What's unique about acute pancreatitis in children: risk factors, diagnosis and management

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Abstract | Pancreatitis in children is an appreciable problem that has become increasingly prevalent. This Review covers the principles related to the definitions, epidemiology, risk factors, diagnosis and management of acute pancreatitis in children and identifies features that are unique among children. Additionally, knowledge gaps related to management principles are identified.

Acute pancreatitis is a disorder of reversible inflammation of the pancreas[1]. At all ages, acute pancreatitis is histologically defined by the presence of pancreatic oedema, an acute inflammatory infiltrate, vacuolization within the main parenchymal cell — the pancreatic acinar cell — and varying degrees of pancreatic necrosis or haemorrhage[1,2]. A pragmatic clinical definition according to the International Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE) group[3] and adopted by most paediatric groups is shown in BOX 1. In this Review, we searched the literature for salient manuscripts, reviews, and position statements relating to paediatric acute pancreatitis and present them below.

Epidemiology of paediatric acute pancreatitis

The incidence of paediatric acute pancreatitis has increased over the past two decades[4] and now stands at 3–13 cases per 100,000 population per year[5–7]. This incidence overlaps with the lower end of the range historically seen in adults, which is 5–45 cases per 100,000 population per year[8,9]. Acute pancreatitis is more common in children >5 years of age than in younger children[10,11]. However, the severity of acute pancreatitis is similar among the paediatric age groups[12].

Risk factors

Park *et al.*[7] identified several risk factors for acute pancreatitis from a large cohort of children at Yale New Haven Children's Hospital, USA, from 1994 to 2007. In rank order, the risk factors comprised: biliary tract disease; medication use; systemic disease; abdominal trauma; metabolic disorders; and inborn errors of metabolism (FIG. 1). Most paediatric cohorts have identified a similar burden of risk factors[4]. Moreover, there are differences in risk factor prevalence across age groups[10] (FIG. 1); inborn errors of metabolism are diagnosed as a risk factor for acute pancreatitis primarily in infants and toddlers (<2 years), whereas biliary risk factors predominate in children >11 years. In the past few years, the contribution of genetic risk has become increasingly recognized, especially in the context of acute recurrent pancreatitis (ARP)[13]. Another important observation is that over one-fifth of patients will have more than one risk factor identified[7]. For this reason, a general recommendation is to use the term risk factor rather than aetiology for pancreatitis, unless the risk factor is a highly penetrant genetic cause (for example, *PRSS1* gene variants, discussed later) or a definite association (for example, impacted gallstone or specific medication). A brief description of key points about each of these risk factors is presented later, and suggested evaluation steps for children with acute pancreatitis are depicted in BOX 2.

Biliary disease

Pancreatitis attributed to biliary obstruction is most often because of an impacted gallstone in the common bile duct (CBD)[14]. The frequency of biliary pancreatitis ranges widely from 3–30% of all acute pancreatitis cases, and in most case series it constitutes the most common risk factor for acute pancreatitis in children[4,12,15–19]. Elevated levels of serum transaminases[14], bilirubin, alkaline phosphatase or γ-glutamyl-transferase are typically seen in paediatric biliary pancreatitis and serve as a helpful indicator for this risk factor. However, one or all of these biochemical indices can be normal in 10–25% of patients with acute biliary pancreatitis[20].

Anatomical variants

Anatomical abnormalities of the pancreaticobiliary system are identified in ~5–20% of cases of acute pancreatitis in children[12,17]. Anomalies include pancreas divisum, pancreaticobiliary maljunction (also known as a common channel), choledochal cyst, annular pancreas and intestinal duplication. The most common finding

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Key points

- Acute pancreatitis is a painful inflammatory process that is growing in incidence in children
- The most common risk factors for acute pancreatitis in children are biliary tract disease and medications, although genetic associations are becoming much more appreciated
- The symptoms of acute pancreatitis differ based on age and developmental stage
- The key principles of management for acute pancreatitis in children are to provide adequate pain control and supportive care and remove the inciting risk factor if known
- About one-quarter of children with acute pancreatitis will develop recurrence and one-third of those children will progress to chronic pancreatitis

