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Insights in pediatric pancreatology 2022

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Insights in pediatric pancreatology 2022

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MINI REVIEW
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Pancreatogenic Diabetes in Children With Recurrent Acute and Chronic Pancreatitis: Risks, Screening, and Treatment (Mini-Review)

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Up to 9% of children with acute recurrent pancreatitis (ARP) or chronic pancreatitis have pancreatogenic diabetes mellitus (DM), and this risk likely increases as they age into adulthood. Risk factors for pancreatogenic DM in children vary depending on the clinical cohort but may include pancreatic atrophy, exocrine insufficiency, pancreatic calcifications, obesity/metabolic syndrome features, or autoimmune diseases. Knowledge regarding disease pathology is extrapolated nearly entirely from studies in adults. Insulin deficiency is the primary defect, resulting from islet loss associated with pancreatic fibrosis and cytokine-mediated β-cell dysfunction. Beta cell autoimmunity (type 1 diabetes) should also be considered as markers for this have been identified in a small subset of children with pancreatogenic DM. Hepatic insulin resistance, a deficient pancreatic polypeptide state, and dysfunctional incretin hormone response to a meal are all potential contributors in adults with pancreatogenic DM but their significance in pediatrics is yet unknown. Current guidelines recommend yearly screening for diabetes with fasting glucose and hemoglobin A1c (HbA1c). Insulin in the first-line pharmacologic therapy for treatment of pancreatogenic DM in children. Involvement of a multidisciplinary team including a pediatric endocrinologist, gastroenterologist, and dietitian are important, and nutritional health and exocrine insufficiency must also be addressed for optimal DM management.

Keywords: DM, T3cD, islet, endocrine, exocrine, pancreatic, insulin

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INTRODUCTION

While rare in childhood, acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are associated with high disease morbidity. Affected children most often present with severe episodic or persistent abdominal pain (1, 2). As the disease progresses, however, these children are at risk for pancreatic dysfunction, namely pancreatic exocrine insufficiency and pancreatogenic diabetes mellitus (DM) (3). Pancreatogenic DM is broadly defined as diabetes resulting from a primary exocrine disease of the pancreas, and includes diabetes that occurs secondary to acute or chronic pancreatitis. There are various synonyms used for this condition in the literature, including type 3c diabetes, pancreatogenous diabetes, or pancreatic diabetes (4). This mini-review will highlight the current knowledge on the potential mechanisms driving pancreatogenic DM, and screening and treatment guidelines for children with ARP and CP who may be at risk (**Table 1**).

TABLE 1 | Summary of the potential risk factors for and pathophysiology of pancreatogenic DM in children with ARP and CP, and screening and treatment recommendations, limited by a small number of studies in children to date.

Potential risk factors	Pathophysiology (suspected)	Screening	Treatment
• Exocrine insufficiency	• Insulin deficiency ± ? (unclear role of)	• Yearly HbA1c and fasting glucose	• Insulin
• Pancreatic atrophy	• *Insulin resistance*	• OGTT as indicated	• Multi-disciplinary team
• Obesity/metabolic syndrome	• *PP deficiency*	• MMTT (research or serial assessments)	• Nutritional management including PERT if indicated
• Pancreatic calcifications	• *Incretin dysfunction*		
• Autoimmune diseases	• β-*cell autoimmunity*		

PREVALENCE OF PANCREATOGENIC DIABETES IN CHILDREN

About 4–9% of children with ARP and CP have pancreatogenic diabetes (1, 3, 5–7). This is much higher than the prevalence of diabetes in the general pediatric population with only around 0.25% of children having any form of diabetes (8). However, considering the rarity of pediatric ARP and CP, probably affecting no more than ∼0.1% of children, pediatric pancreatogenic DM is rare (9). In contrast, in adults with CP, 25–80% have diabetes, with duration of disease, pancreatic surgical history, pancreatic calcifications, and comorbid exocrine insufficiency all impacting risk (4, 10–12). This difference in prevalence between children and adults likely represents the natural progression of pancreatitis, in that the pancreatic parenchyma becomes more damaged with a longer duration of disease, as well as the higher risk in general for diabetes with aging. In hereditary forms of CP, DM prevalence increases steadily with age; available natural history studies suggest at least 60–70% of those with hereditary pancreatitis will develop pancreatogenic diabetes in their lifetime, with a median age of onset around 50 years (13). In addition, adults are at higher risk for type 2 DM and may have an overlap of type 2 DM and pancreatogenic DM (8). Thus, in evaluating children with pancreatitis one must consider the current and future risk for pancreatogenic DM.

In children, pancreatogenic DM risk may be elevated when pancreatic exocrine insufficiency, obesity, or pancreatic atrophy are also present, and at an older age (3, 5, 6). Pancreatic calcifications may also be a risk factor but this has not been consistently shown in children, probably due to the low frequency of advanced calcific disease compared to the adult population (3). Total pancreatectomy with islet autotransplantation (TPIAT) is gaining traction in the U.S. as a treatment for severe forms of hereditary pancreatitis. Because of the resection of the pancreas and islet loss, TPIAT is associated with a high rate of post-surgical insulin dependent diabetes (14). This select group of children undergoing TPIAT for intractable ARP or CP has been specifically excluded when calculating the 4–9% prevalence of pancreatogenic DM in children.

MECHANISMS OF PANCREATOGENIC DIABETES (STUDIES FROM ADULTS)

Insulin Secretion

Current research into the pathophysiology underling pancreatogenic DM has been limited largely to research enrolling adult participants or using adult tissue samples. The primary defect is inadequate insulin secretion from both irreversible islet loss and beta cell dysfunction. Histopathology studies of pancreas tissue in adults with CP demonstrate reduced beta cell area in CP with DM (15). Likewise, stimulatory tests of insulin secretion show reduced insulin secretion compared to healthy controls, and a correlation between reduced islet and reduced exocrine function, supporting the concept that insulin secretory defects occur because of scarring through the exocrine pancreas that incidentally damages the islet tissue (16, 17). Reduced first phase and post-meal insulin secretion is apparent even prior to frank onset of pancreatogenic DM (18). Late in the course of disease, after insulin deficient pancreatogenic DM develops, glucagon secretion from α cells is also reduced, again attributed to an overall islet loss (19). This lack of glucagon production is important clinically, since it may predispose patients to a higher risk for hypoglycemia.

More recently, it has been suggested that beta cell function may be impaired from intrapancreatic inflammation even prior to islet loss. Tissues resected from surgical patients with CP with or without pancreatogenic DM showed elevated pancreatic cytokines in both groups including greatly elevated IL-1β, IL-6, IL-8, TNFα, IL-10, and INFγ compared to healthy control pancreas tissue. Notably, INFγ was significantly higher in the CP- pancreatogenic DM group versus CP without diabetes (20). These observations have led to the hypothesis that β-cell dysfunction may occur from inflammation even before frank loss of islet tissue.

The classic paradigm has been that insulin deficiency results from non-specific pancreatic damage and inflammation, that is the islets are simply an "innocent bystander" that are not directly targeted. However, in the INSPPIRE study, around one quarter of the children with pancreatogenic DM also were reported to have islet autoantibodies and pancreatogenic DM was higher in children with other autoimmunity, raising some speculation for a sub-population of children who develop type 1 DM—an autoimmune attack directed at the β-cells—in the setting of CP or ARP (3). β-cell autoantibodies and insulitis have been incidentally reported in some children with CP undergoing TPIAT (**Figure 1**), and adults in the North American Pancreatitis-2 (NAPS2) study with CP or ARP and pancreatogenic DM had a 10% risk of islet autoantibody positivity, even after excluding insulin autoantibodies (which can be falsely positive with insulin treatment) from the analysis (21, 22). Thus, whether a small portion of children may have autoimmune islet loss in pancreatogenic DM needs additional investigation.

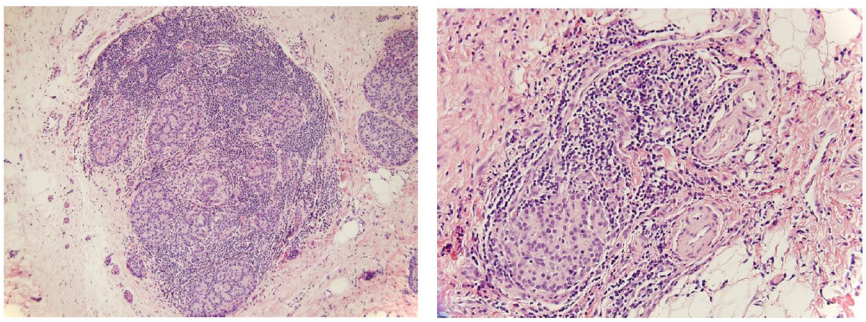

FIGURE 1 | Example of the insulitis characteristic of type 1 diabetes in a patient with chronic pancreatitis. Lymphocytic inflammation surrounds and infiltrates the islet tissue while the exocrine tissue is largely fibrotic from CP.

Insulin Sensitivity

Beta cell function is comprised of both insulin secretion and insulin sensitivity. Individuals who are insulin resistant must secrete more insulin to overcome the impaired insulin responsiveness, and if unable to do so, DM may result (23). In adults with CP in the NAPS-2 cohort, in addition to canonical pancreatitis risk factors, obesity and a family history of DM—classic type 2 DM risk factors—increased the risk for pancreatogenic DM (11). Genetic risk scores for diabetes in pancreatogenic DM also resemble that seen in type 2 diabetes (24). There are conflicting data on measures of peripheral insulin sensitivity, but data from euglycemic clamp techniques differentiating peripheral and hepatic insulin sensitivity suggest specific hepatic insulin resistance may contribute to diabetes pathology, at least in adult studies mostly comprised of men with alcohol-mediated pancreatitis (25, 26). Visceral adiposity has also been shown to be higher in adults with CP who have pancreatogenic DM when compared to their non-diabetic counterparts (27).

Insulin resistance and metabolic syndrome risks have not been directly studied in children, but the children with pancreatogenic DM in INSPPIRE were more likely to also have hypertriglyceridemia (3).

Other Hormones Including Incretins and Pancreatic Polypeptide

Available data from small cross-sectional studies suggest that pancreatic polypeptide (PP) produced and secreted by the PP-cells of the islets is deficient in pancreatogenic DM and may serve as a biomarker in differentiating pancreatogenic DM from type 2 DM (28–30). It has also been proposed that the PP deficiency itself may contribute to the hepatic insulin resistance, as infusion of PP in one small series improved hepatic insulin sensitivity (25). However, the role of PP requires further ongoing study, especially in children.

The incretin hormones glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released by the enteroendocrine cells of the gut and play an important role in glucose homeostasis by augmenting insulin secretion in response to oral nutrient ingestion. GLP-1 and GIP are reduced in CP, presumably due to exocrine insufficiency and malabsorption impairing the usual enteroendocrine response (31, 32). Administration of pancreatic enzyme replacement therapy can improve GLP-1 and GIP levels and increase insulin secretion in CP, but whether this results in improved glycemia is unclear (32). To date the role of PP and incretins as biomarkers or drivers of pancreatogenic DM in children have not been studied.

SCREENING FOR DIABETES IN CHILDREN WITH A HISTORY OF PANCREATITIS

Children diagnosed with ARP and CP should be screened yearly for diabetes given the known high risk in this population. This can be done easily in the clinic with fasting glucose and HbA1c on a yearly basis (33, 34). In cases of pre-DM or high suspicion for pancreatogenic DM, a 2 h oral glucose tolerance test (OGTT) may be considered to detect early DM with better sensitivity. Mixed meal tolerance tests (MMTT) may also be obtained as a more physiologic measure of islet function and glycemia, and are particularly useful in the research setting or for trends over time. However, MMTT lacks the diagnostic cut-offs for pre-DM and DM that have been established for OGTT so are less desirable as a screening tool for DM (34).

The diagnosis of pancreatogenic DM should be made according to standard American Diabetes Association criteria. By ADA criteria, diabetes is diagnosed when two tests on the same or separate mornings are in the abnormal DM range: HbA1c $\geq$ 6.5%, fasting glucose $\geq$ 126 mg/dL, or 2 h OGTT glucose $\geq$ 200 mg/dL. A random glucose $\geq$ 200 mg/dL with classic symptoms of DM is also considered diagnostic (35). Islet autoantibody panels (including insulin autoantibodies, glutamic acid decarboxylase, IA-2, or zinc transporter-8 antibodies) should be considered, especially with symptomatic blood glucose $\geq$ 200 mg/dL. Pre-DM is diagnosed by HbA1c 5.7–6.49% or fasting glucose 100–125 mg/dL, or 2 h OGTT glucose 140–199 mg/dL (35). The risk for progressing from pre-DM to pancreatogenic DM in children with CP or ARP is unknown.

TREATMENT AND SPECIAL CONSIDERATIONS

First-line pharmacologic treatment of pancreatogenic DM in children is typically with insulin therapy. In the INSPPIRE cohort, insulin was the most common treatment (used in 20/24 cases) (3). Insulin addresses the main physiologic defect which is insulin deficiency, and may be administered by subcutaneous injections of basal and/or bolus insulin therapy, or by continuous subcutaneous infusion using an insulin pump. While traditional glucometers remain an acceptable option for blood glucose monitoring, continuous glucose monitors are now preferred for better monitoring and safety in children treated with rapid-acting insulin (35).

Metformin may be considered when features of insulin resistance are present, including obesity, acanthosis nigricans or a strong family history of T2DM (36). Although GLP-1 agonists are now approved for pediatric use in type 2 DM and obesity, this class of medications has not been studied for pancreatogenic DM in adults or children. There is a possible, but controversial, increased risk of pancreatitis (and pancreatic cancer) with GLP-1 agonists which raise a serious safety concern for their use in children who already have ARP or CP (37). Aside from the debated pancreatitis risk, nausea and delayed gastric emptying are common and well-known side effects and thus the tolerability of this class of medications would likely be poor in children with pancreatogenic DM (37). For these reasons, current care guidelines for children and adults with pancreatogenic DM have recommended against their use. Other non-insulin medications are not approved by the FDA for use in children.

A pediatric endocrinologist, diabetes educator, pediatric gastroenterologist, and pediatric dietitian should all be part of the care team for children with pancreatogenic DM. Maintaining a normal body weight, avoiding both underweight and overweight status, should be a target of nutritional management. Co-morbid exocrine insufficiency or malabsorption must be appropriately addressed with pancreatic enzyme replacement therapy. Adherence and adequacy of dosing should be assessed at clinic visits. Because insulin therapy is often dosed based on meal intake (an insulin to carbohydrate ratio), malabsorption could lead to glycemic variability, with inconsistent insulin responses to meal dosed insulin and more hyper- or hypoglycemia episodes (38).

DISCUSSION, CONCLUSION, AND FUTURE DIRECTIONS

In summary, children with ARP and CP should be considered high risk for developing DM. Pancreatogenic DM has an overall prevalence of 4–9% in children with ARP and CP, although the risk will be even higher after pancreatectomy procedures including TPIAT. Pancreatogenic DM results primarily from insulin deficiency, as islets are lost from progressive fibrotic damage to the pancreas and/or are impaired by intrapancreatic inflammation, with a speculative role for directed β cell autoimmunity in a small subset. However, there may be an important contributing role of insulin resistance or dysfunction of associated hormones including PP, GLP1, or GIP. Importantly, nearly all mechanistic studies have been performed to date in adult patients, and thus our direct data regarding pathophysiology of disease in children are limited. Prospectively designed studies are needed in children with ARP and CP.

Children with ARP and CP need to be screened annually for DM and this is easily done by fasting glucose and HbA1c levels. Potential type 1 or type 2 DM should still be considered when assessing the child with pancreatitis who presents with new onset DM. First-line treatment is typically with insulin therapy to address the primary physiologic defect, but clinical trials of diabetes treatment in this unique group are lacking. Other CP factors including pancreatic exocrine insufficiency and nutritional limitations must be considered and addressed by a multi-disciplinary team as part of the management of the child with pancreatogenic DM.

AUTHOR CONTRIBUTIONS

MB drafted the manuscript.

