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Toxic-Metabolic Risk Factors in Pediatric Pancreatitis: Recommendations for Diagnosis, Management and Future Research

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Abstract

Objectives—Pancreatitis in children can result from metabolic and toxic risk factors, but the evidence linking these factors is sparse. We review the evidence for association or causality of these risk factors in pancreatitis, discuss management strategies and their rationale.

Methods—We conducted a review of the pediatric pancreatitis literature with respect to the following risk factors: (a) hyperlipidemia, (b) hypercalcemia, (c) chronic renal failure, (d) smoking exposure, (e) alcohol, and (f) medications. Areas of additional research were identified.

Results—Hypertriglyceridemia of 1000 mg/dl or greater poses an absolute risk for pancreatitis; persistent elevations of calcium are predisposing. Further research is necessary to determine whether end stage renal disease leads to increased pancreatitis in children similar to adults. It is

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unknown whether cigarette smoking exposure, which clearly increases risk in adults, also increases risk in children. The role of alcohol in pediatric pancreatitis, whether direct or modifying, needs to be elucidated. The evidence supporting most cases of medication-induced pancreatitis is poor. Drug structure, improper handling of drug by host, and by-stander status may be implicated. Other pancreatitis risk factors must be sought in all cases.

Conclusions—The quality of evidence supporting causative role of various toxic and metabolic factors in pediatric pancreatitis is variable. Careful phenotyping is essential, including search for other etiologic risk factors. Directed therapy includes correction/ removal of any agent identified, and general supportive measures. Further research is necessary to improve our understanding of these pancreatitis risk factors in children.

Keywords

Acute Pancreatitis; Acute Recurrent Pancreatitis; Chronic Pancreatitis; Hypertriglyceridemia; Hypercalcemia; Chronic renal failure; Alcohol; Smoking; Medications

Introduction

Despite the increased incidence of pediatric acute pancreatitis (AP) in the last two decades (1), data on etiologies, management and outcomes are still evolving. The available data on management is based almost exclusively on adult studies (2). The lack of pediatric data constitutes a major limitation, since adult AP has a different etiologic background compared with pediatric AP (3). While biliary etiologies and alcohol predominate in adult AP (4, 5), pediatric cases of AP include a greater proportion of genetic, anatomic, metabolic, and toxic etiologies.

Although metabolic disturbances such as hyperlipidemia, hypercalcemia, and chronic renal failure (6), environmental toxins such as alcohol and smoking, and exposure to certain medications are risk factors for AP, the role of these factors in pediatric AP has not been well-defined. In this report, we aim to review the role of various metabolic and toxic factors in pediatric pancreatitis, discuss current management strategies and propose future research topics (Table 1).

Methods

Authors for this study have expertise in pediatric pancreatitis and all but one (PH) are members of the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) research consortium which is conducting a multi-center prospective study evaluating children with acute recurrent and chronic pancreatitis. Authors within three main writing groups (metabolic risk factors, smoking and alcohol exposure, medication adverse events) conducted literature reviews using electronic medical search engines for relevant English language literature on the following etiological factors with respect to pediatric pancreatitis: hyperlipidemia/hypertriglyceridemia, hypercalcemia, chronic renal failure, smoking exposure, alcohol, and medications, utilizing these key words within search engines. Articles deemed of high relevance were reviewed with key information noted and summarized. One primary author was named within each writing group and areas lacking

evidence and topics for additional research were identified. The literature was then reviewed and discussed via email, phone or face-to-face meetings amongst all authors to obtain consensus and prepare a preliminary draft. The literature review, key summaries and suggestions for future research was then discussed between the primary authors from each section and the senior author to create a final draft, which was agreed upon by all authors.

