Analysis Following A National Increase In Scarlet Fever In England 2014. BMC Genomics, 18, 224.

90. Davies, M. R. et al (2015). Emergence of Scarlet Fever Streptococcus Pyogenes emm12 Clones In Hong Kong Is Associated With Toxin Acquisition And Multidrug Resistance. Nature Genetics, 47, 84–87.

91. Silva-Costa, C., Carrico, J. A., Ramirez, M. & Melo-Cristino, J.(2014) Scarlet Fever Is Caused By A Limited Number of Streptococcus Pyogenes Lineages And Is Associated With The Exotoxin Genes ssa, speA and speC. Pediatric Infectious Disease Journal. 33, 306–310.

92. Brosnahan, A.,J., Mantz, M.,J., Squier, C.,A., Peterson, M.,L., Schlievert, P.,M.,(2009) Cytolysins Augment Superantigen Penetration of Stratified Mucosa, Journal of Immunology, 182, 2364-2373.

93. Broudy,T.,B., Pancholi,V.,Fischetti, V.,A.(2002) The In Vitro Interaction of Streptococcus Pyogenes With Human Pharyngeal Cells Induces A Phage-Encoded Extracellular DNase, Infection & Immunity,, 70, 2805-2811.

94. Lamagni, T. et al (2018). Resurgence of Scarlet Fever In England, 2014-16: A Population-Based Surveillance Study. Lancet Infectious Diseases, 18, 180–187.

95. Kasper, K. J. et al(2014). Bacterial Superantigens Promote Acute Nasopharyngeal Infection By Streptococcus Pyogenes In A Human MHC Class II-Dependent Manner. PLoS (Public Library of Science) Pathogens. 10, e1004155.

96. Zeppa, J. J. et al (2017). Nasopharyngeal Infection By Streptococcus Pyogenes Requires Superantigen-Responsive Vbeta-Specific T cells. Proceedings of The National Academy of Sciences. USA, 114, 10226–10231.

97. Brouwer, S., Barnett, T.,C., Kasper, K.,J., et al (2020) Prophage Exotoxins Enhance Colonization Fitness In Epidemic Scarlet Fever-Causing Streptococcus Pyogenes, Nature Communications, 6 October.

98. Kamochi,M.,Kamochi,F.,Kim,Y.,B.,Sawh S., Sanders, J.,M.,Sarembock, I., et al (1999) P-Selectin And ICAM-1 Mediate Endotoxin-Induced Neutrophil Recruitment And Injury To The Lung And Liver, American Journal of Physiology, 277, 1310-1319.

99. Herwald, H., Cramer,H., Morgelin,M.,Russell,W.,Sollenberg, U., Norrby-Teglund, A., et al (2004) M- protein, A Classical Bacterial Virulence Determinant, Forms Complexes With Fibrinogen That Induce Vascular Leakage, Cell, 116, 367-379.

100. Menezes, G.,B.,Lee, W.,Y., Zhou,H.,Waterhouse, C,C.,Cara, D.,C.,Kubes,P.,(2009) Selective Down-Regulation of Neutrophil Mac-1 In Endotoxemic Hepatic Microcirculation Via IL-10, Journal of Immunology, 183, 7557-7568.

101. Duffy, M.M., Ritter, T., Ceredig, R. and Griffin, M.D. (2011) Mesenchymal Stem Cell Effects on T-Cell Effector Pathways. Stem Cell Research & Therapy, 2, Article No. 34.

102. Gong, J., Meng, H.B., Hua, J., et al. (2014) SDF-1/CXCR4 Axis Regulates Migration of Transplanted Bone Marrow Mesenchymal Stem Cells towards the Pancreas Rats with Acute Pancreatitis. Molecular Medicine Reports, 9, 1575-1582.

103. Yang, B., Bai, B., Liu, C.X., et al. (2013) Effect of Umbilical Cord Mesenchymal Stem Cells on Treatment of Severe Acute Pancreatitis in Rats. Cytotherapy, 15, 154-162.

104. He, Z., Hua, J., Qian, D., et al. (2016) Intravenous hMSCs Ameliorate Acute Pancreatitis in Mice via Secretion of Tumor Necrosis Factor-α Stimulated Gene/Protein 6. Scientific Reports, 6, Article No. 38438.

105. Fang, J. and Zhang, Y. (2017) Icariin, an Anti-Atherosclerotic Drug from Chinese Medicinal Herb Horny Goat Weed. Frontiers in Pharmacology, 8, 734.

106. Xu, C.Q., Liu, B.J., Wu, J.F., et al. (2010) Icariin Attenuates LPS-Induced Acute Inflammatory Responses: Involvement of PI3K/Akt and NF-κB Signaling Pathway. European Journal of Pharmacology, 642, 146-153.

107. Nurnberger, W., Heying, R., Burdach, S., Gobel, U., et al. (1997) C1 Esterase Inhibitor Concentrate in Capillary Leakage Syndrome Following Bone Marrow Transplantation. Annals of Hematology, 75, 95-101.

108. Schneider, D.T., Nurnberger, W., Stannigel, H., Bonig, H. and Gobel, U. (1999) Adjuvant Treatment of Severe Acute Pancreatitis with C1 Esterase Inhibitor Concentrate after Haematopoietic Stem Cell Transplantation. Gut, 45, 733-736.

109. Smith, M., Kocher, H.M. and Hunt, B.J. (2010) Aprotinin in Severe Acute Pancreatitis. International Journal of Clinical Practice, 64, 84-92.

110. Berling, R., Genell, S. and Ohlsson, K. (1994) High-Dose Intraperitoneal Aprotinin Treatment of Acute Severe Pancreatitis: A Double-Blind Randomized Multi-Center Trial. Journal of Gastroenterology, 29, 479-475.

111. Gillen,C.,M., Towers,R.,J.,McMillan, D.,J.,Delvecchio, A., Sriprakash, K.,S.,Currie, B.,Kreikemeyer, B., Chhatwal,G.S. Walker, M.,J.,(2002) Immunological Response Mounted By Aboriginal Australians Living In The Northern Territory of Australia Against Streptococcus Pyogenes Serum Opacity Factor, Microbiology, 148, 169-178.

112. Courtney,H.,S., Yi-Li, Twal, W.,O.,And Argraves, W.,S.,(2009) Serum Opacity Factor Is A Streptococcal Receptor For The Extracellular Matrix Protein Fibulin-1, Journal of biological Chemistry, 284, 12966-12971.

113. Low,D.,E., (2019) Steptococcus Pyogenes, Infectious Disease Advisor, January 19.

114. Ramachandran (2019) Tropical Infections of The Heart- Special Focus On Rheumatic Fever And Endomyocardial Fibrosis With Clinical Perspectives, 2nd International Summit On Microbiology & Parasitology, Bangkok (Sukosal), Thailand, October, 24-25 (You Tube).