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REFERENCES

1. Perito E, Gonska T, Bellin MD, Schwarzenberg SJ. Complications of chronic pancreatitis in children. *Curr Opin Gastroenterol.* (2021) 37:498–503.
2. Uc A, Andersen DK, Apkarian AV, Bellin MD, Colloca L, Drewes AM, et al. Pancreatic pain-knowledge gaps and research opportunities in children and adults: summary of a National institute of diabetes and digestive and kidney diseases workshop. *Pancreas.* (2021) 50:906–15. doi: 10.1097/MPA.0000000000001899
3. Bellin MD, Lowe M, Zimmerman MB, Wilschanski M, Werlin S, Troendle DM, et al. Diabetes mellitus in children with acute recurrent and chronic pancreatitis: data From the INternational study group of pediatric pancreatitis: in search for a CuRE cohort. *J Pediatr Gastroenterol Nutr.* (2019) 69:599–606. doi: 10.1097/MPG.0000000000002482
4. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol.* (2016) 1:226–37. doi: 10.1016/S2468-1253(16)30106-6
5. Abu-El-Haija M, Hornung L, Denson LA, Husami A, Lin TK, Matlock K, et al. Prevalence of abnormal glucose metabolism in pediatric acute, acute recurrent and chronic pancreatitis. *PLoS One.* (2018) 13:e0204979. doi: 10.1371/journal.pone.0204979
6. Chowdhury SD, Chacko A, Ramakrishna BS, Dutta AK, Augustine J, Koshy AK, et al. Clinical profile and outcome of chronic pancreatitis in children. *Indian Pediatr.* (2013) 50:1016–9. doi: 10.1007/s13312-013-0281-z
7. Schwarzenberg SJ, Uc A, Zimmerman B, Wilschanski M, Wilcox CM, Whitcomb DC, 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. doi: 10.1097/MPG.0000000000002279
8. Centers for Disease Control and Prevention [CDC]. *Diabetes Report Card 2019*. Atlanta, GA: Centers for Disease Control and Prevention (2020). Available from: https://www.cdc.gov/diabetes/library/reports/reportcard/diabetes-in-youth.html
9. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, et al. Nationwide trends in acute and chronic pancreatitis among privately insured children and non-elderly adults in the United States, 2007-2014. *Gastroenterology.* (2018) 155:469–78.e1. doi: 10.1053/j.gastro.2018.04.013
10. Malka D, Hammel P, Sauvanet A, Rufat P, O'Toole D, Bardet P, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology.* (2000) 119:1324–32. doi: 10.1053/gast.2000.19286
11. Bellin MD, Whitcomb DC, Abberbock J, Sherman S, Sandhu BS, Gardner TB, et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. *Am J Gastroenterol.* (2017) 112:1457–65. doi: 10.1038/ajg.2017.181
12. Elliott IA, Epelboym I, Winner M, Allendorf JD, Haigh PI. Population-level incidence and predictors of surgically induced diabetes and exocrine insufficiency after partial pancreatic resection. *Perm J.* (2017) 21:16–095. doi: 10.7812/TPP/16-095
13. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol.* (2004) 2:252–61. doi: 10.1016/s1542-3565(04)00013-8
14. Bellin MD, Schwarzenberg SJ, Cook M, Sutherland DE, Chinnakotla S. Pediatric autologous islet transplantation. *Curr Diabetes Rep.* (2015) 15:67. doi: 10.1007/s11892-015-0639-9
15. Schrader H, Menge BA, Zeidler C, Ritter PR, Tannapfel A, Uhl W, et al. Determinants of glucose control in patients with chronic pancreatitis. *Diabetologia.* (2010) 53:1062–9. doi: 10.1007/s00125-010-1705-0
16. Nyboe Andersen B, Krarup T, Thorsgaard Pedersen NT, Faber OK, Hagen C, Worning H. B cell function in patients with chronic pancreatitis and its relation to exocrine pancreatic function. *Diabetologia.* (1982) 23:86–9. doi: 10.1007/BF01271165
17. Larsen S, Hilsted J, Tronier B, Worning H. Pancreatic hormone secretion in chronic pancreatitis without residual beta-cell function. *Acta Endocrinol.* (1988) 118:357–64. doi: 10.1530/acta.0.1180357
18. Lundberg R, Beilman GJ, Dunn TB, Pruett TL, Freeman ML, Ptacek PE, et al. Early alterations in glycemic control and pancreatic endocrine function in nondiabetic patients with chronic pancreatitis. *Pancreas.* (2016) 45:565–71. doi: 10.1097/MPA.0000000000000491
19. Donowitz M, Hendler R, Spiro HM, Binder HJ, Felig P. Glucagon secretion in acute and chronic pancreatitis. *Ann Intern Med.* (1975) 83:778–81. doi: 10.7326/0003-4819-83-6-778
20. Pavan Kumar P, Radhika G, Rao GV, Pradeep R, Subramanyam C, Talukdar R, et al. Interferon γ and glycemic status in diabetes associated with chronic pancreatitis. *Pancreatology.* (2012) 12:65–70. doi: 10.1016/j.pan.2011.12.005
21. Kharoud HK, Mettler T, Freeman ML, Trikudanathan G, Beilman GJ, Chinnakotla S, et al. Type 1 diabetes mellitus in patients with recurrent acute and chronic pancreatitis: a case series. *Pancreatology.* (2021) 21:95–7. doi: 10.1016/j.pan.2020.12.006
22. Yadav D, Whitcomb DC, Tang G, Slivka A, Bellin M. Autoimmunity may explain diabetes in a subset of patients with recurrent acute and chronic pancreatitis: a pilot study. *Clin Gastroenterol Hepatol.* (2021). [Online ahead of print]. doi: 10.1016/j.cgh.2021.11.011
23. Faerch K, Brøns C, Alibegovic AC, Vaag A. The disposition index: adjustment for peripheral vs. hepatic insulin sensitivity?. *J Physiol.* (2010) 588:759–64. doi: 10.1113/jphysiol.2009.184028
24. Goodarzi MO, Nagpal T, Greer P, Cui J, Chen YI, Guo X, et al. Genetic risk score in diabetes associated with chronic pancreatitis versus type 2 diabetes mellitus. *Clin Transl Gastroenterol.* (2019) 10:e00057. doi: 10.14309/ctg.0000000000000057
25. Brunicardi FC, Chaiken RL, Ryan AS, Seymour NE, Hoffmann JA, Lebovitz HE, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *J Clin Endocrinol Metab.* (1996) 81:3566–72. doi: 10.1210/jcem.81.10.8855802
26. Yki-Järvinen H, Kiviluoto T, Taskinen MR. Insulin resistance is a prominent feature of patients with pancreatogenic diabetes. *Metabolism.* (1986) 35:718–27. doi: 10.1016/0026-0495(86)90239-8
27. Kumar K, Sharma R, Manrai M, Sood AK. Visceral adipose tissue as a risk factor for diabetes mellitus in patients with chronic pancreatitis: a cross-sectional, observational study. *Diabetes Ther.* (2017) 8:1057–64. doi: 10.1007/s13300-017-0304-1
28. Aslam M, Vijayasarathy K, Talukdar R, Sasikala M, Nageshwar Reddy D. Reduced pancreatic polypeptide response is associated with early alteration of glycemic control in chronic pancreatitis. *Diabetes Res Clin Pract.* (2020) 160:107993. doi: 10.1016/j.diabres.2019.107993
29. Qi L, Wei Q, Ni M, Liu D, Bao J, Lv Y, et al. Pancreatic and gut hormone responses to mixed meal test in post-chronic pancreatitis diabetes mellitus. *Diabetes Metab.* (2021) 48:101316. doi: 10.1016/j.diabet.2021.101316
30. Hart PA, Andersen DK, Mather KJ, Castonguay AC, Bajaj M, Bellin MD, et al. 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. doi: 10.1097/mpa.0000000000001168
31. Knop FK. Incretin hormones and beta cell function in chronic pancreatitis. *Dan Med Bull.* (2010) 57:B4163.
32. Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, Holst JJ, 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. doi: 10.1016/j.regpep.2007.07.002
33. Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology.* (2014) 14:27–35. doi: 10.1016/j.pan.2013.10.009
34. Freeman AJ, Maqbool A, Bellin MD, Goldschneider KR, Grover AS, Hartzell C, et al. Medical management of chronic pancreatitis in children: a position paper by the North American Society for pediatric gastroenterology, hepatology, and nutrition pancreas committee. *J Pediatr Gastroenterol Nutr.* (2021) 72:324–40. doi: 10.1097/MPG.0000000000003001
35. Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care.* (2022) 45:S17–38. doi: 10.2337/dc22-S002
36. Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology.* (2013) 13:336–42. doi: 10.1016/j.pan.2013.05.002
37. Consoli A, Formoso G. Potential side effects to GLP-1 agonists: understanding their safety and tolerability. *Expert Opin Drug Saf.* (2015) 14:207–18. doi: 10.1517/14740338.2015.987122
38. Crosby J, Bellin MD, Radosevich DM, Chinnakotla S, Dunn TB, Pruett TL, 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. doi: 10.1097/MPA.0000000000000266

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OPINION
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Endoscopic Advancements in Pediatric Pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) in children occurs with an estimated annual incidence of 3–13/100,000 (1, 2). While some children may have a single episode, others may develop acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP). Children with pancreatic disease can have impacted quality of life due to chronic pain, frequent hospitalizations, and/or nutritional deficiencies. Supportive management is typically indicated for patients with acute pancreatitis, while in some circumstances endoscopic diagnostic evaluation and/or therapy are required. Endoscopy can also be beneficial in patients with ARP or CP (3).

Historically, interventional endoscopy procedures which can benefit patients with pancreatitis, such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS), have been performed by adult gastroenterologists with advanced endoscopic training. Adult physicians certainly have adequate training to perform the procedures, but they often lack formal training in caring for pediatric patients or pediatric pancreatitis. Many are employed in facilities that care exclusively for adult patients and either travel to pediatric institutions to perform procedures in an unfamiliar setting or perform procedures for pediatric patients in adult facilities. This approach, when executed well, can be very successful and provide excellent patient care. However, issues can arise utilizing this model due to limited physician availability, timeliness of care and procedures, and challenges in communication amongst pediatric providers, adult proceduralists and families. In an ideal setting, children should be treated at a center with dedicated pediatric nursing staff, anesthesia, behavioral and child life specialists, and pediatric surgical and intensive care expertise if needed (4).

Over the last 10–15 years, pediatric gastroenterologists have increasingly pursued training in interventional endoscopy. Pediatric ERCP, EUS, and other advanced endoscopic procedures are now performed safely and effectively in specialized centers by pediatric providers worldwide (5–7). New training opportunities for pediatric gastroenterologists in interventional endoscopy continue to arise (8). In conjunction with advancements in interventional endoscopy, the field of pediatric pancreatology continues to evolve through increased recognition of AP and CP and collaborative approaches to research (9–11). It is increasingly important that providers managing children with pancreatitis are aware of the indications for endoscopic evaluations and interventions for pancreatitis, the benefits and risks involved, and when endoscopic therapy is no longer warranted (3).

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasonography allows for highly detailed transgastric and transduodenal sonographic images of the pancreas and peripancreatic anatomy through an echoendoscope and can be safely and effectively performed in children (3, 6, 12, 13). EUS has been established in adults since the 1980s and is sensitive for evaluating changes in the pancreas that reflect CP, including specific

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parenchymal and ductal changes. While traditional cross-sectional imaging often reflects late irreversible changes to the pancreas, EUS can allow the detection of early changes or minimal change CP before irreversible changes occur (14). EUS has been shown to outperform cross-sectional imaging [magnetic resonance imaging (MRI) and computed tomography (CT)] for the detection of CP with a sensitivity of 81% and specificity of 90% (15). To maximize the success of interventions aimed at slowing or stopping disease progression and ameliorating the deleterious downstream effects of pancreatic insufficiency, techniques to identify the early stages of chronic pancreatic disease are imperative.

In adult patients, Rosemont or conventional criteria are used to assess CP parenchymal or ductal changes (14, 16–18). These guidelines are utilized but not accepted universally in adults, with poor reliability amongst different observers (17). These established criteria can be utilized as a guide in assessing the pediatric pancreas *via* EUS, however results in pediatric patients must be interpreted with caution as there is no data to validate its use in children (14, 16, 19).

Endoscopic ultrasonography can also be used in patients with idiopathic ARP or CP, investigating for ductal or anatomic abnormalities not fully delineated by magnetic resonance cholangiopancreatography (MRCP), or even biliary microlithiasis. EUS identifies an etiology in up to 75% of patients with idiopathic ARP (20). More recent innovations in EUS diagnostic imaging include the use of real-time shear wave elastography. EUS elastography allows an indirect assessment of tissue rigidity and may predict pancreatic fibrosis or pancreatic exocrine insufficiency (21, 22). Contrast-enhanced EUS consists of EUS imaging while gas-filled microbubbles are injected into peripheral veins, highlighting vascular lesions within the pancreas and helping distinguish various pancreatic lesions. In benign pancreatitis, contrast-enhanced EUS can identify necrotizing foci of AP at an early stage and may be useful in differentiating focal autoimmune pancreatitis from pancreatic cancer (23, 24).

Autoimmune pancreatitis (AIP) presents a challenging diagnostic dilemma, with convoluted adult diagnostic criteria which include response to therapy (25). Pediatric guidelines from the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) suggest "tissue diagnosis should ideally be obtained prior to initiating therapy," with EUS guided biopsies favored when available (26). Diagnostic sensitivity for EUS guided fine needle biopsy (FNB) is quite low in adults (27). Pediatric patients typically present with type 2, rather than type 1 AIP and there is a paucity of data in children (26, 28). A recent meta-analysis showed the pooled diagnostic yield for histology criteria in AIP to be 55.8% for FNA and 87.2% for FNB despite similar rates of histologic tissue procurement (29). In our practice, cases of suspected autoimmune pancreatitis with classic, diffuse imaging findings are often treated empirically after discussing risks/benefits with the family. Cases that are less clear benefit from extensive discussions with families regarding the typical modest yield of EUS-FNB, along with the risks and benefits of empiric therapy vs. biopsy.

Interventional EUS is a rapidly progressing field utilizing echo endoscopes to perform therapeutic interventions and should be performed at high volume, experienced centers. The predominant use of interventional EUS in pediatric patients is in symptomatic pancreatic walled off necrosis and pseudocysts. EUS-guided transgastric or transduodenal cyst-enterostomy drainage procedures are preferred approaches with superior success rates and risk profiles, decreased length of stay and lower treatment cost as compared to surgical approach (3, 30, 31). Metal and plastic stents have been used in children successfully, along with lumen apposing metal stents (13, 32–34). EUS guided celiac plexus blockade in patients with CP and debilitating pain has been used successfully in adult and pediatric patients (6, 35–37). Pediatric patients with conventional or post-surgical anatomy with dilation of the pancreatic duct but the inability to cannulate the duct *via* ERCP are candidates for pancreatic duct rendezvous *via* EUS (38).

The risk of adverse events in EUS includes bleeding, bacteremia and perforation. FNA or FNB of the pancreatic parenchyma can cause pancreatitis. Diagnostic EUS presents risk rates similar to upper endoscopy, while interventional EUS presents higher risks of infection, bleeding and perforation. The failure rate for complex procedures, such as pancreatic rendezvous, can approach 30% (6, 39, 40).

ENDOSCOPIC PANCREATIC FUNCTION TESTING

Exocrine pancreatic insufficiency (EPI) can occur in patients with cystic fibrosis and other congenital diseases, and CP. Indirect EPI testing is available, but only detects severe EPI. Direct pancreatic function testing with endoscopic pancreatic function testing (ePFT) during conventional esophagogastroduodenoscopy has emerged as a viable test in children. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recently published a position paper outlining a proposed standardized ePFT protocol in children. After aspiration of gastric and duodenal contents, cholecystokinin or secretin are administered and 3 duodenal aspirates are collected at 5-min intervals and sent for laboratory analysis of pancreas enzyme activity. EUS with secretin stimulation (sEUS) has been utilized to assess for structural changes reflective of minimal change chronic pancreatitis (MCCP), and can impact the likelihood of CP following, and predict progression of MCCP to overt CP in patients with abdominal pain thought to be pancreatic in origin with non-diagnostic cross-sectional imaging (41, 42). A multicenter research collaboration is needed to further refine and validate the proposed methods (43).

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Acute recurrent pancreatitis and CP are some of the most frequent indications for pediatric ERCP, which is feasible in children of all ages and sizes (3, 7, 44, 45). Historically diagnostic ERCP had been utilized, however, with the advent

of high quality MRCP and EUS, the vast majority of pediatric patients undergo ERCP for therapeutic indications (7). ERCP is used sparingly for diagnostic purposes, however in cases of suspected pancreatic ductal anatomic abnormalities, such as pancreas divisum, anomalous pancreaticobiliary junction or choledochocele it remains the gold standard (3, 46, 47). Diagnoses of abnormal pancreaticobiliary ductal anatomy can be confirmed and sometimes treated within the same procedure.

Endoscopic retrograde cholangiopancreatography allows numerous therapeutic modalities for ARP and CP in symptomatic patients. Pancreatic duct strictures are managed with catheter or balloon dilation, followed by serial pancreatic duct (PD) stent placements for up to 12 months with close observation (48). Calculi in the PD can also be removed using an extraction balloon during ERCP or for larger refractory stones through extracorporeal shockwave lithotripsy or pancreatoscopy (49). Other anatomical abnormalities such as pancreas divisum associated with ARP or CP can be addressed through a minor papillotomy and/or dorsal pancreatic duct stent placement (50–52).

Pediatric patients with AP may benefit from ERCP as well. ERCP with stent placement may be necessary for AIP with associated pancreatic or bile duct strictures/obstruction. Therapeutic intervention through biliary sphincterotomy and stone extraction is performed if AP is due to biliary etiology, specifically gallstone pancreatitis with suspected persistent bile duct obstruction (53, 54).

Technically successful ERCP may not always alleviate patients' symptoms in the setting of pancreatic disease. Moreover, ERCP is associated with certain risks, including post ERCP pancreatitis (PEP), bleeding, infection, and perforation (5). PEP occurs in up to 12% of children undergoing ERCP and is more likely to occur in patients needing pancreatic sphincterotomy, PD cannulation, PD injection, or prophylactic stent placement (55, 56). Pre-emptive use of IV ketorolac or ibuprofen in children has been performed at the time of ERCP to decrease the rates of PEP, albeit published results have not reached statistical significance (55, 57).

