

Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee

*A. Jay Freeman, †Asim Maqbool, ‡Melena D. Bellin, §Kenneth R. Goldschneider, ||Amit S. Grover, ¶Cheryl Hartzell, #Travis L. Piester, **Flora Szabo, †Bridget Dowd Kiernan, ††Racha Khalaf, ††Rakesh Kumar, §§Mirta Rios, ||||Sohail Z. Husain, ¶¶Veronique D. Morinville, and ###Maisam Abu-El-Haija

ABSTRACT

This position paper summarizes the current understanding of the medical management of chronic pancreatitis (CP) in children in light of the existing medical literature, incorporating recent advances in understanding of nutrition, pain, lifestyle considerations, and sequelae of CP. This article complements and is intended to integrate with parallel position papers on endoscopic and surgical aspects of CP in children. Concepts and controversies related to pancreatic enzyme replacement therapy (PERT), the use of antioxidants and other CP medical therapies are also reviewed. Highlights include inclusion of tools for medical decision-making for PERT, CP-related diabetes, and multimodal pain management (including an analgesia ladder). Gaps in our understanding of CP in children and avenues for further investigations are also reviewed.

Key Words: chronic pancreatitis, nutrition, pain management, position paper, sequelae of chronic pancreatitis

(*JPGN* 2021;72: 324–340)

Received May 21, 2020; accepted October 26, 2020.

From the *Department of Gastroenterology, Hepatology and Nutrition, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA, the †Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, the ‡Department of Pediatrics, Division of Endocrinology and Diabetes, University of Minnesota Masonic Children's Hospital, Minneapolis, MN, the §Pain Management Center, Cincinnati Children's Hospital, the ||Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Harvard Medical School, Boston, MA, the ¶Division of Pediatric Anesthesiology, Department of Anesthesiology, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, the #Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, the **Division of Pediatric Gastroenterology and Nutrition, Children's Hospital of Richmond, Virginia Commonwealth University, Richmond, VA, the ††Digestive Health Institute, Children's Hospital Colorado, Section of Pediatric Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine, Aurora, CO, the †††Department of Gastroenterology, Hepatology and Nutrition, ProMedica Toledo Children's Hospital, Toledo, OH, the §§Food and Nutrition Department, Nicklaus Children's Hospital, Miami, FL, the ||||Department of Pediatrics, Stanford University, and the Lucile Packard Children's Hospital, Palo Alto, CA, the ¶¶Division of Pediatric Gastroenterology and Nutrition, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada, and

The incidence of chronic pancreatitis (CP) among children remains low but continues to increase at a rate that mirrors acute pancreatitis (AP) and acute recurrent pancreatitis (ARP) (1). As defined by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium, CP requires imaging findings characteristic of and consistent with CP (specifically, radiographically evident calcifications, and pancreatic duct irregularities, such as strictures and dilations) along with 1 of the following 3: abdominal pain consistent with pancreatic origin, evidence of exocrine pancreatic insufficiency (EPI), or evidence of endocrine pancreatic insufficiency, or a pancreatic biopsy specimen demonstrating histological evidence of CP (2). Unlike in adults where CP is typically believed to be influenced heavily by alcohol and smoking (3), genetic and obstructive etiologies are far more common in children (4). Chronic pain and clinical manifestations of endocrine and/or exocrine insufficiency may cause impairment in daily functioning and have been shown to result in overall

the ###Division of Pediatric Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Address correspondence and reprint requests to A. Jay Freeman, MD, MSc, Associate Professor of Pediatrics, Director of Digestive Health for the Emory+Children's Pediatric CF Program Director Advanced Pancreatic Care Program @ CHOA, Medical Director GA Chapter of the National Pancreas Foundation, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Emory University School of Medicine, Children's Healthcare of Atlanta, 2015 Uppergate Dr. NE, Atlanta, GA 30322 (e-mail: Afreem6@emory.edu).

A. Jay Freeman and Asim Maqbool denote co-first authors.

Veronique D. Morinville and Maisam Abu-El-Haija denote co-senior authors.

This position paper was supported through NASPGHAN. No additional funding was received.

The authors report no conflicts of interest.

This article has been developed as a Journal CME and MOC Part II Activity by NASPGHAN. Visit <https://learnonline.naspghan.org/> to view instructions, documentation, and the complete necessary steps to receive CME and MOC credits for reading this article.

Copyright © 2020 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0000000000003001

impairment across all domains in health-related quality of life (QOL) among children with CP (5).

Despite the increased incidence, and given the unique risk factors and impact on QOL of CP among children, dedicated guidelines to assist in the medical management of children with CP are lacking. Large pediatric consortiums, such as INSPPIRE have been successful in characterizing this unique population but a lack of quality interventional and natural history studies has resulted in reliance on the adult literature and cystic fibrosis (CF) guidelines (where EPI is common) to direct treatment. Key aspects of management, such as nutrition, pain management, lifestyle modification, and monitoring for sequela of disease, however, seem different than those seen in other populations and require further guidance and study among children with CP.

Herein we summarize relevant literature, present the first recommendations dedicated to the medical care of children with CP, and highlight areas that require future study. Authorized and prepared by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Pancreas Committee, this is 1 of 3 complementary position papers to address management of CP in children: Endoscopic, Surgical, and Medical Managements. The manuscript detailing the roles of EUS and ERCP were recently published (6).

METHODS

The working group involved in the development of this NASPGHAN position paper included members of the NASPGHAN Pancreas Committee under the leadership of the committee Vice Chair (M.A.H.), as well as current Pancreas Committee Chair (S.Z.H.) and past Chair (V.M.) who were available for consultation and editing throughout the process. The authorship included co-first authors (A.J.F. and A.M.), among other experts in the field of pediatric pancreatology. In addition, expertise in pediatric endocrinology (M.B.) was incorporated to address endocrine pancreatic insufficiency and pediatric pain specialists (K.G. and C.H.) to address chronic pain management strategies.

Four subgroups were identified (Nutrition and Endocrine, Pain, Lifestyle, and Sequelae of Disease) with 2 to 3 authors assigned to each subgroup under the supervision of the 2 first authors (A.J.F. and A.M.). All available adult and pediatric publications were reviewed after each subgroup conducted Medline and PubMed searches related to their topics through July 2019. Regular calls and electronic correspondences were conducted between the subgroup leaders and the lead authors. Section paragraphs were written by subgroup members and reviewed by all members of the writing team. Each subgroup proposed clinical practice recommendations related to their review of the literature related to their topic(s). The first manuscript draft was circulated among all authors in December 2019.

Subsequently, tentative summary statements with a modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (7) statement were performed based on the strength of scientific evidence reviewed and available. On the basis of this committee's past work, formally utilizing the GRADE system (8) would not be advised because of the lack of quality literature and lack of a full systematic review. Therefore, we employed an extensive review of each sub-topic by each subgroup's members followed by an iterative consensus building process amongst all the authors. In the first round of consensus building, a vote was conducted for every practice recommendation and evidence level statement was voted upon by each of the authors, using a 5-point scale (5—strongly agree; 4—agree; 3—neutral; neither agree nor disagree; 2—disagree; 1—strongly disagree). It had been agreed ahead of time that consensus could only be reached

if at least 75% of the participants voted “4” (agree) or “5” (strongly agree) on a statement. A conference call was conducted to clarify voting statements and GRADE criteria in February 2020. Voting was anonymous, and no justification was requested for what response category was selected.

The updated draft of the manuscript was recirculated to all participating committee members for further review. A second round of voting was performed in February 2020 to complete the consensus-building process, after which all authors reviewed the manuscript a final time before submission. The final position paper was submitted and subsequently approved by the NASPGHAN Executive Council after all appropriate edits were completed.

Nutritional and Endocrine Complications of Chronic Pancreatitis in Children

As the exocrine gland is responsible for secreting digestive enzymes to support nutrient absorption and the endocrine gland maintains glucose homeostasis through the production of insulin and noninsulin islet hormones, overall destruction of the pancreas during CP can lead to variable levels of EPI and diabetes mellitus. These 2 defining complications of CP can have significant morbidity in children with CP.

Dietary Considerations for Children With Chronic Pancreatitis

Recommendations for acceptable macronutrient distribution in ranges (AMDRs) for healthy children and adults have been established by the National Academy of Sciences, based on international trials and epidemiological evidence (9). For children, differences in recommended AMRD by age are based primarily on a transition from high-fat intake in early infancy to the lower fat intake recommended for adults. For children ages 4 to 18 years, a healthy diet should consist of 45% to 60% carbohydrate, 10% to 30% protein, and 25% to 35% fat (10).

EPI may be overt (with abdominal pain, bloating, gas, malodorous stools, and steatorrhea) or subclinical. Furthermore, consequences of EPI may be immediate as well as with longer term, with implications for complications later in life. Therefore, EPI should be assessed for and addressed in patients with CP.

Although data are lacking regarding the ideal macronutrient composition in the diet for children with CP, many specialists believe that fat restriction may put patients at unnecessary risk. The CF model (given high incidence of EPI) was also used to help develop pediatric CP nutritional recommendations put forth jointly by North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) working groups that also addressed nutritional issues in pediatric acute, acute recurrent, and chronic pancreatitis (11). In patients with CF-associated EPI, insufficient fat absorption has been associated with delay in pubertal development, with comorbidities associated with poor nutritional status, such as CF-related diabetes and CF-associated liver disease imparting the greatest risk for delayed puberty (12). Hence, in pediatric patients with CF, a high-fat diet is recommended, with >35% of total calories from fat, in conjunction with pancreatic enzyme replacement therapy (PERT) (13) and routine monitoring for pubertal delay advised (12). Given children with CP do not appear to have the same concerns with weight gain and lung function but concerns for delayed puberty persist, the current recommendations support a normal fat diet in children with CP unless hypertriglyceridemia is the underlying etiology (11,14).

In addition to caloric and macronutrient deficiencies, children with CP are at risk for micronutrient deficiencies, particularly deficiencies of the fat-soluble vitamins A, D, E, and K. In particular, vitamin D deficiency is a likely contributor to the high prevalence of osteopenia and osteoporosis in adults with CP (15). In the CF disease model, patients may be at risk for essential fatty acid deficiency; it is unclear if this applies to all patients with CP-related EPI. Other micronutrient needs and deficiencies are not well studied in CP patients, requiring a proactive approach in monitoring those levels.

For children with CP, growth parameters should be followed and adequate nutrition provided, by oral diet, or when necessary, by enteral feeding. In a randomized control trial (RCT) involving adults with CP, dietary counseling was found to be as effective as supplementation to improve malnutrition (16). As such, a pediatric dietitian is an integral component to a CP care team.

Recommendations:

1. Patients with CP are at risk for macro- and micronutrient deficiencies. Patients should be monitored for growth and pubertal development, dietary intake, and fat-soluble vitamin deficiencies. Growth and dietary intake should be reviewed at every clinic visit, a minimum of every 6 to 12 months. Fat-soluble vitamin laboratory analysis should occur every 12 to 18 months or as clinically indicated. (Grade 1B)
15/15 = 100% Agreement.
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree
2. A multidisciplinary approach that includes a clinical pediatric dietitian is needed to adequately monitor nutritional status, evaluate nutrient intake and provide education and recommendations to help prevent both malnutrition and obesity. (Grade 1C)
15/15 = 100% Agreement.
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree

Use of Pancreatic Enzyme Replacement Therapy for Exocrine Pancreatic Insufficiency in Children With Chronic Pancreatitis

Patients with CP are at risk of EPI, and the risk increases over time. Among adults with CP, EPI typically develops over 5 to 10 years after the initial diagnosis (3). A recent publication of 442 pediatric patients with pancreatitis, however, showed that 18% developed EPI within 6 years of their initial AP attack (17). EPI may be overt (with abdominal pain, bloating, gas, malodorous stools, and steatorrhea) or subclinical. Furthermore, consequences of EPI may be immediate as well as with longer term, with implications for complications later in life. Therefore, EPI should be assessed for and addressed in patients with CP.

