Guidelines for the diagnosis and management of pancreatitis in children

BSPGHAN Pancreatitis Working Group

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1.0 Scope of the guideline

This guideline covers the diagnosis and management of acute and chronic pancreatitis in children and young people (CYP) in the United Kingdom. It is aimed at medical, surgical, nursing and allied healthcare professionals across secondary, tertiary and quaternary centres who encounter such patients. There continues to be a paucity of evidence in the field of paediatric pancreatitis, especially with regard to fluid management, pain control, dietary interventions and consistency of follow up. Although many questions remain with regard to these areas, we would envisage that this guidance would be used as a framework for the multidisciplinary teams involved with these young people and allow a more standardised approach to care.

The guideline has the following aims:

1. Clearly define the clinical entity of pancreatitis, its definitions, epidemiology, clinical presentation and causes.
2. Understand the most useful investigations at presentation and subsequent useful blood tests, imaging and genetic analyses that may be beneficial in certain cases.
3. Outline the general principles of management focussing on fluid balance, pain control, nutrition and surgical options.
4. Understand the features of acute recurrent pancreatitis, chronic pancreatitis and autoimmune pancreatitis – their presentation, investigation, management and long-term monitoring strategies.

2.0 Definition

Pancreatitis is defined as an inflammatory process affecting the pancreas, the aetiology of which can be variable. As per INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE) the defining criteria of different types of pancreatitis are:

1. Acute Pancreatitis (AP) – requires at least 2 of the following:
    - abdominal pain compatible with AP (i.e. abdominal pain of acute onset, especially in the epigastric region).
    - serum amylase and/or lipase values three times the upper limit of normal.
    - imaging findings consistent with AP (e.g. using [endoscopic] ultrasound, CT, MRI).

2. Acute Recurrent Pancreatitis (ARP)
    - Two distinct episodes of pancreatitis (as defined above) along with:
    - Complete resolution of abdominal pain > 1 month apart or
    - Complete normalisation of amylase/lipase before subsequent episode of AP is diagnosed, along with complete resolution of pain symptoms, irrespective of a specific time interval between AP episodes

3. Chronic Pancreatitis (CP) - the diagnosis of CP includes at least one of the below 3 criteria:
    - abdominal pain consistent with pancreatitis origin and imaging suggestive of CP

- evidence of pancreatic exocrine insufficiency and imaging suggestive of CP
- evidence of pancreatic endocrine insufficiency and imaging suggestive of CP
- pancreatic histology suggestive of CP.

3.0 Acute Pancreatitis

3.1 Incidence

Much of the natural history and management of paediatric acute pancreatitis aligns with acute pancreatitis in adults (although aetiologies often differ), and while there is a lower annual incidence at 4-13 per 100,000, there seems to be a rising trend (possibly due to an increase in multisystem disease and referral bias).

3.2 Signs and Symptoms

Presenting symptoms of pancreatitis include epigastric or diffuse abdominal pain (80-95% of cases), nausea and vomiting (40-80% of cases), abdominal distension, fever, breathlessness, irritability, and impaired consciousness. This can be accompanied by more systemic signs such as pyrexia, low oxygen saturation, tachypnoea, tachycardia, hypotension, abdominal guarding, ileus and/or oliguria. However, it should be noted that often symptoms are vague (especially in younger children) and that pain radiating to the back (which is classically described in older patients) may not always be present.

3.3 Aetiology

There is a myriad of factors associated with acute pancreatitis with the most frequently encountered listed below:

- Idiopathic
- (Systemic) infections
- Multisystem diseases
- Trauma
- Drugs (especially Badalov class I-IV i.e. asparaginase, azathioprine, 6-mercaptopurine, sodium valproate, tetracyclines, aminosalicylic acid, steroids, sulfasalazine, and non-steroidal anti-inflammatory drugs)
- Gallstones
- Hereditary (e.g. *SPINK1*, *PRSS1*, *CFTR* mutations)
- Anatomical variants (e.g. pancreas divisum, pancreaticobiliary ductal abnormalities)
- Hypertriglyceridaemia
- Hypercalcaemia
- Following ERCP
- Autoimmune (refer to Section 7.0)
- Other causes to be considered are viral infections (e.g. mumps, cytomegalovirus, and coxsackie B virus), tumours, metabolic conditions (e.g. methylmalonic acidaemia), cardiac bypass surgery, scorpion bites (notably from Tityus trinitatis) and organophosphate poisoning.