SURGICAL MANAGEMENT

Patients who do not respond to endoscopic therapy and have progressive, debilitating pancreatitis, may require surgical intervention. Traditional surgical drainage procedures such as lateral pancreaticojejunostomy (Puestow), or other surgical drainage variants (Frey or Beger), pancreatic tail resection, or pancreaticoduodenectomy (Whipple) have fallen out of favor in children with ARP and CP, especially in those with genetic risk factors. Endoscopic procedures can improve drainage in cases of pancreatic duct strictures amenable to stenting, usually attempted for up to a year before surgical intervention (48).

Children debilitated by their disease, with chronic pain, frequent hospitalizations, and failure of maximized medical and endoscopic therapy can be considered for total pancreatectomy with islet auto-transplantation (TPIAT) after an extensive evaluation. Total pancreatectomy offers the advantage of pain relief but leads to diabetes. The risk of diabetes is offset by the islet auto-transplantation intraoperatively, with childrens' glycemic outcomes ranging from insulin-independent to diabetic, with contributing factors such as the timing of surgery from the onset of symptoms, body mass index, pancreas mass, and fibrosis (58). Pancreatic enzyme replacement therapy is also needed post-operatively as patients have acquired exocrine pancreatic insufficiency.

PEDIATRIC INTERVENTIONAL ENDOSCOPY: THE FUTURE

While the field of pediatric interventional endoscopy has evolved, many care gaps exist and there are tremendous opportunities for growth and research (3, 45). Awareness of available pediatric diagnostic and interventional procedures will need to continue to increase. Unique research opportunities arise in pediatric pancreatitis, with the ability to study the progression and entire spectrum of disease by following patients from a first episode of AP to CP. EUS findings along the spectrum of disease, including objective findings of shear wave elastography, could lead to the development of a pediatric EUS CP criteria (59).

Endoscopic retrograde cholangiopancreatography and EUS are frequently used to diagnose and treat autoimmune pancreatitis and pancreas divisum, but supporting literature is sparse. Individualized decisions regarding endotherapy related to specific genetic mutations needs further research and randomized studies are needed to further assess PEP prophylaxis.

The volume of interventional endoscopic procedures in children is increasing, however it still does not approach adult volume. Strong collaboration amongst institutions and individual endoscopists remains vital to the advancement of the field. As the field evolves, questions remain regarding appropriate training avenues and the appropriate location and number of centers offering pediatric interventional endoscopic expertise.

CONCLUSION

Increased awareness of pancreatic disease in children has led to improved detection of AP, ARP, and CP in this population. Diagnostic and therapeutic options with EUS and ERCP are available and ideally should be performed at large tertiary centers with high patient volumes. The approach to each patient is individualized, and some may not need endoscopic diagnostic or therapeutic intervention. Surgical options such as TPIAT should be considered in patients with debilitating pain and affected quality of life who also need serial endoscopic therapy with no notable improvement in symptoms or frequency of inflammatory attacks. There are ample research opportunities to advance the fields of pediatric interventional endoscopy and pancreatology as they continue to evolve.

AUTHOR CONTRIBUTIONS

MS and DV contributed to the conceptualization, drafting of the manuscript, and editing of the final manuscript. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Le Marechal C, Hentic O, et al. The natural history of hereditary pancreatitis: a national series. *Gut.* (2009) 58:97–103. doi: 10.1136/gut.2008.149179
2. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas.* (2010) 39:5–8. doi: 10.1097/MPA.0b013e3181baac47
3. Liu QY, Gugig R, Troendle DM, Bitton S, Patel N, Vitale DS, et al. The roles of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the evaluation and treatment of chronic pancreatitis in children: a position paper from the North American society for pediatric gastroenterology, hepatology, and nutrition pancreas committee. *J Pediatr Gastroenterol Nutr.* (2020) 70:681–93. doi: 10.1097/MPG.0000000000002664
4. Troendle DM, Barth BA. ERCP can be safely and effectively performed by a pediatric gastroenterologist for choledocholithiasis in a pediatric facility. *J Pediatr Gastroenterol Nutr.* (2013) 57:655–8. doi: 10.1097/MPG.0000000000000124
5. Troendle DM, Barth BA. Pediatric considerations in endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc Clin N Am.* (2016) 26:119–36. doi: 10.1016/j.giec.2015.08.004
6. Barakat MT, Cagil Y, Gugig R. Landscape of pediatric endoscopic ultrasound in a United States tertiary care medical center. *J Pediatr Gastroenterol Nutr.* (2022) 26:119–36. doi: 10.1097/MPG.0000000000003403
7. Barakat MT, Cholankeril G, Gugig R, Berquist WE. Nationwide evolution of pediatric ERCP indications, utilization and re-admissions over time. *J Pediatr.* (2020) 232:159–65.e1. doi: 10.1016/j.jpeds.2020.11.019
8. Foundation N. *NASPGHAN Foundation Advanced Fellowship In Pediatric Endoscopy* (2020). Available online at: https://naspghan.org/wp-content/uploads/2020/02/AdvancedEndoscopy2020_2720.pdf (accessed April 14, 2022).
9. Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology.* (2019) 156:1969–78. doi: 10.1053/j.gastro.2018.12.043
10. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, et al. Nationwide trends in acute and chronic pancreatitis among privately insured children and non-elderly adults in the United States, 2007–2014. *Gastroenterology.* (2018) 155:469–78.e1. doi: 10.1053/j.gastro.2018.04.013
11. Schwarzenberg SJ, Bellin M, Husain SZ, Ahuja M, Barth B, Davis H, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr.* (2015) 166:890–6 e1. doi: 10.1016/j.jpeds.2014.11.019
12. Lakhole A, Liu QY. Role of endoscopic ultrasound in pediatric disease. *Gastrointest Endosc Clin N Am.* (2016) 26:137–53. doi: 10.1016/j.giec.2015.08.001
13. Nabi Z, Lakhtakia S, Basha J, Chavan R, Ramchandani M, Gupta R, et al. Endoscopic ultrasound-guided drainage of walled-off necrosis in children with fully covered self-expanding metal stents. *J Pediatr Gastroenterol Nutr.* (2017) 64:592–7. doi: 10.1097/MPG.0000000000001491
14. Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the rosemont classification. *Gastrointest Endosc.* (2009) 69:1251–61. doi: 10.1016/j.gie.2008.07.043
15. Issa Y, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur Radiol.* (2017) 27:3820–44. doi: 10.1007/s00330-016-4720-9
16. Rajan E, Clain JE, Levy MJ, Norton ID, Wang KK, Wiersema MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. *Gastrointest Endosc.* (2005) 61:401–6. doi: 10.1016/S0016-5107(04)02758-0
17. Pungpapong S, Wallace MB, Woodward TA, Noh KW, Raimondo M. Accuracy of endoscopic ultrasonography and magnetic resonance cholangiopancreatography for the diagnosis of chronic pancreatitis: a prospective comparison study. *J Clin Gastroenterol.* (2007) 41:88–93. doi: 10.1097/MCG.0b013e31802dfde6
18. Gardner TB, Taylor DJ, Gordon SR. Reported findings on endoscopic ultrasound examinations for chronic pancreatitis: toward establishing an endoscopic ultrasound quality benchmark. *Pancreas.* (2014) 43:37–40. doi: 10.1097/MPA.0b013e3182a85e1e
19. Gress FG. The early history of interventional endoscopic ultrasound. *Gastrointest Endosc Clin N Am.* (2017) 27:547–50. doi: 10.1016/j.giec.2017.06.015
20. Guo A, Poneros JM. The role of endotherapy in recurrent acute pancreatitis. *Gastrointest Endosc Clin N Am.* (2018) 28:455–76. doi: 10.1016/j.giec.2018.05.001
21. Iglesias-Garcia J, Larino-Noia J, Dominguez-Munoz JE. New imaging techniques: endoscopic ultrasound-guided elastography. *Gastrointest Endosc Clin N Am.* (2017) 27:551–67. doi: 10.1016/j.giec.2017.06.001
22. Dominguez-Muñoz JE, Iglesias-Garcia J, Castiñeira Alvariño M, Luaces Regueira M, Lariño-Noia J. EUS elastography to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. *Gastrointest Endosc.* (2015) 81:136–42. doi: 10.1016/j.gie.2014.06.040
23. Ripolles T, Martinez MJ, Lopez E, Castello I, Delgado F. Contrast-enhanced ultrasound in the staging of acute pancreatitis. *Eur Radiol.* (2010) 20:2518–23. doi: 10.1007/s00330-010-1824-5
24. Cho MK, Moon SH, Song TJ, Kim RE, Oh DW, Park DH, et al. Contrast-enhanced endoscopic ultrasound for differentially diagnosing autoimmune pancreatitis and pancreatic cancer. *Gut Liver.* (2018) 12:591–6. doi: 10.5009/gnl17391
25. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the international association of pancreatology. *Pancreas.* (2011) 40:352–8. doi: 10.1097/MPA.0b013e3182142fd2
26. Scheers I, Palermo JJ, Freedman S, Wilschanski M, Shah U, Abu-El-Haija M, et al. Recommendations for diagnosis and management of autoimmune pancreatitis in childhood: consensus from INSPPIRE. *J Pediatr Gastroenterol Nutr.* (2018) 67:232–6. doi: 10.1097/MPG.0000000000002028
27. de Pretis N, Crinò SF, Frulloni L. The role of EUS-guided FNA and FNB in autoimmune pancreatitis. *Diagnostics.* (2021) 11:8–10. doi: 10.3390/diagnostics11091653
28. Scheers I, Palermo JJ, Freedman S, Wilschanski M, Shah U, Abu-El-Haija M, et al. Autoimmune pancreatitis in children: characteristic features, diagnosis, and management. *Am J Gastroenterol.* (2017) 112:1604–11. doi: 10.1038/ajg.2017.85
29. Yoon SB, Moon SH, Song TJ, Kim JH, Kim MH. Endoscopic ultrasound-guided fine needle aspiration vs. biopsy for diagnosis of autoimmune pancreatitis: systematic review and comparative meta-analysis. *Dig Endosc.* (2021) 33:1024–33. doi: 10.1111/den.13866
30. Lerch MM, Stier A, Wahnschaffe U, Mayerle J. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? *Dtsch Arztebl Int.* (2009) 106:614–21. doi: 10.3238/arztebl.2009.0614
31. Farias GFA, Bernardo WM, De Moura DTH, Guedes HG, Brunaldi VO, Visconti TAC, et al. Endoscopic vs. surgical treatment for pancreatic pseudocysts: systematic review and meta-analysis. *Medicine.* (2019) 98:e14255. doi: 10.1097/MD.0000000000014255
32. Brimhall B, Han S, Tatman PD, Clark TJ, Wani S, Brauer B, et al. Increased incidence of pseudoaneurysm bleeding with lumen-apposing metal stents compared to double-pigtail plastic stents in patients with peripancreatic fluid collections. *Clin Gastroenterol Hepatol.* (2018) 16:1521–8. doi: 10.1016/j.cgh.2018.02.021
33. Trindade AJ, Inamdar S, Bitton S. Pediatric application of a lumen-apposing metal stent for transgastric pancreatic abscess drainage and subsequent necrosectomy. *Endoscopy.* (2016) 48 Suppl 1:E204–5. doi: 10.1055/s-0042-108573
34. Giefer MJ, Balmadrid BL. Pediatric application of the lumen-apposing metal stent for pancreatic fluid collections. *Gastrointest Endosc.* (2016) 84:188–9. doi: 10.1016/j.gie.2016.01.045
35. Moutinho-Ribeiro P, Costa-Moreira P, Caldeira A, Leite S, Marques S, Moreira T, et al. Endoscopic ultrasound-guided celiac plexus interventions. *GE Port J Gastroenterol.* (2020) 28:32–8. doi: 10.1159/000508293
36. Gress F, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol.* (2001) 96:409–16. doi: 10.1111/j.1572-0241.2001.03551.x

37. Membrillo-Romero A, Rascon-Martinez DM. [Celiac block in pediatric patients using endoscopic ultrasound for management of severe pain due to chronic pancreatitis. Review of the technique in 2 cases]. *Cir Cir.* (2017) 85:264–8. doi: 10.1016/j.circen.2017.05.006
38. Yoshimura Y, Yamashita S, Sato M, Iwano K, Kurita A, Hata D. The first successful rendezvous procedure for pancreatic duct drainage in a pediatric case with obstructive pancreatitis. *Pancreas.* (2021) 50:e37–9. doi: 10.1097/MPA.0000000000001775
39. Early DS, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Evans JA, et al. Adverse events associated with EUS and EUS with FNA. *Gastrointest Endosc.* (2013) 77:839–43. doi: 10.1016/j.gie.2013.02.018
40. Saumoy M, Kahaleh M. Safety and complications of interventional endoscopic ultrasound. *Clin Endosc.* (2018) 51:235–8. doi: 10.5946/ce.2017.081
41. DeWitt JM, Al-Haddad MA, Easler JJ, Sherman S, Slaven J, Gardner TB, et al. Pancreatic function testing and dynamic pancreatic duct evaluation for the diagnosis of exocrine pancreatic insufficiency and chronic pancreatitis. *Gastrointest Endosc.* (2021) 93:444–53. doi: 10.1016/j.gie.2020.06.029
42. Monachese M, Lee PJ, Harris K, Jang S, Bhatt A, Chahal P, et al. EUS and secretin endoscopic pancreatic function test predict evolution to overt structural changes of chronic pancreatitis in patients with non-diagnostic baseline imaging. *Endosc Ultrasound.* (2021) 10:116–23. doi: 10.4103/2303-9027.313801
43. Patel N, Sellers ZM, Grover A, Liu QY, Maqbool A, Morinville VD, et al. Endoscopic pancreatic function testing (ePFT) in children: a position paper from the NASPGHAN pancreas committee. *J Pediatr Gastroenterol Nutr.* (2021) 72:144–50. doi: 10.1097/MPG.0000000000002931
44. Pant C, Sferra TJ, Barth BA, Deshpande A, Minocha A, Qureshi WA, et al. Trends in endoscopic retrograde cholangiopancreatography in children within the United States, 2000–2009. *J Pediatr Gastroenterol Nutr.* (2014) 59:57–60. doi: 10.1097/MPG.0000000000000333
45. Vitale DS, Lin TK. Trends in pediatric endoscopic retrograde cholangiopancreatography and interventional endoscopy. *J Pediatr.* (2021) 232:10–2. doi: 10.1016/j.jpeds.2020.12.078
46. Agarwal J, Nageshwar Reddy D, Talukdar R, Lakhtakia S, Ramchandani M, Tandan M, et al. ERCP in the management of pancreatic diseases in children. *Gastrointest Endosc.* (2014) 79:271–8. doi: 10.1016/j.gie.2013.07.060
47. Lin TK, Vitale DS, Abu-El-Haija M, Anton CG, Crotty E, Li Y, et al. Magnetic resonance cholangiopancreatography vs endoscopy retrograde cholangiopancreatography for detection of anatomic variants of the pancreatic duct in children. *J Pediatr.* (2022) 244:120–4. doi: 10.1016/j.jpeds.2022.01.008
48. Dumonceau JM, Delhaye M, Tringali A, Arvanitakis M, Sanchez-Yague A, Vaysse T, et al. Endoscopic treatment of chronic pancreatitis: European society of gastrointestinal endoscopy (ESGE) guideline—updated August 2018. *Endoscopy.* (2019) 51:179–93. doi: 10.1055/a-0822-0832
49. Dumonceau JM, Delhaye M, Tringali A, Dominguez-Munoz JE, Poley JW, Arvanitaki M, et al. Endoscopic treatment of chronic pancreatitis: European society of gastrointestinal endoscopy (ESGE) clinical guideline. *Endoscopy.* (2012) 44:784–800. doi: 10.1055/s-0032-1309840
50. Lin TK, Pathak SJ, Hornung LN, Vitale DS, Nathan JD, Abu-El-Haija M. Clinical outcomes following therapeutic endoscopic retrograde cholangiopancreatography in children with pancreas divisum. *J Pediatr Gastroenterol Nutr.* (2021) 72:300–5. doi: 10.1097/MPG.0000000000002996
51. Lin TK, Abu-El-Haija M, Nathan JD, Palermo JP, Barth B, Bellin M, et al. Pancreas divisum in pediatric acute recurrent and chronic pancreatitis: report from INSPPIRE. *J Clin Gastroenterol.* (2019) 53:e232–8. doi: 10.1097/MCG.0000000000001063
52. Pan G, Yang K, Gong B, Deng Z. Analysis of the efficacy and safety of endoscopic retrograde cholangiopancreatography in children with symptomatic pancreas divisum. *Front Pediatr.* (2021) 9:761331. doi: 10.3389/fped.2021.761331
53. Buxbaum JL, Abbas Fehmi SM, Sultan S, Fishman DS, Qumseya BJ, Cortessis VK, et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. *Gastrointest Endosc.* (2019) 89:1075–105.e15. doi: 10.1016/j.gie.2018.10.001
54. Zakko L, Gardner TB. Endoscopic management of recurrent acute pancreatitis. *Clin Gastroenterol Hepatol.* (2019) 17:2167–70. doi: 10.1016/j.cgh.2019.04.069
55. Troendle DM, Gurram B, Huang R, Barth BA. IV ibuprofen for prevention of post-ERCP pancreatitis in children: a randomized placebo-controlled feasibility study. *J Pediatr Gastroenterol Nutr.* (2020) 70:121–6. doi: 10.1097/MPG.0000000000002524
56. Troendle DM, Abraham O, Huang R, Barth BA. Factors associated with post-ERCP pancreatitis and the effect of pancreatic duct stenting in a pediatric population. *Gastrointest Endosc.* (2015) 81:1408–16. doi: 10.1016/j.gie.2014.11.022
57. Mark JA, Kramer RE. Ketorolac is safe and associated with lower rate of post-endoscopic retrograde cholangiopancreatography pancreatitis in children with pancreatic duct manipulation. *J Pediatr Gastroenterol Nutr.* (2021) 73:542–7. doi: 10.1097/MPG.0000000000003252
58. Balamurugan AN, Elder DA, Abu-El-Haija M, Nathan JD. Islet cell transplantation in children. *Semin Pediatr Surg.* (2020) 29:150925. doi: 10.1016/j.sempedsurg.2020.150925
59. Yamashita Y, Tanioka K, Kawaji Y, Tamura T, Nuta J, Hatamaru K, et al. Utility of elastography with endoscopic ultrasonography shear-wave measurement for diagnosing chronic pancreatitis. *Gut Liver.* (2020) 14:659–64. doi: 10.5009/gnl19170

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The Exocrine Pancreas in Cystic Fibrosis in the Era of CFTR Modulation: A Mini Review

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Cystic fibrosis (CF) is a common disorder of autosomal recessive inheritance, that once conferred a life expectancy of only a few months. Over recent years, significant advances have been made to CF therapeutic approaches, changing the face of the disease, and facilitating the partial restoration of pancreatic function. This mini review summarizes the current landscape of exocrine pancreatic management in CF and explores areas for future direction and development.