I. Metabolic Risk Factors

Metabolic risk factors of pancreatitis for this review include the most common causes such as hypertriglyceridemia, hypercalcemia, and chronic renal failure. It is understood that other, but extremely rare, metabolic risk factors of pancreatitis include methylmalonic acidemia (7), propionic acidemia (8), and some urea cycle disorders, such as ornithine carbamoyltransferase deficiency (9). Metabolic syndromes typically present with multisystem involvement and associated symptoms that lead to their consideration. For example, methylmalonic acidemia presents with failure to thrive, vomiting, anemia, thrombocytopenia, hypotonia, renal disease, and developmental delay (10). Propionic acidemia is associated with protein intolerance leading to symptoms of vomiting, lethargy, ketosis, neutropenia, thrombocytopenia, and developmental delay (11). Ornithine carbamoyltransferase deficiency, like all urea defects, is associated with episodic hyperammonemia and neurologic deterioration (12). A thorough review of these metabolic disorders is outside the scope of this document; however, obtaining serum ammonia level, urine organic acid screen, and genetic testing in consultation with a genetics specialist may be considered in children with acute recurrent or chronic pancreatitis and symptoms and signs suggestive of a metabolic disorder.

(a) Hypertriglyceridemia—Hypertriglyceridemia (HTG), a relatively rare cause of AP, is estimated to account for up to 6% of AP cases (6, 13). Data in children for HTG-associated pancreatitis are limited and mainly extrapolated from single case reports (14–17). A triglyceride level of 1000 milligrams per deciliter (mg/dl) or higher is generally accepted as an absolute risk factor for AP (16, 18). However, even levels above 500 mg/dl confer an increased relative risk (19). In a prospective study of 33,000 Swedish adult patients, elevated triglycerides were associated with an increased graded risk of AP (hazard ratio 1.21 for each 18 mg/dl increase in triglycerides) (20). In patients with familial hypertriglyceridemia and recurrent bouts of AP, genetic defects in lipoprotein lipase (LPL) and apolipoprotein C-II should be considered (21).

While the mechanism of hyperlipidemia-associated pancreatitis is not clear, two postulates predominate (22). First, hyperviscosity from chylomicrons might directly impair circulatory flow in small pancreatic vessels, resulting in ischemia (22). Second, pancreatic lipases metabolizing excess triglycerides to free fatty acids within the pancreas could trigger acinar and capillary injury (23–25). While HTG is more often considered in a single episode AP, it can also result in acute recurrent pancreatitis (ARP) and occasionally chronic pancreatitis (CP) when triglyceride levels are inadequately controlled (26, 27).

Treatment of HTG associated with pancreatitis can be separated into two phases: (1) treatment to resolve HTG during an AP attack, and (2) ongoing management of HTG after

an acute AP episode has resolved to prevent future recurrences. Supportive measures, similar to those used in any episode of AP, apply to patients with HTG. In addition, acute management of severe HTG in a patient with AP is directed at reducing the triglyceride level. Multiple case reports in adults and children describe successful use of a continuous intravenous infusion of insulin and dextrose, alone or in combination, with subcutaneous or intravenous heparin boluses (14–17, 28). Both insulin and heparin increase lipoprotein lipase (LPL) activity, thereby accelerating triglyceride deposition (29). The effect of heparin is transient (30–120 minutes) and can cause rebound inhibition of LPL; therefore, this approach is used only in combination with insulin therapy. Plasmapheresis (lipoprotein apheresis) has been successfully used in children (30). However, according to the American Society for Apheresis, the optimum role of apheresis therapy in HTG-associated pancreatitis is not established and, therefore, decision-making should be individualized (31, 32).

Familial HTG requires specific pharmacologic treatment options (33), while the management of secondary HTG is geared towards first identifying and then mitigating the underlying factor. For example, type 1 diabetes with diabetic ketoacidosis (30) requires ongoing lipid reduction therapy to reduce risk of subsequent AP attacks. Based on the National Cholesterol Education Program (NCEP) treatment guidelines established for adults, treatment of HTG should be administered when triglyceride levels exceed 500 mg/dl. Non-pharmacologic treatments include weight reduction as appropriate, increased physical activity, a diet low in fat (15% of the caloric intake) and low in simple carbohydrates. Pharmacologic therapy most commonly includes a fibrate medication, or alternatively nicotinic acid, with omega-3 fatty acids (2– 4 grams/day) (23, 34, 35), in addition to making dietary changes and increasing exercise. While statin therapies are not conventionally indicated for lowering serum triglyceride levels, one large meta-analysis of more than 100,000 adult patients found that statins were protective against the development of AP compared with placebo (RR 0.77 (0.62–0.997)) (36, 37). A child with familial hyperlipidemia was reported to achieve successful long-term remission from AP with a biliopancreatic diversion to induce fat malabsorption (38). Controlled trials to compare effectiveness of management protocols are clearly needed in HTG-associated AP.