3.4 Investigations

3.4.1 On admission

- Vital signs including oxygen saturations, heart rate, respiratory rate, temperature and blood pressure should be measured frequently. If possible, a validated early-warning system (such as a PEWS chart) should be utilised; trends in vital signs should be monitored closely not just single values.
- Serum amylase and/or lipase (NV usually <110 IU/L), triglyceride levels, full blood count, CRP, renal and liver function tests (e.g. ALT/AST, GGT, bilirubin, ALP), glucose, calcium and capillary blood gas should be obtained at presentation – these should be acted on accordingly. Even if antibiotics are not indicated during initial review, caregivers should strongly consider taking blood cultures if pyrexial and a full coagulation screen (e.g. PT, APTT, Fibrinogen) if there are concerns about DIC/SIRS at initial presentation.
- Immunoglobulins, IgG subclasses (1-4) and autoantibodies (i.e. liver screen [e.g. anti-SMA, anti-LKM1, ANA, anti-mitochondrial] and diabetes screen [e.g. anti-GAD, anti-IA2, anti-ZnT8]), especially if suggestive pancreatic imaging and/or past medical or family history of autoimmune disorders

3.4.2 Radiology

- Transabdominal ultrasound (fasted) should be performed in all CYP with a clinical diagnosis of pancreatitis looking for evidence of pancreatic abnormalities (parenchymal and ductal) and local complications.
- Chest x-ray if clinical concerns to identify any pleural effusion.
- If the diagnosis remains uncertain or there is persistence/worsening of clinical and/or biochemical picture, then MRI/MRCP or CT are indicated during the initial presentation admission. This will help to identify features of acute pancreatitis (oedema of the pancreas, inflammatory fat-stranding, peri-pancreatic fluid collections, and ductal abnormalities) or any other contributing factors.
- There is no clear indication for axial imaging (CT/MRI) within the first week of presentation in uncomplicated cases. However, in patients with evidence of chronicity on initial US examination an MRCP would be beneficial within the first 6-8 weeks following presentation as an outpatient.
- In contrast, if the child is pyrexial and jaundiced with bile duct dilatation on US, suggestive of cholangitis, early MRCP or endoscopic ultrasound (EUS), with a view or proceeding straight to ERCP, sphincterotomy and stone extraction should be considered. In these cases, early discussion with either a specialist paediatric centre (or local adult colleagues depending on the age/weight of the child) is strongly recommended.

3.5 Management

- Organ support in a critical care setting, treatment of infection, pancreatic exocrine and endocrine insufficiency, necrosectomy, and the prevention of recurrence, are dependent on the severity of disease and needs of individual patients. Overall, acute

pancreatitis has a mortality of 4%, recurs in 14% and is classed as severe disease in 17%.

- There is not a fully validated, clinically useful, scoring system for assessing the severity of paediatric pancreatitis as modification of adult scores/criteria have been hampered by issues with defining blood pressure criteria, the rarity of upper GI bleeding and the inability to monitor arterial blood gases outside the PICU setting.
- However, the majority of consensus statements focus on local complications (e.g. pancreatic pseudocysts, abscesses, and necrosis), organ dysfunction such as systolic blood pressure and creatinine measurements, upper GI bleeding and low PaO_2 as measures of severity.

3.5.1 Fluid Management

- At present crystalloids or Ringer's lactate are the preferred solutions for fluid resuscitation in acute pancreatitis.
- Based on assessment of hydration status/hemodynamic status, if evidence of hemodynamic compromise, a bolus of 10 to 20 mL/kg is recommended.
- Children with diagnosis of acute pancreatitis should be provided 1.5 to 2 times maintenance IV fluids with hourly monitoring of urine output over the initial 24-48 hours. Adjust fluid intake based on overall fluid balance.
- Reduction of intravenous fluids and initiation of enteral feeds depending on tolerance and clinical status.

