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A review of acute pancreatitis in the era of COVID-19

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Abstract
Acute pancreatitis is uncommon in childhood with an estimated incidence of approximately 1 in 10,000 children per year. It is an important condition, which may escape prompt diagnosis and is associated with significant morbidity and mortality. Most often, it will result in an acute hospital admission. The course of this disease is unpredictable and ranges from self-resolving mild illness to significantly severe disease with high risk of mortality or complications due to progression to multi-organ failure. Considerable advances have occurred in management which is now focused on multidisciplinary approach with extensive investigation and minimally invasive endoscopic interventions resulting in improved prognosis. In recent years, incidence of acute pancreatitis in children has risen, either due to improved awareness or reflective of true rise. Since 2020 there are emerging data suggesting an association of COVID-19 with acute pancreatitis. The best approach to diagnosis and management of acute pancreatitis in children and young people is largely extrapolated from adult practice. This review presents a brief summary of normal physiology and pathophysiology relating to pancreatitis, a suggested approach to investigation and diagnosis and summarizes available evidence to inform management in children and young people. We will also explore the latest data collected linking COVID-19 to pancreatitis.

Keywords COVID-19; diagnosis; disease pathogenesis; epidemiology; genetics; paediatric pancreatitis

Clinical scenarios
A 16-year-old girl, previously fit and well, presented to our emergency department with two weeks history of gradually worsening abdominal pain. This was accompanied by vomiting, diarrhea and appetite loss. She also had history of PCR confirmed covid-19 infection a month ago from which she recovered completely without needing hospitalization. Past medical and family history was unremarkable. She was not on any regular medications and denied alcohol consumption. On examination, she looked pale and was mildly tachycardiac. Abdomen was soft but tender in epigastric region. Blood investigations were carried out which showed high level of lipase. Suspecting acute pancreatitis, an urgent ultrasound abdomen was done which showed mild bulkiness of pancreatic head but no evidence of obstruction, cholelithiasis or peri-pancreatic collection. The girl was admitted in hospital and symptomatic treatment with rehydration and pain killers was given. She recovered completely a few days later and was discharged from hospital. Extensive investigations were carried out including genetic workup to look for the etiology but nothing could be identified.

Two weeks later, she presented again with same complaint. This time her ultrasound abdomen showed echogenic pancreatic head and uncinate process in keeping with pancreatic oedema (Figure 1). Repeat imaging and blood tests remained normal and she recovered completely with supportive treatment. Later, an MRI choleangiogram was performed and findings were within normal range. She is still under follow up and remains asymptomatic.

A second case of 17-year-old boy was observed in our hospital with similar presentation. He also had history of previous covid-19 infection but without confirmatory PCR. Investigations were suggestive of acute pancreatitis but no specific cause could be identified. He also responded well to conservative management, remains well and is being followed up as outpatient.

Introduction
Pancreatitis is the inflammation of pancreas which results in associated oedema and tissue necrosis. It can cause pancreatic scarring and organ damage. This inflammation is commonly self-limiting and reversible. However, it can potentially progress to complicated disease following local and systemic inflammatory response with secondary infection of the pancreas or peri-pancreatic necrosis resulting in multi-organ failure. Mortality in children is reported as 4%. Moreover, a significant number of children can develop chronic pancreatitis (CP) or acute recurrent episodes (ARP). It is essential therefore to investigate the cause of acute pancreatitis as it is closely related to management and prognosis of disease. The aetiology in children is different from adults.

Historically, acute pancreatitis (AP) was considered to be more prevalent in adults but recent studies estimate its incidence at approximately 1 in 10,000 children per year which is approaching that seen in adults. More recently, a number of AP cases have been reported in children diagnosed with Covid-19 which suggests that SARS-CoV-2 has a strong association with AP. According to a study done in New York, point prevalence of AP in Covid-19 infected children was found to be 1.8%.

Normal physiology of pancreatic enzymes production and secretion
The exocrine pancreas is responsible for producing digestive enzymes (protease, amylase and lipase) along with bicarbonate and water. These enzymes are secreted into pancreatic duct.
which merges with the bile duct at the head of pancreas and enters the duodenum through the ampulla of Vater. This is essential for normal digestion of food and effective absorption of nutrients. Water and bicarbonates are required to neutralize gastric acid.