(b) Hypercalcemia—Both clinical and experimental evidence link hypercalcemia with pancreatitis (39, 40). The most common reason for hypercalcemia (i.e. above 10.7 mg/dl total serum calcium) is a parathyroid gland adenoma leading to primary hyperparathyroidism (PHPT). At least eight retrospective studies since 1980, each with greater than 50 PHPT patients, have reported a positive association between PHPT and pancreatitis (reviewed in (41)). The prevalence of pancreatitis among PHPT patients ranged from 3% to 15%. About 70% of these patients had AP or ARP, and the remaining 30% had CP (42). It is notable that about 30–50% of PHPT patients with pancreatitis had co-existing risk factors for pancreatitis, such as genetic mutations predisposing for AP, ARP, and CP (43, 44).

While PHPT is the most common etiology for hypercalcemia, other hypercalcemia etiologies are associated with pancreatitis. For example, high intravenous calcium exposure during cardiac surgery (45) or parenteral nutrition use has been shown to cause pancreatitis.

Ectopic secretion of calcium-mobilizing hormones (i.e. acute lymphoblastic leukemia) has also been associated with pancreatitis (46).

In several studies, serum calcium levels in PHPT patients with pancreatitis were slightly greater than PHPT patients without pancreatitis (e.g. about 1 mg/dl higher), suggesting that even mild hypercalcemia in the setting of PHPT can predispose to pancreatitis (41). Hypoalbuminemia, often seen in patients with severe pancreatitis or in malnourished patients, can underestimate hypercalcemia. In such clinical scenarios, either calculating a corrected calcium to compensate for a low albumin or, preferably, measuring a free ionized calcium is indicated.

The acute management of hypercalcemic pancreatitis includes treatment of hypercalcemia by restricting calcium intake, providing adequate intravenous hydration to promote renal perfusion and calcium excretion, and potentially pursuing pharmacological measures and parathyroidectomy for PHPT associated with persistently elevated calcium levels. After parathyroidectomy, over half of PHPT-patients have no further recurrences of AP (41). One study reported that symptoms of CP improved following parathyroidectomy (47), although another study showed no improvement in this subset of patients (48).

(c) Chronic renal failure—Any discussion of pancreatitis associated with renal failure must begin with appreciation of the pitfall of utilizing serum amylase and lipase alone as diagnostic markers of pancreatic disease among patients with end-stage renal disease (ESRD), as both amylase and lipase exhibit impaired clearance through renal filtration in ESRD (49). Elevation of either enzyme is a common finding among patients with ESRD without pancreatitis (50–52). In general, ESRD patients without pancreatitis will have serum amylase and lipase levels <3X the upper limit of normal (ULN). However, distinguishing these laboratory changes from patients with pancreatitis who have amylase and/or lipase levels >3X the ULN can be difficult. These confounders notwithstanding, an increased prevalence of pancreatitis is a recognized complication among patients with ESRD compared with the general population. The autopsy studies have been most informative, as histopathological examination of the pancreas is considered the gold standard for diagnosis, but this option is very rarely available in clinical practice. Avram conducted an analysis of 21 uremic patients who had undergone autopsy and compared them to 60 patients who had undergone autopsy with no concomitant renal or pancreatic disease. Significant pancreatic disease, including pancreatitis, was found in 56% of patients with chronic renal failure compared to 12% of controls (53). Vaziri et al similarly found that at autopsy 60% of patients with ESRD had pancreatic abnormalities; histologic pancreatitis was the most common lesion noted (in 28% of patients), and other changes included fibrosis, calcifications, and cystic lesion (54).