3.5.2 Pain management

The management of pain in CYP with pancreatitis is poorly studied with guidance often extrapolated from adult practice. Pain is often the predominant feature in patients with pancreatitis therefore a focus on pain relief should be paramount at every clinical review.

- Consider starting with paracetamol (intravenous administration may be more effective and better tolerated) and NSAIDs and if no meaningful clinical response escalate to opioids as per local chronic pain protocol.
- Ideally, at presentation, patients should be urgently reviewed by a local pain team for consideration of patient-controlled or nurse-controlled analgesia or optimisation of non-opioid preparations.
- Neuropathic pain agents (such as gabapentin) are a recommended alternative in an attempt to minimize opioid intake. Other interventions such as Transcutaneous Electrical Nerve Stimulation (TENS) are advisable as adjuvant supportive measures.
- In adults, more invasive techniques such as percutaneous celiac plexus block (CPB) either via percutaneous or endoscopic ultrasound (EUS) guided route are an option followed by thoracoscopic splanchnicectomy for more refractory to conservative treatment cases.
- Always liaise closely with local clinical psychology team in an attempt to address pain-derived anxiety issues and to help patients with short, medium and potentially long-term problems.
- Charts to scale pain severity (0-10) and anxiety (0-10) should be available, introduced early on in the management plan, reviewed regularly, and acted upon. These charts

often remain useful in acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) cases after the patient is discharged home.

3.5.3 Antimicrobials and other drugs

Antimicrobials

- Acute pancreatitis alone is not an indication for empirical antimicrobial use; however, pragmatic clinical judgement is advised.
- If the patient develops local infective complications or SIRS then antimicrobials are advised. In very unwell patients not responding to antimicrobial escalation, antifungals should be considered.

Somatostatin analogues

The use of somatostatin or its analogue, octreotide, in acute pancreatitis has shown to reduce mortality in adults in terms of complications in patients treated on a high dose.

- The effect on pain from the inhibition of pancreatic secretion by octreotide has not been conclusive. However, following discussion with a specialist centre, especially in those with refractory pain, octreotide may be considered.
- There is some evidence that octreotide may be useful in the treatment of pancreatic pseudocysts, a common complication of pancreatitis, although again specialist advice should be sought.

3.5.4 Endoscopic procedures

Prior to deciding on invasive endoscopic procedures axial imaging will most likely be necessary (preferably MRI/MRCP) and discussion with either a specialist paediatric or adult hepatobiliary service. Exploring options with local adult colleagues can often be very helpful and can avoid unnecessary transfer of unwell patients, especially older children and adolescents. However, in the majority of patients discussions should be limited to specialist paediatric centres in the first instance.

- If the child has evidence of ductal (biliary and/or ductal) irregularities, anatomical variants, cholelithiasis or evidence of obstruction discuss with a specialist centre (paediatric or adult) about the indication and feasibility for ERCP.
- Discuss with a specialist centre about the indication for Endoscopic Ultrasound (EUS) if: the diagnosis is not clear and there is indication for tissue diagnosis (Fine Needle Biopsy) or there is pseudocyst formation that requires draining (cyst gastrostomy).

3.5.5 Surgery

- In the current era, the vast majority of interventional management for pancreatitis or its associated complications is done via ERCP and /or EUS and referral to a specialist paediatric hepatobiliary surgical team is highly recommended.
- A pancreaticojejunostomy or Puestow procedure may be indicated in patients with ARP or CP and ductal abnormalities, which are refractory to endoscopic management.

- Pancreatectomy is rarely indicated in children. Pancreatectomy and Islet Auto-transplantation is not within the scope of this document and is currently only commissioned for adults in England and Wales.