Keywords: cystic fibrosis, exocrine pancreas, CFTR modulators, pancreatitis, precision medicine

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INTRODUCTION

Cystic fibrosis (CF) is one of the most common recessive genetic disorders worldwide, with wide-ranging health implications. While CF is characterized as an illness of pulmonary morbidity and mortality, it is a multisystem disorder encompassing sequelae in the gastrointestinal, hepatobiliary, and pancreatic systems (1). CF occurs due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Over 2,000 mutations, with varying functional consequences, have been identified to date, resulting in a spectrum of disease phenotypes. The CF gene encodes the CFTR protein responsible for driving chloride, bicarbonate and fluid secretion in affected epithelial surfaces. Dysfunction in the CFTR protein results in thick, inspissated secretions which in turn leads to obstruction, infection, inflammation and ultimately destruction of affected organs (2). These processes result in clinical manifestations such as chronic sinopulmonary diseases, exocrine and endocrine pancreatic diseases, intestinal obstruction, cirrhosis and obstructive azoospermia from atrophic or absent vasa deferens (3). This mini-review will focus on the exocrine pancreatic disease in CF, and how presentation and management has evolved with the introduction of CFTR-modulating therapies.

PATHOPHYSIOLOGY OF CYSTIC FIBROSIS IN THE PANCREAS

Pancreatic dysfunction in CF is a result of ductal obstruction from early in life. The specific mechanisms behind this process are multifactorial and incompletely understood, but are thought to hinge on dysregulated bicarbonate buffering, altered chloride flux and the production of pro-inflammatory pancreatic secretions. Our understanding of the pathophysiology has evolved exponentially in recent years, and is continuing to expand rapidly. The first pathological descriptions of "fibrocystic disease" of the pancreas were published by Dr. Dorothy Andersen in 1938 (4), but it was not until 1989, almost four decades later, that the CFTR gene was first recognized by Riordan and colleagues, demonstrating the clear genetic basis for the multisystem phenotype of CF (5).

In the 30 years since, our understanding of the role of CFTR in pancreatic function has deepened, guiding CF management beyond a "blanket" approach and toward more directed therapy. Today, CFTR has been established as a key modulator of chloride and bicarbonate transport, with downstream implications for several organ systems. In the small pancreatic ducts, this ionic flux is crucial in the production of alkaline fluid, the neutralization of gastric acid and the maintenance of a functional environment for digestive enzymes (2).

In the pancreatic ductal epithelia, defective CFTR results in ductal secretions with a lower pH (secondary to reduced bicarbonate buffering), a lower volume (secondary to reduced sodium chloride-driven osmosis) and an increased viscosity (secondary to protein hyperconcentration) (6, 7). This process begins *in utero*, resulting in early acinar plugs consisting mainly of zymogen material. As exocrine atrophy progresses, the ability of the pancreas to produce zymogens decreases, and these plugs come to contain a higher proportion of mucins secondary to ductal metaplasia (8). Ultimately, the end effects of CFTR dysregulation have been widely observed to result in pancreatic ductal obstruction and zymogen accumulation, leading to fibroinflammatory changes and parenchymal injury (2, 9).

GENOTYPE-PHENOTYPE CORRELATIONS OF THE EXOCRINE PANCREAS IN CF

The spectrum of phenotypic presentation of exocrine pancreatic disease in CF closely correlates with individual genotype. While >2,000 mutations have been identified to date, with more expected to be uncovered with time, they can be broadly categorized into six classes in relation to the degree of CFTR protein production and function. These classes are summarized in **Table 1** below.

Genotype classes I, II and III are commonly associated with pancreatic insufficiency, due to a greater degree of CFTR deficiency and dysfunction. Genotype classes IV, V, and VI or compound heterozygous individuals with one less severe allele, tend to retain some level of exocrine function as CFTR is still produced to some extent (**Table 1**). Response to therapeutic interventions varies between genotype classes, and varies further within each class itself. While genotype provides one method of classifying CF disease to guide investigation and management, it is important to recognize that outcomes in CF are also influenced by a number of other determinants including epigenetic factors, genetic modifiers, environmental factors and socioeconomic status (11).

CFTR MODULATOR THERAPY OVERVIEW

The identification of CFTR as the genetic basis for CF disease has turned scientific research toward precision medicine, and the early 2000s saw the introduction of CFTR modulator drugs. CFTR modulators are designed to support or restore the functionality of CFTR, and are classified into five key groups based on mechanism: potentiators, correctors, stabilizers, read-through agents, and amplifiers (3). Currently, only four agents have been made available on the pharmaceutical market, and are approved for use only in specific genotypes.

Potentiators

Potentiators restore or augment the cAMP mediated CFTR gating, allowing for some degree of CFTR-dependent transport to occur. Approximately 5% of CF mutations are a gating or conductance deficit, and it is this proportion of the CF population that will benefit from potentiator therapy. These mutations tend to fall within Classes III and IV (**Table 1**). Currently, the only available potentiator is ivacaftor, which is approved use either as a monotherapy, or as combination therapy with the correctors tezacaftor or lumacaftor. While the mechanism of action is yet to be fully elucidated, clinical outcomes demonstrate significant improvement amongst eligible patients commenced on therapy, ranging from decreased frequency of pulmonary exacerbations, to nutritional improvement and rescued pancreatic function (14, 15). While there are several other potentiators currently under clinical evaluation, ivacaftor remains the only potentiator available for patient use.

Correctors

Correctors (e.g., tezacaftor, lumacaftor, and elexacaftor) assist CFTR protein structuring and trafficking. While the specifics of activity vary between individual agents, the mechanism of the corrector class is considered to be either direct (binding to the misfolded protein itself and "chaperoning" it through the endoplasmic reticulum) or indirect (through proteostasis regulation) (3). Mistrafficking is the most common mutation type in CF, notably including the F508del mutation.

Stabilizers

Stabilizing therapies target Class VI mutations, wherein the CFTR protein is present at the plasma membrane but has reduced availability due to increased lysosomal degradation. Stabilizers function to anchor the protein at the cell surface, preventing premature removal and destruction. While lumacaftor has been shown to transiently increase CFTR stability, ongoing investigation into agents with longer-term benefits are ongoing (16).

Read-Through Agents

One of the more severe phenotypes in CF results from defective CFTR synthesis in the first instance, usually due to the introduction of a premature termination codon (PTC) into the protein mRNA (Class I mutations). Read-through agents allow the protein translation process to "skip over" the PTC through recruiting an alternative amino acid in its place, facilitating the production of a full-length protein (17). Aminoglycosides such as gentamicin have demonstrated read-through capabilities in early experimental studies, but the practical application of these properties is limited by the toxicity profile seen with longer-term dosing. While some trials are currently examining aminoglycoside derivatives with stronger read-through capability

TABLE 1 | An overview of the genotype classes in CF, with their associated pancreatic phenotype (11–13).

Class	CFTR function	Pancreatic status	Example Mutations
I *"Protein synthesis defect"*	No CFTR is synthesized due to stop codons or splicing defects.	Insufficient	G542X, W1282X, R553X, 3950delT
II *"Maturation defect"*	CFTR is synthesized but in an immature form which is degraded intracellularly.	Insufficient	F508del, N1303K
III *"Gating defect"*	Despite synthesis of CFTR, activation and regulation by ATP or cAMP are disrupted.	Insufficient	G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D
IV *"Conductance defect"*	CFTR is synthesized and expressed at the plasma membrane, but chloride conductance is reduced.	Insufficient	R334W, G314E, R347P, D1152H
V *"Reduced quantity"*	CFTR synthesis is normal but produced in quantities too small to be effective at the cell surface.	Sufficient	3849+ 10 kb C→ T, 3272-26 A→ G, 2789+5G→ A
VI *"Reduced stability"*	CFTR stability is reduced so protein synthesis at the cell surface cannot occur in quantities high enough to be effective.	Variable	c. 120del123, rPhe580del
Unclassified			All other mutations, including those unknown

and less toxicity, nothing has been approved for use in CF to date (18, 19).

Amplifiers

Class V mutations encompass those genotypes resulting in reduced synthesis or maturation of the CFTR protein. Amplifiers target this class of mutation, increasing the expression of CFTR mRNA and the downstream protein production load (20). Nesolicaftor is currently in the midst of phase 3 trials (Proteostasis Therapeutics), having shown promising results throughout earlier studies with significantly higher CFTR mRNA levels when used in combination with existing corrector and potentiator therapies (21, 22).

THE EXOCRINE PANCREATIC PHENOTYPES IN CF

Two key clinical manifestations present themselves as hallmarks of exocrine pancreatic disease in CF: (1) pancreatic insufficiency, and (2) symptomatic pancreatitis among a subset of people with pancreatic sufficient (PS) CF. Each of these confer a distinct disease burden and occur within a specific subset of the CF population, shaping presentation and management.

Pancreatic Insufficiency

Approximately 85% of people with CF are pancreatic insufficient (PI) from early in life (23). A near absolute loss in exocrine output results in a disease of maldigestion, characterized by steatorrhoea, failure to thrive, and fat-soluble vitamin deficiencies. Left unrecognized, this population historically died in early infancy from malnutrition, before the now-familiar pulmonary manifestations of CF even took root (24). Under- or malnutrition (as measured by BMI) has been shown in epidemiological studies to be closely linked with poor pulmonary and survival outcomes in CF (25). Nowadays, the appropriate and timely initiation of pancreatic enzyme replacement therapy (PERT), coupled with a high energy diet, allows these individuals to facilitate nutritional digestion and maintain adequate growth and development; hence early recognition and management are essential. Even with PERT treatment, the clinical consequences of PI are ongoing and continues to represent a large proportion of CF morbidity and mortality, leading to malnutrition, poor weight gain and a decreased ability to withstand intercurrent clinical insults (26).

The PI status should always be confirmed on testing. Fecal elastase is the most commonly utilized test in clinical practice for assessing exocrine pancreatic function. Traditionally, a fecal elastase cutoff of $<200\,\mu g/g$ as indicative of PI is used although a lower cutoff of $100\,\mu g/g$ has been reported to be of greater predictive value for ruling out PI and minimize false positive results due to dilution of feces caused by non-pancreatic intestinal causes (e.g., short gut syndrome) (27). Other indirect measures of exocrine pancreatic function include fecal chymotrypsin and serum trypsinogen. These latter two tests have a lower sensitivity and specificity than fecal elastase, and their use in the diagnostic setting is curbed by some key clinical limitations. Fecal chymotrypsin is a commercially available enzyme, so it cannot be reliably measured in patients prescribed PERT (28). Serum trypsinogen is not specific for exocrine pancreatic function, and can be elevated in other states of disease including acute pancreatitis and is not widely available (29). Direct tests of pancreatic function, such as secretin or cholecystokinin testing (using a dreiling tube or endoscope), are more sensitive and specific, but less commonly used due to their technical nature and poor patient tolerance and/or need for general anesthesia (in children) (30).

CFTR-Related Pancreatitis

Approximately 15% of the CF cohort are PS, born with at least 2% of residual pancreatic reserve, enough to adequately digest and absorb nutrients (26). While PS individuals tend to exhibit a less severe phenotype overall, it is in this population that symptomatic pancreatitis may occur, at a proportion of ∼20%. It is thought to result from an altered ratio of acinar reserve and

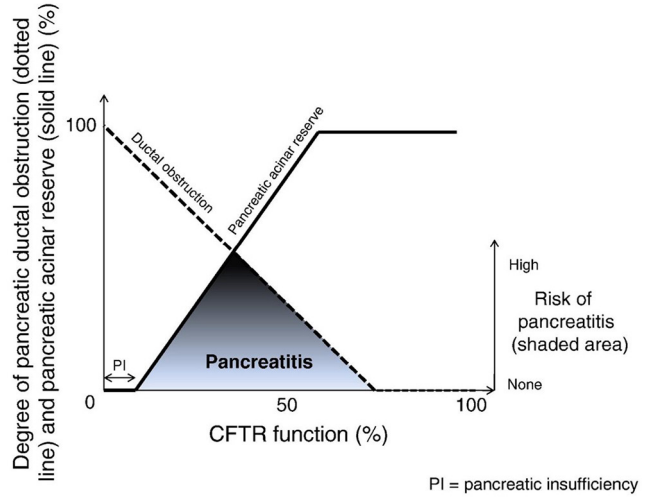

FIGURE 1 | The development of pancreatitis in the context of CFTR-related contributors. Adapted from Ooi et al. (10).

ductal obstruction, as conceptualized in **Figure 1**. Compounding this process, impaired bicarbonate secretion leads to altered luminal pH, promoting ongoing acute tissue inflammation and the perpetuation of pancreatitis in the chronic period (31). This pathology relies on a degree of acinar function to be preserved in the presence of significant ductal obstruction, hence a negligible prevalence of pancreatitis amongst the PI group.

As well as genotype being a key determinant, risk of pancreatitis is also amplified in the context of cigarette or alcohol use, both of which independently decrease CFTR function (32, 33). Pancreatitis in the CF cohort is diagnosed with classical criteria of archetypal symptomatology, serum amylase/lipase greater than three times the upper limit of normal, and/or consistent findings on imaging (34).

It is also worth noting that in the context of the progressive nature of pancreatic disease in CF, a percentage of PS individuals will become PI later in life. The likelihood of this level of pancreatic destruction is largely informed by genotype (e.g., carriage of classes I, II or III mutations on both alleles) and previous bouts of symptomatic pancreatitis (10). This suggests that recurrent attacks of symptomatic pancreatitis heralds progressive deterioration in exocrine function, underscoring the importance of serially monitoring function amongst the PS group.

THREE DISTINCT CFTR MODULATOR TREATMENT GROUPS IN CF PANCREATIC DISEASE

CFTR modulator treatment eligibility and planning is generally based on genotype classing (as described in **Table 1**). However, this patient classification system does not incorporate likely pancreatic response into the decision-making process. As CFTR modulator use has increased, longitudinal evidence comes forth, describing three different patient groups with distinct pancreatic presentations and response to therapy.

Pancreatic Insufficient Individuals May Recover Pancreatic Function

Pancreatic dysfunction in CF begins *in utero*, and while PERT prescription can assist in mitigating some of the clinical ramifications, exocrine disease persists throughout life (35). As CFTR modulators have become established as a key tenet of CF management, their wide-ranging effects on health beyond pulmonary capacity have been brought to the fore. Emerging evidence has demonstrated improvement and recovery in exocrine pancreatic function, with implication for growth and nutritional outcomes later in life. The ARRIVAL trial noted improvements in measured pancreatic markers such as fecal elastase (FE) and immunoreactive trypsinogen (IRT) when ivacaftor was introduced in young children between 12 and 24 months (36), and the KIWI/KLIMB studies demonstrated similar improvements amongst a group in early childhood (aged 2–5 years) (37, 38). However, the magnitude of these benefits is curbed as the introduction age of ivacaftor increases, and ferret models have demonstrated that withdrawal of therapy reinstates exocrine disease (39, 40). Ultimately, these findings support the concept that the "window of opportunity" to rescue exocrine pancreatic function in CF occurs early in life, hinging on early and sustained modulator therapy.

The "window of opportunity" in initiating CFTR modulator treatment is likely to be from as early in life as possible. However, a recent ivacaftor study in ferret models demonstrated partial protection from disease progression when the therapy was commenced *in utero*. Ferrets in the treatment group demonstrated similar growth rates as wild-type animals, and continued on a normal growth trajectory while nursing even without PERT treatment (40). Corroborating this proof-of-concept, a recent human case report provides details of a child born to a F508del homozygous mother on elexacaftor/tezacaftor/ivacaftor treatment. Despite inheriting a F508del homozygous genotype themselves, this child did not meet the laboratory criteria for the IRT CF newborn screening, and was born PS with growth tracking along the 85th centile (41). Together, these studies support the finding that pancreatic disease begins *in utero*, and raises the possibility that modulator treatment commenced even prior to birth may slow or perhaps prevent exocrine disease from taking hold. Currently, no modulator therapy is approved for use earlier than 2 years of age.

