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The Causal Evaluation of Acute Recurrent and Chronic Pancreatitis in Children: Consensus From the INSPPIRE Group

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Abstract

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Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) have been diagnosed in children at increasing rates over the past decade. However, as pediatric ARP and CP are still relatively rare conditions, little quality evidence is available on which to base the diagnosis and determination of etiology. Objectives: To review the current state of the literature regarding the etiology of these disorders and to developed a consensus among a panel of clinically active specialists caring for children with these disorders to help guide the diagnostic evaluation and identify areas most in need of future research. Methods: A systematic review of the literature was performed and scored for quality, then consensus statements developed and scored by each individual in the group for level of agreement and strength of the supporting data using a modified Delphi method. Scores were analyzed for the level of consensus achieved by the group. Results: The panel reached consensus on 27 statements covering the definitions of pediatric ARP and CP, evaluation for potential etiologies of these disorders, and long-term monitoring. Statements for which the group reached consensus to make no recommendation or could not reach consensus are discussed. Conclusion: This consensus helps define the minimal diagnostic evaluation and monitoring of children with ARP and CP. Even in areas in which we reached consensus, the quality of the evidence is weak, highlighting the need for further research. Improved understanding of the underlying cause will facilitate treatment development and targeting.

Keywords

hereditary pancreatitis; CFTR; PRSS1; autoimmune pancreatitis; pancreatic insufficiency

Introduction

Because acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are relatively uncommon in the pediatric population, studies providing high-quality evidence for their evaluation do not exist. Pediatric ARP and CP share common risk factors that are often quite distinct from those for adults (for example, alcohol and tobacco), making the more extensive adult literature of limited value in the evaluation and management of these children.[1]

The **In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE** (INSPPIRE) consortium was formed to collect detailed information on a cohort of children with ARP and CP with the aim to fill gaps in knowledge and improve clinical care.[2] The INSPPIRE database was populated by surveys completed by each patient/patient's family and by the managing pediatric gastroenterologist. In the first iteration of the data collection tool, we collected study physician opinions regarding the cause of pediatric ARP/CP with "idiopathic" being one of the choices. We also collected specific clinical data including detailed information regarding patient demographics, events associated with pancreatitis, abdominal pain history, alcohol and tobacco history, medication use, family history, imaging history, history of genetic testing, history of exocrine or endocrine pancreatic insufficiency, and treatment. In a subsequent review of the data, we noted that many children were labeled as having "idiopathic" ARP or CP in the absence of genetic testing. In addition, many children who were found to have pancreas divisum did not have additional evaluation despite an ongoing debate regarding a direct role for pancreas divisum in the development of ARP and CP.[3]

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Our aim with this current effort was to reach expert consensus recommendations on the minimal evaluation of the risk factors for ARP and CP in pediatric patients. After a systematic literature review by pediatric gastroenterologists with expertise in pediatric pancreatitis, recommendation statements were developed and submitted to all the authors for consideration using the Delphi method.[4] We present the agreed consensus recommendations followed by a brief summary of the relevant background literature or expert discussion on each topic. We also address important areas where we reached a consensus to make no recommendation or where we were unable to reach consensus to help guide future research directions for pediatric ARP and CP.

Methods

Panel selection

The INSPPIRE consortium is made up of individuals with a wide array of backgrounds including a pediatric endocrinologist, nurses, research coordinators, pediatric gastroenterologists and trainees. A *core* group of 6 senior pediatric gastroenterologists at academic medical centers in the United States and Israel initiated this effort, performed the literature review, and developed the recommendation statements through e-mail communications and 3 conference calls. The statements were then submitted to the individual members of the entire INSPPIRE group (*consensus* group). Individual members of the consensus group scored the statements and returned them to one member of the core group (CEG) who functioned as the Delphi process facilitator. The consensus group consisted of 18 members of INSPPIRE who are practicing pediatric gastroenterologists with an interest in pediatric pancreatic disease. The consensus group included the 6 members of the core group with the addition of pediatric gastroenterologists from the United States, Canada, and Australia.

Search Strategy and Grading Criteria

The literature regarding the evaluation of ARP and CP in adults has recently been reviewed.[5,6] Therefore, we concentrated our efforts on literature specifically related to children.