Safety processes, mentioned below, are necessary to prevent pancreatic tissue damage by its own enzymes.

Normal pancreatic acinar cells synthesize and secrete zymogen granules which contain digestive enzymes in an inactivated form, called pro-enzymes; such as trypsinogen. Synthesis and secretion of these pro-enzymes is highly regulated neurally and hormonally to ensure appropriate supply of inactive enzymes and prevent accumulation and auto-digestion.

For further protection, Pancreatic Secretory Trypsin Inhibitor or PSTI (also known as Serine Protease Inhibitor Kazal - Type 1 or SPINK-1) is present in pancreatic cells to cleave prematurely activated trypsin. Similarly, alpha-1 antitrypsin and alpha-2 macroglobulin is present in blood to suppress trypsin activity if inappropriately activated.

Finally, the normal anatomy of the ampulla of Vater and the higher pressure in the pancreatic duct than the duodenum helps to ensure forward flow into duodenum and prevents its reflux.

Pathophysiology of acute pancreatitis and its complications

Excessive stimulation of the pancreas or direct destruction of tissue results in obstruction to outflow of zymogen granules, exposing them to the proteolytic action of lysosomal enzymes (particularly cathepsin B) in acinar cells. This culminates in a cascade of proteolytic reactions leading to activation of many zymogen granules and causing acute cell injury. This reaction is further potentiated by neutrophilic enzymes and activation of trypsinogen by the proteolytic activity of trypsin itself — a phenomenon also referred to as auto-digestion.

Additional mechanisms of injury include: reflux of entero-kinase from the duodenum (a potent activator of pro-enzymes), reactive oxygen species injury due to lipid peroxidation; or compromised blood flow to pancreas which may result in hypoxic injury to acinar cells. Impairment of the cytoprotective mechanism for maintaining homeostasis of cellular function in the pancreas as described earlier in this section is understood to be the key triggering factor.

In cases of severe necro-inflammation of pancreas, release of inflammatory cytokines including histamine and bradykinin cause a systemic inflammatory response. This involves widespread vasodilation and third spacing of fluids, leading to ARDS, oliguria, and eventually hypovolaemic shock and multi organ failure if untreated.

In addition, spillage of activated enzymes into surrounding area can also result in local complications such as formation of a pseudocyst: a fluid filled sac that forms around diseased pancreas comprising of pancreatic enzymes, blood and necrotic tissue. Necrotic pancreatic tissue (Figure 2) and pseudocysts (Figure 3), both, form a nidus of infection. Compensatory anti-inflammatory response from the immune system may result in compromised immune function, leading to secondary infection and sepsis.

A hypercoagulable state resulting in venous thrombosis is a common finding with complicated acute pancreatitis; splanchnic veins being involved most frequently. This phenomenon is attributed to release of proteolytic enzymes into a vessel resulting in extensive endothelial damage. Elevated plasma fibrinogen level, fibrinogen degradation product (FDP) and thrombocytosis also contribute towards intravascular coagulation. Severe complications such as, pulmonary embolus and disseminated intravascular coagulation (DIC) have been reported.

Clinical presentation and approach

Acute pancreatitis typically presents with sudden onset of severe abdominal pain — usually in the epigastric region radiating to back or between shoulder blades indicating diaphragmatic irritation. More variable associated features include vomiting, nausea, diarrhoea and, or fever.

Detailed and specific history taking with focused examination is essential; not only for diagnosis but to assess severity, identify aetiology and to plan treatment. In paediatrics the most common causes are infections, drugs, trauma or anatomic abnormality. Less common are genetic factors and autoimmune disease. In contrast, adults present with gallstones and alcohol as the most common aetiologies. Differentials include gastritis, appendicitis, acute intestinal obstruction or intussusception.

The abdomen may look normal or distended depending upon severity. A tender epigastrium and tachycardia are the most common and sometimes the only findings. Fever is associated with necrosis however secondary infection should be excluded.