Individuals With Recovered Pancreatic Function May Develop Symptomatic Pancreatitis

Rescuing exocrine pancreatic function in CF has clear benefits for nutrition and growth. However, increasing pancreatic reserve in CF poses its own risks, as a growing body of evidence highlights links to the development of symptomatic acute pancreatitis amongst a subset of patients who were PI prior to commencement of modulators, corroborated by the findings of recent case reports. Gould et al. describe a series of five

patients, all PI, who developed a classical presentation of acute pancreatitis at a median of 30 months following commencement of modulator therapy. Of these five, three had regained some level of exocrine function with FE measurements above 100 μg/g (42). Megalaa et al. describe a similar case report of a 10 year old child, realized to have regained PS status only after an episode of acute pancreatitis (43). In keeping with the model conceptualized by Ooi and colleagues in 2011 (**Figure 1**), this suggests that while CFTR modulators may effectively increase pancreatic acinar reserve, in the setting of ongoing ductal obstruction, this can result in a heightened risk of pancreatitis (10). This speaks to the risk profile of CFTR modulators, highlighting that their health benefits must be considered in the context of potential serious complications which clinicians must remain vigilant for amongst this population.

Pancreatic Sufficient Individuals May Have a Reduced Risk of Symptomatic Pancreatitis

Conversely, PS patients commenced on modulator treatment appear to accelerate beyond this critical ratio of acinar reserve and ductal obstruction (**Figure 1**), with a subsequent decline in the prevalence of pancreatitis amongst this group. Akshintala et al. retrospectively reviewed a small cohort of adult CF patients with a history of pancreatitis in the preceding 2 years, highlighting that none of these 15 individuals developed pancreatitis during their follow up period (mean 36 months) (44). Ramsey and colleagues supported these findings 3 years onwards, demonstrating a significant reduction in pancreatitis-related hospitalizations amongst those commenced on CFTR modulators amongst both PI and PS patients, with a greater relative risk reduction within the PS group (45). Overall, these findings suggest that in those suffering from recurrent pancreatitis, or who have a pre-existing risk of pancreatitis, CFTR modulators may assist in shifting away from this "risk window," alleviating ductal obstruction enough to improve pancreatic output without inducing further inflammation.

CONCLUSION

Pancreatic disease represents a significant proportion of CF-related morbidity and mortality. Where treatment previously focused mitigating the effects of downstream sequalae, the research landscape has shifted now to focus on addressing the central CFTR mutation at the root. As CFTR modulators become established as a cornerstone of CF management, the limitations of these novel agents are brought to the fore. The risk-benefit profile of these therapies varies for three CF cohort subsets, depending on pre-existing pancreatic function and risk of pancreatitis. This classification of modulator-eligible patients encourages a patient-centered treatment approach, where a distinct risk monitoring process may facilitate the early recognition of key complications unique to each population. The temporal outcomes of CFTR modulator use in the context of longer-term pancreatic complications including CF-related diabetes and malignancy are yet to be established, but with demonstrable benefits in the short-term setting, positive effects may be anticipated.

AUTHOR CONTRIBUTIONS

IM and CO conceptualized the topic and drafted review design. IM analyzed the literature and drafted the manuscript. CO refined the manuscript and provided guidance on literature interpretation. All authors made significant and direct contributions to the work and approve it for publication.

REFERENCES

1. Donaldson SH, Boucher RC. Pathophysiology of cystic fibrosis. *Annales Nestlé.* (2006) 64:101–9. doi: 10.1159/000095374
2. Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. *J Pathol.* (2016) 238:311–20. doi: 10.1002/path.4634
3. Lopes-Pacheco M. CFTR modulators: shedding light on precision medicine for cystic fibrosis. *Front Pharmacol.* (2016) 7:275. doi: 10.3389/fphar.2016.00275
4. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *Am J Dis Child.* (1938) 56:344–99. doi: 10.1001/archpedi.1938.01980140114013
5. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science.* (1989) 245:1066–73. doi: 10.1126/science.2475911
6. Kopelman H, Corey M, Gaskin K, Durie P, Weizman Z, Forstner G. Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. *Gastroenterology.* (1988) 95:349–55. doi: 10.1016/0016-5085(88)90490-8
7. Kopelman H, Durie P, Gaskin K, Weizman Z, Forstner G. Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis. *N Engl J Med.* (1985) 312:329–34. doi: 10.1056/NEJM198502073120601
8. Angyal D, Bijvelds MJC, Bruno MJ, Peppelenbosch MP, de Jonge HR. Bicarbonate Transport in cystic fibrosis and pancreatitis. *Cells.* (2021) 11:54. doi: 10.3390/cells11010054
9. Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. *Gut.* (2007) 56:1153–63. doi: 10.1136/gut.2004.062786
10. Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. *Gastroenterology.* (2011) 140:153–61. doi: 10.1053/j.gastro.2010.09.046
11. Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol.* (2020) 10:1662. doi: 10.3389/fphar.2019.01662
12. Durda-Masny M, Gozdzik-Spychalska J, John A, Czaiński W, Strózewska W, Pawłowska N, et al. The determinants of survival among adults with cystic fibrosis—a cohort study. *J Physiol Anthropol.* (2021) 40:19. doi: 10.1186/s40101-021-00269-7
13. Marson FAL, Bertuzzo CS, Ribeiro JD. Classification of *CFTR* mutation classes. *Lancet Respir Med.* (2016) 4:e37–8. doi: 10.1016/S2213-2600(16)30188-6
14. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *Lancet Respir Med.* (2014) 2:902–10. doi: 10.1016/S2213-2600(14)70218-8
15. Nichols A, Davies J, Jones D, Carr S. Restoration of exocrine pancreatic function in older children with cystic fibrosis on ivacaftor.

Paediatr Respir Rev. (2020) 35:99–102. doi: 10.1016/j.prrv.2020.04.003
16. He L, Kota P, Aleksandrov AA, Cui L, Jensen T, Dokholyan NV, et al. Correctors of ΔF508 CFTR restore global conformational maturation without thermally stabilizing the mutant protein. *FASEB J.* (2013) 27:536–45. doi: 10.1096/fj.12-216119
17. Pranke I, Bidou L, Martin N, Blanchet S, Hatton A, Karri S, et al. Factors influencing readthrough therapy for frequent cystic fibrosis premature termination codons. *ERJ Open Res.* (2018) 4:00080-2017. doi: 10.1183/23120541.00080-2017
18. Leubitz A, Frydman-Marom A, Sharpe N, van Duzer J, Campbell KC, Vanhoutte F. Safety, tolerability, and pharmacokinetics of single ascending doses of ELX-02, a potential treatment for genetic disorders caused by nonsense mutations, in healthy volunteers. *Clin Pharmacol Drug Dev.* (2019) 8:984–94. doi: 10.1002/cpdd.647
19. Sharma J, Keeling KM, Rowe SM. Pharmacological approaches for targeting cystic fibrosis nonsense mutations. *Eur J Med Chem.* (2020) 200:112436. doi: 10.1016/j.ejmech.2020.112436
20. Giuliano KA, Wachi S, Drew L, Dukovski D, Green O, Bastos C, et al. Use of a high-throughput phenotypic screening strategy to identify amplifiers, a novel pharmacological class of small molecules that exhibit functional synergy with potentiators and correctors. *SLAS Discov.* (2018) 23:111–21. doi: 10.1177/2472555217729790
21. Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From ivacaftor to triple combination: a systematic review of efficacy and safety of CFTR modulators in people with cystic fibrosis. *Int J Mol Sci.* (2020) 21:5882. doi: 10.3390/ijms21165882
22. Molinski SV, Ahmadi S, Ip W, Ouyang H, Villella A, Miller JP, et al. Orkambi® and amplifier co-therapy improves function from a rare CFTR mutation in gene-edited cells and patient tissue. *EMBO Mol Med.* (2017) 9:1224–43. doi: 10.15252/emmm.201607137
23. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc.* (2008) 108:832–9. doi: 10.1016/j.jada.2008.02.020
24. Reid DW, Blizzard CL, Shugg DM, Flowers C, Cash C, Greville HM. Changes in cystic fibrosis mortality in Australia, 1979–2005. *Med J Australia.* (2011) 195:392–5. doi: 10.5694/mja10.11229
25. Lai H-C, Corey M, FitzSimmons S, Kosorok MR, Farrell PM. Comparison of growth status of patients with cystic fibrosis between the United States and Canada. *Am J Clin Nutr.* (1999) 69:531–8. doi: 10.1093/ajcn/69.3.531
26. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. *J Cystic Fibrosis.* (2017) 16:S70–8. doi: 10.1016/j.jcf.2017.06.011
27. Beharry S, Ellis L, Corey M, Marcon M, Durie P. How useful is fecal pancreatic elastase 1 as a marker of exocrine pancreatic disease? *J Pediatr.* (2002) 141:84–90. doi: 10.1067/mpd.2002.124829
28. Niederau C, Grendell JH. Diagnosis of chronic pancreatitis. *Gastroenterology.* (1985) 88:1973–95. doi: 10.1016/0016-5085(85)90029-0
29. Couper RT, Corey M, Durie PR, Forstner GG, Moore DJ. Longitudinal evaluation of serum trypsinogen measurement in pancreatic-insufficient and pancreatic-sufficient patients with cystic fibrosis. *J Pediatr.* (1995) 127:408–13. doi: 10.1016/S0022-3476(95)70072-2
30. Lankisch PG, Schreiber A, Otto J. Pancreolauryl test. Evaluation of a tubeless pancreatic function test in comparison with other indirect and direct tests for exocrine pancreatic function. *Dig Dis Sci.* (1983) 28:490–3. doi: 10.1007/BF01308149
31. Behrendorff N, Floetenmeyer M, Schwiening C, Thorn P. Protons released during pancreatic acinar cell secretion acidify the lumen and contribute to pancreatitis in mice. *Gastroenterology.* (2010) 139:1711–20.e5. doi: 10.1053/j.gastro.2010.07.051
32. Raju SV, Jackson PL, Courville CA, McNicholas CM, Sloane PA, Sabbatini G, et al. Cigarette smoke induces systemic defects in cystic fibrosis transmembrane conductance regulator function. *Am J Respir Crit Care Med.* (2013) 188:1321–30. doi: 10.1164/rccm.201304-0733OC
33. Maléth J, Balázs A, Pallagi P, Balla Z, Kui B, Katona M, et al. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. *Gastroenterology.* (2015) 148:427–39.e16. doi: 10.1053/j.gastro.2014.11.002
34. Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. *J Pediatr Gastroenterol Nutr.* (2012) 55:261–5. doi: 10.1097/MPG.0b013e31824f1516
35. Bass R, Brownell JN, Stallings VA. The impact of highly effective CFTR modulators on growth and nutrition status. *Nutrients.* (2021) 13:2907. doi: 10.3390/nu13092907
36. Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to 24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med.* (2018) 6:545–53. doi: 10.1016/S2213-2600(18)30202-9
37. Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5 years (KLIMB). *J Cyst Fibros.* (2019) 18:838–43. doi: 10.1016/j.jcf.2019.03.009
38. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med.* (2016) 4:107–15. doi: 10.1016/S2213-2600(15)00545-7
39. Stallings VA, Sainath N, Oberle M, Bertolaso C, Schall JI. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. *J Pediatr.* (2018) 201:229–37.e4. doi: 10.1016/j.jpeds.2018.05.018
40. Sun X, Yi Y, Yan Z, Rosen BH, Liang B, Winter MC, et al. *In utero* and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis. *Sci Transl Med.* (2019) 11:eaau7531. doi: 10.1126/scitranslmed.aau7531
41. Fortner CN, Seguin JM, Kay DM. Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy. *J Cyst Fibros.* (2021) 20:835–6. doi: 10.1016/j.jcf.2021.03.018
42. Gould MJ, Smith H, Rayment JH, Machida H, Gonska T, Galante GJ. CFTR modulators increase risk of acute pancreatitis in pancreatic insufficient patients with cystic fibrosis. *J Cystic Fibrosis*. (2021). doi: 10.1016/j.jcf.2021.09.010. [Epub ahead of print].
43. Megalaa R, Gopalareddy V, Champion E, Goralski JL. Time for a gut check: pancreatic sufficiency resulting from CFTR modulator use. *Pediatr Pulmonol.* (2019) 54:E16–8. doi: 10.1002/ppul.24353
44. Akshintala VS, Kamal A, Faghih M, Cutting GR, Cebotaru L, West NE, et al. Cystic fibrosis transmembrane conductance regulator modulators reduce the risk of recurrent acute pancreatitis among adult patients with pancreas sufficient cystic fibrosis. *Pancreatology.* (2019) 19:1023–6. doi: 10.1016/j.pan.2019.09.014
45. Ramsey ML, Gokun Y, Sobotka LA, Wellner MR, Porter K, Kirkby SE, et al. Cystic fibrosis transmembrane conductance regulator modulator use is associated with reduced pancreatitis hospitalizations in patients with cystic fibrosis. *Am J Gastroenterol.* (2021) 116:2446–54. doi: 10.14309/ajg.0000000000001527

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Congenital etiologies of exocrine pancreatic insufficiency

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Congenital exocrine pancreatic insufficiency is a rare condition. In a vast majority of patients, exocrine dysfunction occurs as part of a multisystemic disease, the most prevalent being cystic fibrosis and Shwachman-Bodian-Diamond syndrome. Recent fundamental studies have increased our understanding of the pathophysiology of these diseases. Exocrine pancreatic dysfunction should be considered in children with failure to thrive and fatty stools. Treatment is mainly supportive and consists of pancreatic enzyme replacement and liposoluble vitamins supplementation.

KEYWORDS

exocrine pancreatic insufficiency, cystic fibrosis, Shwachman-Bodian-Diamond syndrome, Pearson syndrome, Johanson-Blizzard syndrome, pancreas agenesis

Introduction

The pancreas is a mixed endocrine and exocrine gland. The exocrine tissue comprises acinar cells that produce and store pancreatic enzymes; and ductal cells that secrete fluid and electrolytes. Digestive pro-enzymes flow into the duodenal lumen where they are activated and ensure nutrient digestion. The exocrine pancreatic function is immature at birth (1–3). Pancreatic amylase activity is nearly absent in premature and term neonates, remains low in the first year of life to progressively reach adult values around 3 years of age. Trypsin and lipase activity are markedly lower (10x and 20x, respectively) at birth but progressively reach adult values within the first year of life. The functional exocrine reserve is impressively large as more than 98% of the pancreatic enzyme production must be lost before steatorrhea develops (4, 5). Exocrine pancreatic insufficiency (EPI) is usually evidenced in infants with clinical features of malabsorption such as failure to thrive, chronic diarrhea, anemia or hypoalbuminemia. Fecal elastase-1 is the most frequent test used to identify pancreatic insufficient (PI) patients.

Although a wide variety of conditions may be associated with EPI, most are syndromic and exceedingly rare. Etiologies of congenital EPI can be subdivided in 3 groups based on underlying pathophysiologic mechanisms: i.e., related to (a) exocrine pancreatic tissue injury, (b) pancreatic hypoplasia or agenesis or (c) isolated enzyme deficiency. Cystic fibrosis (CF) represents by far the most frequent cause of inherited EPI (90–95%) followed by Shwachman-Bodian-Diamond syndrome (SBDS, ∼4%). The differential diagnosis and main cardinal features are summarized in Table 1.

TABLE 1 Etiologies and main clinical features of congenital exocrine pancreatic insufficiency.

	Genetic defect	Main clinical features
Exocrine pancreas tissue injury		
Cystic fibrosis	*CFTR*	Chronic sinopulmonary disease (e.g.,)
		-Chronic cough and sputum production
		-Chronic wheezing and air trapping
		-Obstructive lung disease
		-Nasal polyps
		-Chronic pansinusitis
		Digestive system (e.g.,)
		-EPI or pancreatitis
		-Meconium ileus
		-Liver disease (cholestasis, steatosis, portal HT)
		-Failure to thrive
		-Distal intestinal obstruction
		Obstructive male infertility
		-Hypoplasia, aplasia of vas deferens
		-Hypoplasia, aplasia of seminal vesicles
		Other
		-Diabetes mellitus
Shwachman-Bodian-Diamond syndrome type 1	*SBDS*	Hematologic anomalies related to bone marrow dysfunction (e.g.,)
		-Hypoproductive cytopenia
		-Pancytopenia
		-Leukemia
		EPI
		Skeletal dysplasia
		-Short stature
		-Thoracic dystrophy
		-Chondrodysplasia
		Other
		-Hearing loss, ear malformation
		-Cardiac defects
		-Increased liver enzymes, hepatomegaly
		-Delayed teeth eruption, dysplastic teeth
		-Kidney tubulopathy
		-Psychomotor delay
		-Ichthyosis
		-Eye anomalies (strabismus, coloboma, keratitis)
Shwachman-Bodian-Diamond syndrome type 2	*EFL1*	(See SBDS type 1)
		Specific features
		-Myopia
		-Arched palate
SBDS-like	*eIF6*	(See SBDS type 1)
SBDS-like	*DNAJC21*	(See SBDS type 1)
		Specific features
		-Retinal dystrophy
		-Hypermobile joints

(Continued)

TABLE 1 Continued

	Genetic defect	Main clinical features
		-Hip dysplasia
		-Cryptorchidism
SBDS-like	*SRP54*	(See SBDS type 1)
		Specific features
		-Congenital profound neutropenia
Pearson syndrome	mt-Deletion	Hematologic anomalies
		-Sideroblastic anemia
		-Vacuolization of marrow precursors
		Digestive system
		-EPI
		-Hepatomegaly, increased liver enzymes
		Other
		-Muscle weakness (ptosis, limb weakness)
		-Endocrinologic disturbance (hypothyroidy, hypoparathyroidy, growth hormone deficiency, adrenal Insufficiency, diabetes mellitus)
		-Splenic atrophy
		-Impaired cardiac function
		-Renal insufficiency
		-Cardiac conduction block
Johanson Blizzard syndrome	*UBR1*	Nasal alea hypoplasia/agenesis
		EPI
		Mental or psychomotor retardation
		Other
		-Short stature
		-Scalp defects, alopecia, abnormal hair implantation
		-Oligodontia, microdontia
		-Imperforate anus
		-Genito-urinary anomalies (vesico-ureteral reflux hypospadias)
		-Endocrinologic disturbance (hypothyroidy, hypopituitarism, diabetes mellitus)
Shteyer syndrome	*COX4I2*	Dyserythropoietic anemia
		EPI
		Calvarial hyperostosis
		Other
		-Delayed psychomotor development
		-Hepatomegaly
		-Splenomegaly
		-Muscle weakness
		-Dental anomalies (maldentition, caries)
Pancreas hypoplasia/agenesis	*PDX1*	Neonatal diabetes mellitus
		EPI

(Continued)

TABLE 1 Continued

	Genetic defect	Main clinical features
	PTF1A	Neonatal diabetes mellitus EPI Cerebellar agenesis/hypoplasia Other -Optic nerve hypoplasia -Joint stiffness -Dysmorphic facial features (triangular face, beaked nose, low set dysplastic ears) -Little subcutaneous fat.
	GATA6	Congenital heart disease Neonatal diabetes mellitus EPI Developmental delay Other -Bile tract anomalies (biliary atresia, gallbladder agenesis) -Endocrine anomalies -Diaphragmatic hernia
Isolated enzyme deficiency	*PNLIP*	Steatorrhea

EPI, exocrine pancreatic insufficiency; HT, hypertension; SBDS, Shwachman-Bodian-Diamond syndrome.