is pancreas divisum (FIG. 2), in which pancreatic ductal drainage occurs through the proximally located minor duct of Santorini rather than the main duct of Wirsung. The condition is theorized to predispose to acute pancreatitis owing to poor drainage of pancreatic juice from the minor duct[21]. Whether pancreas divisum is a definite risk factor for ARP is unclear. Part of the controversy stems from the fact that pancreas divisum is a common anomaly that is seen in ~7% of the general population, and only a few studies report an increased prevalence among patients with pancreatitis[22,23]. However, there are reports of reduced frequency of pancreatitis after minor papilla sphincterotomy[22,24]. Pancreas divisum in the setting of acute pancreatitis is often concomitant with a genetic predisposition[25,26] (for example, with *CFTR*, *SPINK1* and even *PRSS1* gene variants; these variants are discussed in greater detail later). The other ductal anomalies (pancreaticobiliary maljunction, choledochal cyst, annular pancreas and intestinal duplication) are more clearly linked to pancreatic outflow obstruction. Cross-sectional imaging is an essential component of the evaluation of ARP in children[27].

Systemic disease

Acute pancreatitis is often associated with systemic disease[4]. The most common associations include sepsis and haemolytic uraemic syndrome[28]. Autoimmune disorders associated with acute pancreatitis include systemic lupus erythematosus, Henoch–Schönlein purpura, Kawasaki disease and IBD[29,30]. Reasons for an increased risk of acute pancreatitis in patients with IBD are medications that predispose to pancreatitis, primary sclerosing cholangitis with distal common bile duct narrowing, and autoimmune pancreatitis[30]. Patients with Crohn's disease can develop pancreatitis from duodenal inflammation causing periampullary oedema and an increased frequency of gallstones[30]. 30% of patients with a younger onset of autoimmune pancreatitis (AIP), known as type II AIP or idiopathic duct centric pancreatitis (IDCP), are diagnosed with IBD[31,32].

Medications

The most common medications leading to paediatric acute pancreatitis are valproic acid, asparaginase, prednisone, metronidazole, tetracycline, 6-mercaptopurine and mesalamine[33]. Approximately one-third of children with medication-associated pancreatitis have a second concomitant risk factor[33]. Mechanisms underlying medication-associated pancreatitis are largely unclear, but could include immune-mediated or hypersensitivity reactions, or a direct toxic effect on pancreatic acinar cell stress responses[34,35].

Trauma

Acute pancreatitis resulting from blunt abdominal trauma should prompt a search for pancreatic duct disruption. Common traumatic events in children include bicycle handlebar injuries, motor vehicle accidents, sports injuries, falls and non-accidental trauma[4,12,36].

Genetic associations

The contribution of genetic variants to acute pancreatitis in children with a single isolated episode of pancreatitis is unclear. However, genetic risk factors are enriched in children with ARP[13], as will be discussed later.

Infections

Infections are a common consideration in paediatric medicine. However, only select case reports have linked infections to acute pancreatitis, and these include the viruses responsible for mumps, influenza, hepatitis, herpes[4] and bacterial pathogens such as *Salmonella enterica* subsp. *enterica* serovar Typhi (the causative agent of typhoid fever)[37]. A diagnosis is most often based on the history of an infectious prodrome, the systemic findings of the infection itself and the temporal diagnosis of acute pancreatitis in the absence of other risk factors. However, pancreatic histology demonstrating invasion of the pathogen is rarely available. An experimental mouse model of pancreatitis is induced by infection with Coxsackie B virus in conjunction with alcohol feeding[38], yet clinical reports with this pathogen are sparse[39,40].

Metabolic factors

Metabolic abnormalities are uncommon risk factors for acute pancreatitis[4,12,15–17,19,28]. Diabetic ketoacidosis is the most frequent cause of acute pancreatitis in this category, followed by hypertriglyceridaemia and hypercalcaemia[4,12,15–19,28]. Most patients with hypercalcaemia-associated pancreatitis have primary hyperparathyroidism[41].

AIP and IDCP

AIP occurs in two forms[31,42]. Type I AIP is associated with IgG4-related disorders. The type II variant (more appropriately termed IDCP) is most common in young

Box 1 | **Definition of acute pancreatitis in children**

Acute pancreatitis in children is diagnosed by the presence of at least two of the following three criteria[3]:

- Abdominal pain suggestive of, or compatible with, acute pancreatitis*
- Serum amylase or lipase level at least three times greater than the upper limit of normal
- Imaging findings characteristic of, or compatible with, acute pancreatitis

*Can be absent in very young children (patients <3 years of age) or children who are moribund.