A PubMed search was performed on January 2, 2016 using the following the criteria included in supplement 1. This search yielded 315 English language publications involving humans since 1975, of which 306 were available as whole text. Of these, 51 were review articles and therefore were excluded. The remaining 255 articles were equally distributed and evaluated by one of the 6 core group pediatric gastroenterologists. Publications were graded regarding the level of evidence based on the Oxford Criteria for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group*, “The Oxford Levels of Evidence 2″ Oxford Centre for Evidence-Based Medicine (OCEBM) http://www.cebm.net/index.aspx?o=5653). Articles that were judged to have Level 1 or 2 data were re-reviewed by an additional investigator in the core group to confirm the scoring.

Based on the results of this literature review, additional literature related to pancreatitis in adults and personal experience, the core group developed recommendation statements.

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These statements were sent to the consensus group with instructions on the GRADE system.[7] Members of the consensus group were asked to independently score each statement on a 5-point scale: 5=definitely yes, 4=probably yes, 3=no specific recommendation, 2=probably no, 1=definitely no and also submit a GRADE strength of recommendation (1=strong, 2=weak) and quality of evidence (A=high, B=moderate, C=low). They were asked to submit comments regarding the recommendation statement and evidence to support the score to the facilitator. A summary report was generated by the facilitator of scores, comments, and high-quality references relevant to areas of disagreement and distributed back to the entire group for input/discussion. New statements were developed, statements were reworded, and some statements were eliminated based on feedback from the group and distributed again for scoring and input. This process was repeated through 3 rounds with the aim to reach consensus on as many statements as possible. At least 14 members of the consensus group participated in each round of scoring. Strong agreement or consensus was defined as a standard deviation (SD) of ≤ 0.5 on the 5-point scale. Moderate agreement was defined as a SD>0.5 when the highest and lowest scores were excluded with all scores leaning either positive (3–5) or negative (1–3). Poor consensus statements were defined as having the SD of scores from experts >0.5, and both positive and negative responses remained after exclusion of the lowest and highest scores. Items achieving consensus were considered settled and not included in subsequent scoring rounds. Between the second and third rounds of scoring, 11 members of the consensus group met in person to try to reach consensus on final items.

Results

The 255 articles evaluated as a result of the PubMed search contained many case reports or dealt with surgical treatment of pancreatitis. Only 76 articles were judged to address risk factors for pediatric ARP or CP and had at least Level 4 evidence. None of articles identified by the search results were deemed to provide Level 1 or 2 evidence regarding risk factors for pediatric ARP or CP.

The first round of statements developed by the core group and distributed to the consensus group included definitions of ARP and CP, 29 statements regarding etiologic evaluation, and 6 statements regarding long-term monitoring of patients with ARP and CP. The second round included 1 definition, 27 statements regarding etiologic evaluation and 6 statements regarding long-term monitoring. The final round included 7 statements regarding etiologic evaluation. Consensus was reached on 27 statements and 25 statements were endorsed (Table 1A). The panel either could not reach consensus or reached a consensus to not make a recommendation regarding 8 statements (Table 1B).

All statements with poor consensus received a mean score of *no specific recommendation.*

Definitions—DEFINITION: Pediatric ARP is at least two discrete episodes of acute pancreatitis (AP) as defined by the INSPPIRE criteria in the absence of evidence of irreversible, structural changes in the pancreas.[8] The patient must fail to meet criteria for AP for a period after the first episode.

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The INSPPIRE Criteria for AP is the presence of at least two of the following:

1. Characteristic abdominal pain
2. Imaging consistent with AP
3. Lipase or amylase ≥ 3 times the upper limit of normal (3x ULN)

Strong consensus, definitely yes

DEFINITION: Pediatric CP is the presence of at least one of the following:

1. Irreversible, structural changes in the pancreas such as diffuse or focal destruction, sclerosis, pancreatic duct abnormalities/obstruction with some periods of consistent abdominal pain or lipase or amylase ≥ 3x ULN
2. Irreversible, structural changes in the pancreas such as diffuse or focal destruction, sclerosis, pancreatic duct abnormalities/obstruction with exocrine pancreatic insufficiency
3. Irreversible, structural changes in the pancreas such as diffuse or focal destruction, sclerosis, pancreatic duct abnormalities/obstruction with endocrine pancreatic insufficiency

Strong consensus, probably yes

Statements—STATEMENT: Pediatric patients with ARP are at risk for progressing to CP over time.

Strong consensus, probably yes

STATEMENT: Pediatric CP and ARP have common etiologies.