The purpose of the present mini-review is to depict the differential diagnosis in EPI and summarize advancing knowledge on the pathophysiologic mechanisms leading to EPI in those conditions.

Congenital exocrine pancreatic insufficiency due to exocrine injury

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive, multisystemic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. CF has an estimated prevalence of 1/3.000 in Caucasians. The CFTR gene codes for a cAMP-responsive chloride channel at the apical surface of secreting epithelia (6, 7). More than 2000 *CFTR* mutations were described to date. The most frequent, occurring at least on 1 allele in >65% CF patients, is a 3-base-pair deletion causing the loss of a phenylalanine at position 508 of the protein (F508del). *CFTR* mutations have been classified in 6 classes based on their predominant effect on CFTR function or processing (Figure 1A) (8, 9).

Pancreatic damage in CF already begins in utero (10). As from 32 weeks of gestation, the acinar and duct lumen were found to be dilated by inspissation of proteinaceous material. This duct plugging causes intrapancreatic enzyme activation, gland inflammation and leads to acinar injury; a process that progresses through infancy until the exocrine tissue is replaced by fibrotic cells. Initially, endocrine cells are relatively preserved. Functional testing confirms reduced fluid, and subsequently, enzyme secretion in CF patients (11). In pancreatic sufficient (PS) children, this process is delayed as mutations have a milder functional impact on CFTR.

CF is diagnosed in many countries by newborn screening evidencing high serum trypsinogen levels. Later in life, CF patients present with chronic cough, rectal prolapse, steatorrhea, failure to thrive or male infertility. The final diagnosis of CF is based on sweat-test and *CFTR* sequencing (12). Transepithelial nasal potential difference may help to classify patients with mutations of unknown functional impact. Most clinical symptoms of CF arise from the dehydration of sweat, mucus or digestive fluids. The CFTR defective gene causes the secretions to become sticky and thick. Instead of acting as lubricants, the secretions clog up tubes and ducts, especially in the lungs, gut and pancreas. Cardinal features are summarized in Table 1. CF patients with identical CFTR genotypes show a high variability in disease severity, complication rates and survival. These differences are largely attributable to genetic modifiers (variants in other genes such as *SLC26A9 or TGFB1*) and environmental factors (such as cigarette smoke exposure or bacterial pathogens).

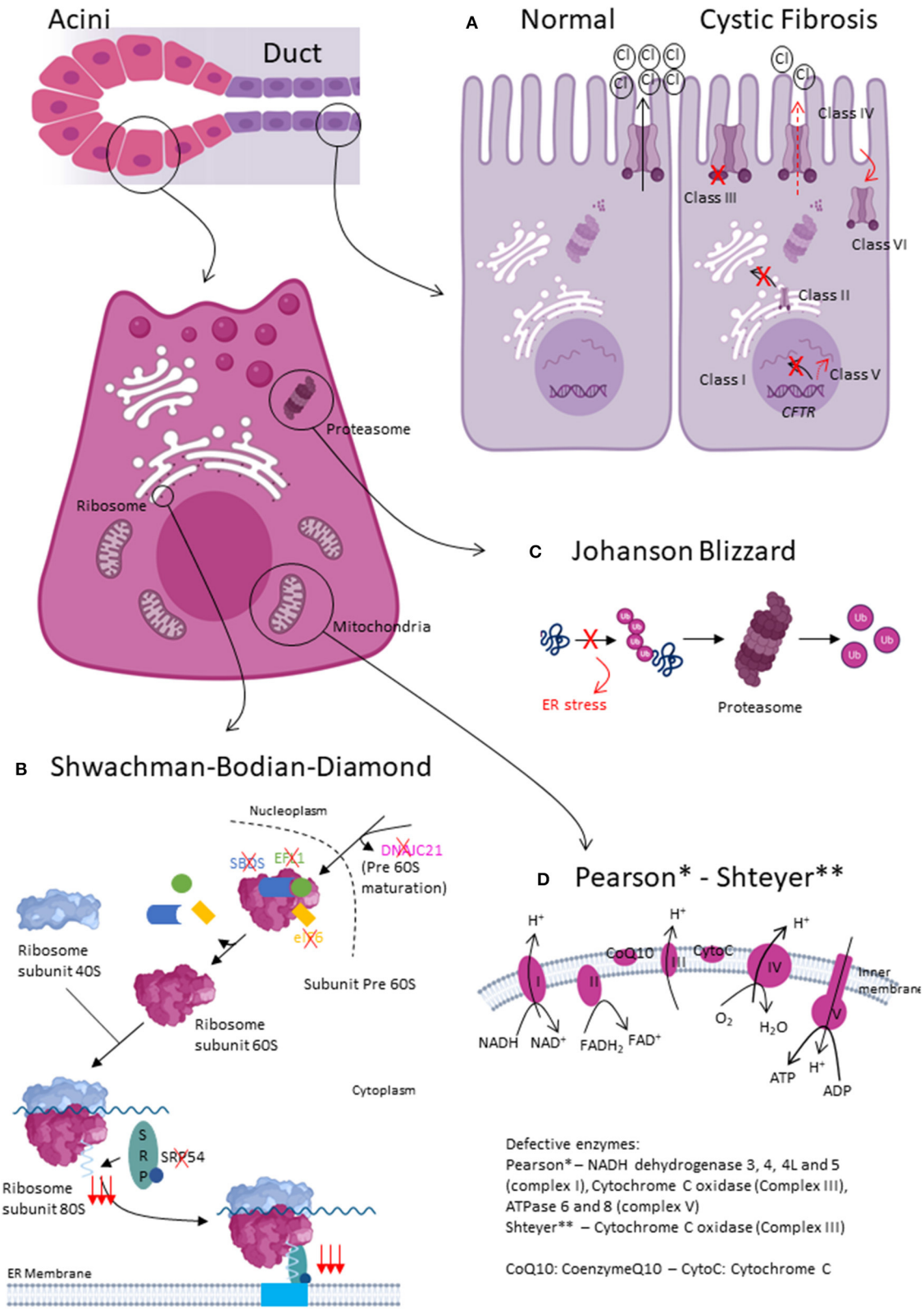

FIGURE 1
Pathophysiology of exocrine pancreatic insufficiency due to pancreatic exocrine tissue injury. **(A)** Normal and altered CFTR function. In Class I *CFTR* mutations, no CFTR protein is synthetized. In Class II, CFTR protein trafficking is defective. Class III mutations lead to impaired gating,

(Continued)

FIGURE 1
whereas Class IV lead to impaired conductance. In Class V and VI, there is, respectively, less CFTR protein or the protein is less stable. **(B)** Shwachman-Bodian-Diamond type1, type2 and SBDS-like syndromes mainly impact acinar cell function. All disease-causing mutations impact the final maturation steps of ribosome biogenesis. **(C)** Johanson Blizzard syndrome mainly effects acinar cell function. UBR1 mutations cause defective recognition of misfolded proteins, which can therefore not be degraded by the proteasome. **(D)** Pearson and Shteyer syndrome lead to mitochondrial dysfunction. Acini seem more affected than ductal cells.

Cross sectional studies of CF cohorts evidenced that almost 85% of patients present EPI (13, 14). Before the advent of CFTR modulators, CF children carrying two class I (reduced or absent synthesis) or II (block in protein processing) mutations became pancreatic insufficient (PI) within the first year of life (15).

EPI management encompasses nutritional support, pancreatic enzyme replacement therapy (PERT) and liposoluble vitamin supplementation following existing guidelines (16). Recent major therapeutic advances in CF care concern a more fundamental and targeted treatment of the disease, using CFTR modulators. CFTR modulators are small molecules which act specifically at the level of the defective mechanisms causing CF. The effects of these modulators on exocrine pancreatic function have not yet been studied as primary outcomes but rather as secondary or exploratory outcomes. Nevertheless, several data suggest that CFTR modulators may at least partially restore the exocrine pancreatic function in CF patients. Fecal elastase-1 rose above the clinical cutoff of 200 μg/g at least once in >25% of CF children with a CFTR gating-mutation treated with Ivacaftor for 24 weeks (17). Ivacaftor is a CFTR modulator that increases the open probability of CFTR, leading to enhanced chloride transport. Moreover, a reduction in immunoreactive trypsinogen (IRT) concentrations, a marker of pancreatic stress, has also been observed. Another study showed that the increase of fecal eslastase-1 and the decrease of serum IRT were maintained for an additional 84 weeks in CF children with a CFTR gating-mutation treated with Ivacaftor, suggesting that early CFTR modulation can potentially delay the decline of pancreatic function (18). The same tendency has been observed in CF children homozygous for F508del and treated with Ivacaftor/Lumacaftor combination therapy for 24 weeks (19). The effect of the triple combination (Elexacaftor/Tezacaftor/Ivacaftor) on the exocrine pancreatic function has not been studied yet. However, a significant increase in BMI in CF patients (heterozygous carriers for F508del and a minimal function CFTR mutation as well as in CF patients homozygous for F508del-CFTR mutation) treated with this medication has been described. The effect of CFTR modulators on BMI can be explained by different factors including a decreased resting energy expenditure, decreased gut inflammation, increased exocrine pancreatic function and an increased appetite (20–22). Other authors observed similar effects on growth parameters (23–25). Additional research is needed to further understand the specific effect of these modulators on exocrine pancreatic function.

Long-term survival of patients with CF is mainly dictated by the decline in lung function and by the occurrence of cirrhosis (8). Over the past decades, earlier diagnosis and careful disease management led to a dramatic improvement of patient quality of life and life expectancy which may now reach 50 years (26).

Shwachman-Bodian-Diamond syndrome type 1, type 2 and SBDS-like syndromes

Shwachman-Bodian-Diamond syndrome (SBDS) is the second most frequent cause of congenital EPI. Although originally described by Nezelof in 1961, the disease was named after physicians Shwachman, Bodian and Diamond in 1964. SBDS prevalence is estimated at 1/76.000 (27).

Approximately 90% of SBDS patients carry biallelic mutations in the Shwachman-Bodian-Diamond syndrome gene (*SBDS*, SBDS type1). More recently, the molecular spectrum of SBDS has been extended with biallelic mutations evidenced in elongation factor-like GTPase 1 (*EFL1*, SBDS type2), DnaJ heat shock protein family member C21 (*DNAJC21*), eukaryotic initiation factor (*eIF6*) or heterozygous mutation in signal recognition particle 54 (*SRP54*) genes. Although SBDS might seem genetically heterogeneous, all encoded dysfunctional proteins affect the final maturation steps of the large ribosomal subunit (Figure 1B). Ribosome biogenesis is a highly conserved and tightly regulated process involving more than 200 ribosomal proteins, ribosomal RNAs and small nuclear RNA molecules. Ribosome synthesis takes place in the cytoplasm and nucleolus. DNAJC21 seems involved in the biogenesis of nucleolar rRNA and in the cytoplasmic recycling of a factor involved in the nuclear export of the 60S ribosomal subunit. Furthermore, SBDS cooperates with EFL1 to release eIF6, an anti-association factor, from the 60S ribosomal subunit; enabling the 40S and 60S subunits to assemble and form the 80S ribosome. Finally, SRP54 is part of the SRP complex that escorts the nascent polypeptide of the 80S ribosome to the endoplasmic reticulum (ER) (28).

Pancreas necropsy in SBDS patients evidenced acinar hypoplasia and extensive fat infiltration without fibrosis or inflammation; the ductal cells and Langerhans islets were conserved. In parallel, quantitative pancreatic function tests in SBDS patients showed, in relation to the total acinar secretion,

normal fluid and anion outputs but severely reduced enzyme secretion (29). Conditional *SBDS* KO and hypomorphic mutants phenocopied SBDS in mice. Progressive acinar cell atrophy and reduction in number and size of zymogen granules, organelles storing pancreatic enzymes in acinar cells, were evidenced as from the post-natal period. These pathologic findings correlate with reduced pancreatic enzyme production. Acinar depletion was shown to result from p53 dependent senescence cell cycle arrest. However, the precise mechanism by which impaired ribosome biogenesis activates p53 remains unclear (30, 31).

A vast majority of patients with biallelic SBDS mutations are diagnosed during infancy with more or less severe infections and/or signs of malabsorption and failure to thrive (90%). Pancreatic ultrasound may show fatty gland changes.

The cardinal features of SBDS are bone marrow failure, EPI and skeletal anomalies (Table 1).

The management of EPI in SBDS patients is supportive and relies on PERT and liposoluble vitamin supplementation. A modest improvement in exocrine function can be seen over time in about 45% of patients to an extent they could discontinue PERT (32, 33). Reasons for this improvement remain obscure, although it is believed to be related to the physiologic maturation of pancreatic enzyme secretion with age. Regular pancreatic function monitoring is therefore warranted to diagnose patients that converted from PI to PS status. Serum trypsinogen has been shown to be a reliable marker to follow exocrine function in SBDS patients (34). Trypsinogen concentration below 50 μg/L (normal values 140–400 μg/L) are seen in PI patients and rise above 50 μg/L in PS patients, sometimes reaching normal values.

Long-term survival in SBDS patients is primarily dictated by severe infections and hematologic malignancies. Early development (24 and 38 years) (35, 36) of pancreatic cancer was also described in SBDS type1. Survival at 20 years was 87.4% (95%CI 75.3–93.8) in an Italian SBDS cohort (37) but remains poorly investigated beyond that age.

Johanson-Blizzard syndrome

Johanson-Blizzard syndrome (JBS) is a multisystemic autosomal recessive disorder with a prevalence estimated at 1/250.000 (38). JBS was first described in 1967 by Morris and Fisher (39), but was ultimately named after Drs Johanson and Blizzard in 1971 who delineated the syndromic spectrum of the disease (40). JBS was later found to be caused by homozygous or compound heterozygous mutations in the ubiquitin-protein ligase E3 component N-recognin 1 (*UBR1*) gene encoding one of a handful ligases of the N-end rule pathway (38). As such, wild-type UBR1 recognizes, binds and mark N-terminal residue of proteins ultimately leading to protein degradation by the proteasome. Mutated *UBR1* is hypothesized to interfere with proper protein degradation and result in unfolded protein accumulation in the ER, causing ER stress (Figure 1C).

Pancreas necropsy in JBS patients evidenced progressive acinar tissue loss and inflammatory infiltrates (41). This pathogenic process was shown to start during fetal life. Functional tests in pancreas of UBR1$^{-/-}$ mice showed markedly decreased zymogen outputs compared to controls following cholecystokinin injection, as well as increased susceptibility to pancreatitis. These findings suggest that the N-end rule pathway may be involved in zymogen processing or export (38) and that defective zymogen trafficking play a role in pancreatitis. Similarly, quantitative pancreatic function tests in JBS patients showed significantly decreased enzyme secretion but preserved fluid and anion outputs (29). Furthermore, serum trypsinogen concentration were markedly below normal ranges.

The cardinal features of JBS are EPI and hypo- or aplasia of the nasal wings (Table 1). EPI is invariably diagnosed during early infancy and doesn't improve over time. As *UBR1* expression is ubiquitous, all organs may be affected. Other facultative features include cranio-facial anomalies (dentition anomalies, scalp defects, microcephaly, cleft palate), short stature, developmental delay, congenital heart disease, endocrine glands dysfunction (hypothyroidism, diabetes mellitus), raised liver enzymes, genito-urinary and kidney defects.

The management of EPI in JBS patients include PERT and liposoluble vitamin supplementation. Endocrine hormone supplementation may further be required.