Jaundice with history of clay colored stools suggests obstruction or abnormality to biliary flow such as choledochal cyst. In severe cases, periumbilical or flank ecchymosis, known as Cullen’s sign or Grey Turner Sign respectively, may be present indicating significant peritoneal or retroperitoneal hemorrhage. Non-specific signs, such as irritability, lethargy and respiratory distress due to ARDS may appear as the widespread inflammatory response ensues. Fluid redistribution may lead to ascites, oliguria and other signs of impending circulatory shock which can progress to multiorgan failure.
Aetiology

Several aetiological factors have been identified for acute pancreatitis in pediatrics but the cause may remain unidentified for many (Table 1). Extensive investigations are required to establish the cause so that the possibility of recurrence and progression to chronic pancreatitis can be minimized.

Viral infections have been extensively described in literature – the most common causative agents being mumps, coxsackie and mycoplasma. Mechanism of injury may be direct invasion or secondary to auto-antibodies production (mycoplasma). More recently, SARS-CoV-2 has been found to have an association with acute pancreatitis in adults and children but prevalence and incidence in children is yet to be determined. Viral pancreatitis usually resolves spontaneously and completely.

Evidence of association with SARS-CoV-2

Liu et al. analyzed association of ACE-2 receptors in pancreas and pancreatic injury in SARS-CoV-2 infection. These receptors are expressed slightly more in the pancreas than lungs which suggests that SARS-CoV-2 infection can cause direct damage to pancreas. Pancreatic injury is reported in 1–2% of non-severe compared to 17% of severe Covid-19 patients.3

During 2003 outbreak due to SARS-CoV, we learnt about organ distribution of the virus using immunohistochemistry and in situ hybridization on tissue samples from deceased patients. High levels of SARS-CoV PCR were detected in many organs including Pancreas and other parts of the gastrointestinal tract (GIT).4 According to Peng Zhou, SARS-CoV-2 has 79.6% genomic sequence identical to SARS-Cov and termed both of them as ‘almost identical’.5

Data suggests that not only respiratory system but many parts of GIT including the pancreas can be affected directly by SARS-CoV-2 but exact pathogenesis and incidence remains unclear. It must be emphasized that the consequences of pancreatic injury can be potentially very serious in covid-19 because this will potentiate the systemic inflammation and ARDS already affected by direct infection of SARS-CoV-2.

Laboratory investigations

Diagnosis depends on the triad of characteristic symptoms, pancreatic enzyme elevation and distinct radiological findings. In children characteristic symptoms can vary, hence acute pancreatitis should be ruled out in any child with severe and persistent abdominal pain.

There is no gold standard laboratory test for acute pancreatitis. Serum amylase and lipase are commonly elevated but reported sensitivity and specificity of both the tests vary. Radiologically diagnosed pancreatitis in presence of normal pancreatic enzyme levels have also been reported. Moreover, elevated levels may be found in other diseases especially salivary gland disease and renal failure. Finally, there is significant fluctuation of levels which do not correlate with the course of illness and recovery. Lipase, however, has superior sensitivity to amylase hence considered as an important tool for diagnosis supported with clinical correlation. In a prolonged episode of acute pancreatitis, it is prudent to investigate and rule out pancreatic insufficiency.

Imaging

Ultrasound abdomen is often the most convenient and reliable initial investigation of choice for evidence of acute or chronic insult to pancreatic tissue. An inflamed pancreas may appear hypertrophied or bulky. Obstruction to pancreatic flow, gross
Common aetiologies for acute pancreatitis in children and young people