Several additional autopsy studies have documented an increased incidence of AP among adult patients with ESRD. Incidence estimates for AP among hemodialysis recipients range from 1.6–10 episodes per 1000 person years and 18–37 episodes per 1000 person years for peritoneal dialysis patients (55–57). These rates are markedly increased compared to the rate of AP among the general United States population of 0.44 episodes per 1000 person years (58). The mechanisms which underlie the increased incidence of AP among patients with

ESRD are variable. In addition to the etiologies of AP present in the general population, systemic vascular disease, medication use linked to AP as adverse effects, hyperparathyroidism, and hyperlipidemia have been postulated to play a combined role in the evolution of pancreatitis in ESRD patients. Increased circulating levels of enteric hormones have been documented in patients with ESRD, which may increase pancreatic enzyme secretion and eventual pancreatic injury (59, 60). Factors hypothesized to explain the excess hazard of pancreatitis among patients receiving peritoneal dialysis mainly involve direct toxic effects of the dialysate, including pH, hypertonicity, contaminating foreign particulate debris, and other additives (55, 56, 61, 62).

When considering diagnosis of pancreatitis in patients with renal disease, clinicians have to consider confounding elevations of serum amylase and lipase associated with impaired renal function as well as transient changes of serum amylase and lipase in relation to dialysis procedures. Clinical and radiographic findings are essential in diagnosing AP in this population. In one series, computed tomography was superior to ultrasound for diagnosing AP in patients with ESRD, primarily because about 30% of ultrasound exams were technically unsatisfactory (63). Serum amylase >3X ULN has been proposed as a cutoff for AP among adults with ESRD (51). This cutoff is congruent with diagnostic criteria proposed for use in healthy children and adolescents (64). We thus propose that elevations of amylase and/or lipase 3 times upper limits of normal similarly be required to make a diagnosis of acute pancreatitis in children with ESRD.

Supportive measures are the cornerstone of the management of AP patients with ESRD as with other patients with AP (57, 61). The role of discontinuing peritoneal dialysis in the face of AP is unclear (65), as some patients are reported to have AP while receiving either peritoneal dialysis or hemodialysis, casting some doubt on the hypothesis that the mode of dialysis is the primary determinant of pancreatitis in susceptible patients. It has been suggested that stopping heparin, when feasible, should be considered during AP for patients with ESRD to minimize the theoretical risk of hemorrhagic pancreatitis (57).

Key points and future research questions for HTG-, hypercalcemia-, and chronic renal failure-induced pancreatitis in children:

1. HTG, hypercalcemia and chronic renal failure are encountered as etiologies for pancreatitis and have to be included in diagnostic evaluation.
2. Serum triglyceride levels of 1000 mg/dl or greater pose an absolute risk for pancreatitis, while levels between 500 and 1000 mg/dl may contribute as a predisposing factor. Studies are needed to define the levels of HTG that lead to pancreatitis in the pediatric population.
3. Persistent elevations in serum calcium, such as with PHPT, predispose to pancreatitis, and even mild elevations in calcium above the ULN should prompt physicians to pursue a work up for underlying etiologies of hypercalcemia (above 10.7 mg/dl).
4. Adult patients with ESRD have an increased incidence of pancreatitis. This association needs to be defined in the pediatric population.

5. Optimal management strategies for pancreatitis resulting from high triglyceride or calcium levels or in the setting of renal disease need to be more rigorously studied.

II. Environmental Risk Factors

Various environmental risk factors such as conditions contributing to hypertriglyceridemia and renal disease, as well as adverse drug reactions, can cause ARP and CP and are covered elsewhere in this review. This section will review 2 common environmental exposures in the pediatric population, namely, tobacco (smoking) and alcohol exposure.