The use of PERT in CP has been evaluated, particularly in adult populations. Although the majority of the studies focus on the effect of PERT on pain management, its primary role remains in treating EPI. In patients with CP and EPI, PERT therapy is often indicated with dosing suggestions similar to those utilized in EPI associated with CF (11). Dosing is based on the patient's weight, tailored to the fat content of a meal/snack or based on the volume and content of enteral tube feeds (see Table 1). Formulations of PERT vary in different countries. Online tools and resources are available to provide guidance for prescribing PERT for children with EPI (An example of which is provided in Figure 1 (18)). For

TABLE 1. Recommended pancreatic enzyme replacement therapy dosing for children with chronic pancreatitis-associated exocrine pancreatic insufficiency

PERT dosing method	Feeding and dose considerations
Weight-based	Oral feeding Start at 500 to 1000 lipase units/kg/meal May increase by 1 cap/meal or snack till symptoms resolve or maximum dose reached Maximum dose is 3000 lipase units/kg/meal Should not exceed 10,000 lipase units/kg/day
Fat-based	Oral or enteral feeding Consider if suboptimal response to weight-based dosing Dose range: 500 to 4000 lipase units/g fat
Volume-based	Enteral feeding Consider if on continuous/night time feeds with ongoing poor weight gain and/or malabsorption* Enteral feeding in line cartridge: 1 cartridge for the first 500 cc formula Add second cartridge up to 1000 cc formula (no more than 2 cartridges may be used per feed)

*Pancreatic enzyme replacement therapy (PERT) can be used with tube feeding; consultation with a pancreatologist, and/or an experienced registered dietitian is recommended.

patients requiring continuous or nighttime enteral nutrition, inline lipase cartridges may be considered but are not yet available in all countries (19).

There are multiple ways to measure exocrine pancreatic sufficiency. Indirect testing modalities are the most commonly employed. The most practical and commonly used clinically is the fecal elastase test. The monoclonal antibody test is the preferred assay to measure fecal elastase and is performed on formed to semi-formed stool. This test was initially validated for patients with CF but remains the most commonly used assay to measure fecal elastase regardless of etiology. The upper limit of the reported reference range is $>500 \mu\text{g/g}$ and the lower limit is $<15 \mu\text{g/g}$. Reference laboratories, however, usually cite $<100 \mu\text{g/g}$ stool as abnormal, 100 to $200 \mu\text{g/g}$ as indeterminate or with moderate EPI, with $>200 \mu\text{g/g}$ as normal, with the same reference ranges utilized for CP in children (20,21). Fecal elastase is a spot test that varies with age or may be transiently decreased and may require multiple measurements over time during clinical decision making to account for progression to EPI and account for the multiple variables, which may impact results (22,23). Additionally, transient EPI can occur after pancreatic injury, viral infection or for unclear reasons. As such, repeat testing of fecal elastase may be influenced by clinical symptoms (22). Fecal elastase tends to perform best at the ends of the reference ranges (24), with intermediate values often requiring more investigation to correlate with EPI; this may be in particularly true in patients with chronic pancreatitis. Therefore, interpretation of fecal elastase to diagnose EPI in patients with CP for intermediate values and insufficient range should occur cautiously using greater than 1 measurement, possibly with additional markers of EPI and in consultation with a specialist."

Coefficient of fat absorption (CFA) may also be utilized to measure exocrine function, however, it requires a strict high-fat diet, a 72-hour stool collection, and involvement of a dietitian familiar with its administration and interpretation to account for the

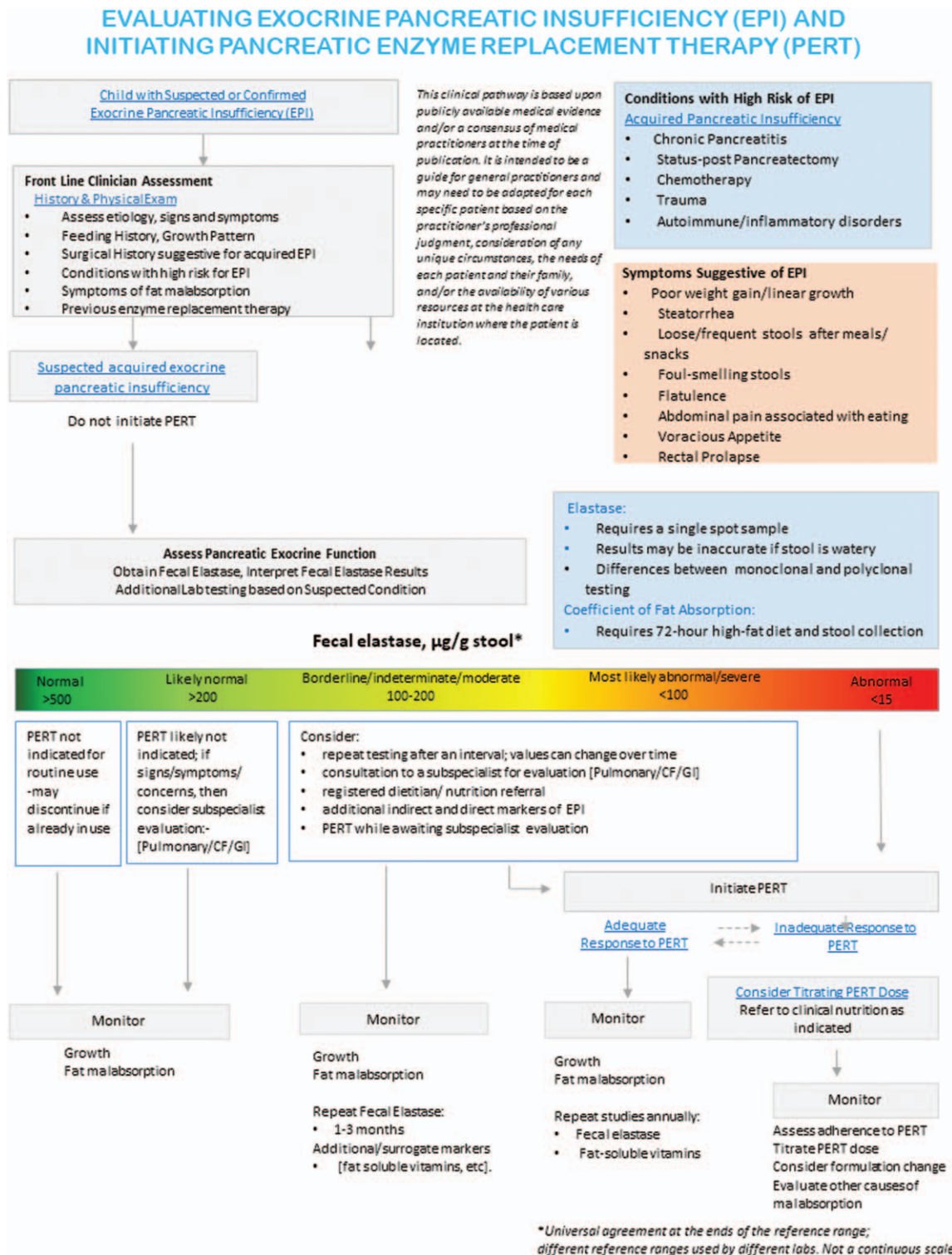


FIGURE 1. An example of an institutional clinical pathway for testing and diagnosing exocrine pancreatic insufficiency in children. Modified from Padula et al (18).

child's fat intake. A malabsorption blood test is available for research and is currently undergoing validation for clinical use. Direct pancreatic function testing (eg, Dreilling tube method and endoscopic pancreatic function testing) is available at some centers

as covered in a separate NASGHAN-ESPGHAN position paper (25). These tests, however, are more invasive or require an endoscopy, which to date have limited broad application in children.

Recommendation:

- There is a clear role for PERT in children with CP who have EPI with steatorrhea, poor growth and/or nutritional deficiencies. PERT dosing for CP associated EPI is similar to that used in patients with CF. (Grade 1B)
14/15 = 93% Agreement
Voting results: 10 strongly agree; 4 agree; 1 neutral; 0 disagree; 0 strongly disagree.

Pancreatogenic Diabetes Mellitus in Children With Chronic Pancreatitis

Compared with CP among adults, the literature on pancreatogenic diabetes mellitus (DM), also referred to as Type 3c DM, in children with CP is sparse. Published series suggest the prevalence of DM in children with CP is around 4% to 9% (17,26,27). Presumably many more patients with childhood CP are, however, at risk for developing DM later as adults, as exemplified from the natural history of hereditary pancreatitis, in which nearly half of all patients are diabetic by age 50 years (28). Calcific CP, BMI above the 85th percentile, older age, and history of severe AP may be risk factors for pre-diabetes or DM in children with CP (27,29). DM often co-exists with EPI, as a marker of late stages of disease and extensive damage to the pancreatic parenchyma (30).

Because of the high risk for diabetes, it has been advocated that children with CP be screened yearly for DM with a simple fasting glucose and hemoglobin A1c (HbA1c) level (31). Annual screening is recommended for adults with CP, and has also been incorporated into screening recommendations for children enrolled in the INSPPIRE studies (31,32). Two-hour oral glucose tolerance testing should be considered to evaluate for impaired glucose tolerance and diabetes based on a 2-hour postprandial glucose, particularly in those patients with pre-DM range fasting glucose or HbA1c (32). Diabetes is diagnosed based on standard American Diabetes Association guidelines (fasting plasma glucose ≥ 126 mg/dL, 2 hour OGTT glucose ≥ 200 mg/dL, or HbA1c $\geq 6.5\%$), which, in the absence of classic diabetes symptoms, should be confirmed with a second positive test (33).

Mixed meal tolerance testing (MMTT) is an alternate approach to assessing glycemic and islet hormonal responses to a meal. MMTT protocols typically use a Boost or Ensure beverage to mimic a typical meal, in contrast to the simple carbohydrate stimulus of an OGTT. MMTT may be advantageous in some settings, particularly for research of islet dysfunction in CP, as it is more physiologic (34). Postprandial glycemic thresholds to diagnose DM are, however, only established for OGTT, and thus OGTT is preferred if the goal is to establish a diagnosis of DM or pre-DM (35).

The underlying pathophysiology leading to pancreatogenic DM is extrapolated mainly from research in adult populations. Insulin deficiency is the primary defect leading to hyperglycemia (36–39). Impaired insulin secretion may result from islet (and beta cell) loss as a consequence of irreversible damage from pancreatic fibrosis or from beta cell dysfunction resulting from intrapancreatic inflammatory cytokines (36,40,41). Small series in adults, usually with alcoholic pancreatitis, also suggest a role of hepatic insulin resistance, with conflicting studies on whether peripheral body insulin sensitivity is impaired (42–46). Finally, as appropriate nutrient breakdown is integral to proper stimulation of the incretin hormones Glucagon-like Peptide-1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) in the small intestine, a potential defect in the incretin axis has been proposed. In adults with CP, administration of PERT results in increased GLP-1 and GIP levels after a meal, but it

is unknown whether this impacts glycemic control in a clinically meaningful way (47,48).