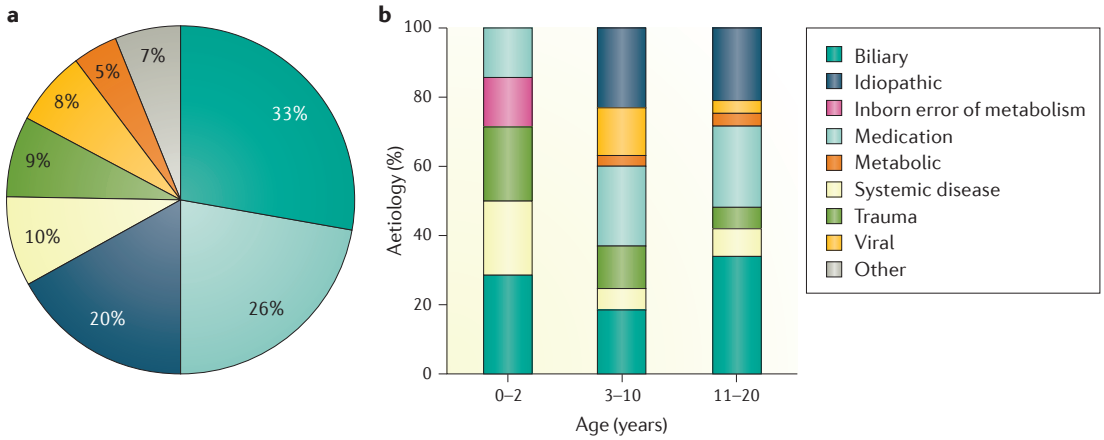

Figure 1 | **Aetiology of acute pancreatitis in children. a** | Aetiology in all children. **b** | Aetiology by age group[7,10].

adults, manifests with normal serum IgG4 levels, is steroid responsive, has a low recurrence rate and is associated with IBD[32]. One or both AIP entities might have been diagnosed by paediatric surgeons in previous decades as idiopathic fibrosing pancreatitis in young children who presented with jaundice and were found to have an inflammatory obstructing mass at the head of the pancreas. Although more comprehensive studies are necessary, an increased awareness of this disorder might obviate the need for surgical procedures such as a diverting duodenostomy for affected patients.

Idiopathic pancreatitis

About one-quarter of paediatric acute pancreatitis cases are still labelled as being idiopathic, although the proportion will probably shrink owing to increased efforts in identifying structural and genetic risk factors[4].

Diagnosis of paediatric acute pancreatitis

Each of the clinical criteria used to diagnose acute pancreatitis (BOX 1) are discussed here, with special notes relating to children.

Abdominal pain

Very young children (<3 years) with acute pancreatitis are less likely than older children to report classic epigastric pain radiating to the back. Nevertheless, the most common symptom is abdominal pain, albeit nonfocal by description[4,10]. Nonspecific irritability is a frequent complaint in nonverbal children and might serve as a proxy for abdominal pain when corroborated with some degree of abdominal tenderness on physical examination.

Serum amylase or lipase level

Although using the cutoff of a greater than threefold elevation in serum amylase or lipase level is probably an accurate method of diagnosing pancreatitis, this threshold has interestingly not been systematically validated in children. The serum lipase level is both more sensitive and more specific than the serum amylase level in making a diagnosis of acute pancreatitis among all paediatric age groups[4]. Pancreatic amylase expression does not fully mature until late infancy[43]. For this reason, the serum amylase level will miss the diagnosis of acute pancreatitis in one-third of infants compared with the serum lipase level[10].

Imaging findings

Indications for imaging when a patient presents for evaluation with suspected acute pancreatitis are: to make a diagnosis of pancreatitis; to exclude other causes for an acute abdomen; to identify pancreatitis risk factors, particularly biliary disease; and to determine the presence of localized pancreatic complications, particularly necrosis. Medical culture in paediatrics advocates first-line imaging tests that avoid or minimize ionizing radiation, such as transabdominal ultrasonography[44]. The additional benefit of ultrasonography is that it is widely accessible and relatively inexpensive compared with other imaging modalities. However, the efficacy of ultrasonography is dependent on operator skill, unlike the other modalities mentioned here. In addition, an obese body habitus or overlying bowel gas can obscure visualization with transabdominal ultrasonography. Cross-sectional imaging by CT, MRI or magnetic resonance cholangiopancreatography (MRCP) is an immediate next option to adequately evaluate for pancreatic complications such as necrosis, acute fluid collections, duct disruption, pseudocyst or to exclude biliary pancreatitis[45,46].