Strong consensus, definitely yes

STATEMENT: More than one risk factor for ARP or CP may be identified in the same patient

Strong consensus, definitely yes

STATEMENT: Pain associated with CP can be intermittent (similar in character to ARP), chronic, or resolved.

Moderate consensus, definitely yes

Two related issues covered by the above statements generated discussion. While good consensus was achieved, primarily based on anecdotal experience, that ARP can progress to CP, the boundary between these two entities and the clinical usefulness of maintaining the boundary were questioned. Because of the current weakness of the evidence connecting the two conditions, we elected to maintain the traditional separate definitions. In many individual cases however, ARP may be an early manifestation of an underlying disorder that will eventually manifest as CP.[9,10] Review of the INSPPIRE database indicated that genetic

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factors were more commonly found in subjects with CP while toxic/metabolic factors were more commonly identified in subjects with ARP, but there also was significant overlap.[11]

The other area of discussion was the role of abdominal pain in the definition of CP. While abdominal pain is a primary hallmark of CP in adults, it is common for children with irreversible, destructive structural changes to the pancreas (CP) to complain only of mild or intermittent pain. It is not clear if this finding is because of inherent differences in the disease process in children or differences in the way children experience or report pain. The definition we adopted for CP relies heavily on imaging finding, pancreatic function, or biochemical evidence of pancreatitis while relying less on the nature of the reported pain.

Clinical laboratory testing—STATEMENT: Initial evaluation of recurrent pancreatitis should include the following:

aspartate aminotransferase (AST)

alanine aminotransferase (ALT)

gamma glutamyltransferase (GGT)

Total bilirubin (with fractionation if total is elevated)

Fasting lipids

Total serum calcium

Strong consensus, definitely yes

STATEMENT: In the initial evaluation of ARP one should consider testing for stool ova and parasites in patients who are immunosuppressed, have been traveling to areas where *Ascaris lumbricoides* or *Strongyloides stercoralis* is endemic, or have peripheral blood eosinophilia.

Strong consensus, probably yes

STATEMENT: If there is a concern for undiagnosed metabolic disease, serum ammonia and urine organic acids should be obtained on presentation.

Moderate consensus, probably yes

Measurement of serum transaminases (AST, ALT, GGT) can help in the evaluation for metabolic and obstructive pancreatic lesions. Underlying metabolic abnormalities are more likely to be found in ARP or CP than acute pancreatitis.[12] Members of the INSPPIRE consortium recently published a review of toxic and metabolic risk factors in pediatric pancreatitis including recommendations for diagnosis and management.[13] Triglyceride levels greater than or equal to 1000 milligrams per deciliter (mg/dL) are accepted as an absolute risk factor for ARP. Genetic defects in lipoprotein lipase and apolipoprotein C-II should be considered in patients with hypertriglyceridemia and ARP or CP.

A causal link between hypercalcemia (total serum calcium above 10.7 mg/dL) and pancreatitis is supported by experimental evidence[14] and this association is well established clinically, primarily in patients with parathyroid gland adenomas leading to primary

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hyperparathyroidism, such as in the multiple endocrine neoplasia syndrome type I.[15,16] Primary hyperparathyroidism can lead to both ARP and CP.[17]

A number of rare metabolic disorders including organic acidosis syndromes and maple syrup urine disease are associated with pancreatitis in case reports or case series. The availability of extensive newborn screening for metabolic diseases in the United States makes the yield of metabolic evaluation lower than in the past for this country. In areas of the world where newborns are not routinely screened, testing for these conditions should be strongly considered.

Imaging Studies and Endoscopy—STATEMENT: Initial evaluation of ARP should include imaging of the pancreas.

Strong consensus, definitely yes

STATEMENT: Patients with ARP should have magnetic resonance cholangiopancreatography (MRCP) imaging. Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) may be alternatives depending on the clinical scenario.

Strong consensus, definitely yes

STATEMENT: Detailed imaging of the pancreatic ducts and biliary tree (MRCP) should be undertaken acutely if the GGT> 2x ULN or the direct bilirubin fraction is elevated, even in the absence of evidence of obstructive etiology on ultrasound.

Moderate consensus, probably yes

STATEMENT: The choice of modality to image the pancreas of children should minimize radiation exposure.

Strong consensus, definitely yes

STATEMENT: Pancreas divisum is a risk factor for ARP but alone is not sufficient to prevent evaluation for concomitant causes of ARP or CP.