Studies on treatment approaches for pancreatogenic DM are lacking in children, and even adult treatment guidelines are largely based on expert consensus and known pathophysiology, rather than any direct research in CP (32). Insulin injections are often the most appropriate pharmacologic therapy for children with pancreatogenic DM, as insulin replacement therapy addresses the primary issue of insulin deficiency. Pancreatogenic diabetes is, however, believed to occur secondary to a number of mechanisms resulting in hyperglycemia and alternatives to insulin may need to be considered (49). In children who are obese or have mild DM, metformin might be considered as a first-line treatment, or metformin may be used alongside insulin in children with pancreatogenic DM who have clinical signs of insulin resistance (32). Occasionally, sulfonyleurea has been utilized off-label as it is currently not an FDA-approved medication for the treatment of diabetes in children (49). Given the complexities of glucose control in pancreatogenic diabetes, and its potential effect on growth and development, pediatric endocrinology should be involved in insulin management whenever feasible. Lifestyle modifications should be considered if needed to target a normal BMI. Although very little is known about risk of diabetic microvascular complications (retinopathy, nephropathy) in pancreatogenic DM, monitoring per ADA guidelines established for type 1 or type 2 DM with yearly eye exams and urine microalbumin should be considered (50).

A special consideration in the treatment of pancreatogenic DM is that 1 should ensure that co-existing EPI is appropriately managed. When prandial insulin is administered, it is important to ensure that malabsorption is treated with PERT therapy, because malabsorption may contribute to glycemic lability (51).

Recommendations:

- Children with CP should be screened yearly for pancreatogenic DM with a fasting glucose and HbA1c level. (GRADE 1C)
15/15 = 100% Agreement
Voting results: 10 strongly agree; 5 agree; 0 neutral; 0 disagree; 0 strongly disagree
- Consider OGTT if pre-diabetes is present based on abnormal fasting glucose (100–125 mg/dL) and/or HbA1c level (5.7%–6.4%). OGTT should be performed annually once a patient is considered to have pre-diabetes. (GRADE 1C)
14/15 = 93% Agreement
Voting results: 10 strongly agree; 4 agree; 1 neutral; 0 disagree; 0 strongly disagree
- Chronic pancreatitis patients with diabetes should be referred to a pediatric endocrinologist to optimize glucose management and determine if evaluation for other forms of DM should be considered. (GRADE 1B)
15/15 = 100% Agreement
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree
- It is important to address clinical symptoms of malabsorption and PERT in children with CP and DM to improve glycemic control. (GRADE 1C)
15/15 = 100% Agreement
Voting results: 10 strongly agree; 5 agree; 0 neutral; 0 disagree; 0 strongly disagree

Use of Antioxidants in Chronic Pancreatitis

The fibro-inflammatory pathophysiology of CP involves oxidative stress and depletion of antioxidants. Thus, the use of antioxidants has been hypothesized as a strategy for the treatment,

and prevention of progression, in CP (52,53). Proposed antioxidant agents include Vitamin A, Vitamin C, Vitamin E, selenium, zinc, and methionine, although consistency in formulations and dosage across studies is lacking.

Supplementation of specific antioxidants as essential cofactors to potentially ameliorate the malnutrition or inflammation of the pancreas that results from CP has not been adequately studied. Potential mechanisms by which antioxidants impede the progression or spread of the inflammatory cascade have not yet been elucidated (53). A theoretical reduction in inflammation might slow or halt the progression of pancreatic acinar cell burnout leading to EPI over an extended period of time, making the effect difficult to measure or demonstrate in trials.

More research is needed to elucidate pathways involved in the complex interplay of nutritional supplements, cofactors, and antioxidants in CP. This is especially crucial as pancreatic fibrosis in CP can progress sub-clinically until severe clinical consequences surface, which may be irreversible at that stage.

Recommendations:

8. Insufficient data exists to recommend the use of antioxidants as a treatment to prevent EPI or other disease progression in children with CP. (GRADE 2C)
15/15 = 93% Agreement
Voting results: 10 strongly agree; 4 agree; 1 neutral; 0 disagree; 0 strongly disagree

Medical Management of Pain in Chronic Pancreatitis

The pathophysiology of CP pain is multifactorial with multiple mechanisms that are incompletely understood (54). It may include pancreatic causes (eg, acute and chronic inflammation, increased pressure in ducts, ischemia and fibrosis) as well as extrapancreatic causes including duodenal or common bile duct stenosis (54,55). Interestingly, a large prospective cohort study of 518 patients found that the severity and temporal pain patterns in CP were independent of the corresponding abdominal imaging findings (56), suggesting other pain mechanisms are involved as well.

Repetitive pain attacks because of recurrent pancreatitis may lead to sensitization and increased excitability of pancreatic nociceptors, resulting in amplification of pain with subsequent attacks. The increased excitability seen in the periphery also occurs in the central nociceptive pathways of the spinal cord. This leads to central sensitization, which involves neural remodeling and recruitment of nerves not typically involved in pain signaling (57). The result is reduction of pain thresholds, pain to nonnoxious stimuli (allodynia) and more diffuse pain. The complex interplay of pain mechanisms creates the basis for the multidisciplinary and multimodal approach to CP pain management.

Multidisciplinary Approach

Interdisciplinary pain care is held as the standard in pediatric pain care (58). The literature supports the efficacy of this approach to chronic pain in children (59). The field lacks studies in pediatric AP or CP pain management; however, the foundation of the approach to pain management is based on what is known as the biopsychosocial model of pain, in which the patient's pain is influenced by the interplay of genetic, biological, psychological, anatomic, functional, psychological, and social forces. From that perspective, the coordination of CP pain care must occur across multiple disciplines, as for any severe chronically painful condition. The team ideally would include not only physicians and nurses but also psychologists, physical therapists, social

workers, and school staff, to address all aspects of the patient's life that may be affected by the patient's disease. Clearly, effective multimodal pain treatment includes medications, interventional treatments, psychology, physical rehabilitation, and complementary modalities (60). Pain cannot always be completely eliminated but function and related QOL can be improved. Therefore, education, anticipatory guidance, and expectation management of the various types of pain and treatments associated with CP is essential. Such education aims not to only improve the success of treatments by setting realistic goals and fostering a good understanding of the treatment plan but also to provide comfort and support to patients and families. Introducing a multimodal pain treatment plan early on, following the diagnosis of ARP or CP (and in particular, with hereditary etiologies) will likely increase the effectiveness of the treatment plan.

Role of Psychology

Pain-focused psychology is a psycho-educational approach aimed at teaching patients' new ways of coping. The most well-researched and established method is cognitive behavioral therapy (CBT). CBT can be adapted to a multitude of disorders but pain-focused CBT targets the impact of dysfunctional thoughts on unhealthy or avoidant behavior as they relate to pain. It utilizes cognitive restructuring to increase functional ability, while decreasing psychosocial impairment and pain intensity (61). Psychologists also teach mindfulness and techniques, such as progressive muscle relaxation and diaphragmatic breathing to modulate the physiological response of a pain experience (heart rate, breathing, muscle tension). They also work with parents to teach strategies on how to respond to their child's pain, especially in a crisis, in a more constructive and beneficial way to help increase their child's function. Although there are no studies of the effect of CBT on CP, there are several on functional abdominal pain in children. Positive effects of CBT are apparent both in the short-term and long-term (6–12 months) (62–64). The internet has been shown to be an effective way to bring CBT to pediatric patients and their families and may be useful for patients in remote or under-resourced locations (65).

Role of Physical Therapy

Patients may present overall physically deconditioned with limited ability to participate in school and simple activities of daily living due to pain. Increasing a patient's function is essential to decrease pain signaling and overcome a patient's social impairment (66). Physical therapy (PT) provides a safe and structured environment to start functioning again, while providing accountability to a provider. The overall goal of PT is to increase strength, stamina, and confidence so the patient can transition to a daily workout program. Additionally, a patient can trial other complementary therapies, such as a transcutaneous electronic nerve stimulation (TENS) unit or myofascial release, aimed at improving musculoskeletal pain that can develop because of increased muscle tension (66). TENS use for pancreatitis pain has not been studied; however, our modest anecdotal experience and the minimal risk of TENS therapy support considering the modality as part of a multi-modal pain care plan.

Recommendations:

9. Treatment of pain in children with CP requires a multidisciplinary approach, ideally involving a pediatric pain physician, pediatric gastroenterologist, psychologist, nurse, and physical therapist. (GRADE 1B)
15/15 = 100% Agreement
Voting results: 12 strongly agree; 3 agree; 0 neutral; 0 disagree; 0 strongly disagree

10. Cognitive Behavioral Therapy (CBT) should be considered in management of children with CP pain. (GRADE 1B)
15/15 = 100% Agreement
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree
11. Physical therapy may be considered as an adjunct therapy for pain management in children with CP. (Grade 2B)
15/15 = 100% Agreement
Voting results: 8 strongly agree; 7 agree; 0 neutral; 0 disagree; 0 strongly disagree

Nonanalgesic Pharmacologic Options

A potential secondary and controversial role for PERT is for pain management in CP. PERT use for pain in CP is long standing and has a theoretical pathophysiologic basis. Nutrients are known to stimulate cholecystokinin releasing factor (CCK-RF) from the duodenum (67). In the fasting state, pancreatic enzymes, such as trypsin degrade CCK-RF, preventing the pancreatic stimulatory effects brought about by cholecystokinin (CCK) release (3,55). Hypothetically, inhibiting CCK release, thus preventing pancreatic stimulation, should mitigate any increased intraductal pressure and associated pain. During the fed state, endogenous pancreatic enzymes act on digested nutrients and not CCK-RF, which is then able to stimulate pancreatic stimulation in an unopposed manner via CCK release. Elevated levels of CCK have been reported in CP patients and may generate pain by increasing pancreatic ductal pressures (CCK-A), as well as through direct activation of nociceptive pathways in the central nervous system (68). The theoretical mechanism of PERT as an analgesic is by inactivating CCK-RF thereby preventing CCK-induced pancreatic stimulation.

The clinical efficacy of PERT in the management of CP without EPI remains, however, unclear. In a Technical Review by the American Gastroenterology Association (AGA), 6 trials examining the benefit of PERT in adults with CP were evaluated; pain relief was noted in only 2 of the trials, both of which utilized nonenteric-coated enzymes (69). Additionally, a meta-analysis of 5 randomized controlled trials showed no significant difference in the mean daily pain score or average weekly analgesic consumption between PERT and placebo, ultimately concluding that PERT did not relieve abdominal pain in patients with CP and should not be prescribed for this primary purpose (70). A more recent meta-analysis reported improvements in pancreatic pain as a secondary outcome but did not further address the basis for this improvement (71).

Antioxidant therapy (AOT) has also been postulated to aid in inflammatory pain treatment of CP by addressing oxidative stress as a mechanism (55). Patients with CP have elevated free radical activity and oxidative stress indices (lipid peroxide levels) in blood and duodenal secretions, and decreased antioxidants, precursors, and cofactors in blood (72–74). Common components of AOT include vitamins C, E, A, selenium, and methionine (75). Rustagi et al compared 8 studies involving nearly 450 patients. Patients treated with AOT had significant pain reduction compared with controls; however, subgroup analysis demonstrated that this benefit was limited to patients with a mean age of greater than 42 years or those patients with alcoholic pancreatitis (76). A previous Cochrane review examined 12 randomized controlled trials that reported significantly less pain after 1 to 6 months among the treatment group; however, the number of pain-free participants was not significantly different (75). In addition, more adverse events were reported in the AOT group. These included mild symptoms of headache or gastrointestinal distress that were enough to force trial participants to stop taking the antioxidants. The authors concluded that while AOT reduced pain slightly, the clinical benefit remained

uncertain. Studies of AOT are further complicated by heterogeneity of study designs (eg, number/type of antioxidants, length of exposure, and concomitant therapies) and inconsistent or unknown dosages of commonly used antioxidant and multivitamin formulations that lack FDA oversight.

Corticosteroids have also been proposed to address inflammation in patients with pancreatitis. In a meta-analysis of adult patients with severe AP, corticosteroid therapy was associated with decrease in length of hospital stay, surgical interventions, and mortality (77). Studies on the use of corticosteroids in pediatric patients or CP are, however, lacking.