(a) Smoking (Active and Passive)—There are no published data on the effect of active smoking of tobacco (and other substances) and pancreatitis in children. Therefore, this review and the recommendations are mainly based on adult studies. In the North American Pancreatitis Study 2 (NAPS2) cohort, there was a dose-dependent risk of ARP and CP with cigarette smoking that was independent of alcohol use (66). The cigarette consumption ranging from 12 to 35 pack-years (p.y.) conferred 1.4-fold and 2.2-fold risk for ARP and CP respectively, while a greater than 35 p.y. increased the risk to 2–4.6-fold. In a French study, patients with both type 1 and type 2 autoimmune pancreatitis who were heavy smokers (greater than 10 p.y.) had a higher rate of CP and pancreatic exocrine insufficiency, compared to less heavy smokers and non-smokers (67). Similarly, in patients with alcohol-induced CP, a smoking history of 15 p.y. was associated with an earlier onset of CP; subjects with a 20 p.y. smoking history had more pancreatic calcifications, while those with 30 p.y. history demonstrated a higher rate of exocrine pancreatic insufficiency (68). Other studies have also demonstrated a dose-dependent effect of increased smoking and pancreatitis, and this effect was likely exacerbated by a concomitant alcohol use (69). In an Indian cohort with CP, histopathological changes (specifically, calcifications) correlated with underlying diabetes mellitus and smoking (70).

It is unclear why active smoking contributes to pancreatitis (71). Nicotine and a tobacco-specific nitrosamine derived from nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), appear to be key toxins in tobacco. It is thought at least some of the toxic effects of smoking on the pancreas are through nicotine- and NNK-mediated activation of cellular damage pathways. The events appear to begin in the pancreatic acinar cell and, in CP, also involve pancreatic stellate cells. Another putative mechanism may be through inducing the release of endothelin-1 which then causes pancreatic ischemia and vasoconstriction (72). Additionally, cigarette smoking could induce pancreatitis by inhibiting the cystic fibrosis transmembrane conductance regulator (CFTR) function (73).

There are no pediatric or adult studies showing a correlation of passive tobacco smoke exposure and pancreatitis. Passive smoking includes both second-hand exposure (tobacco smoke permeating any environment, causing inhalation within that environment) and third-hand exposure (tobacco smoke permeating hair, skin, clothes, furniture, drapes, walls, bedding, carpets, dust, vehicles and other surfaces, long after smoking has stopped). Animal models may prove a potential link between passive smoke exposure and development of pancreatitis. For example, a rat model that was exposed to second-hand smoking demonstrated a higher ratio of pancreatic trypsinogen expression relative to the trypsin

inhibitor, suggesting that passive inhalation of cigarette smoke might lead to pancreatic auto-digestion (74). Rat models of smoking exposure have also demonstrated pancreatic fibrotic changes with increased pro-collagen 1 gene expression and increased production of proinflammatory mediators including IL-1 and TGF-beta (74). Fetal exposure of tobacco smoke is a risk factor for respiratory disease in children, but there are no data in regards to fetal smoke exposure and pancreatic disease (75).

Key Points and future research questions for smoking-induced pancreatitis in children:

1. The adult literature shows an increased risk of pancreatitis from cigarette smoking that correlates with pack-years. It is unknown whether active smoking increases the risk of pancreatitis in children or the effects can manifest later in adulthood.
2. There are no studies showing causality between passive smoking exposure and pancreatitis in adults and children. Studies are needed to clarify any possible correlation.
3. The relationship of both second-hand exposure and third-hand exposure to pancreatitis in children is unknown.
4. The effects of smoking on the developing pancreas in utero should be determined.
5. Children and adults with predisposition to pancreatitis (i.e. genetic risk factors) should be advised against smoking.

(b) Alcohol Use—In adults, the long-term alcohol abuse is correlated with an increased risk of pancreatitis and higher mortality (76, 77). Up to 44.1% of AP and 44.5% of CP cases in the adult literature are due to alcohol abuse, with a higher risk of both AP and CP correlating with heavy alcohol consumption. Moreover, if alcohol intake is combined with tobacco smoking, the risk of CP is even higher, with an estimated prevalence of 74.8% (78–80). Therefore, screening adult patients with pancreatitis for alcohol abuse is essential for early intervention and preventive therapy (81).

In adults with AP, an alcoholic etiology is considered in the presence of alcohol abuse within the last two weeks (82). CP may be caused by alcohol if a minimum of 80 grams or more of alcohol intake has been documented daily for at least 6–12 years (82). It is not known whether these definitions can be applied to pediatrics, but alcohol consumption is not commonly reported in children with CP (83). The amount of alcohol that would lead to increased risk of pancreatitis in children is unknown. Binge drinking is more common in the pediatric age and increases with age (84). In Tables 2&3, we provide the definition for binge drinking and risk level estimates for alcohol use in children (85, 86).