Management of paediatric acute pancreatitis

General principles

The principles of management for acute pancreatitis are fourfold: provide adequate pain control; remove inciting risk factors, such as a persistently impacted gallstone in the distal CBD, suspected medications thought to predispose to pancreatitis or elevated serum triglyceride or calcium levels; halt the progression to severe acute pancreatitis, manifested by multi-organ failure or pancreatic fluid collections, particularly necrosis; and control for the complications of pancreatitis, which include peptic ulcer disease and gastrointestinal bleeding, portal vein thrombosis or intestinal ileus. It is important to also consider the complications from comorbidities for each individual patient. Offering adequate pain

Box 2 | **Suggested risk factor investigations for acute pancreatitis in children**

Single episode

- Serum levels of alanine transaminase, aspartate transaminase, bilirubin, γ-glutamyl-transferase, triglycerides and calcium
- Right upper quadrant ultrasonography or cross-sectional imaging

Recurrent episodes

In addition to the single episode risk factors, the following investigations can also be carried out:

- Magnetic resonance cholangiopancreatography (preferably with secretin to enhance imaging)
- Evaluation for genetic variants associated with ARP

control with opioids is prudent. Additional endoscopic, pharmacological, or surgical strategies are based on individualized factors.

Severe pancreatitis develops in about one-fifth of adults with acute disease, and about one-tenth to one-third of severely affected adult patients with pancreatitis succumb to death[47]. However, the proportion of severe cases among children is much lower than among adults, depending on how severity is defined, and mortality rates are overall <5%[4].

Intravenous fluids

The management of acute pancreatitis in children is currently modified from adult guidelines[48,49]. These guidelines include aggressive, or at least optimized, intravenous hydration in the first 12–24 h (with 10–20 ml/kg body weight boluses of crystalloid fluids, particularly lactated Ringer's solution), followed by continuous fluids at greater than maintenance levels for 24 h or more. A decision to reduce the infusion rate is thereafter based on adequate urine output and balanced by the child's ability to tolerate oral or enteral fluids and to handle a large cumulative volume. Abu-El-Haija *et al.*[50] noted paediatric provider variability in hydration practices for acute pancreatitis. The group prospectively examined patients with mild acute pancreatitis at their centre and randomly assigned them to aggressive versus maintenance hydration in the first 24 h of presentation. They found that fluid rate in the first 24 h as a single management strategy had no effect on outcomes such as length of stay, intensive care unit transfer rates or readmission rates[51]. Lactated Ringer's solution was found to reduce markers of systemic inflammation over normal saline in adults[52], but the tangible benefits in a reduction of serum inflammatory indices or progression to systemic inflammatory response syndrome needs to be validated in children.

Nutritional management

Several trials have reported a survival benefit in the use of early enteral nutrition compared with total parenteral nutrition for patients with predicted severe acute pancreatitis[53–56]. Enteral nutrition in this context is usually given within 24–48 h of presentation as a hypocaloric nasojejunal feeding regimen of a polymeric or elemental formula[57]. Before strict recommendations about early enteral feeding can be made in children, paediatric clinical trials are necessary to know whether this regimen (via either nasogastric or nasojejunal routes) will affect not only severity outcomes but also other important quality measures, such as length of stay, duration and severity of abdominal pain, recrudescence of pancreatitis or pain upon refeeding. In cases of hypertriglyceridaemia, intravenous fluid therapy and a brief period of fasting are usually effective interventions in reducing serum levels. If necessary, insulin can also be given to further reduce serum triglyceride levels. Persistent elevations might require plasmapheresis[58]. Anecdotally, patients with methylmalonic acidaemia or propionic acidaemia who develop pancreatitis seem to have fewer episodes of pancreatitis with correction of their acid–base balance[59].

Support and prevent complications

Additional supportive measures include gastric acid suppression as gastrointestinal bleeding is an important, albeit uncommon, complication of severe acute pancreatitis[49]. In cases of biliary pancreatitis, endoscopic retrograde cholangiopancreatography (ECRP) should be performed within 24–72 h of suspecting a persistent impacted stone, or sooner if cholangitis is suspected[60,61]. Published in 2015, a randomized controlled trial in adults confirmed that cholecystectomy should be performed on the same admission[62]. However, patients with pancreatic fluid collections should wait for 6–8 weeks until resolution of these complications[63].