| Category             | Example                                                                 |
|----------------------|--------------------------------------------------------------------------|
| Drugs                | Steroids, Valproate, Some antibiotics e.g. Metronidazole, Tetracycline, Isoniazid, Some immunosuppressants e.g. Mescalazine, Azathioprine, Some chemotherapy e.g. L-Asparaginase, Mercaptopurine, Cytarabine, Didanosine |
| Biliary tract abnormalities | Choledochal cyst, Cholelithiasis (Gall stones), Cholecystitis, Anomalous junction of biliary and pancreatic ducts |
| Pancreatic anatomy abnormalities | Annular pancreas, pancreas divisum, ampullary obstruction, diverticulum or cyst of pancreatic duct, pancreatic tumor |
| Infections           | Viruses e.g. measles, mumps, coxsackie, Epstein Barr virus and possibly SARS-CoV-2 (COVID-19), Bacteria e.g. Mycoplasma, Salmonella, Premature newborns |
| Trauma               | Blunt abdominal injury (accidental/NAI), Duodenal haematoma, Post – ERCP |
| Systemic disease     | Crohn's disease, Sepsis, Haemolytic ureamic syndrome, Kawasaki disease, Auto-immune disorders (e.g. systemic lupus/Poly arteritis nodosa/Henoch-Schoenlein purpura/AI pancreatitis), Anorexia nervosa/malnutrition, Cystic fibrosis |
| Genetic              | CFTR, CASR, PRSS1, SPINK-1 or CTRC gene mutation, Cystic fibrosis |
| Metabolic            | Hyperlipidemia, Hypercalcaemia, Glycogen storage disease, Organic acidemias, Re-feeding syndrome |
| Irritant             | Alcohol                                                                   |

Table 1

appearance of hepato-pancreato-biliary system and/or abnormality in the peri-pancreatic area can be visualized. However, obesity and presence of bowel gas may limit the ability of ultrasound to provide complete and reliable information.

Plain and contrast-enhanced CT Scans of abdomen are considered as gold standard to provide extensive information about the hepato-pancreato-biliary system. It can provide evidence for obstruction, abnormalities in the collecting system and/or complications developing in and around pancreas. Serial CT scans are useful to follow the progress of complicated acute pancreatitis.

Other valuable imaging tools are Endoscopic Retrograde Choleangio-pancreatography (ERCP) and Magnetic Resonance Choleangio-pancreatography (MRCP) but due to the need for anaesthesia, their use is limited in children than in adult age group. ERCP however is widely used for therapy of gall stones or duct anomalies. Endoscopic Ultrasonography (EUS) may be useful to determine the presence of microlithiasis in gallbladder or distal common bile duct which are not visualized by conventional methods.

Specific investigations to identify aetiology should be carried out extensively once obstruction is ruled out.

Management

Medical care

Management depends on the severity of disease. Mild cases may recover completely merely by pain management and hydration; provided the cause is identified and treated. Conversely, severe pancreatitis may need extensive treatment under multidisciplinary team; including pain specialist, dietician, surgery, interventional radiology, intensive care team, hepatopancreato-biliary team and primary care services for follow up – in accordance with NICE guidelines. Psychiatrist support may be needed since hospital stay may last longer than months.

Supportive care, pain control, fluid resuscitation and managing complications are the mainstay of treatment. Delaying surgical interventions is safer as there is potential for spontaneous resolution.

Fluid resuscitation: AP is a condition which is complicated by widespread alteration of the microcirculation. As mentioned above, massive cytokine release can occur and if it does, this results in increased capillary permeability and hence relative hypovolemia and impending shock. The importance of aggressive fluid resuscitation cannot be over-emphasized in such scenario.

In paediatrics, generally either balanced isotonic crystalloid solutions or 0.9% saline with 5% dextrose remain the fluids of choice. Use of colloids (fresh frozen plasma/albumin/packed RBC) is discouraged but justifiable if albumin is <2g/dl or the haematocrit is <25%. In severe cases, children may need 1.5–2 times the maintenance fluid, in the initial 24–48 hours, with strict fluid monitoring for signs of overload. There is strong evidence in adults that early and prompt fluid resuscitation significantly improves prognosis.

Pain control: acute Pancreatitis is known for its excruciating pain. Prolonged need for morphine or fentanyl infusion is common since pain does not respond to acetaminophen or ibuprofen except in mild cases. Pain specialist teams should be involved from the outset.