The alcohol use can modify the small bowel microflora and chronic alcohol abuse may prolong the intestinal transit time. Thus, bacterial overgrowth has been postulated in the development of alcoholic pancreatitis, although the mechanism is not clear (87).

Alcohol may be an additional risk factor in patients with predisposition to pancreatitis. For example, alcohol use may be associated with an earlier onset of AP in people with *SPINK1*

mutations (specifically, the p.N34S mutation) (88). Pancreatic ductal stone formation also appears to be accelerated in the setting of alcohol-associated CP (89).

There are no studies evaluating the association of alcohol with pancreatitis in children. It is also not known whether alcohol can be an additional risk factor in children with predisposition to other forms of pancreatitis.

Prenatal alcohol exposure can cause fetal alcohol spectrum disorder. It is not known whether fetal alcohol exposure will have a detrimental effect on the pancreas (90).

Key Points and future research questions for alcohol-induced pancreatitis in children:

1. There appears to be an association with long-term alcohol abuse and pancreatitis in adults. There are no studies to establish the amount of alcohol exposure causing pancreatitis in the pediatric population.
2. Further studies are needed to determine whether alcohol use in children is associated with pancreatitis, specifically as a modifying factor in the presence of genetic risk factors or pancreatic structural abnormalities.
3. The effects of prenatal alcohol exposure on the prevalence of pediatric onset pancreatic disease require further investigation.
4. Children with genetic risk factors for pancreatitis should be counseled not to consume alcohol.

III. Medications

In general, an estimated 0.3 % to < 2 % of AP cases are believed to be drug-induced (13, 91–94). Some populations (pediatric patients, geriatric age range, patients with inflammatory bowel disease, AIDS or immune deficiencies) have higher incidences (93, 95). Medication-induced pancreatitis is generally under-reported. (93, 96–98). The reasons behind under-reporting include limited knowledge or uncertainty as to the causative effect of the medication, lack of prospective clinical trials investigating pancreatitis risk for various drugs and absence of consistent diagnostic criteria. Conversely, published cases of drug-induced pancreatitis frequently consist of single case-reports. These case reports often lack proper documentation for diagnosing AP, determining the latency of effect, and investigating other potential causes including anatomic or genetic factors. The pediatric literature relating to medication-induced pancreatitis is also sparse (99, 100).

Several medications have been implicated in the development of pancreatitis. These include antibiotics, psychiatric medications, anti-convulsants, non-steroidal anti-inflammatory medications, chemotherapeutic agents, anti-lipemics, anti-hypertensives, anti-hyperglycemics, and anti-viral agents (40, 93, 96, 101–107). Most cases lack a re-challenge with the suspected drug, therefore it is uncertain whether the medication was indeed *the cause* of pancreatitis, a *co-factor* or an “*innocent bystander*”. The Naranjo Algorithm, a questionnaire developed by Naranjo et al, may be helpful in determining the likelihood of an adverse drug reaction for the drug in question (108). Caution must be exercised before

considering a medication as a cause of AP because of possible interactions of multiple drugs, environmental, and patient-related factors.

Several classification systems have been published in recent decades to better categorize the risk for drug-induced pancreatitis (109–112). Karch and Lasagna classified medications as “definite” risk if the drug reaction followed a reasonable temporal sequence from the administration of the drug in question, followed by resolution of pancreatitis with the drug being discontinued, and recurrence of pancreatitis symptoms upon repeat exposure to the drug (109). A medication was classified as a “probable” risk if the drug reaction followed a reasonable temporal sequence and a known pattern, confirmed by stopping the medication. A “possible” risk involved a drug reaction following a reasonable temporal sequence and a known pattern, but could have been produced by other risk factors (93, 109).

Upon reviewing the cases of drug-induced pancreatitis from 1996 to 2004, Trivedi et al. proposed the following classification system (93):

- Class I: 20 reported cases of APs; at least 1 case with positive re-challenge;
- Class II: > 10 but < 20 reported cases of AP (with or without positive re-challenge);
- Class III: all medications implicated in AP (i.e., Class I, Class II) and those with 10 reported cases, or unpublished reports (i.e. in pharmaceutical or Food and Drug Administration files).