The management of pancreatic fluid collections depends on their contents. Non-necrotic collections will usually resolve spontaneously[64]. Necrotic collections should be allowed to develop into walled-off necrosis, which usually takes >4 weeks[49]. A decision to endoscopically, percutaneously or surgically drain necrotic foci is based on group practice and available technical expertise. Antimicrobial therapy is indicated when infected necrosis is either established or highly suspected and can be tailored to the microorganisms identified from the necrosectomy specimen. Pseudocysts form weeks after resolution of acute pancreatitis and are most often managed conservatively. However, pancreatic duct stents are often placed to treat pseudocysts, as they are thought to arise at least in part from ductal disruption. Symptomatic pseudocysts that cause extra-intestinal obstruction or pain can be drained[65,66].

Hospital course in children

The median hospital stay for children with acute pancreatitis is ~5 days[4]. About one-quarter of patients will go on to develop acute recurrence[4].

Aetiology of acute pancreatitis versus ARP

ARP in children has been studied by the INSPPIRE consortium. The group published survey results outlining a reasonable approach to evaluate patients with ARP[3]. The consensus was to perform genetic testing for gene variants (discussed later) known to be associated with pancreatitis and to perform cross-sectional imaging to evaluate for biliopancreatic structural anomalies[3]. These two modalities alone have helped to narrow the gap on idiopathic pancreatitis. Our overall suggested risk factor evaluation for patients with ARP is depicted in BOX 2.

Genetic

From an INSPPIRE study published in 2016, at least one genetic risk factor was present in about half of children with ARP. These risk factors included gene variants in *PRSS1*, *SPINK1*, *CFTR,* or *CTRC*[13].

PRSS1. *PRSS1* encodes cationic trypsinogen, which is the most abundant pancreatic proenzyme, or zymogen, in the pancreatic acinar cell. The *PRSS1* variants that are associated with pancreatitis are thought to confer gain-of-function[67]. Thus, these variants predispose the pancreas to pathological intra-acinar trypsinogen activation. The *PRSS1* variants lead to a highly penetrant[68] (up to 80%) autosomal dominant form of familial pancreatitis called hereditary pancreatitis[69]. Patients develop a first attack of pancreatitis at a median age of 10 years. Most of the patients who are affected progress to chronic pancreatitis by 20 years of age. Patients with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer[70] compared with an equivalent 1.5% risk in the general population[71]. This increased risk is rivalled only by patients with Peutz–Jeghers Syndrome (30%)[72]. In the INSPPIRE cohort[13], 17% of children with ARP had a *PRSS1* variant. The high rate of *PRSS1* variants in this study, however, could have been influenced by referral patterns.

SPINK1. *SPINK1* encodes serine protease inhibitor Kazal-type 1, an endogenous trypsin inhibitor, which is highly upregulated in response to pancreatitis. In the original reports, *SPINK1* gene variants were identified in about one-quarter to one-third of patients with chronic pancreatitis[73,74]. The most common sequence variant is Asn34Ser. This and other less common variants are thought to lead to loss-of-function, although, to date, empiric evidence for this notion is lacking. These variants confer mild to moderate susceptibility to pancreatitis, evidenced by the fact that they are also found in 1–3% of the general population[75]. For this reason, *SPINK1* is considered a susceptibility gene for pancreatitis rather than a causative gene. In the INSPPIRE cohort, 13% of the children with ARP or chronic pancreatitis who were tested had at least one *SPINK1* gene variant[13].

CFTR. The *CFTR* gene encodes the cystic fibrosis transmembrane conductance regulator[76], which functions as a chloride and bicarbonate transporter at the apical, or luminal, membrane of pancreatic duct cells. In conjunction with several ion transport pumps, anion exchangers and an intricate system of feedback regulation, *CFTR* is central in orchestrating ductal fluid and bicarbonate secretion into pancreatic juice. Pancreatitis is a *CFTR*-related disease because compound heterozygous variants in *CFTR* are associated with pancreatitis, and these variants are often a combination of one disease-causing and another non-disease-causing variant allele[77,78]. Children with *CFTR*-related pancreatitis are found to be relatively pancreas sufficient, compared with patients with cystic fibrosis, who have profound pancreatic insufficiency[79]. 34% of the INSPPIRE cohort that was tested had at least one *CFTR* gene variant of any type[13]. The significance of the multitude of CFTR gene variants to pancreatitis is currently unclear, and determining pathogenicity will require a systematic approach. Other pressing questions are how to optimally diagnose CFTR-associated pancreatitis and the role of sweat chloride testing or other more sensitive functional tests in the decision-making process.