The use of somatostatin analogs (eg, octreotide) and leukotriene antagonists has been proposed but the evidence supporting these therapies is weak and associated with numerous side effects as well as high cost. As such, these therapies have not been recommended for the treatment of pain in CP (57).

Recommendations:

12. There is insufficient data to recommend PERT as therapy for pain in children without EPI. (GRADE 1B)
14/15 = 93% Agreement
Voting results: 10 strongly agree; 4 agree; 1 neutral; 0 disagree; 0 strongly disagree
13. There is insufficient data to recommend antioxidants, steroids, leukotriene antagonists, or somatostatins in the management of pain for children with CP. (GRADE 2C)
14/15 = 93% Agreement
Voting results: 9 strongly agree; 5 agree; 1 neutral; 0 disagree; 0 strongly disagree

Outpatient Interventions

Analgesic Therapies

The goals of a successful medication regimen are aimed at decreasing a patient's pain to allow for increase in function. Proposed stepwise medication regimens modeled after the World Health Organization pain ladder for cancer pain relief have reported decreases in inpatient admissions for pain control (68,78). For CP, however, it is likely more appropriate to conceive of the analgesic regimen as a layering process, rather than a stepwise ascension. Anti-inflammatory and neuromodulating medications are used as interventions for nociceptive and centrally mediated pain, respectively, and opioids are layered on top for more severe bouts of nociceptive pain, rather than replacing the nonopioids. The advantage of utilizing a multimodal approach consisting of pain medications with different mechanisms of action is that it allows for lower doses of each medication, decreasing the risk of adverse side effects of each individual medication (79). Of note, because of lack of pediatric safety and efficacy data for analgesics in general, all medications discussed, with the exception of ibuprofen and acetaminophen, are used off-label for treatment of pain in children.

Proposed Analgesic Ladder

On the basis of pain management experience and by summarizing approaches in effective management of pain, we concluded that a tool would be helpful to clinical care providers. The proposed analgesic ladder for treating pain in children with CP is shown in Figure 2. Note that this schema refers to pharmacologic interventions. It is assumed that appropriate psychological or other nonpharmacologic treatments can and should be used through all phases of pain management. Level I consist of nonopioid medications, including NSAIDs (eg, ibuprofen or naproxen) and acetaminophen. This should be the first-line therapy for acute intermittent abdominal pain. If the patient's pain continues to be

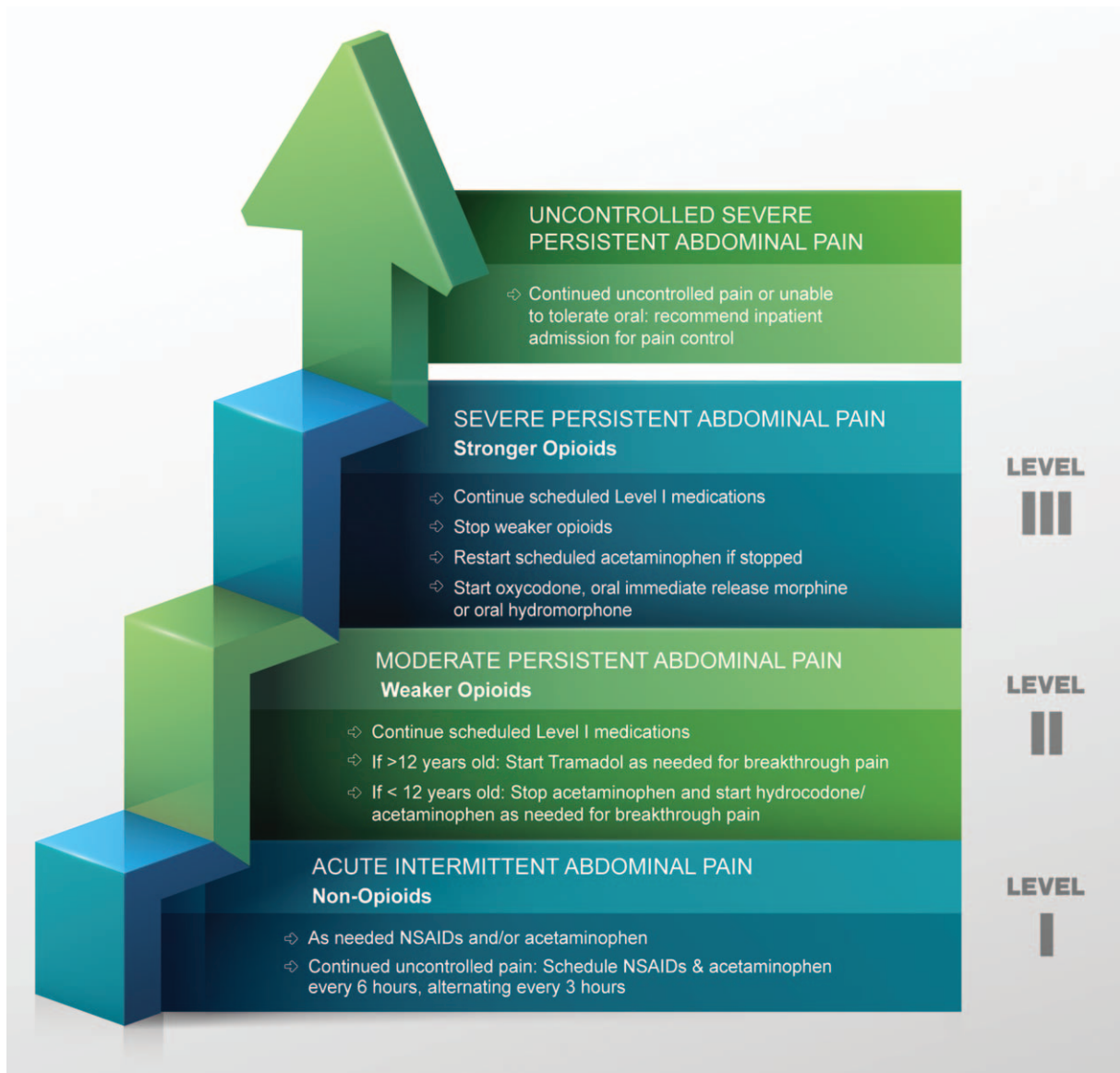


FIGURE 2. Proposed analgesic ladder for the treatment of pain in children with chronic pancreatitis. Graphics courtesy of Ms. Natalie Alexander. Nonpharmacologic pain care is assumed to be provided at all points in the ascension of analgesic potency.

uncontrolled with intermittent dosing, the patient should be counseled to schedule NSAIDs and acetaminophen. Acetaminophen is safe for short-term use in pediatrics (80) but there is concern about the effects on the liver. In adults, evidence for adverse effects of long-term acetaminophen use is mixed (81); while there is a paucity of pediatric literature, dosing limits should be strictly observed. If long-term scheduled NSAID use is required, starting an acid suppression medication, such as H2-blockers or proton pump inhibitors, is reasonable to decrease the risk of NSAID-induced gastritis (82).

Level II starts with weaker opioids, including tramadol. The patient should continue with scheduled level I medications while starting as needed level II medications. Tramadol can be useful for pancreatitis pain, and has less gastrointestinal slowing than standard opioids. A small study found tramadol compared favorably with oral morphine in regards to analgesia in adults with CP and had less effect on GI transit time (83). Unfortunately, tramadol has a Food

and Drug Administration (FDA) boxed warning for children under 12 years of age related to concerns about pharmacogenetic variability in metabolism and potential safety effects deriving from that and is used off-label in older pediatric patients. An alternative weaker opioid would be hydrocodone. Limitations of hydrocodone include the fact that it is rarely used outside of the United States and is only available in combination form with acetaminophen. Thus, prescribers should counsel patients to stop taking acetaminophen in addition to the hydrocodone/acetaminophen.

Level III is indicated if the patient’s pain control continues to be inadequate. Level III consists of the addition of more potent oral opioids, such as oxycodone, immediate release morphine or hydromorphone, which are all used off-label in pediatrics. The patient should replace the weaker opioid with the stronger opioid, and continue the nonopioid medications. It is important to counsel both the patient and their family on appropriate opioid handling, including dosing, storage in a locked area, and disposal as according to the

local law. Strategies should be implemented to prevent opioid dependence and multiple opioid prescriptions that include, but are not limited to: identifying a single prescriber of all opioids for the patient; development of patient care contracts; and reviewing local drug-monitoring programs. If the patient's pain continues to be uncontrolled despite the above regimen or if enteral medications are not possible or desired, it is recommended for the patient to be considered for inpatient admission for pain control with subsequent outpatient follow-up (see Inpatient Treatment Section).

Neuromodulating Medications

Tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitors (SNRI), and anticonvulsants have been long established through a multitude of studies as effective agents in treating chronic neuropathic pain. These medications provide pain relief by modulating central pain signaling, thus reducing central sensitization. TCAs include amitriptyline and nortriptyline. Both are equally effective; however, nortriptyline is associated with fewer side effects (84). SNRIs include duloxetine and anticonvulsants, such as gabapentin and pregabalin. Ketamine has been used to treat both acute and chronic pain of numerous types in patients of all ages, and there is modest evidence to support its use in inpatient pancreatitis care (85). Note that regulations on its use vary widely from 1 institution to another, so practical recommendations are difficult to make. To date, there are no studies evaluating the efficacy of these medications in CP in the pediatric population, and all are used off-label in the pediatric population. One randomized control trial examining pregabalin's analgesic effect in adults with CP, however, found significant decrease in pain intensity in the pregabalin group compared with placebo (86). Despite the wide use of gabapentin in patients with chronic pain, there are no studies assessing gabapentin's efficacy in patients with CP.

There are no studies to date in CP patients evaluating the risk factors associated with the development of chronic pain following AP, or when to start neuromodulator medications. Despite this, several factors have to be assessed to determine the patient's need, including the patient's frequency of pain, functional disability, effect of the patient's pain on their overall QOL, and pain flares in the absence of chemical or radiologic evidence of active inflammation.

Concurrently, a discussion with patient's gastroenterologist regarding the most likely course of their disease process may also help in deciding whether to start a daily medication.

Repetitive pain insults, along with the chronicity of pain can potentially cause the central sensitization with the associated hyperalgesia and allodynia. Perioperative administration of gabapentin has been shown to significantly decrease the incidence of chronic postsurgical pain (CPSP) in children and adults alike following surgeries with a high risk for developing CPSP (87,88). On the basis of this, one could extrapolate that gabapentin may also prevent chronic abdominal pain following a major pain insult, such as acute pancreatitis. Further studies are needed to examine the risk factors that correlate with increased incidence of CP pain.

Considerations remain for which neuromodulating agent is appropriate for the patient. Gabapentin requires a patient to take it 3 times a day, which may not be realistic for all patients. If the patient's sleep is impacted greatly, TCAs can normalize sleep patterns; however, they can also prolong a patient's QTc, so many practices obtain EKG before starting. SNRIs can provide concurrent mood stabilization, which may be beneficial in patients with depression or anxiety.

Interventional Procedures for Pain Control

Celiac plexus blockade has been used in adults for CP for decades. Overall results have been mixed and largely short-term, based on moderate levels of data (89,90). No evidence has been published in the pediatric literature, and the technical expertise and experience to perform this procedure in children is limited to a few centers worldwide. Furthermore, extrapolation from adults to children is further confounded by the fact that the etiologies of pancreatitis in the 2 populations are different, so may respond differently.