Strong consensus, definitely yes

STATEMENT: Annular pancreas is a risk factor for ARP but alone is not sufficient to prevent evaluation for concomitant causes of ARP.

Strong consensus, definitely yes

STATEMENT: Once the diagnosis of ARP or CP is made, laboratory evaluation and imaging on presentation for ARP events depends on the overall clinical situation and disease pattern.

Strong consensus, probably yes

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STATEMENT: When available, a secretin-enhanced MRCP or sMRCP (rather than a standard MRCP) should be obtained to evaluate pancreatic ductal abnormalities.

Moderate consensus, probably yes

STATEMENT: An esophagogastroduodenoscopy with biopsies to evaluate for mucosal abnormalities (such as peptic ulcer disease, Crohn disease, or eosinophilic enteritis) or duplications should be considered in patients with ARP or CP of unclear etiology.

No consensus, no recommendation

The review by Schwarzenberg, *et al* of children with CP in the INSPPIRE database reported obstructive lesions of the pancreas in 33% of cases. The majority of the identified lesions were congenital (i.e., pancreas divisum and pancreatic duct malunion), whereas gallstones were implicated in CP in only 4% of subjects.[3] Similar results are seen with ARP. Lucidi, *et al* reported structural abnormalities in 19% of their pediatric cohort with ARP, 47% of whom had a choledochal cyst (which is strongly associated with pancreatic duct malunion).[18] We found obstructive lesions in about one third of our cohort of >300 children, distributed evenly between the CP and ARP, with ~ 40% of these children identified as having pancreatic divisum. However, overall the frequency of identified pancreatic divisum in the INSPPIRE cohort was 8–9%, similar to the percentage reported in the general population.[11,19] Because of this finding, a consensus was reached that pancreatic divisum may play a role in the development of ARP or CP, but this finding may not be causative in itself and further investigation is warranted.

sMRCP has been studied in adults, and at many centers sMRCP is now the standard accepted technique for identifying early changes of the pancreatic duct.[5,20] sMRCP can provide dynamic images of the pancreatic duct to differentiate fixed from non-fixed lesions. It also is being explored as a technique to assess exocrine function of the pancreas.[21] However, studies in children are limited, secretin is often unavailable, and this technique has not been as widely adopted by pediatric radiologists compared to adult radiologists.[22]

Statements of special consideration/controversy

Genetic testing: STATEMENT: The search for a genetic cause of ARP or CP should include a sweat chloride test (even if newborn screening for cystic fibrosis (CF) is negative) and *PRSS1* gene mutation testing. Genetic testing for CF should be considered if a sweat test is unable to be performed.

Strong consensus, definitely yes

STATEMENT: Mutation analysis of the genes *SPINK1*, *CFTR* and *CTRC* may identify risk factors for ARP or CP.

Strong consensus, definitely yes

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STATEMENT: Patients with ARP or CP and a sweat test <=60 mmol/L should have expanded *CFTR* mutation testing done if there is no other identified cause of their pancreatic disease (such as a *PRSS1* mutation or a clear obstructive etiology)

No consensus, No specific recommendation

The INSPPIRE research consortium recently published a cross-sectional study of CP patients in the registry and reported that one or more pancreatitis-predisposing genetic mutations were identified in 67% of study subjects despite the fact that 17% of subjects had no genetic test results available.[3] The most common CP-associated mutations involved the cationic trypsinogen gene (*PRSS1*). Of the 11 subjects (14%) with CF transmembrane regulator gene (CFTR) mutations, 91% had one or more mutations associated with CF or a *CFTR*-related disorder [23,24] and only 1 had a positive sweat chloride test.[3] ARP and CP also have been associated with loss-of-function mutations in genes that encode the serine peptidase inhibitor Kazal type 1 (*SPINK1*), chymotrypsin C (*CTRC*), the calcium-sensing receptor gene (*CASR*) and the lipase gene CEL.[12,25]

While knowing potential genetic mutations is desired by the patient, family, treating physician, and interested investigators, these recommendations are meant to guide the minimal evaluation for the etiology of ARP and CP. Therefore, the group consensus was to give two levels of recommendation. We elected to strongly recommend genetic testing when positive results provide clear etiologic information and therefore alter the direction and extent of further causal investigations. We strongly recommend testing for PRSS1 mutations and for cystic fibrosis.