With adequate treatment, JBS patients survive into adulthood.

Pearson syndrome

Pearson syndrome is a very rare mitochondrial cytopathy, with an estimated prevalence <1/1.000.000. The disease was first described by Pearson in 1979 (42).

Rotig et al. discovered in 1995 that Pearson syndrome was caused by deletions ranging from 1.1-10kb in mitochondrial DNA (mtDNA) (43). Deletions give rise to 3 overlapping phenotypes: Pearson syndrome, Kearns Sayre and progressive external ophtalmoplegia. The disease expressivity doesn't seem related to the size or location of mtDNA deletion but rather to heteroplasmy (i.e., relative abundance of mitochondria carrying the mutation in each cell), tissue distribution (random partitioning of mitochondria) and tissue-specific vulnerability to oxidative stress. In Pearson syndrome, the deletion was found to be more abundant in blood compared to other cells. MtDNA encodes amongst others ATPases 6 and 8, cytochrome c oxidase III and NADH dehydrogenase 3, 4, 4L and 5. Hence, MtDNA deletion results in defective oxidative phosphorylation and impaired translation of messenger RNAs to proteins (Figure 1D). Pearson syndrome occurs sporadically which is suggestive for mutations arising de novo during either oogenesis or early embryonic development.

Histopathology of the patients' pancreas is characterized by acinar cell loss which are replaced by connective tissue and blood vessels. Ductal cells and Langerhans islets seem largely unaltered. However, functional pancreatic tests show not only decreased acinar function but also impaired fluid and electrolyte secretion (42).

Cardinal clinical features of Pearson syndrome are refractory sideroblastic anemia, bone marrow precursors vacuolization and EPI (Table 1). Patients with Pearson syndrome invariably develop EPI during infancy. The diagnosis is further comforted by increased serum lactate/pyruvate and ketone body ratios (44).

Patient management is mainly based on the symptomatic treatment of EPI (PERT and liposoluble vitamins supplementation), pancytopenia (folic acid, transfusion) and, although not evidenced-based, some authors have suggested to support the mitochondrial electron transport chain (L-carnitine, coenzyme Q). Of note, hypercaloric diets, high glucose containing diets and parenteral nutrition might precipitate mitochondrial dysfunction (44–46).

Pearson syndrome is often fatal in early childhood. Patient surviving this period develop symptoms of Kearns Sayre Syndrome; a neuromuscular disease characterized by early onset ophtalmoplegia and pigmentary retinopathy.

Shteyer syndrome

Shteyer syndrome is an exceptional multisystemic autosomal recessive disorder caused by biallelic mutations in the *COX4I2* gene coding for a component of the cytochrome c oxidase, the terminal enzyme in the mitochondrial respiratory chain (Figure 1D).

Cardinal disease features are exocrine pancreatic insufficiency, dyserythropoietic anemia and calvarial hyperostosis (Table 1). To date 4 patients have been described with the disease (47), all presenting failure to thrive and steatorrhea soon after birth. On imaging, the pancreas appeared atrophic and fatty.

The disease management is mainly based on the symptomatic treatment of EPI (pancreatic enzyme and liposoluble vitamins supplementation) and iterative transfusions for anemia.

Follow-up data is lacking to determine the outcome of affected patients.

Congenital pancreatic hypoplasia or agenesis

A handful patients present isolated or syndromic pancreas agenesis and subsequent exocrine and endocrine pancreatic insufficiency related to mutations in genes coding for transcription factors playing a critical role in early cell fate and pancreas development.

Isolated pancreas hypoplasia/agenesis

Pancreas agenesis is caused by biallelic mutations in *PDX1* gene (48), a transcription factor critical for pancreas development (49). Heterozygous patients develop maturity onset diabetes of the young type 4 (MODY4).

Syndromic pancreatic agenesia and congenital heart defects

The syndrome is caused by heterozygous mutations in *GATA6*, an important zinc-finger transcriptional regulator in the development and differentiation of numerous tissues (50). It has been suggested that heterozygous *GATA6* mutations result in protein loss of function and cause pancreatic agenesis through haploinsufficiency. Less than 40 patients were reported to date and most patient harbored *de novo* mutations (50–52).

The patient phenotype associates pancreas hypoplasia or agenesis, cardiac defects (ventricular septal defects, atrial septal defects, pulmonary stenosis, tetralogy of Fallot) and developmental delay (Table 1).

Syndromic pancreatic and cerebellar agenesis

Pancreas and cerebellar agenesis syndrome is caused by biallelic mutations in *PTF1A* gene encoding a transcription factor involved in cell fate during early pancreas development (53). The disease was described to date in 6 individuals (53–56), all born from consanguineous parents.

The patient's phenotype mainly associates EPI, neonatal diabetes mellitus and cerebellum agenesis (Table 1).

Patient life expectancy is short (<6 months).

Congenital isolated enzyme deficiency

Congenital pancreatic lipase deficiency is an exceptional mono-enzymatic cause of EPI. The disease results from by biallelic mutations in *PNLIP* gene (57). Only a handful patients have been described with the disease world-wide.

Dietary fat digestion relies on the joint action of pancreatic lipase, colipase and bile salts. In the duodenum, triglycerides are emulsified by bile salts. Colipase enables lipase to anchor the surface of lipid micelles and hydrolyze dietary long chain triglycerides to free fatty acids and monoacylglycerols. The main clinical symptom is steatorrhea and treatment relies on PERT.

Patients with isolated colipase (*CLPS* gene) (58) or combined lipase-colipase (59, 60) deficiency have historically been described but none were confirmed genetically.

Summary and perspectives

This mini-review illustrates the remarkable complexity and diversity of pathways leading to inherited EPI. The improvement of genetics has allowed to define the etiology of congenital EPI in a majority of patients. These progresses have led to a better understanding of the relationship between those gene mutations and the pathophysiologic mechanisms leading to altered pancreatic function. Until a decade ago, the treatment of EPI was essentially symptomatic. Since then, the discovery of targeted treatments in cystic fibrosis raises many hopes to slow down the exocrine function decline. The development of specific treatments for other rare causes of EPI remains a great challenge for the future.

Author contributions

SB drafted the CF part of the manuscript and reviewed the manuscript for intellectual content. IS drafted the rest of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

References

1. Zoppi G, Andreotti G, Pajno-Ferrara F, Njai DM, Gaburro D. Exocrine pancreas function in premature and full term neonates. *Pediatr Res.* (1972) 6:880–6. doi: 10.1203/00006450-197212000-00005

2. Fomon SJ, Ziegler EE, Thomas LN, Jensen RL, Filer LJ Jr. Excretion of fat by normal full-term infants fed various milks and formulas. *Am J Clin Nutr.* (1970) 23:1299–313. doi: 10.1093/ajcn/23.10.1299

3. Delachaume-Salem E, Sarles H. Normal human pancreatic secretion in relation to age. *Biol Gastroenterol.* (1970) 2:135–46.

4. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med.* (1973) 288:813–5. doi: 10.1056/NEJM197304192881603

5. Gaskin KJ, Durie PR, Lee L, Hill R, Forstner GG. Colipase and lipase secretion in childhood-onset pancreatic insufficiency. Delineation of patients with steatorrhea secondary to relative colipase deficiency. *Gastroenterology.* (1984) 86:1–7. doi: 10.1016/0016-5085(84)90582-1

6. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science.* (1989) 245:1066–73. doi: 10.1126/science.2475911

7. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science.* (1989) 245:1073–80. doi: 10.1126/science.2570460

8. Elborn JS. Cystic fibrosis. *Lancet.* (2016) 388:2519–31. doi: 10.1016/S0140-6736(16)00576-6

9. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell.* (1993) 73:1251–4. doi: 10.1016/0092-8674(93)90353-R

10. Oppenheimer EH, Esterly JR. Cystic fibrosis of the pancreas. Morphologic findings in infants with and without diagnostic pancreatic lesions. *Arch Pathol.* (1973) 96:149–54.

11. Kopelman H, Durie P, Gaskin K, Weizman Z, Forstner G. Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis. *N Engl J Med.* (1985) 312:329–34. doi: 10.1056/NEJM198502073120601

12. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros.* (2018) 17:153–78. doi: 10.1016/j.jcf.2018.02.006

13. Cade A, Walters MP, McGinley N, Firth J, Brownlee KG, Conway SP, et al. Evaluation of fecal pancreatic elastase-1 as a measure of pancreatic exocrine function in children with cystic fibrosis. *Pediatr Pulmonol.* (2000) 29:172–6. doi: 10.1002/(SICI)1099-0496(200003)29:3<172::AID-PPUL3>3.0.CO;2-1

14. Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr.* (1982) 100:857–62. doi: 10.1016/S0022-3476(82)80501-5

15. Walkowiak J, Sands D, Nowakowska A, Piotrowski R, Zybert K, Herzig KH, et al. Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations. *J Pediatr Gastroenterol Nutr.* (2005) 40:199–201. doi: 10.1097/00005176-200502000-00022

16. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clin Nutr.* (2016) 35:557–77. doi: 10.1016/j.clnu.2016.03.004

17. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med.* (2016) 4:107–15. doi: 10.1016/S2213-2600(15)00545-7

18. Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2–5years (KLIMB). *J Cyst Fibros.* (2019) 18:838–43. doi: 10.1016/j.jcf.2019.03.009

19. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2–5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med.* (2019) 7:325–35. doi: 10.1016/S2213-2600(18)30460-0

20. Griese M, Costa S, Linnemann RW, Mall MA, McKone EF, Polineni D, et al. Safety and efficacy of elexacaftor/tezacaftor/ivacaftor for 24 weeks or longer in

people with cystic fibrosis and one or more f508del alleles: interim results of an open-label phase 3 clinical trial. *Am J Respir Crit Care Med.* (2021) 203:381–5. doi: 10.1164/rccm.202008-3176LE

21. Gelfond D, Heltshe S, Ma C, Rowe SM, Frederick C, Uluer A, et al. Impact of CFTR Modulation on intestinal pH, motility, and clinical outcomes in patients with cystic fibrosis and the G551D mutation. *Clin Transl Gastroenterol.* (2017) 8:e81. doi: 10.1038/ctg.2017.10

22. Stallings VA, Sainath N, Oberle M, Bertolaso C, Schall JI. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. *J Pediatr.* (2018) 201:229–37 e4. doi: 10.1016/j.jpeds.2018.05.018

23. Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single phe508del allele. *N Engl J Med.* (2019) 381:1809–19. doi: 10.1056/NEJMoa1908639

24. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet.* (2019) 394:1940–8. doi: 10.1016/S0140-6736(19)32597-8

25. Burgel PR, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med.* (2021) 204:64–73. doi: 10.1164/rccm.202011-4153OC

26. MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the cystic fibrosis foundation patient registry. *Ann Intern Med.* (2014) 161:233–41. doi: 10.7326/M13-0636

27. Myers KC, Bolyard AA, Otto B, Wong TE, Jones AT, Harris RE, et al. Variable clinical presentation of shwachman-diamond syndrome: update from the north american shwachman-diamond syndrome registry. *J Pediatr.* (2014) 164:866–70. doi: 10.1016/j.jpeds.2013.11.039

28. Tummala H, Walne AJ, Williams M, Bockett N, Collopy L, Cardoso S, et al. DNAJC21 mutations link a cancer-prone bone marrow failure syndrome to corruption in 60s ribosome subunit maturation. *Am J Hum Genet.* (2016) 99:115–24. doi: 10.1016/j.ajhg.2016.05.002

29. Jones NL, Hofley PM, Durie PR. Pathophysiology of the pancreatic defect in johanson-blizzard syndrome: a disorder of acinar development. *J Pediatr.* (1994) 125:406–8. doi: 10.1016/S0022-3476(05)83286-X

30. Tourlakis ME, Zhong J, Gandhi R, Zhang S, Chen L, Durie PR, et al. Deficiency of Sbds in the mouse pancreas leads to features of shwachman-diamond syndrome, with loss of zymogen granules. *Gastroenterology.* (2012) 143:481–92. doi: 10.1053/j.gastro.2012.04.012

31. Tourlakis ME, Zhang S, Ball HL, Gandhi R, Liu H, Zhong J, et al. *In Vivo* senescence in the Sbds-deficient murine pancreas: cell-type specific consequences of translation insufficiency. *PLoS Genet.* (2015) 11:e1005288. doi: 10.1371/journal.pgen.1005288

32. Hill RE, Durie PR, Gaskin KJ, Davidson GP, Forstner GG. Steatorrhea and pancreatic insufficiency in shwachman syndrome. *Gastroenterology.* (1982) 83:22–7. doi: 10.1016/S0016-5085(82)80279-5

33. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR. Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology.* (1996) 111:1593–602. doi: 10.1016/S0016-5085(96)70022-7

34. Moore DJ, Forstner GG, Largman C, Cleghorn GJ, Wong SS, Durie PR. Serum immunoreactive cationic trypsinogen: a useful indicator of severe exocrine dysfunction in the paediatric patient without cystic fibrosis. *Gut.* (1986) 27:1362–8. doi: 10.1136/gut.27.11.1362

35. Dhanraj S, Manji A, Pinto D, Scherer SW, Favre H, Loh ML, et al. Molecular characteristics of a pancreatic adenocarcinoma associated with shwachman-diamond syndrome. *Pediatr Blood Cancer.* (2013) 60:754–60. doi: 10.1002/pbc.24453

36. Nakaya T, Kurata A, Hashimoto H, Nishimata S, Kashiwagi Y, Fujita K, et al. Young-age-onset pancreatoduodenal carcinoma in shwachman-diamond syndrome. *Pathol Int.* (2014) 64:75–80. doi: 10.1111/pin.12133

37. Cesaro S, Pegoraro A, Sainati L, Lucidi V, Montemitro E, Corti P, et al. A prospective study of hematologic complications and long-term survival of Italian patients affected by shwachman-diamond syndrome. *J Pediatr.* (2020) 219:196–201 e1. doi: 10.1016/j.jpeds.2019.12.041

38. Zenker M, Mayerle J, Lerch MM, Tagariello A, Zerres K, Durie PR, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-blizzard syndrome). *Nat Genet.* (2005) 37:1345–50. doi: 10.1038/ng1681

39. Morris MD, Fisher DA. Trypsinogen deficiency disease. *Am J Dis Child.* (1967) 114:203–8. doi: 10.1001/archpedi.1967.02090230133019

40. Johanson A, Blizzard R. A syndrome of congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. *J Pediatr.* (1971) 79:982–7. doi: 10.1016/S0022-3476(71)80194-4

41. Vanlieferinghen PH, Borderon C, Francannet CH, Gembara P, Dechelotte P. Johanson-blizzard syndrome. A new case with autopsy findings. *Genet Couns.* (2001) 12:245–50.

42. Pearson HA, Lobel JS, Kocoshis SA, Naiman JL, Windmiller J, Lammi AT, et al. A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. *J Pediatr.* (1979) 95:976–84. doi: 10.1016/S0022-3476(79)80286-3

43. Rotig A, Cormier V, Blanche S, Bonnefont JP, Ledeist F, Romero N, et al. Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. *J Clin Invest.* (1990) 86:1601–8. doi: 10.1172/JCI114881

44. Farruggia P, Di Marco F, Dufour C. Pearson syndrome. *Expert Rev Hematol.* (2018) 11:239–46. doi: 10.1080/17474086.2018.1426454

45. Kerr DS. Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. *Mol Genet Metab.* (2010) 99:246–55. doi: 10.1016/j.ymgme.2009.11.005

46. Seneca S, De Meirleir L, De Schepper J, Balduck N, Jochmans K, Liebaers I, et al. Pearson marrow pancreas syndrome: a molecular study and clinical management. *Clin Genet.* (1997) 51:338–42. doi: 10.1111/j.1399-0004.1997.tb02484.x

47. Shteyer E, Saada A, Shaag A, Al-Hijawi FA, Kidess R, Revel-Vilk S, et al. Exocrine pancreatic insufficiency, dyserythropoeitic anemia, and calvarial hyperostosis are caused by a mutation in the COX4I2 gene. *Am J Hum Genet.* (2009) 84:412–7. doi: 10.1016/j.ajhg.2009.02.006

48. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. *Nat Genet.* (1997) 15:106–10. doi: 10.1038/ng0197-106

49. Jonsson J, Carlsson L, Edlund T, Edlund H. Insulin-promoter-factor 1 is required for pancreas development in mice. *Nature.* (1994) 371:606–9. doi: 10.1038/371606a0

50. Allen HL, Flanagan SE, Shaw-Smith C, De Franco E, Akerman I, Caswell R, et al. GATA6 haploinsufficiency causes pancreatic agenesis in humans. *Nat Genet.* (2011) 44:20–2. doi: 10.1038/ng.1035

51. Yorifuji T, Kawakita R, Hosokawa Y, Fujimaru R, Yamaguchi E, Tamagawa N. Dominantly inherited diabetes mellitus caused by GATA6 haploinsufficiency: variable intrafamilial presentation. *J Med Genet.* (2012) 49:642–3. doi: 10.1136/jmedgenet-2012-101161

52. Yu L, Bennett JT, Wynn J, Carvill GL, Cheung YH, Shen Y, et al. Whole exome sequencing identifies de novo mutations in GATA6 associated with congenital diaphragmatic hernia. *J Med Genet.* (2014) 51:197–202. doi: 10.1136/jmedgenet-2013-101989

53. Hoveyda N, Shield JP, Garrett C, Chong WK, Beardsall K, Bentsi-Enchill E, et al. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. *J Med Genet.* (1999) 36:700–4.