Recommendations:

14. Analgesic pain management in CP should follow an "analgesic ladder" that incorporates the layering of nonopioid and opioid medications. Ideally this should be directed by a pain specialist working in partnership with a pancreatologist or gastroenterologist. (GRADE 1B)
15/15 = 100% Agreement
Voting results: 13 strongly agree; 2 agree; 0 neutral; 0 disagree; 0 strongly disagree
15. Neuromodulators may be effective in treating pain in children with CP as part of a multidisciplinary approach. (GRADE 1C)
15/15 = 100% Agreement
Voting results: 9 strongly agree; 6 agree, 0 neutral, 0 disagree; 0 strongly disagree
16. Celiac plexus block for pain has not been shown to be effective in children with CP and cannot be recommended currently. (GRADE 1C)
14/15 = 93% Agreement
Voting results: 9 strongly agree; 5 agree; 1 neutral; 0 disagree; 0 strongly disagree

Inpatient Treatment

On occasion, pain from CP or ARP will flare beyond a level that patients can treat at home. Admission for such flares would then follow treatment guidelines for AP (91). Pain-specific consideration include discouraging the use of opioids in the absence of concrete markers of inflammation (chemical or radiographic) and maximizing coping and functioning. At times, brief use of opioids is reasonable while evaluation is ongoing. Unless a patient is NPO for medical or surgical reasons, and outside of the presence of ileus, intravenous medications are rarely indicated. Finally, if patients have a history of chronic opioid use, then they will display varying amounts of tolerance, which will require adjustments in dosing. Such patients will need to be weaned to pre-admission opioid dosing levels at the time of discharge, barring new developments. All adjunct medications and nonpharmacologic therapies should continue, following the layering model noted above.

Recommendation:

17. Children with CP suffering from pain refractory to standard medical management should be evaluated at a center with pediatric experience in pain management. (GRADE 1C)
15/15 = 100% Agreement
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree

Lifestyle Modification in Children With Chronic Pancreatitis

Lifestyle modifications have been shown in adult cohorts to alter the course of CP. Specifically, chronic alcohol use and smoking are independent risk factors for developing CP. Furthermore,

obesity has been linked with worse outcomes in CP amongst pediatric and adult cohorts. The proposed pathophysiology of these modulators is expanded below.

Alcohol Consumption

Heavy alcohol consumption is a well-established risk factor for the development of pancreatitis and progression from AP to CP, especially in patients with genetic etiologies (92–97). Long-term alcohol abuse is the primary risk factor for the development of CP in adults, accounting for up to 44.5% of cases (98,99). When co-abused, alcohol and tobacco use account for a combined prevalence of CP of approximately 74.8% (98,100). There is only scant pediatric data regarding the effects of alcohol consumption in children. A retrospective analysis of 146 pediatric patients with CP from INSPIRRE consortium revealed alcohol consumption in 5/137(4%) patients; however, the quantity and frequency of consumption was not specified (101). The adult literature and animal models suggest that alcohol increases the sensitivity of the pancreas to injury in patients with other underlying genetic or anatomic risk factors (102,103) but no studies have evaluated the association between alcohol use and pancreatitis in children.

Recommendation:

18. On the basis of long-term adult data, providers should caution patients about the acute and chronic negative effects of alcohol abuse on pancreatic health. (GRADE 1B)
15/15 = 100% Agreement
Voting results: 13 strongly agree; 2 agree; 0 neutral; 0 disagree; 0 strongly disagree

Smoking

Tobacco smoking has been identified as an independent, dose-dependent risk factor for CP and ARP among adults (98,104–106). In idiopathic CP, smoking is associated with disease progression as measured by the appearance of pancreatic calcification and new onset diabetes in a dose-dependent manner (107,108). Among 540 patients with CP in the North American Pancreatitis Study 2 (NAPS 2) cohort, long-term heavy cigarette consumption was associated with a 2.2 times greater risk of CP (106). The amount of smoking was significantly higher in patients with CP (26.6 pack-years) compared with ARP subjects (19.5 pack-years) and controls (16.2 pack-years) (106).

Patients with CP also had significantly longer smoking duration (median 30.5 years) than patients with ARP (median, 22.7 years) and controls (median 21.9 years) (106). The mechanism of how smoking accelerates the progression of CP and acts as an independent risk factor for CP is not well understood (104).

No studies have examined the role of smoking in the pathophysiology of CP in pediatrics. A retrospective review by Ballengee et al (109), of 134 pediatric patients admitted for pancreatitis revealed that hospital admission and length of stay were significantly higher for those exposed to second hand smoking indoors compared with those exposed to smoking outdoors or with no exposure. Although the impact of e-cigarettes on CP has not been evaluated, their use has gained popularity in the past several years, especially among adolescents, and represents an additional potential nicotine exposure. The National Youth Tobacco Survey in 2018 reported that 20.8% of high school students and 4.9% of middle school students use e-cigarettes (one e-cigarette at least 1 day in the past 30 days) (110). Exposure to smoking and other nicotine sources is likely to be under reported because of social stigmas, and thus

other biomarkers will likely be required to assess the true impact of smoking.

Recommendation:

19. Health-care providers should caution patients about the dose-dependent response of tobacco smoking on the development and progression of CP among adult patients and should advise against smoking. (GRADE 1A)
15/15 = 100% Agreement
Voting results: 12 strongly agree; 3 agree; 0 neutral; 0 disagree; 0 strongly disagree

Obesity

Truncal obesity has been shown to be an important risk factor for severe AP in adults compared with individuals with a normal BMI (111–117). Peripancreatic fat or intrapancreatic fat deposition directly correlate with the severity of AP in obese patients, as fat has a higher susceptibility for the development of necrosis in adult studies (114,118). Data regarding the effects of obesity in CP are, however, limited. A retrospective study of 118 patients with CP showed a positive correlation between increased pancreatic fat, higher abdominal visceral fat content, and pancreatic fat fraction compared with those with no CP (119). A retrospective study by the Zurich Pancreatitis Group found that overweight status (BMI >25) at disease onset did not affect the progression of EPI and diabetes in patients with alcoholic CP (120). Among children, the INSPIRRE study found patients with a BMI in the overweight range and greater were less likely to develop CP, EPI, or have additional medical or endoscopic interventions when compared with those with a normal BMI (118). This study also reports that obese patients had their first episode of AP at a later age when compared with nonobese pediatric patients. Patients, however, defined as overweight or obese with no evidence of CP had overwhelming acute inflammation on imaging of the pancreas indicative of a prolonged pro-inflammatory state albeit delayed, likely secondary to the obesity (118). The differences in CP outcomes between children and adults may be because of differences in underlying etiologies but require additional explorations, especially pertaining to potential insulin resistance, which may overlap with pancreatogenic diabetes.

Recommendation:

20. Data are limited regarding the impact of weight and BMI on CP outcomes, as such, providers should counsel patients and parents about a balanced healthy diet and lifestyle. (GRADE 1C)
15/15 = 100% Agreement
Voting results: 8 strongly agree; 7 agree; 0 neutral; 0 disagree; 0 strongly disagree

Quality of Life

Impaired QOL is commonly seen in pediatric patients with CP (5,121). A single center study assessed the health-related QOL (HRQOL) through the PedsQL 4.0 Generic Core Scales and the PedsQL Multidimensional Fatigue Scale in children with longstanding pancreatitis using a patient self-report as well as parent proxy report. Investigators reported that in 38 subjects, pediatric patients with CP have significantly worse HRQOL and fatigue scores compared with matched healthy subjects (5). This study established that pediatric patients with CP have diminished functioning across both physical and psychosocial domains with pain being one of the most significant contributors (5). The Short Form 36 (SF-36) is a widely used HRQOL

measure, mostly in adult patients to assess physical functioning, bodily pain, role limitations because of physical and emotional health problems, general mental health, social functioning, energy/fatigue or vitality, and general health perceptions. SF-36 has been used in pediatric patients to assess quality of life before and after total pancreatectomy with islet autotransplantation (TPIAT) (121). Other validated disease-specific QOL assessment tools, such as the Pancreatitis Quality of Life Instrument (PAN-QOLI) are available for adults but have not been studied in pediatric patients (122).

Directed efforts are needed to develop impactful interventions that mitigate the effect of CP on QOL in the pediatric population. Although endoscopic and/or surgical interventions may improve QOL (123), some patients are not surgical candidates and further interventions are needed to improve their QOL and functioning before surgery.

Recommendation:

21. Administering a survey tool to assess QOL and/or functional assessment among pediatric patients is helpful to assess degree of impairment and drive targeted interventions indicated. (GRADE 2C)
15/15 = 100% Agreement
Voting results: 8 strongly agree; 7 agree; 0 neutral; 0 disagree; 0 strongly disagree

Sequelae of Chronic Pancreatitis

Beyond the common findings that define CP, such as EPI or endocrine pancreatic insufficiency, several other sequelae may be appreciated. To provide thorough care for pediatric patients with CP, understanding and managing these issues is vital. Amongst the other sequelae that may develop are fluid collections, ductal disease, vascular and gastric/intestinal issues.

Pancreatic/Peripancreatic Fluid Collections

Pancreatic fluid collections (PFC) include acute more mature fluid collections. Acute fluid collections are those <4 weeks old and divided into acute peri-pancreatic fluid collections and acute necrotic fluid collections. More mature fluid collections >4 weeks old are divided into walled off necrosis and pancreatic pseudocysts. Pancreatic pseudocysts are typically a consequence of AP, pancreatic trauma, and/or CP (124). Among adults, the prevalence of pseudocysts in CP have been reported to be between 10% and 40%, though this is likely overestimated because of previous inclusion of acute fluid collections and walled off necrosis within the definition of pancreatic pseudocysts (125–127). Although usually asymptomatic, mass effect from pancreatic pseudocysts can cause abdominal pain, early satiety, nausea, vomiting, jaundice, weight loss; secondary complications, such as gastric outlet obstruction, biliary obstruction, infection, or vascular complications, such as splenic vein thrombosis or intra-cystic hemorrhage can also present with pain (128). Asymptomatic pseudocysts are usually managed conservatively (5) with observation, and pain control. Drainage, however, should be considered when fluid collection becomes clinically symptomatic (uncontrolled nausea/vomiting or pain), infected, causes obstructive complications (blood vessels, common bile duct, gastric outlet obstruction), bleeding, or fistula formation. Even when asymptomatic, endoscopic drainage has been proposed if the pseudocyst measures >5 cm in diameter without spontaneous regression (129). Previously walled off necrosis was felt to require definite intervention via surgery or advanced endoscopic techniques

but recently care has evolved and many of these collections may also be managed conservatively (130) if the patient remains clinically stable during the course.

Pancreatic Duct Disease

Pancreatic duct abnormalities are most often characterized by strictures and intraductal stone formation (131,132). For some patients, ductal obstruction may cause increased pressure resulting in ductal dilation, and is the assumed cause of pain. Endoscopic therapy is often offered for decompression of these strictures and removal of pancreatic duct stones when this is believed to be the cause of pain or for recurrent pancreatitis episodes (132,133). Recommendations related to advanced endoscopy are covered in a complementary NASPGHAN position statement (6).

Vascular Complications

Splenic vein thrombosis is a reported complication in about 10% to 20% of adult patients with CP and is often related to the presence of a pancreatic pseudocyst or severe acute pancreatitis, in general (132,134,135). Most patients with splenic vein thrombosis are asymptomatic but they may develop varices, which are at high risk of gastrointestinal bleeding (2). Less commonly, deep vein thrombosis and pulmonary embolism have been reported, although are more typical in acute pancreatitis. Management is usually conservative. The use of anticoagulation is not well studied in CP though no significant difference has been demonstrated in AP patients with regard to recanalization rate (136). The rates and impact of thrombotic events in children with CP has not been studied.