The presence of a *PRSS1* mutation has implications for future health of the patient as well as close relatives and future children of the patient. Identifying a known gain-of-function *PRSS1* mutation (p.N29I or p.R122H) suggests the patient has hereditary pancreatitis and has a high likelihood of progressive disease to CP and pancreatic cancer. Because the disease penetrance of *PRSS1* mutations is quite high (unlike the other currently identified mutations in other genes) additional investigation for other potential causes of ARP or CP may not be necessary as family members are more likely to be affected. Genetic counseling should play a central role in the care of patients with *PRSS1* mutations.

Many children in the INSPPIRE cohort had an incomplete evaluation for CFTR-related disease. While diagnosing CF in patients presenting with pancreatitis is uncommon with genotyping alone, more extensive testing increases the yield.[26–28] Many individuals with non-classical CF pancreatitis carry at least one *CFTR* mutation that is less functionally deleterious than those found in classical CF.[29] However, clinical testing for these mutations is controversial as it remains unclear how to identify *CFTR* mutations that increase the risk of ARP/CP. Only a few mutations have been identified in a sufficient number of individuals to determine if they contribute significantly to the risk of developing pancreatitis. Data are often analyzed as total *CFTR* mutations in the pancreatitis population compared to a control population. The same comparison with individual mutations is not statistically significant because the numbers are small.

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It also is unclear how dysfunction of a *CFTR* mutation should be determined. Two recent reports complicate the issue. Ooi et al (2014) demonstrate discordance between two methods to functionally test the CFTR protein, including sweat testing and nasal potential difference (NPD).[27] Larusch et al (2014) suggest that *CFTR* mutations that alter bicarbonate transport but not chloride transport increase the risk for CP.[30] It is not clear that these mutations would produce abnormal results on functional testing with sweat test or NPD. Presently, *CFTR* mutation analysis may be useful to help identify a risk factor for the development of ARP and CP, but such analysis will not demonstrate a clear etiology. The advent of "read-through agents" and medications that improve the function of specific CF-causing mutant CFTR proteins, suggests that identification of rare genetic mutations may be critical in the future for targeted therapy.[31,32] Currently, we recommend that individuals with a positive or borderline sweat test be referred to a CF center to allow for complete evaluation of CF.

The identification of *SPINK1* mutations in patients with ARP or CP may provide important prognostic information in the presence of other risk factors.[33] Importantly, the *SPINK1* p.N34S variant is a risk factor for rapid progression to CP particularly if the *SPINK1* variants are bi-allelic.[34–36] *SPINK1* variants may also increase the risk of progression to CP when found alone or in combination with other risk factors.[11,37]

Many polymorphisms have been identified in the *CTRC* gene. These include a number of missense and deletion variants that do not have a clear association with CP.[38] Furthermore, the mutations associated with risk may be affected by ethnicity. Studies on patients in a German database found that only the p.254W and p.K247_R254del mutations were associated with an increased risk of CP.[39,40] Studies of patient cohorts from India found that the p.A73T, p.I64LfsX69, p.V235I and c.180C>T mutations increased the risk of CP in this population.[40,41] In the INSPPIRE population, *CTRC* mutations were significantly more common in children with onset of disease <6 y/o, compared to later onset (42). Because there is less evidence that *SPINK1* and *CTRC* mutations are causative of ARP and CP, the consensus was to recommend testing for mutations in these genes in a separate statement. New genetic risk factors are being identified and testing for them may be warranted in the future.

Autoimmune pancreatitis: STATEMENT: Autoimmune pancreatitis (AIP) is a systemic disease that rarely causes ARP or CP in children.

Strong consensus, probably yes

STATEMENT: IgG4 positive ampullary biopsies are neither sensitive nor specific for pediatric AIP.

Strong consensus, no specific recommendation

STATEMENT: Empiric trials of corticosteroids should not be done for pediatric ARP or CP in the absence of evidence suggesting AIP

Moderate consensus, probably yes

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STATEMENT: Measurement of serum IgG4 levels in children with ARP or CP in the absence of associated systemic disease or suggestive imaging for AIP is unlikely to be useful.