Chymotrypsin C (CTRC). *CTRC* encodes the pancreatic zymogen chymotrypsin C (CTRC). On the basis of *in vitro* enzymatic studies, CTRC is thought to protect against unchecked trypsin activation by degrading active trypsin[80,81]. Pancreatitis is associated with loss-of-function variants in *CTRC*. 10% of the INSPPIRE cohort who were tested had loss-of-function *CTRC* variants[13]. The prevalence of *CTRC* variants associated with ARP was probably underestimated, as only 30% of the ARP cohort underwent testing for CTRC variants[13].

Other gene variants. Other emerging gene variants associated with ARP in children include those in *CPA1*, which encodes carboxypeptidase A1 (REF. 82). Most paediatric centres perform individualized gene variant analysis by PCR or by full gene sequencing. Emerging gene chips and more cost-effective whole-exome sequencing tools will provide a more comprehensive array of gene testing and novel discovery platforms.

Strategies to prevent recurrence

Does cholecystectomy reduce recurrence in patients with suspected microlithiasis? Some paediatric pancreatologists will consider cholecystectomy in children with unremitting attacks of idiopathic ARP, even in the absence of visualized gallstones or distinct evidence of microlithiasis. Although the assumption is that these

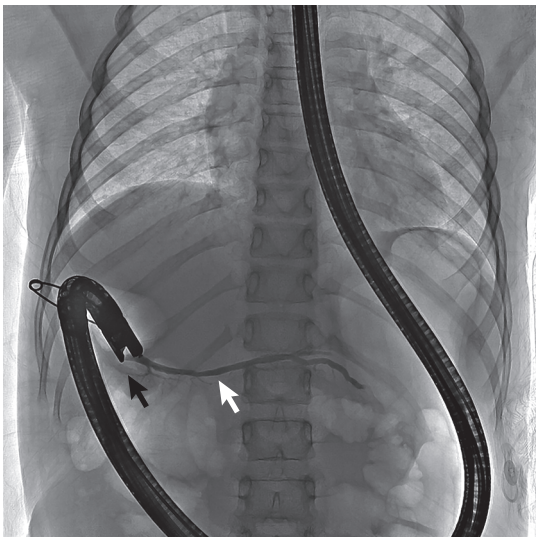

Figure 2 | **Pancreas divisum visualized by endoscopic retrograde cholangiopancreatography.** Injection of contrast agent through the major papilla causes filling only of the head of the pancreas (black arrow). However, the pancreatic duct is opacified (white arrow) to the tail following injection of contrast into the minor papilla. Permission obtained from Elsevier Ltd © Troendle, D. M. & Barth, B. A. *Gastrointest. Endosc. Clin. N. Am.* **26**, 119–136 (2016).

children might have undiagnosed microlithiasis, it is unclear whether empiric cholecystectomy improves pancreatitis outcomes[83–85].

Is there a role for antioxidants? Antioxidants are often prescribed to patients with ARP. A small placebo-controlled crossover trial of an antioxidant cocktail (Antox, comprising *N*-acetylcysteine, selenium and vitamin C) in adult patients with idiopathic ARP and chronic pancreatitis showed some benefit in reducing recurrent bouts of pancreatitis and chronic pain[86]. Although larger, controlled trials have either confirmed[87] or negated[88] the findings of a reduction in chronic pancreatitis pain with antioxidants, there has been no follow-up study to assess whether antioxidants reduce recurrence in patients with ARP. A large, randomized controlled trial conducted in Manchester, UK[88], showed no difference in severe acute pancreatitis outcomes with the same antioxidant cocktail.

What is the risk of progression from ARP to chronic pancreatitis? Estimates from the literature are that 20–40% of patients with ARP progress to a diagnosis of chronic pancreatitis within 2–5 years of an initial diagnosis of acute pancreatitis[89–91]. Risk factors for progression include alcohol consumption and smoking[92]. Longitudinal paediatric studies are needed to provide crucial information about the risk factors that mediate the sobering progression from ARP to chronic pancreatitis.

Conclusions

The past decade has seen substantial progress in defining and characterizing pancreatitis in children. Incidence of the disease has increased and seems to approach the lower end of the range seen among adults. Risk factors for paediatric acute pancreatitis are divided into biliary, anatomical, systemic disease, medications, trauma, genetic, infectious and metabolic factors. The proportion of patients with idiopathic disease has reduced owing to the discovery of genetic and anatomic variants associated with acute pancreatitis. Management of acute pancreatitis in children requires early aggressive fluid and nutritional therapy and adequate pain control, along with addressing inciting factors. Patients with ARP are of particular interest to study because of the high apparent risk for progression to chronic pancreatitis.

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Author contributions
Both authors contributed equally to this Review.

Competing interests statement
The authors declare no competing interests.