Gastroparesis

The frequency of gastroparesis in adult patients with CP is ~3.6% (137). It is frequently seen in patients with small duct CP and can present with similar symptoms as seen in AP. Gastroparesis may also cause confusion in diagnosis, and affect the efficacy of PERT, complicating both evaluation and treatment of CP (138). As per 1 publication, patients with abdominal pain who do not respond to PERT or express early satiety should be evaluated for gastroparesis (138). Treatment of gastroparesis is challenging in patients with CP. Management for mild cases includes dietary modifications, such as small and frequent meals and prokinetic agents such as erythromycin and metoclopramide. Severe gastroparesis may require intrapyloric botulinum toxin injections, gastrostomy feeding tube placement, or implantation of gastric electrical stimulator (137).

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is defined as excessive bacteria in the small intestine. EPI, impaired motility secondary to inflammation/narcotic use, and/or PPIs can predispose patients with CP to SIBO (132,139,140). Various adult studies have shown of the prevalence of SIBO in CP patients to be between 22% and 67% (12,139,141–145). The presentation of SIBO may mimic EPI or constipation and includes abdominal pain, bloating, diarrhea, steatorrhea, weight loss, weakness, neuropathy, and excessive flatulence (146). SIBO should be considered in patients with CP and suggestive symptoms not responsive to other therapy (140). Diagnostic modalities for SIBO for children are invasive or lacking sensitivity and specificity. As such, decision to treat has commonly been based on clinical judgement.

Pancreatic Cancer

Meta-analysis reveals a relative risk of 13.3 for the development of pancreatic cancer among adults with CP (132,147,148). The risk for the development of pancreatic cancer among children with CP is not yet known. Genetic etiologies account for the most common cause of CP among children. These are associated with a lifetime risk as high as 40% to 50% for the development of pancreatic cancer among adults, although genetic predisposition may be confounded by smoking, drinking, and other factors (137,149). More recent analysis controlling for smoking exposure showed relative risk for the development of pancreatic cancer to be ~7% with those patients with a PRSS1 mutation (150), whereas certain CFTR mutations were associated with a more modest risk (OR = 1.41) and SPINK1 mutations showing no increased association (151). Cigarette smoking, alcohol, and diabetes mellitus may further increase the risk for the development of pancreatic cancer in CP, and appropriate education must be provided (137,152).

Whether chronic/recurrent inflammation or the genetic mutations alone account for the increased risk of cancer is unknown. No reliable screening tests or screening recommendations have been developed to distinguish sub-groups of patients with CP who are at risk for developing pancreatic cancer or whether age of diagnosis impacts future risk. Recently, the intestinal microbiota or more precisely, the mycobiota have been implicated in the pathogenesis of pancreatic cancer (153). Future studies are critical to determine the impact of hereditary pancreatitis among children on long-term pancreatic cancer risk especially as it pertains to earlier surgical intervention to potentially decrease this risk.

Recommendations:

22. The majority of pancreatic fluid collections will resolve spontaneously with supportive care. Intervention is reserved for complications from mass-effect, infection/necrosis or if spontaneous regression of the collection is thought to be unlikely. (GRADE 1B)
15/15 = 100% Agreement
voting results: 10 strongly agree; 5 agree; 0 neutral; 0 disagree; 0 strongly disagree
23. Children with CP that continue to exhibit abdominal pain, bloating or other GI concerns deserve an appropriate GI workup to evaluate for other etiologies that may explain their symptoms. (GRADE: 1C)
15/15 = 100% Agreement
Voting results: 11 strongly agree; 4 agree; 0 neutral; 0 disagree; 0 strongly disagree

SUMMARY OF RECOMMENDATIONS

This report provides evidence-based guidance on the medical management of CP in children based on existing literature. Table 2 summarizes the recommendations made by the writing group. All 23 of the recommendations received at least 75% support (5 = strongly agreed or 4 = agreed). The majority of recommendations are supported by a Grade of 1B or 1C (strong recommendation but moderate to low-quality evidence with several recommendations based on expert opinion). This highlights the need for focused, high-quality studies in a number of key aspects of management for CP in children.

FUTURE DIRECTIONS

Although this report provides guidance on the medical management of CP based on existing literature, it also recognizes directions of much needed future investigation into concepts and

controversies that require further elucidation and resolution. These include but are not limited to the following:

1. Environmental factor assessments:
 - a. The effect of tobacco exposure in children with CP—primary, secondary, and tertiary.
- Evaluation of clinical tools application in CP management:
2.
 - a. pain evaluation tools;
 - b. multimodal pain management efficacy;
 - c. performance of clinical pathways on clinically relevant outcomes;
 - d. dynamic surveillance for development of EPI and for consequences.
3. Mechanisms and progression of disease
 - a. to garner a better understanding of the pathophysiology and risk factor for vascular complications associated with CP;
 - b. the impact of genetic and other risk factors (including the microbiome and mycobiome in CP need to be further explored to determine the long-term risk of cancer and other sequelae from CP.
4. Prospective controlled studies to investigate:
 - a. antioxidant use in the context of reducing inflammation and pain are indicated;
 - b. the use of PERT for pain control independent of management of EPI would help to advance our understanding of the mechanisms and management of pain;
 - c. the role of an organized lipid matrix and the efficacy of enteral in-line feeding cartridges in the management of EPI;
 - d. assessment for the consequences of EPI beyond micronutrient deficiencies, such as on bone health;
 - e. the impact of pain medications (eg, neuropathic medications) on CP should be studied through RCTs as well.
5. Assessment of changes to the natural history of chronic pancreatitis, such as to lifelong risk for pancreatic cancer.

CONCLUSIONS

Well-established pediatric consortia continue to highlight the disease burden experience by children with CP. A lack of pediatric-focused interventional studies dictates that recommendations are largely based on adult literature or expert opinion as we have reported here. This highlights the need for focused, high-quality studies in a number of key aspects of management for CP dedicated to pediatric patients.

DISCLAIMER

The NASPGHAN practice guidelines and position papers are evidence-based decision-making tools for managing health conditions. They are authorized by the NASPGHAN Executive Council, peer reviewed, and periodically updated. They are not to be construed as standards of care and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. All decisions regarding the care of a patient should be made by the health care team, patient, and family in consideration of all aspects of the individual patient's specific medical circumstances. Although NASPGHAN makes every effort to present accurate and reliable information, these guidelines are provided "as is" without any warranty of accuracy, reliability, or otherwise, either expressed or implied. NASPGHAN does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither NASPGHAN nor its officers, directors, members, employees, or

TABLE 2. Summary of recommendations

Category	Recommendation	Grade
Nutrition and endocrine	1. Patients with CP are at risk for macro- and micronutrient deficiencies. Patients should be monitored for growth and pubertal delay, dietary intake, and fat-soluble vitamin deficiencies. Growth and intake should be reviewed at every clinic visit, a minimum of every 6 to 12 months. Fat-soluble vitamin laboratory analysis should occur every 12 to 18 months or as clinically indicated	1B
	2. A multidisciplinary approach that includes a clinical pediatric dietitian is needed to adequately monitor nutritional status, evaluate nutrient intake and provide education and recommendations to help prevent both malnutrition and obesity	1C
	3. There is a clear role for PERT in children with CP who have EPI with steatorrhea, poor growth and/or nutritional deficiencies. PERT dosing for CP-associated EPI is similar to that used in patients with CF	1B
	4. Children with CP should be screened yearly for pancreatogenic DM with a fasting glucose and HbA1c level	1C
	5. Consider OGTT if pre-diabetes is present based on abnormal fasting glucose (100–125 mg/dL) and/or HbA1c level (5.7%–6.4%). OGTT should be performed annually once a patient is considered to have pre-diabetes	1C
	6. Chronic pancreatitis patients with diabetes should be referred to a pediatric endocrinologist to optimize glucose management and determine if evaluation for other forms of DM should be considered	1B
	7. It is important to address clinical symptoms of malabsorption and PERT in children with CP and DM to improve glycemic control	1C
	8. Insufficient data exists to recommend the use of antioxidants as a treatment to prevent EPI or other disease progression in children with CP	2C
Pain management	9. Treatment of pain in pediatric CP requires a multidisciplinary approach, ideally involving a pediatric pain physician, pediatric gastroenterologist, psychologist, nurse, and physical therapist	1B
	10. Cognitive behavioral Therapy (CBT) should be considered in management of pediatric CP pain	1B
	11. Physical therapy may be considered as an adjunct therapy for pain management in children with CP	2B
	12. There is insufficient data to recommend PERT as therapy for pain in children without EPI	1B
	13. There is insufficient data to recommend antioxidants, steroids, leukotriene antagonists, or somatostatins in the management of pain for children with CP	2C
	14. Analgesic pain management in CP should follow an “analgesic ladder” that incorporates the layering of non-opioid and opioid medications. Ideally this should be directed by a pain specialist working in partnership with a pancreatologist or gastroenterologist	1B
	15. Neuromodulators may be effective in treating pain in children with CP as part of a multidisciplinary approach	1C
	16. Celiac plexus block for pain has not been shown to be effective in children with CP and cannot be recommended	1C
	17. Children with CP suffering from pain refractory to standard medical management should be evaluated at a center with pediatric experience in pain management	1C
Lifestyle modifications	18. On the basis of long-term adult data, providers should caution patients about the acute and chronic negative effects of alcohol abuse on pancreatic health	1B
	19. Health-care providers should caution patients about the dose-dependent response of tobacco smoking on the development and progression of CP among adult patients and should advise against smoking	1A
	20. Data are limited regarding the impact of weight and BMI on CP outcomes, as such, providers should counsel patients and parents about a balanced healthy diet and lifestyle	1C
	21. Administering a survey tool to assess QOL and/or functional assessment among pediatric patients to assess degree of impairment and drive targeted interventions indicated	2C
Sequelae of disease	22. The majority of pancreatic fluid collections will resolve spontaneously with supportive care. Intervention is reserved for complications from mass-effect, infection/necrosis or if spontaneous regression of the collection is thought to be unlikely	1B
	23. Children with CP that continue to exhibit abdominal pain, bloating or other GI concerns deserve an appropriate GI workup to evaluate for other etiologies that may explain their symptoms	1C

CP = chronic pancreatitis; DM = diabetes mellitus; EPI = exocrine pancreatic insufficiency; GI = gastrointestinal, OGTT = oral glucose tolerance test; PERT = pancreatic enzyme replacement therapy; QOL = quality of life.

agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, nor consequential damages, incurred in connection with the guidelines or reliance on the information presented.