Moderate consensus, no specific recommendation

While the group agreed that AIP is rare in children, opinion regarding which pediatric patients should be evaluated for the disorder and how to diagnose AIP varied widely. Generally, it was judged that not enough data or experience are available to guide a consensus in this disorder in children although adult diagnostic criteria for the diagnosis of AIP exist including the HISORt criteria.[42] Serum IgG_4 levels can be checked in pediatric patients with suspicion of AIP although elevated IgG_4 levels are elevated only in Type I AIP (lymphoplasmacytic sclerosing pancreatitis type) but not in Type II AIP (neutrophilic infiltration of duct epithelium type), which is seen more commonly in younger patients.[43] Only three cases of pediatric probable type 1 AIP are reported in the literature and only one of these presented with pain or elevated lipase.[44,45]

Bile collection, metabolic disease, and celiac disease: STATEMENT: Patients without an etiology for ARP or CP after evaluation for obstructive, genetic and metabolic causes should have bile collected for micro-crystal analysis.

No consensus, no specific recommendation

STATEMENT: Patients with ARP that only have pancreatitis in the setting of a clear metabolic derangement (diabetic ketoacidosis, toxic drug exposure, diagnosed metabolic disease, severe hypertriglyceridemia (>1000mg/dL), or hypercalcemia) require no further evaluation regarding the etiology of the pancreatitis.

No consensus, no specific recommendation

STATEMENT: Patients with ARP or CP should be screened for celiac disease

Strong consensus, probably yes

A large population-based study identified an 2.6-fold risk of ARP or CP in individuals who subsequently were diagnosed with celiac disease.[46] Case reports associate celiac disease with pancreatitis in children. Because early diagnosis of celiac disease can impact not only the recurrence or progression of pancreatic disease but also the general health and growth of the child, celiac disease screening is recommended.

Long-term monitoring: STATEMENT: Pediatric patients with CP should be evaluated for fat-soluble vitamin deficiency at least annually.

Strong consensus, probably yes

STATEMENT: Pediatric patients with ARP should be evaluated for fat-soluble vitamin deficiency at least annually.

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Moderate consensus, probably yes

STATEMENT: Pediatric patients with CP should be evaluated for the development of pancreatic exocrine insufficiency at least annually.

Strong consensus, definitely yes

STATEMENT: Pediatric patients with ARP should be evaluated for the development of pancreatic exocrine insufficiency at least annually.

Moderate consensus, probably yes

STATEMENT: Pediatric patients with CP should be evaluated for the development of pancreatic endocrine insufficiency at least annually.

Moderate consensus, probably yes

STATEMENT: Pediatric patients with ARP should be evaluated for the development of pancreatic endocrine insufficiency at least annually.

No consensus, No specific recommendation

The group could not agree on annual evaluation of ARP patients regarding the development of endocrine pancreatic insufficiency but did reach moderate consensus that pediatric patients with ARP should be evaluated for exocrine pancreatic insufficiency annually.

After several rounds, consensus was reached that patients with CP should be monitored annually for the development of exocrine and endocrine pancreatic insufficiency. Patients with CP can develop pancreatic exocrine and endocrine insufficiency over time. Our experience is that ARP is frequently a precursor to CP, and the exact timing of the development of irreversible pancreatic damage may not be clinically apparent. The time course for the transition to exocrine or endocrine insufficiency is not clearly established. The group consensus was that patients with CP require more direct testing for pancreatic insufficiency, but the weaknesses of the currently widely available, non-invasive tests for exocrine insufficiency made us hesitant to recommend such testing formally.[47] Many of us routinely screen with fecal elastase-1, fasting blood sugar and HbA1c.[48] Fat soluble vitamin deficiencies are frequently found even in patients with exocrine insufficiency treated with pancreatic enzyme replacement therapy.[49,50]

Discussion

ARP and CP in children are relatively rare but are being recognized more frequently in the last decade. In addition, new underlying causes of pediatric ARP and CP, specifically autoimmune and genetic etiologies, are being better defined. There are few rigorously conducted studies on which to base the evaluation of children suffering from these disorders and diversity of opinion exists as to what constitutes an adequate evaluation. We used a formal group consensus method to provide guidance regarding the *minimum* evaluation that should be undertaken in search of a specific etiology. As such, statements/evaluation that we

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have not endorsed as part of the minimum evaluation, such as upper gastrointestinal endoscopy, may be appropriate and would be recommended by experts in specific clinical situations. It is not our intention that recommendation statements not endorsed by the panel should be proscribed.