4.0 Acute Recurrent & Chronic Pancreatitis Investigations

All of the above investigations and management plans are applicable to all CYP suffering an acute episode of pancreatitis whether it is their first presentation or a recurrence of their pre-existing condition. You must also consider the following when reviewing a patient who fulfils criteria for ARP and/or CP.

4.1 Pancreatic Exocrine Insufficiency (PEI)

4.1.1 Definition

PEI, characterised by reduced pancreatic exocrine function and a reduction in the release of digestive enzymes lipase, amylase and protease into the gastrointestinal tract, is associated with the malabsorption of macronutrients and malnutrition. PEI is diagnosed based on the presence of abnormally low faecal elastase (<100µg/g stool on two separate stool samples ≥1 month apart) without the presence of watery stools.

4.1.2 Signs and Symptoms

- Lower abdominal pain / bloating worse after eating
- Offensive loose stools
- Excessive flatulence
- Steatorrhea
- Floating Stool
- Pale coloured stool
- Low serum fat-soluble vitamins (A, D, E, K)
- Poor weight gain and/or linear growth
- Unintentional weight loss

4.1.3 Pancreatic Enzyme Replacement Therapy (PERT)

PERT is available in a variety of formulations (refer to Children's British National Formulary for up-to-date prescribing options) and is designed to be given via enteral route with all oral or enteral intake containing fat. Extrapolated guidelines for the Cystic Fibrosis population advise the following starting dose:

- Infants: 2,000 - 4,000iu lipase per breastfeed or per 120ml of formula
- Children under 4 years: 1,000iu lipase/kg/meal + 500iu lipase/kg/snack
- Children >4 years: 1,000-2,500iu lipase/kg/meal + 500iu lipase/kg/snack
- Adolescents and those adult size 40000-50000iu lipase/meal + 20,000iu lipase/snack

- Dosing can be increased as required up to 10,000 IU lipase/kg/day if there are ongoing symptoms of steatorrhea despite good compliance.

4.1.4 Monitoring

- Monitor for PEI every 6-12 months in children with ARP and CP.
- For patients on PERT, review dose in line with weight gain and symptoms at each follow up appointment.
- Monitor serum fat-soluble vitamin levels every 6 months and supplement as necessary.

4.2 Diabetes

Pancreatogenic diabetes mellitus or T3DM is estimated to affect 4-9% of children and young people with CP and is typically associated with concurrent PEI.

- Serum HbA1c levels should be checked every 6 months.
- In patients with HbA1c results in the pre-diabetic range (HbA1c 5.7-6.4%) or fasting blood sugar (100–125 mg/dL or 5.6–6.9 mmol/L), oral glucose tolerance test (OGTT) is recommended.

4.3 Anthropometry

- Weight and height should be measured every 3-6 months due to higher risk of malnutrition in this group.

5.0. Nutritional Management

5.1 Nutritional Management of AP

During an acute episode of pancreatitis extended periods of fasting, pain, vomiting, elevated metabolic requirements and reduced appetite can lead to rapid weight loss. Encouragement with oral intake within the first 24 hours is strongly advised once the patient has been safely fluid resuscitated. If oral intake is not tolerated in this time an alternative safe route of enteral feeding, (e.g. NG tube) should be considered within the first 48-72 hours of presentation.

5.1.1 Initiating Feeding

- Except in the presence of direct contraindications to enteral feeding (including but not limited to ileus, pancreatic laceration/transection/fracture or duct disruption), children with acute pancreatitis should be encouraged to attempt oral and/or enteral nutrition (EN) via the gastric route (even if only trophic feeds initially) within 24 hours to reduce the risk of bacterial translocation.

5.1.2 Choice of Feed

- There is no evidence for the need to use a specialist feed; choice of feed may be a first line whole protein option in line with local enteral feeding guidelines.

- Supplementation with medium chain triglycerides (MCT) is not indicated unless there is a known biliary obstruction or bile flow issue.

5.1.3 Route of feeding

- In cases of worsening epigastric pain, high gastric aspirates, a significant spike in pancreatic amylase or lipase directly associated with feeding or vomiting with oral or nasogastric (NG) feeding, feeding via the jejunal route (NJ) feeding may be indicated.