REFERENCES

- Oracz G, Wejnarska K, Kolodziejczyk E, et al. Pediatric acute and chronic pancreatitis: increase in incidence or increasing awareness? *Pancreas* 2017;46:e55–6.
- Morinville VD, Husain SZ, Bai H, et al., INSPPIRE Group. Definitions of pediatric pancreatitis and survey of present clinical practices. *J Pediatr Gastroenterol Nutr* 2012;55:261–5.
- Pham A, Forsmark C. Chronic pancreatitis: review and update of etiology, risk factors, and management. *F1000Res* 2018;7:F1000 Faculty Rev-607.
- Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr* 2015;166:890.e1–6.e1.
- Pohl JF, Limbers CA, Kay M, et al. Health-related quality of life in pediatric patients with long-standing pancreatitis. *J Pediatr Gastroenterol Nutr* 2012;54:657–63.
- Liu QY, Gugig R, Troendle DM, et al. The roles of EUS and ERCP in the evaluation and treatment of chronic pancreatitis in children: a position paper from the NASPGHAN Pancreas Committee. *J Pediatr Gastroenterol Nutr* 2020;70:681–93.
- Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest* 2006;129:174–81.
- Guyatt GH, Oxman AD, Vist GE, et al., GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. Washington: The National Academies Press; 2005. <http://doi.org/10.17226/10490>. Accessed June 11, 2019.
- Zello GA. Dietary Reference Intakes for the macronutrients and energy: considerations for physical activity. *Appl Physiol Nutr Metab* 2006;31:74–9.
- Abu-El-Hajja M, Uc A, Werlin SL, et al. Nutritional considerations in pediatric pancreatitis: a position paper from the NASPGHAN Pancreas Committee and ESPGHAN Cystic Fibrosis/Pancreas Working Group. *J Pediatr Gastroenterol Nutr* 2018;67:131–43.
- Buyken AE, Karaolis-Danckert N, Remer T. Association of pre-pubertal body composition in healthy girls and boys with the timing of early and late pubertal markers. *Am J Clin Nutr* 2009;89:221–30.
- Kolodziejczyk E, Wejnarska K, Dadalski M, et al. The nutritional status and factors contributing to malnutrition in children with chronic pancreatitis. *Pancreatol* 2014;14:275–9.
- Kocher HM, Kadaba R. Chronic pancreatitis. *BMJ Clin Evid* 2011;2011:0417.
- Lindkvist B, Dominguez-Munoz JE, Luaces-Regueira M, et al. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatol* 2012;12:305–10.
- Singh S, Midha S, Singh N, et al. Dietary counseling versus dietary supplements for malnutrition in chronic pancreatitis: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2008;6:353–9.
- Schwarzenberg SJ, Uc A, Zimmerman B, et al. Chronic pancreatitis: pediatric and adult cohorts show similarities in disease progress despite different risk factors. *J Pediatr Gastroenterol Nutr* 2019;68:566–73.
- Padula L, Brownell J, Reid E, et al. Clinical Pathway for Children with/ at Risk for Exocrine Pancreatic Insufficiency (EPI) Who May Need Pancreatic Enzyme Replacement Therapy (PERT). <https://www.chop.edu/clinical-pathway/initiating-pancreatic-enzyme-replacement-therapy-pert-clinical-pathway>. Published 2019. Accessed.
- Stevens J, Wyatt C, Brown P, et al. Absorption and safety with sustained use of RELIZORB Evaluation (ASSURE) Study in patients with cystic fibrosis receiving enteral feeding. *J Pediatr Gastroenterol Nutr* 2018;67:527–32.
- Glasbrenner B, Schon A, Klatt S, et al. Clinical evaluation of the faecal elastase test in the diagnosis and staging of chronic pancreatitis. *Eur J Gastroenterol Hepatol* 1996;8:1117–20.
- Puttaiah Kadyada S, Thapa BR, Kaushal K, et al. Incomplete functional and morphological recovery after acute and acute recurrent pancreatitis in children. *J Gastroenterol Hepatol* 2019;34:293–301.
- Garah J, Rosen I, Shaoul R. Transient exocrine pancreatic insufficiency in children: an existing entity? *J Pediatr Gastroenterol Nutr* 2019;68:574–7.
- Lohr JM, Panic N, Vujasinovic M, et al. The ageing pancreas: a systematic review of the evidence and analysis of the consequences. *J Intern Med* 2018;283:446–60.
- Vanga RR, Tansel A, Sidiq S, et al. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:1220.e4–8e.
- Taylor CJ, Chen K, Horvath K, et al. ESPGHAN and NASPGHAN Report on the assessment of exocrine pancreatic function and pancreatitis in children. *J Pediatr Gastroenterol Nutr* 2015;61:144–53.
- Poddar U, Yachha SK, Borkar V, et al. Clinical profile and treatment outcome of chronic pancreatitis in children: a long-term follow-up study of 156 cases. *Scand J Gastroenterol* 2017;52:773–8.
- Chowdhury SD, Chacko A, Ramakrishna BS, et al. Clinical profile and outcome of chronic pancreatitis in children. *Indian pediatrics* 2013;50:1016–9.
- Howes N, Lerch MM, Greenhalf W, et al., European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC). Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2004;2:252–61.
- Abu-El-Hajja M, Hornung L, Denson LA, et al. Prevalence of abnormal glucose metabolism in pediatric acute, acute recurrent and chronic pancreatitis. *PLoS One* 2018;13:e0204979.
- Hao L, Wang T, He L, et al. Risk factor for steatorrhea in pediatric chronic pancreatitis patients. *BMC Gastroenterol* 2018;18:182.
- Uc A, Perito ER, Pohl JF, et al. International Study Group of Pediatric Pancreatitis: In Search for a CuRE Cohort Study: Design and Rationale for INSPPIRE 2 From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas* 2018;47:1222–8.
- Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatol* 2013;13:336–42.
2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S13–28.
- Hart PA, Andersen DK, Mather KJ, et al., Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Evaluation of a mixed meal test for diagnosis and characterization of PancreaTogEniC DiabeTes secondary to pancreatic cancer and chronic pancreatitis: rationale and methodology for the DETECT Study From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas* 2018;47:1239–43.
- American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S14–31.
- Schrader H, Menge BA, Zeidler C, et al. Determinants of glucose control in patients with chronic pancreatitis. *Diabetologia* 2010;53:1062–9.
- Domschke S, Stock KP, Pichl J, et al. Beta-cell reserve capacity in chronic pancreatitis. *HepatoGastroenterology* 1985;32:27–30.
- Lundberg R, Beilman GJ, Dunn TB, et al. Early alterations in glycemic control and pancreatic endocrine function in nondiabetic patients with chronic pancreatitis. *Pancreas* 2016;45:565–71.
- Nyboe Andersen B, Krarup T, Thorsgaard Pedersen NT, et al. B cell function in patients with chronic pancreatitis and its relation to exocrine pancreatic function. *Diabetologia* 1982;23:86–9.
- Sasikala M, Talukdar R, Pavan kumar P, et al. beta-Cell dysfunction in chronic pancreatitis. *Digest Dis Sci* 2012;57:1764–72.
- Pondugala PK, Sasikala M, Guduru VR, et al. Interferon-gamma decreases nuclear localization of Pdx-1 and triggers beta-cell dysfunction in chronic pancreatitis. *J Interferon Cytokine Res* 2015;35:523–9.
- Seymour NE, Brunicaudi FC, Chaiken RL, et al. Reversal of abnormal glucose production after pancreatic resection by pancreatic polypeptide administration in man. *Surgery* 1988;104:119–29.

43. Brunnicardi FC, Chaiken RL, Ryan AS, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *The Journal of clinical endocrinology and metabolism* 1996;81:3566–72.
44. Niebisz-Cieslak AB, Karnafel W. Insulin sensitivity in chronic pancreatitis and features of insulin resistance syndrome. *Pol Arch Med Wewn* 2010;120:255–63.
45. Nosadini R, del Prato S, Tiengo A, et al. Insulin sensitivity, binding, and kinetics in pancreatogenic and type I diabetes. *Diabetes* 1982;31 (4 Pt 1):346–55.
46. Yki-Jarvinen H, Kiviluoto T, Taskinen MR. Insulin resistance is a prominent feature of patients with pancreatogenic diabetes. *Metabolism* 1986;35:718–27.
47. Knop FK, Vilsboll T, Hojberg PV, et al. The insulinotropic effect of GIP is impaired in patients with chronic pancreatitis and secondary diabetes mellitus as compared to patients with chronic pancreatitis and normal glucose tolerance. *Regul Pept* 2007;144:123–30.
48. Knop FK, Vilsboll T, Larsen S, et al. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. *Am J Physiol Endocrinol Metab* 2007;292:E324–30.
49. Hart PA, Bellin MD, Andersen DK, et al., Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer(CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol* 2016;1:226–37.
50. 13. Children and adolescents: standards of medical care in diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S148–64.
51. Crosby J, Bellin MD, Radosevich DM, et al. Gastrointestinal symptoms before and after total pancreatectomy with islet autotransplantation: the role of pancreatic enzyme dosing and adherence. *Pancreas* 2015;44:453–8.
52. Armstrong JA, Cash N, Soares PM, et al. Oxidative stress in acute pancreatitis: lost in translation? *Free Radic Res* 2013;47:917–33.
53. Grigsby B, Rodriguez-Rilo H, Khan K. Antioxidants and chronic pancreatitis: theory of oxidative stress and trials of antioxidant therapy. *Dig Dis Sci* 2012;57:835–41.
54. Di Sebastiano P, di Mola FF, Bockman DE, et al. Chronic pancreatitis: the perspective of pain generation by neuroimmune interaction. *Gut* 2003;52:907–11.
55. Drewes AM, Bouwense SAW, Campbell CM, et al., Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatol* 2017;17:720–31.
56. Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. *Clin Gastroenterol Hepatol* 2015;13:552–60.
57. Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. *Pain Rep* 2017;2:e625.
58. Miro J, McGrath PJ, Finley GA, et al. Pediatric chronic pain programs: current and ideal practice. *Pain Rep* 2017;2:e613.
59. Lioffi C, Johnstone L, Lilley S, et al. Effectiveness of interdisciplinary interventions in paediatric chronic pain management: a systematic review and subset meta-analysis. *Br J Anaesth* 2019;123:e359–71.
60. Martin SR, Zeltzer LK. Prioritizing pediatric chronic pain and comprehensive pain treatment in the context of the opioid epidemic. *Pain Manag* 2018;8:67–70.
61. Nelson S, Coakley R. The pivotal role of pediatric psychology in chronic pain: opportunities for informing and promoting new research and intervention in a shifting healthcare landscape. *Curr Pain Headache Rep* 2018;22:76.
62. Levy RL, Langer SL, Walker LS, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. *Am J Gastroenterol* 2010;105:946–56.
63. Robins PM, Smith SM, Glutting JJ, et al. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. *J Pediatr Psychol* 2005;30:397–408.
64. Youssef NN, Rosh JR, Loughran M, et al. Treatment of functional abdominal pain in childhood with cognitive behavioral strategies. *J Pediatr Gastroenterol Nutr* 2004;39:192–6.
65. Lalouni M, Ljotsson B, Bonnert M, et al. Clinical and cost effectiveness of online cognitive behavioral therapy in children with functional abdominal pain disorders. *Clin Gastroenterol Hepatol* 2019;17:2236.e11–44.e11.
66. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. *Rheumatol Int* 2017;37:29–42.
67. Owyang C, Louie DS, Tatum D. Feedback regulation of pancreatic enzyme secretion. suppression of cholecystokinin release by trypsin. *J Clin Invest* 1986;77:2042–7.
68. Olesen SS, Juel J, Graversen C, et al. Pharmacological pain management in chronic pancreatitis. *World J Gastroenterol* 2013;19:7292–301.
69. Warshaw AL, Banks PA, Fernandez-Del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. *Gastroenterology* 1998;115:765–76.
70. Yaghoobi M, McNabb-Baltar J, Bijarchi R, et al. Pancreatic enzyme supplements are not effective for relieving abdominal pain in patients with chronic pancreatitis: meta-analysis and systematic review of randomized controlled trials. *Can J Gastroenterol Hepatol* 2016;2016:8541839.
71. de la Iglesia-Garcia D, Huang W, Szatmary P, et al., NIHR Pancreas Biomedical Research Unit Patient Advisory Group. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. *Gut* 2017;66:1354–5.
72. Dziurkowska-Marek A, Marek TA, Nowak A, et al. The dynamics of the oxidant-antioxidant balance in the early phase of human acute biliary pancreatitis. *Pancreatol* 2004;4:215–22.
73. Guyan PM, Uden S, Braganza JM. Heightened free radical activity in pancreatitis. *Free Radic Biol Med* 1990;8:347–54.
74. Uden S, Schofield D, Miller PF, et al. Antioxidant therapy for recurrent pancreatitis: biochemical profiles in a placebo-controlled trial. *Aliment Pharmacol Ther* 1992;6:229–40.
75. Ahmed Ali U, Jens S, Busch OR, et al. Antioxidants for pain in chronic pancreatitis. *Cochrane Database Syst Rev* 2014:CD008945.
76. Rustagi T, Njei B. Antioxidant therapy for pain reduction in patients with chronic pancreatitis: a systematic review and meta-analysis. *Pancreas* 2015;44:812–8.
77. Dong LH, Liu ZM, Wang SJ, et al. Corticosteroid therapy for severe acute pancreatitis: a meta-analysis of randomized, controlled trials. *Int J Clin Exp Pathol* 2015;8:7654–60.
78. Giesen HJ. Cancer pain: therapy according to the pain relief ladder. *MMW Fortschr Med* 2010;152:91–395; quiz 96.
79. Kaye AD, Cornett EM, Helander E, et al. An update on nonopioids: intravenous or oral analgesics for perioperative pain management. *Anesthesiol Clin* 2017;35:e55–71.
80. Lavonas EJ, Reynolds KM, Dart RC. Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* 2010;126:e1430–44.
81. McCrae JC, Morrison EE, MacIntyre IM, et al. Long-term adverse effects of paracetamol - a review. *Br J Clin Pharmacol* 2018;84:2218–30.
82. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther* 2013;15(Suppl 3):S3.
83. Wilder-Smith CH, Hill L, Osler W, et al. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci* 1999;44:1107–16.
84. Wilson PR. Multidisciplinary management of chronic pain. A practical guide for clinicians. *Pain Med* 2016;17:1376–8.
85. Sheehy KA, Lippold C, Rice AL, et al. Subanesthetic ketamine for pain management in hospitalized children, adolescents, and young adults: a single-center cohort study. *J Pain Res* 2017;10:787–95.
86. Gurusamy KS, Lusk C, Davidson BR. Pregabalin for decreasing pancreatic pain in chronic pancreatitis. *Cochrane Db Syst Rev* 2016;2:CD011522.
87. Clarke H, Bonin RP, Orser BA, et al. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesth Analg* 2012;115:428–42.
88. Baxter KJ, Haffling J, Sterner J, et al. Effectiveness of gabapentin as a postoperative analgesic in children undergoing appendectomy. *Pediatr Surg Int* 2018;34:769–74.
89. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer

- pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009;54:2330–7.
90. Stevens T, Costanzo A, Lopez R, et al. Adding triamcinolone to endoscopic ultrasound-guided celiac plexus blockade does not reduce pain in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol* 2012;10:186–91191.e1.
 91. Abu-El-Haija M, Kumar S, Quiros JA, et al. Management of acute pancreatitis in the pediatric population: a clinical report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Pancreas Committee. *J Pediatr Gastroenterol Nutr* 2018;66:159–76.
 92. Yang H, Wang L, Shi YH, et al. Risk factors of acute pancreatitis in the elderly Chinese population: a population-based cross-sectional study. *J Dig Dis* 2014;15:501–7.
 93. Razvodovsky YE. Alcohol consumption and pancreatitis mortality in Russia. *JOP* 2014;15:365–70.
 94. Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. *JOP* 2009;10:387–92.
 95. Lankisch PG, Breuer N, Bruns A, et al. Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009;104:2797–805.
 96. Nojgaard C, Becker U, Matzen P, et al. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. *Pancreas* 2011;40:1195–200.
 97. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol* 2012;107:1096–103.
 98. Cote GA, Yadav D, Slivka A, et al., North American Pancreatitis Study Group. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. *Clin Gastroenterol Hepatol* 2011;9:266–73quiz e227.
 99. Spanier B, Bruno MJ, Dijkgraaf MG. Incidence and mortality of acute and chronic pancreatitis in the Netherlands: a nationwide record-linked cohort study for the years 1995–2005. *World J Gastroenterol* 2013;19:3018–26.
 100. Dominguez-Munoz JE, Lucendo A, Carballo LF, et al. A Spanish multicenter study to estimate the prevalence and incidence of chronic pancreatitis and its complications. *Rev Esp Enferm Dig* 2014;106:239–45.
 101. Kumar S, Ooi CY, Werlin S, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. *JAMA Pediatr* 2016;170:562–9.
 102. Zhang GW, Lin JH, Qian JP, et al. Analysis of risk factors for pancreatic duct stones formation in patients with alcoholic chronic pancreatitis. *Pancreatol* 2014;14:109–13.
 103. Pandolfi SJ, Lugea A, Mareninova OA, et al. Investigating the pathobiology of alcoholic pancreatitis. *Alcohol Clin Exp Res* 2011;35:830–7.
 104. Greer JB, Thrower E, Yadav D. Epidemiologic and mechanistic associations between smoking and pancreatitis. *Curr Treat Options Gastroenterol* 2015;13:332–46.
 105. Rebours V, Vullierme MP, Hentic O, et al. Smoking and the course of recurrent acute and chronic alcoholic pancreatitis: a dose-dependent relationship. *Pancreas* 2012;41:1219–24.
 106. Yadav D, Hawes RH, Brand RE, et al., North American Pancreatic Study Group. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 2009;169:1035–45.
 107. Maisonneuve P, Frulloni L, Mullhaupt B, et al. Impact of smoking on patients with idiopathic chronic pancreatitis. *Pancreas* 2006;33:163–8.
 108. Lee JW, Kim HG, Lee DW, et al. Association between smoking and the progression of computed tomography findings in chronic pancreatitis. *Gut Liver* 2016;10:464–9.
 109. Ballengee CR, Brooks P, Leong T, et al. Effects of second-hand smoke on pancreatitis in children. *Pancreas* 2019;48:706–10.
 110. Cullen KA, Ambrose BK, Gentzke AS, et al. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students - United States, 2011–2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1276–7.
 111. Tsai CJ. Is obesity a significant prognostic factor in acute pancreatitis? *Dig Dis Sci* 1998;43:2251–4.
 112. Papachristou GI, Papachristou DJ, Avula H, et al. Obesity increases the severity of acute pancreatitis: performance of APACHE-O score and correlation with the inflammatory response. *Pancreatol* 2006;6:279–85.
 113. Premkumar R, Phillips AR, Petrov MS, et al. The clinical relevance of obesity in acute pancreatitis: targeted systematic reviews. *Pancreatol* 2015;15:25–33.
 114. Navina S, Acharya C, DeLany JP, et al. Lipotoxicity causes multi-system organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med* 2011;3:107ra110.
 115. Shin KY, Lee WS, Chung DW, et al. Influence of obesity on the severity and clinical outcome of acute pancreatitis. *Gut Liver* 2011;5:335–9.
 116. Martinez J, Johnson CD, Sanchez-Paya J, et al. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatol* 2006;6:206–9.
 117. Martinez J, Sanchez-Paya J, Palazon JM, et al. Obesity: a prognostic factor of severity in acute pancreatitis. *Pancreas* 1999;19:15–20.
 118. Uc A, Zimmerman MB, Wilschanski M, et al. Impact of obesity on pediatric acute recurrent and chronic pancreatitis. *Pancreas* 2018;47:967–73.
 119. Tirkes T, Jeon CY, Li L, et al. Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus. *Pancreas* 2019;48:420–6.
 120. Ammann RW, Raimondi S, Maisonneuve P, et al. Is obesity an additional risk factor for alcoholic chronic pancreatitis? *Pancreatol* 2010;10:47–53.
 121. Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis. *Clin Gastroenterol Hepatol* 2011;9:793–9.
 122. Wassef W, DeWitt J, McGreevy K, et al. Pancreatitis quality of life instrument: a psychometric evaluation. *Am J Gastroenterol* 2016;111:1177–86.
 123. Dominguez-Munoz JE, Drewes AM, Lindkvist B, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. *Pancreatol* 2018;18:847–54.
 124. Banks PA, Bollen TL, Dervenis C, et al., Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
 125. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2012;44:784–800.
 126. Wang W, Liao Z, Li ZS, et al. Chronic pancreatitis in Chinese children: etiology, clinical presentation and imaging diagnosis. *J Gastroenterol Hepatol* 2009;24:1862–8.
 127. Andren-Sandberg A, Dervenis C. Pancreatic pseudocysts in the 21st century. Part I: classification, pathophysiology, anatomic considerations and treatment. *JOP* 2004;5:8–24.
 128. Hao L, Pan J, Wang D, et al. Risk factors and nomogram for pancreatic pseudocysts in chronic pancreatitis: a cohort of 1998 patients. *J Gastroenterol Hepatol* 2017;32:1403–11.
 129. Lerch MM, Stier A, Wahnschaffe U, et al. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? *Dtsch Arztebl Int* 2009;106:614–21.
 130. Dalsania R, Willingham FF. Treatment of walled-off pancreatic necrosis. *Curr Opin Gastroenterol* 2019;35:478–82.
 131. Adler JM, Gardner TB. Endoscopic therapies for chronic pancreatitis. *Dig Dis Sci* 2017;62:1729–37.
 132. Rosch T, Daniel S, Scholz M, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. *Endoscopy* 2002;34:765–71.
 133. Kleeff J, Whitcomb DC, Shimosegawa T, et al. Chronic pancreatitis. *Nat Rev Dis Primers* 2017;3:17060.
 134. Agarwal AK, Raj Kumar K, Agarwal S, et al. Significance of splenic vein thrombosis in chronic pancreatitis. *Am J Surg* 2008;196:149–54.
 135. Bernades P, Baetz A, Levy P, et al. Splenic and portal venous obstruction in chronic pancreatitis. A prospective longitudinal study of a medical- surgical series of 266 patients. *Dig Dis Sci* 1992;37:340–6.

136. Harris S, Nadkarni NA, Naina HV, et al. Splanchnic vein thrombosis in acute pancreatitis: a single-center experience. *Pancreas* 2013;42:1251–4.
137. Nassar Y, Richter S. Gastroparesis in non-diabetics: associated conditions and possible risk factors. *Gastroenterol Res* 2018;11:340–5.
138. Chowdhury RS, Forsmark CE, Davis RH, et al. Prevalence of gastroparesis in patients with small duct chronic pancreatitis. *Pancreas* 2003;26:235–8.
139. Capurso G, Signoretti M, Archibugi L, et al. Systematic review and meta-analysis: small intestinal bacterial overgrowth in chronic pancreatitis. *United European Gastroenterol J* 2016;4:697–705.
140. Ni Chonchubhair HM, Bashir Y, Dobson M, et al. The prevalence of small intestinal bacterial overgrowth in non-surgical patients with chronic pancreatitis and pancreatic exocrine insufficiency (PEI). *Pancreatology* 2018;18:379–85.
141. Choung RS, Ruff KC, Malhotra A, et al. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. *Aliment Pharmacol Ther* 2011;33:1059–67.
142. Gubergrits NB, Linevskiy YV, Lukashevich GM, et al. Morphological and functional alterations of small intestine in chronic pancreatitis. *JOP: Journal of the pancreas* 2012;13:519–28.
143. Casellas F, Guarner L, Vaquero E, et al. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. *Pancreas* 1998;16:481–6.
144. Trespi E, Ferrieri A. Intestinal bacterial overgrowth during chronic pancreatitis. *Curr Med Res Opin* 1999;15:47–52.
145. Lembcke B, Kraus B, Lankisch PG. Small intestinal function in chronic relapsing pancreatitis. *Hepatogastroenterology* 1985;32:149–51.
146. Singh VV, Toskes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. *Curr Treat Options Gastroenterol* 2004;7:19–28.
147. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:2964–70.
148. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010;24:349–58.
149. Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology* 2019;156:1969–78.
150. Shelton CA, Umaphathy C, Stello K, et al. Hereditary pancreatitis in the United States: survival and rates of pancreatic cancer. *Am J Gastroenterol* 2018;113:1376.
151. Cazacu IM, Farkas N, Garami A, et al. Pancreatitis-associated genes and pancreatic cancer risk: a systematic review and meta-analysis. *Pancreas* 2018;47:1078–86.
152. Ramsey ML, Conwell DL, Hart PA. Complications of chronic pancreatitis. *Dig Dis Sci* 2017;62:1745–50.
153. Aykut B, Pushalkar S, Chen R, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature* 2019;574:264–7.