In general, the strength of each recommendation is reflected in the level of consensus and the numerical OCEBM score while our assessment of the quality of the evidence is reflected in the strength of agreement (that is, “definitely yes” versus “probably yes”) and the alphabetic OCEBM score. However, there is likely overlap as each member of the panel scored each item independently and was not required to provide justification. In addition, the strength of our recommendations reflects the extent to which we are confident that the desirable effects of a recommendation will outweigh possible undesirable effects. For example, one factor we considered when we chose not to recommend routine screening for autoimmune pancreatitis was whether such a recommendation would lead to overuse of immunosuppressive medication.

The consensus statements presented here are the first to provide expert guidance regarding the evaluation of CP and ARP in children. We expect that with the development of multicenter studies and patient databases, such as those coming from the INSPPIRE research collaborative, these guidance statements will change and be more evidence based in the relatively near future. The evidence on which we base these recommendations is generally weak and highlights the need for further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ARP
Acute recurrent pancreatitis

CP
chronic pancreatitis

In search for a cuRE: INSPPIRE
International Study Group of Pediatric Pancreatitis

sMRCP
secretin-enhanced magnetic resonance cholangiopancreatography

ERCP

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endoscopy retrograde cholangiopancreatography

EUS
endoscopic ultrasound

GRADE
Grades of Recommendation, Assessment, Development and Evaluation

AST
aspartate aminotransferase

ALT
alanine aminotransferase

GGT
gamma glutamyltransferase

ULN
upper limit of normal

CF
cystic fibrosis

AIP
autoimmune pancreatitis

OCEBM
Oxford Centre for Evidence-Based Medicine

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What is known

1. Acute recurrent (ARP) and chronic pancreatitis (CP) are increasingly diagnosed in children.
2. Children with ARP and CP often undergo little evaluation for the cause of their disease.
3. Children with CP have a high incidence of pancreatitis-predisposing genetic mutations.

What is new

1) Guidance regarding the minimal evaluation related to pediatric ARP and CP is provided.
3) Sweat chloride testing and *PRSS1* mutation analysis are recommended for the evaluation for hereditary ARP and CP.
4) High-level evidence for the evaluation of children with ARP and CP is lacking and should be addressed with further research.

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Table 1

Statements endorsed by the panel

	Position and level of consensus	OCEBM strength of recommendation and level of evidence*
Pediatric patients with ARP are at risk for progressing to CP over time.	*probably yes strong consensus*	*2C*
Pediatric CP and ARP have common etiologies.	*definitely yes strong consensus*	*2C*
More than one risk factor for ARP or CP may be identified in the same patient.	*definitely yes strong consensus*	*1B*
Pain in CP can be intermittent (similar in character to ARP), chronic or resolved	*definitely yes moderate consensus*	*2C*
Initial evaluation of ARP should include: AST, ALT, GGT, total bilirubin (fractionation if total is elevated), fasting lipids, and total serum calcium.	*definitely yes strong consensus*	*1B*
In the initial evaluation of ARP or CP one should consider testing for stool ova and parasites in patients who are immunosuppressed, have been traveling to areas where Ascaris lumbricoides is endemic, or have peripheral blood eosinophilia.	*probably yes strong consensus*	*2C*
If there is a concern for undiagnosed metabolic disease, a serum ammonia and urine organic acids should be obtained on presentation.	*probably yes moderate consensus*	*1C*
Initial evaluation of ARP should include imaging of the pancreas.	*definitely yes strong consensus*	*1B*
Detailed imaging of the pancreatic ducts and biliary tree (MRCP) should be undertaken acutely if the GGT> 2x ULN or the direct bilirubin fraction is elevated, even in the absence of evidence of obstructive etiology on ultrasound.	*definitely yes moderate consensus*	*1B*
Patients with ARP should have MRCP imaging of the pancreas. ERCP and EUS may be alternatives depending on clinical situation.	*definitely yes strong consensus*	*1A*
The choice of modality to image the pancreas of children should consider and minimize radiation exposure.	*definitely yes strong consensus*	*1A*
When available, a secretin-enhanced MRCP (as opposed to a standard MRCP) should be obtained to evaluate pancreatic ductal abnormalities.	*probably yes moderate consensus*	*2B*
Pancreas divisum is a risk factor for ARP and CP but alone is not sufficient to prevent evaluation for concomitant causes of ARP or CP.	*definitely yes strong consensus*	*1C*
Annular pancreas is a risk factor for ARP and CP but alone is not sufficient to prevent evaluation for other concomitant causes of ARP or CP.	*definitely yes strong consensus*	*1C*
Once the diagnosis of ARP or CP is made, laboratory work-up and imaging on presentation for recurrent symptoms depends on the overall clinical situation and disease pattern.	*probably yes strong consensus*	*1C*
The search for a genetic cause of ARP or CP should include a sweat chloride test (even if newborn screening for cystic fibrosis is negative) and PRSS1 gene mutation testing. Genetic testing for cystic fibrosis should be considered if a sweat test is unable to be performed.	*definitely yes strong consensus*	*1A*
Mutation analysis of the genes SPINK1, CFTR and CTRC may identify risk factors for ARP or CP.	*definitely yes strong consensus*	*1B*
Autoimmune pancreatitis is a systemic disease that rarely causes ARP and CP in children	*probably yes strong consensus*	*1B*
Empiric trials of corticosteroids should not be done for pediatric ARP or CP in the absence of evidence suggesting autoimmune pancreatitis.	*probably yes moderate consensus*	*1C*
Patients with ARP or CP should be screened for celiac disease.	*probably yes moderate consensus*	*1B*
Pediatric patients with CP should be evaluated for fat-soluble vitamin-deficiency at least annually.	*probably yes strong consensus*	*1C*