- Parenteral nutrition should be only considered in cases where enteral nutrition is not possible for a prolonged period (longer than 5–7 days) such as in ileus, complex fistulae, abdominal compartment syndrome with the theoretical benefit of reduced pancreatic stimulation

5.2 Low Fat Diet

- There is no published evidence for the benefit of a low-fat diet on disease course and fat should not be restricted during an acute episode of pancreatitis unless a clear symptomatic link has been identified in an individual case.

If a patient experiences a clear worsening of symptoms associated with fat intake, a diet with reduced total fat can be used in the short term with faecal elastase to be sent to exclude exocrine insufficiency. In these patients a gradual re-introduction of fat within one week of the onset of acute pancreatitis is recommended to prevent a prolonged hypocaloric intake, and risk of fat-soluble vitamin and essential fatty acid deficiency.

- A normal diet should be maintained between acute episodes where tolerated. Exceptions will include cases of hypertriglyceridaemia or children who experience severe pain or vomiting as fat is increased. Dietetic follow up is essential in such cases.

6.0 Genetic investigations

6.1 Indication for genetic investigations

The indications for genetic testing in the setting of pancreatitis are not absolute but in general, patients with evidence of chronicity on imaging, those with ARP/CP and those with evidence of pancreatic insufficiency should have genetic analyses performed based on local guidance and availability.

6.2 Known genes

1. PRSS1 cationic trypsinogen gene (R122H and N29I)
2. Enzyme inhibitors (serine protease inhibitor Kazal type 1, SPINK1) Chymotrypsin C (CTRC)

3. Secretory channels (cystic fibrosis transmembrane conductance regulator, CFTR) Carboxypeptidase A1 (CPA1)
4. Consider expanding genetic work up including other genes implicated in acinar cell secretion such as CTRCB1, CTRCB2, PNLIP, CEL or ductal integrity such as TRPV6, CLDN2, and CASR. Liaise with your regional genomics services, as these genes are not part of the standard clinical genomic service.

7.0 Psychology support

There have already been reports that chronic pancreatitis can affect Health Related Quality Of Life (HRQOL) outcomes and fatigue scores in children but the condition can also have an effect in their families. This suggests that chronic pancreatitis mainly due to chronic pain impacts upon all areas of young people's lives, with some of the largest effect sizes seen for the Psychosocial Health Summary Score, largely due to greatest differences in school functioning relative to healthy peers. Psychology intervention can be aimed towards thoughts and behaviors that can increase cognitive behavior enhance coping mechanisms, reduce stress and improve compliance with treatment.

Psychology input is advisable from the early stages after diagnosis and local resources would be better positioned to maintain regular contact with the patients and their families.

8.0 Autoimmune Pancreatitis (AIP)

Although the precise incidence/prevalence of AIP in CYP is unknown it is likely to be a rare entity overall in the paediatric population.

There are two types of AIP:

- Type 1 or lymphoplasmacytic sclerosing pancreatitis
- Type 2, idiopathic duct centric chronic pancreatitis, or autoimmune pancreatitis with granulocytic epithelial lesions.

Consider the condition in your differential if there is any of the below and proceed accordingly:

- Suggestive family or past medical history of autoimmune disorders
- Suggestive appearances of AIP on USS, MRI, CT such as pancreatic head/uncinate process swelling, lack of downstream (body, head) pancreatic duct irregularities, intraperitoneal lymphadenopathy.
- Proceed with full autoimmune work up (IgG, IgM, IgA, IgG subclasses, complement and extensive autoantibody profile)
- If serology not supportive but there is still a strong clinical suspicion, consider EUS and fine needle biopsy; discuss with specialist paediatric/adult centre.
- Occasionally pancreatic head swelling in AIP can resemble that of pancreatic tumours and if such suspicion is, raised further discussion with respective specialist paediatric/adult team is highly recommended.
- Avoid treating blindly with steroids for the risk of developing IDDM on the background of chronic pancreatitis.