Trivedi et al. also proposed an algorithm to diagnose drug-induced pancreatitis (89).

Another classification system was described by Badalov et al based on a literature review from 1955–2006 (102):

- Class 1a: at least 1 case report with positive challenge, excluding all other causes such as HTG, alcohol, gallstones, other drugs;
- Class 1b: at least 1 case report with positive re-challenge, but other causes such as HTG, alcohol, gallstones other drugs not ruled out;
- Class II: at least 4 cases in literature and with consistent latency in 75% of cases;
- Class III: at least 2 cases in literature; no consistent latency among cases and no re-challenge;
- Class IV: drugs not fitting into earlier –described classes, single case reports without re-challenge.

The concept of *latency* was introduced by Badalov et al, which refers to a certain time-frame from the initiation of medication to the onset of pancreatitis. Latencies may range from less than 24 hours to greater than 30 days. Class III and IV medications with no apparent latency are considered as low risk for causing AP.

Even among the more plausible examples of drug-induced pancreatitis, most reactions may be idiosyncratic rather than dose-related (96). Acetaminophen, erythromycin, and carbamazepine have been implicated in overdose-related acute AP (96). In some cases,

genetic risk factors may predispose patients to drug-induced pancreatitis, such as thiopurines causing AP in patients with certain HLA haplotypes (113).

The management of medication-induced pancreatitis consists of immediate discontinuation of the suspected drug and general supportive measures as for other causes of AP (109). One must exercise caution when implicating a medication as the sole cause of pancreatitis which may lead to life-long avoidance of potentially life-saving drug. Table 4 summarizes our recommendations for the diagnosis and management of drug-induced pancreatitis in children.

Key Points and future research questions for medication-induced pancreatitis in children—

1. There is limited evidence for “medication-induced” pancreatitis in children. Future studies should include evaluation of other pancreatitis-associated risk factors (i.e. genetic and anatomical) or predisposing factors for “medication-induced” pancreatitis (i.e. HLA-DQA1-HLA-DRB1 testing in thiopurine-induced pancreatitis) (113).
2. There are 3 possible scenarios for “medication-induced” pancreatitis: i) drug structure itself is responsible; ii) risk factors for improper handling of the drug; and iii) drug is a co-factor or a by-stander in those with other specific risk factors for pancreatitis. These respective groups must be systematically investigated to truly understand relative risks.
3. In order to create a common language for clinical care and research, standardized diagnostic criteria and a classification system are needed to define pediatric drug-induced pancreatitis.
4. This should be followed by pediatric studies with proper description of diagnostic criteria for AP, ARP, and CP, the latency of drug effect and exclusion of other causes of pancreatitis to determine the true prevalence of drug-induced pancreatitis.

Conclusions

As our knowledge of pancreatitis continues to evolve, the risk factors are now better defined and re-classified. Children are being increasingly diagnosed with AP, ARP, and CP, and investigations are expanded to search for causality. Although genetic and anatomic risk factors are common in pediatric pancreatitis, metabolic predispositions including HTG, hypercalcemia, and chronic renal failure should also be considered. Previously “adult”-centered risk factors, such as alcohol and smoking, are being re-visited to define their roles in pediatric pancreatic disease. The increasing diversity of medications utilized in children appears to be leading to pancreatitis where a drug is involved- whether as main toxin, as co-factor, or innocent bystander. Better understanding of the potential genotype / phenotype associations in children with pancreatitis should be anticipated by improved data collection and research on metabolic, environmental, and medication exposures. We anticipate that these risk factors will be better elucidated with future clinical research.

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What is Known

- Hypertriglyceridemia, hypercalcemia, chronic renal failure, cigarette smoking, alcohol, and various medications (“toxic-metabolic risk factors”) have all been implicated in adult pancreatitis.
- There is limited knowledge as to whether these toxic-metabolic risk factors are also found in pediatric pancreatitis.

What is New

- This document summarizes the pediatric literature regarding toxic-metabolic risk factors with respect to their roles in acute, acute recurrent and chronic pancreatitis in children, and proposes diagnostic and management guidelines, as well as suggestions for future research to address gaps in knowledge.