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	Position and level of consensus	OCEBM strength of recommendation and level of evidence*
Pediatric patients with CP should be evaluated for the development of pancreatic exocrine insufficiency at least annually.	*definitely yes strong consensus*	*1B*
Pediatric patients with CP should be evaluated for the development of pancreatic endocrine insufficiency at least annually.	*probably yes moderate consensus*	*1B*
Pediatric patients with ARP should be evaluated for fat-soluble vitamin-deficiency at least annually.	*probably yes moderate consensus*	*2C*
Pediatric patients with ARP should be evaluated for the development of pancreatic exocrine insufficiency at least annually.	*probably yes moderate consensus*	*2C*

*OCEBM Levels of Evidence Working Group is Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson. Strength of recommendation: 1 = strong, 2 = weak. Quality of evidence: A=high, B=moderate, C=low.

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Table 2

Statements not endorsed by the panel

	Position and strength of recommendation
IgG4 positive ampullary biopsies are neither sensitive nor specific for pediatric autoimmune pancreatitis.	*no specific recommendation strong consensus*
Measurement of serum IgG4 levels in children with ARP or CP in the absence of associated systemic disease or suggestive imaging for autoimmune pancreatitis is unlikely to be useful.	*no specific recommendation moderate consensus*
Patients with ARP or CP and a sweat test 60 mmol/L should have expanded CFTR mutation testing done if there is no other identified cause of their pancreatic disease (such as a PRSS1 mutation or clear obstructive etiology)	*no specific recommendation no consensus*
Patients with ARP that only have pancreatitis in the setting of a clear metabolic derangement (diabetic ketoacidosis, toxic drug exposure, diagnosed metabolic disease, severe hypertriglyceridemia (>1000mg/dL), or hypercalcemia) require no further evaluation regarding the etiology of the pancreatitis.	*no specific recommendation no consensus*
Patients without an etiology for ARP or CP after evaluation for obstructive, genetic and metabolic causes should have bile collected for micro-crystal analysis.	*no specific recommendation no consensus*
Pediatric patients with ARP should be evaluated for endocrine pancreatic insufficiency at least annually.	*no specific recommendation no consensus*
Pediatric patients with ARP or CP should have an upper endoscopy to look for mucosal abnormalities in the duodenum if other clear etiology has not been identified.	*no specific recommendation no consensus*
An esophagogastroduodenoscopy with biopsies to evaluate for mucosal abnormalities (such as peptic ulcer disease, Crohn's or eosinophilic enteritis) or duplications should be considered in patients with ARP or CP of unclear etiology.	*no specific recommendation no consensus*

Members of the consensus group were asked to independently score each statement on a 5 point scale: 5=definitely yes, 4=probably yes, 3=no specific recommendation, 2=probably no, 1=definitely no and also submit a GRADE strength of recommendation (1=strong, 2=weak) and quality of evidence (A=high, B=moderate, C=low).

Endorsement is defined as Strong Consensus (a standard deviation (SD) of ≤ 0.5 on the 5 point scale) or Moderate Consensus (SD>0.5 but ≤ 1 when the highest and lowest scores were excluded and all scores were on the positive or negative end of the scale). No Consensus statements are those where the SD of scores from experts was >0.5 and both positive and negative responses remained after exclusion of the lowest and highest scores.