Nutrition: in adults it is established that early enteral nutrition i.e. within first 72 hours of presentation even in complicated cases improves prognosis, and reduces incidence of gastrointestinal, intestinal ileus and bacterial translocation. Hence food is rightfully considered as ‘active therapeutic intervention’ in management of AP.
Jejunal and gastric feeds are equally effective. The choice should be made according to whichever is tolerated better, (signs of intolerance include abdominal distension, vomiting or large residual feed volumes). Parenteral nutrition should only be used when enteral feeds are not tolerated. There is no evidence in either paediatric or adult populations to support use of any specific feed preparation such as whole protein vs elemental formulas, addition of immune enhanced nutrients or probiotics.

Supportive care for possible complications: in view of the wide range of possible complications, severe pancreatitis should be managed in an intensive care unit. Frequent blood investigations and appropriate imaging to direct therapy is of paramount importance.

Worsening tachycardia, decreased urine output, development of acute respiratory distress (ARDS), pulmonary edema, effusion and ascites is indicative of progressive systemic inflammatory response (SIRS). Patients will need standard symptomatic support as per ICU standard.

Hypocalcemia is another frequent occurrence and is associated with poorer outcome. Most commonly explained mechanisms for this phenomenon is formation of calcium salts with free fatty acids released from auto-digestion of mesenteric fat by pancreatic enzymes. Transient hypoparathyroidism and hypomagnesemia may also contribute. In later stages, high levels of catecholamines can cause intracellular shifting of circulating calcium, further potentiating hypocalcemia. Clinically this may present with neuromuscular and cardiovascular complications and tetanic spasms in severe cases. Careful replacement of calcium with monitoring is advisable but controversial as sustained rise in cytosolic calcium may result in further pre mature acti-

vated with monitoring is advisable but controversial as sustained rise in cytosolic calcium may result in further pre mature acti-

cation of trypsinogen.

Hypophosphatemia is also reported in acute pancreatitis but its aetiology and clinical impact is not well understood. Hypo-

phosphatemia occur possibly due to third space fluid shift.

Provoked hypercoagulable state as explained above will need treatment with anticoagulants and monitoring of complications. Untreated cases are frequently associated with thrombi in splanchic veins, pulmonary emboli and infaracts.

Pseudocysts and necrotic debris collections are common breeding grounds for infection but prophylactic antibiotic use is not recommended. Cultures obtained from debris drainage alongside blood cultures should be used for judicious antibiotic administration.

There is no data to support use of protease inhibitors, anti-

oxidants or probiotics for treatment of severe AP in children.

Surgical management
The current NICE guidelines recommend a minimally invasive approach. Similarly, according to 2013 American College of Gastroenterology Guidelines, surgical intervention is advisable only for gall stone pancreatitis and debridement of necrosis if not approachable by non-invasive methods.

Interventional radiology
Endoscopic ultrasonography-guided drainage: the indications for EUS-guided drainage are: pseudocyst larger than 5cm, necrotic collections with evidence of infection or cysts persistent for > 4–6 weeks; since these are less likely to self-resolve. This effective procedure can also be used for creation of a cystgas-
trostomy and has effectively replaced surgical cystgastrostomy.

Therapeutic endoscopic retrograde cholangiopancreatography (ERCP): ERCP has a role where imaging suggests an obstruction. It can also be used in placing transpapillary drainage stents to drain a pseudocyst communicating with the pancreatic duct. Despite the risk of post ERCP AP, it’s a useful diagnostic and therapeutic tool; but there is no guideline regarding ideal timing of this procedure in children.

Prognosis
Outcome in severe complicated pancreatitis has improved significantly since the advent of minimally invasive approach. However, complete recovery with no further episodes of pancre-

atitis cannot be achieved without the definitive treatment of aetiology therefore, children with genetic mutation remain at high risk for recurrent pancreatitis and eventually chronic pancreatitis.

Conclusion
Severe complicated paediatric AP can be life threatening and is associated with significant morbidity; but as our knowledge about the disease is improving, prognosis is also improving. We have learnt that key to complete recovery is: early diagnosis, MDT involvement with ICU care and minimally invasive approach. Further research specific to the paediatric population is required to inform incidence, prevalence and evidence-based practice, particularly in light of its association with COVID-19. ◆

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