Table 1
Toxic-Metabolic Risk Factors In Pediatric Pancreatitis-Diagnosis and Management

	Involved in AP/ARP/CP			Diagnosis	Further considerations	Treatment
	AP	ARP	CP			
Hypertriglyceridemia	Yes	Yes	Unclear	Serum TG >1000 mg/dl (absolute risk); or > 500 mg/dl (relative risk)	Consider LPL and apoC-II mutations; Consider other risk factors if TG is 500–1000 mg/dl	Lower serum TG levels (diet, lifestyle, medications)
Hypercalcemia	Yes	Yes	Yes	Serum Calcium > 10.7 mg/dl	Consider primary hyperparathyroidism	IV hydration, lower calcium intake, parathyroidectomy
Chronic Renal Failure	Yes	Yes	Yes	Serum amylase or lipase >3 ULN in a patient with ESRD	Amylase/lipase elevations may be due to decreased renal clearance	Treat underlying problem
Cigarette smoking	Yes	Yes	Yes	Smoking history >10 p.y.	Alcohol has additive effects	Smoking cessation
Alcohol	Yes	Yes	Yes	Children with binge drinking or with moderate & high risk drinking habits (Table 2&3)	Smoking, genetic risk factors have additive effects	Alcohol cessation
Medications	Yes	Yes	Unclear	Temporal sequence is present (latency for AP to occur, resolution of pancreatitis after discontinuing drug and recurrence of AP with reintroduction of the drug)	Consider other risk factors, especially with Class III and IV drugs	Discontinue drug and never use again if strong association with AP is present

Table 2

Binge Drinking in the Youth (86)

	9–13 y/o	14–15 y/o	>16 y/o
Male	3 drinks	4 drinks	5 drinks
Female	3 drinks	3 drinks	3 drinks

1 drink: 12 oz beer; 5 oz wine; 8–9 oz of malt liquor;
1.5 oz of hard liquor (whiskey, gin, rum, vodka, tequila etc.)

Table 3

Risk Assessment for Drinking in the Youth (86)

Ages (y/o)	Moderate Risk (Days of drinking/past year)	High Risk (Days of drinking/past year)
11	1	1
12-15	1	6 (~ every other month)
16	6 (~ every other month)	12 (~ monthly)
17	6 (~ every other month)	24 (~ twice monthly)
18	12 (~ monthly)	52 (~ weekly)

Table 4**Diagnosis and management of drug-induced pancreatitis in children**

	Investigations/ Diagnosis/ Management
First episode AP	<p><u>Initial evaluation</u> Detailed history of present illness, past medical history, family history of pancreatitis; imaging (ultrasound, or computed tomography (CT) or magnetic resonance imaging and cholangiopancreatography (MRI/MRCP)); biochemistry (serum transaminases, total/direct bilirubin, calcium, fasting triglycerides, amylase, lipase).</p> <p><u>Drug information</u> Detailed information regarding any suspected medication: onset of use, dosing, duration of use before onset of AP.</p> <p><u>Management</u> Any possible causal medication should be discontinued with strong consideration to never use it again.</p>
Acute Recurrent Pancreatitis	<p><u>Initial evaluation</u> As above, plus more detailed imaging, in particular MRI/ MRCP.</p> <p><u>Drug information</u> If patient is re-challenged with the medication and latency period is supportive of drug-induced AP → strongly suggests a causative role. Medication plays a role, but may not be the sole cause of AP → test for other risk factors (i.e. genetic, obstructive).</p> <p><u>Management</u> If same medication is present along with 2 separate AP episodes and implicated in published classification systems, it should be discontinued.</p>
Chronic Pancreatitis	<p><u>Initial evaluation</u> Similar to ARP. Due to rarity of drug-induced CP, full evaluation for risk factors of CP should be undertaken.</p> <p><u>Drug information/Management</u> If CP developed subsequent to a severe single episode of drug-induced AP consistent with SAPE (sentinel acute pancreatitis event) hypothesis → medication should be discontinued with extremely strong consideration to never use it again.</p>