54. Sellick GS, Barker KT, Stolte-Dijkstra I, Fleischmann C, Coleman RJ, Garrett C, et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat Genet.* (2004) 36:1301–5. doi: 10.1038/ng1475

55. Al-Shammari M, Al-Husain M, Al-Kharfy T, Alkuraya FS. A novel PTF1A mutation in a patient with severe pancreatic and cerebellar involvement. *Clin Genet.* (2011) 80:196–8. doi: 10.1111/j.1399-0004.2010.01613.x

56. Tutak E, Satar M, Yapicioglu H, Altintas A, Narli N, Herguner O, et al. A Turkish newborn infant with cerebellar agenesis/neonatal diabetes mellitus and PTF1A mutation. *Genet Couns.* (2009) 20:147–52.

57. Lowe ME, Rosenblum JL, Strauss AW. Cloning and characterization of human pancreatic lipase cDNA. *J Biol Chem.* (1989) 264:20042–8. doi: 10.1016/S0021-9258(19)47215-3

58. Hildebrand H, Borgstrom B, Bekassy A, Erlanson-Albertsson C, Helin I. Isolated co-lipase deficiency in two brothers. *Gut.* (1982) 23:243–6. doi: 10.1136/gut.23.3.243

59. Ghishan FK, Moran JR, Durie PR, Greene HL. Isolated congenital lipase-colipase deficiency. *Gastroenterology.* (1984) 86:1580–2. doi: 10.1016/S0016-5085(84)80175-4

60. Ligumsky M, Granot E, Branski D, Stankiewicz H, Goldstein R. Isolated lipase and colipase deficiency in two brothers. *Gut.* (1990) 31:1416–8. doi: 10.1136/gut.31.12.1416

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Risk factors for the progression from acute recurrent to chronic pancreatitis among children in China

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Background: Risk factors for progression from acute recurrent pancreatitis (ARP) to chronic pancreatitis (CP) in children are poorly understood.

Aim: To summarize the clinical characteristics of children with ARP and CP, identify the risk factors of CP, and investigate the factors associated with rapid progression from initial onset of ARP to CP.

Methods: The following variables were included in the risk factor analysis: sex, age at onset, family history, pancreas or biliary tract structural abnormalities, and genetic variations. Univariate and multivariate logistic regression analyses were used to assess the risk factors of CP. The Kaplan–Meier curves of the ARP progression to CP for various risk factor groupings were constructed and compared using the log-rank test. The Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR) of progression to CP for each risk variable.

Results: In total, 276 children were studied, of whom 136 progressed to CP. Among them, 41 had pancreatic duct obstructive disease; 105 underwent genetic testing, of whom 68 were found to have genetic variations. Among the remaining 140 patients who did not progress to CP, 61 had biliary obstructions. Forty-three of these children underwent genetic testing, and 15 were found to have genetic variations. Risk factor analysis showed that children with gene mutations were at a higher risk of progressing to CP [odds ratio (OR) = 3.482; 95% confidence interval (CI): 1.444–8.398; P = 0.005]; children with pancreas divisum (PD) had a higher risk of CP than those without (OR = 8.665; 95% CI: 1.884, 9.851; P = 0.006). Further, children whose first ARP occurred at an older age might develop CP faster (HR = 1.070; 95% CI: 1.003, 1.141; P = 0.039). Children with gene mutations had a faster rate of progression to CP after onset than children without gene mutations (HR = 1.607; 95% CI: 1.024, 2.522; P = 0.039), *PRSS1* gene mutations were more associated (P = 0.025). There was no

difference in the rate of progression from ARP to CP in children with PD (P = 0.887); however, endoscopic retrograde cholangiopancreatography (ERCP) intervention delayed the progression to CP in ARP patients with PD (P = 0.033).

Conclusion: *PRSS1* gene mutations and PD are key risk factors for ARP progression to CP in children. PD itself does not affect the disease progression rate, but therapeutic ERCP can be beneficial to patients with ARP with symptomatic PD and delay the progression to CP.

KEYWORDS

acute recurrent pancreatitis, chronic pancreatitis, pediatrics, pancreas divisum, risk factors

Introduction

Pediatric pancreatitis is often associated with high disease burden for children and families, especially for acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP), with multiple emergency room visits and hospitalizations, and medical, endoscopic and surgical procedures. Moreover, patients with CP have an increased lifetime risk for pancreatic adenocarcinoma (1, 2). ARP is defined as two or more distinct episodes of acute pancreatitis (AP). Studies have shown that approximately 9–35% of children with AP develop ARP (1, 3). CP is a chronic inflammatory process that occurs in the pancreas, which leads to irreversible morphological changes and progressive impairment of exocrine and endocrine functions (4, 5). Pediatric ARP and CP are relatively rare conditions; CP has an incidence of approximately 0.5 cases per 100,000 children per year. ARP occurs frequently as a precursor of CP and is thought to be on the same disease continuum (3, 5, 6).

Most of the published findings regarding risk factors of ARP and CP are studies involving adults. However, the etiologies of ARP and CP in children are different from those in adults; they mainly involve genetic and anatomical factors in children, whereas the contribution of environmental risks, such as smoking, is negligible (1, 6, 7). A few studies have analyzed risk factors for children with CP; however, these pediatric studies are limited in that the cohorts are small, a cohort of Chinese children is rare. The factors contributing to AP recurrence and the progression from ARP to CP in children remain poorly understood and controversial.

This study aimed to characterize the demographic and clinical characteristics of children with ARP and CP to identify the risk factors of CP and the factors that accelerate the progress from the first episode of ARP to CP in Chinese children.

Materials and methods

Study design and participants

The clinical data of children with ARP and CP admitted to Shanghai Children's Medical Center (SCMC) from January 2014 to March 2021 were retrospectively analyzed, including sex, age of onset, age at CP diagnosis, family history, imaging examination of the pancreatic duct or biliary tract, and genetic variation. We aimed to identify the risk factors contributing to CP and investigate the factors associated with rapid progression from the first episode of AP to CP.

Inclusion criteria: (1) children aged <18 years; (2) children was consistent with the diagnostic criteria of ARP or CP; and (3) patients who had been hospitalized at SCMC. Exclusion criteria: patients with incomplete clinical data or those without follow-up data.

The diagnostic criteria used were those of the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) (8). ARP is defined as two or more episodes of AP occurring at least 1 month apart with the resolution of symptoms between episodes, or complete normalization of pancreatic enzyme levels with the complete resolution of clinical symptoms between episodes of AP irrespective of the interval between episodes. Children with irreversible structural changes in the pancreas, with or without abdominal pain, exocrine pancreatic insufficiency, or diabetes, were classified as having CP.

Pancreatic and bile duct images of all patients were obtained using magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP), computerized tomography (CT), or endoscopic retrograde cholangiopancreatography (ERCP).

Genetic testing was performed by the Genetic Diagnosis Center of SCMC. All patients were evaluated with targeted next-generation sequencing (NGS) as described previously (9).

The targeted-NGS panel used in this study contains 2,742 disease-causing genes, covering all known causative genes for pancreatitis. Briefly, the sequencing library was prepared using the Agilent SureSelect XT Inherited Disease Panel (for targeted-NGS) or SureSelect XT Human All Exon V6 kit (Agilent Technologies, Santa Clara, CA, United States), and sequencing was performed by the Illumina Hiseq 2500. The sequence reads were aligned to a reference human genome (Human 37.3; SNP135) by NextGENe® (SoftGenetics LLC, State College, PA, United States), and were then uploaded to the Ingenuity® Variant Analysis™ (Ingenuity Systems, Redwood City, CA, United States) for filtering and annotation. The variants identified by targeted-NGS were validated by Sanger sequencing using the ABI 3700 sequencer (Applied Biosystems, Foster City, CA, United States), in indicated patient and their parents. This study was approved by the Ethics Committee of SCMC and informed consent was obtained from the patients and their parents.

Statistical analysis

The median and interquartile range (IQR) were used to characterize non-normally distributed data, and the Mann–Whitney U test was used for between-group comparisons. Categorical variables are expressed as frequencies and percentages and were compared between groups using the Chi-square test or Fisher's exact test. The risk factors for CP were assessed using univariate and multivariate logistic regression analyses. Using the log-rank test, we constructed and compared the Kaplan–Meier curves of disease progression from the first onset of ARP to the diagnosis of CP in different risk factor groups. The progression time, which is the time taken to progress from ARP to CP, was determined by setting the time of the first AP onset as the starting time and the time of CP diagnosis as the ending time. However, for those who did not progress to CP, the end time was the study deadline. Cox proportional hazards regression was performed by fitting the progression time to obtain the hazard ratio (HR) and 95% confidence interval (CI) of each variable affecting the progression of ARP to CP. All statistical analyses were performed using the SPSS software (version 26.0). Two-sided *P*-values < 0.05 were considered statistically significant.

Results

The characteristics of acute recurrent pancreatitis and chronic pancreatitis

In total, 276 children were enrolled in this study; 140 patients were diagnosed with ARP without progression to CP, and 136 were diagnosed with CP. Demographic and etiological analyses are shown in **Table 1**. The possibilities of male and female patients with ARP developing CP are not significantly different. The median age at ARP and CP diagnoses were 5.0 and 5.8 years, respectively. Approximately 0.7% of the children with ARP and 8.1% of those with CP had a family history of pancreatitis, and the difference was statistically significant ($P = 0.003$).

Etiology analysis

Of the 276 children included in this study, 148 completed genetic testing, including 43 children with ARP and 105 children with CP. The results of the etiological analysis are presented in **Table 1**. Genetic and biliary obstructions were the most common causes of ARP. Fifteen of the 43 (34.9%) children with ARP who completed genetic testing had pathogenic or clinically significant probable pathogenic variants: 12 had *SPINK1* mutations, two had *PRSS1* mutations, and one had both. Of the 140 children with APR, 61 had bile duct obstruction (43.6%), including 11 with choledochal cysts, 28 with pancreaticobiliary maljunction (PBM) with bile duct stone formation, 14 with both choledochal cyst and PBM, and the remaining eight patients with tumor compression or infiltration of the bile duct, including three patients with neuroblastomas, one intraperitoneal lymphangioma, and four lymphomas.

Gene mutations and structural abnormalities in the pancreatic duct are CP's most common etiological causes. Of the 105 children with CP who underwent genetic testing,

TABLE 1 Demographic characteristics and etiology analysis of children with ARP or CP.

Demographic characteristics	ARP	CP	*P*-value
Number	140	136	0.916
Male, *N* (%)	65 (46.4)	64 (47.1)	
Female, *N* (%)	75 (53.6)	72 (52.9)	
Age at onset			
Median (IQR)	5.0 (3.0, 8.0)	5.8 (3.5, 9.0)	0.094
≤6 years of age at first attack	91 (65.0)	77 (56.6)	0.154
Family history of pancreatitis, *N* (%)	1 (0.7)	11 (8.1)	**0.003**
Risk factors, *N* (%)			**<0.001**
Genetic*	15/43 (34.9)	68/105 (64.8)	
Biliary obstruction	61 (43.6)	10 (7.4)	
Pancreatic duct obstruction	7 (5.0)	41 (30.1)	
Medications	22 (15.7)	4 (2.9)	
Systemic disease	6 (4.3)	1 (0.7)	
Infection	3 (2.1)	0	
Trauma	1 (0.7)	1 (0.7)	
Inborn errors of metabolism	1 (0.7)	2 (1.47)	
Unknown	24 (17.1)	28 (20.6)	

Values are presented as frequencies (%) or medians (interquartile ranges). Statistically significant differences are indicated in bold.
*In total, 148 patients with completed genetic testing, including 43 children with ARP and 105 children with CP.

68 (64.8%) had genetic mutations: 40 had *SPINK1* mutation, among them, 37 cases were c.194 + 2T > C variations; 23 had *PRSS1* mutation, mainly c.365G > A (p.R122 H) and c.623 G > C (p.Gly208Ala) variations; two had both *SPINK1* and *PRSS1* mutations, one had *CFTR* mutation, one had *PKHD1* gene mutation, and one had both *PRSS1* and *CFTR* mutations. Forty-one children with CP had pancreatic duct obstructive disease, including 35 with pancreas divisum (PD) and 6 with annular pancreases.

In addition, 22 children with ARP experienced recurrent pancreatitis due to drug-related factors. One of them had a nephrotic syndrome that may be related to prednisone use, and the remaining 21 had chemotherapy drug L-asparaginase-induced pancreatitis. The results showed that other congenital metabolic diseases, systemic diseases, infections, and trauma can also cause ARP or CP, which are rare. Congenital metabolic diseases included two cases of familial hypercholesterolemia (FH) caused by an *LDLR* gene mutation and one case of hypertriglyceridemia caused by an *APOB* gene mutation; systemic diseases included three cases of Henoch–Schonlein purpura (HSP), two cases of systemic lupus erythematosus (SLE), one case of autoimmune pancreatitis (AIP) with ARP, and one case AIP with CP.

However, 24 cases (17.1%) of ARP had unknown etiology, 12 (50.0%) of whom had not undergone genetic testing; and 28 (20.6%) cases of CP had unknown etiologies, 15 (53.6%) of whom had not undergone genetic testing.

Risk factors for chronic pancreatitis

The present study included sex, family history, gene mutations, and congenital pancreatic or bile duct structural abnormalities as in the risk factor analysis. Based on the data analysis of 136 children with CP, family history, genetic abnormalities, and structural abnormalities of the pancreatic duct or bile duct were high-risk factors for CP in the univariate analysis ($P < 0.05$).The results of the multivariate analysis showed that, compared with children without gene mutations, children with genetic abnormalities had a higher risk of developing CP (OR = 3.482, 95% CI: 1.444, 8.98; $P = 0.005$).In order to clarify the significance of a single gene mutation type for CP, we added a multivariate model 2, the *SPINK1* and *PRSS1* gene mutations were used as independent variables. There was no significant difference in the risk of developing CP in children with ARP with or without *SPINK1* mutation. However, both univariate and multivariate analysis indicated that *PRSS1* was a higher risk factor for CP ($P = 0.026$ and $P = 0.03$, respectively). Second, children with pancreatic duct obstruction, especially children with PD, had a higher risk of CP than those without PD (OR = 8.665, 95% CI: 1.884, 39.851; $P = 0.006$) (Table 2). Due to the small number of cases of annular pancreas and the large statistical bias, risk factor analysis was not performed separately.

Factors that contribute to the progression from the first onset acute recurrent pancreatitis to chronic pancreatitis

The mean [standard deviation (SD)] follow-up time for ARP was 2.5 (1.4) years, ranging from 0.5 to 7.0 years; the mean (SD) time for CP was 1.4 (1.6) years, ranging from 0 to 7.0 years. Of the 136 children with CP, 26 were diagnosed with CP at the first visit, and 110 (80.9%) had a history

TABLE 2 Logistic regression analysis results for CP risk factors in children.

Variables	Univariate model		Multivariable model 1		Multivariable model 2	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex	0.975 (0.608, 1.565)	0.916				
Age of onset	1.043 (0.977, 1.113)	0.212				
Family history	**12.232 (1.557, 96.099)**	**0.017**				
Pancreatic duct obstruction*	**17.707 (5.314, 59.007)**	**<0.001**				
Pancreas divisum	**15.825 (4.734, 52.899)**	**<0.001**	**8.665 (1.884, 39.851)**	**0.006**	**7.391 (1.660, 32.906)**	**0.009**
Biliary obstruction	**0.210 (0.111, 0.397)**	**<0.001**	0.728 (0.255, 2.079)	0.553		
Pancreaticobiliary maljunction	**0.185 (0.088, 0.388)**	**<0.001**				
Biliary cyst	**0.250 (0.104, 0.599)**	**0.002**				
Genetic variation	**3.524 (1.679, 7.395)**	**0.001**	**3.482 (1.444, 8.398)**	**0.005**		
SPINK1	1.478 (0.692, 3.160)	0.313				
PRSS1	**4.167 (1.186, 14.634)**	**0.026**			**4.121 (1.151, 14.757)**	**0.030**

*Pancreatic duct obstruction includes pancreatic division and annular pancreas. The number of annular pancreas cases was too small to be statistically analyzed separately.
Statistically significant differences ($P < 0.05$) are indicated in bolded *P*-value.
OR, odds ratio; *PRSS1*, cationic trypsinogen; *SPINK1*, serine protease inhibitor Kazal-type 1.

of recurrent pancreatitis. The median progression time from the initial onset of ARP to CP was 1.4 years (IQR 0.6–3.0 years). In the univariate analysis, family history (P = 0.015), abnormal pancreatic duct structure (P = 0.002), and gene mutation (P = 0.015) were all risk factors. Multivariate Cox hazard ratio model analysis showed that onset age and gene mutations were statistically significant. The older the age at the first onset, the faster the rate of progression to CP (HR = 1.070; 95% CI: 1.003, 1.141; P = 0.039), whereas gene mutation was an independent risk factor, with the occurrence of a more rapid progression to CP with genetic variation (HR = 1.607; 95% CI: 1.024, 2.522; P = 0.039) (**Table 3** and **Figure 1**). We added multivariate model 2 to clarify the significance of gene mutation type for pancreatitis progression. The role of *SPINK1* in disease progression was not statistically significant; however, *PRSS1* mutation was a risk factor for the progression from ARP to CP in the multivariate analysis (P = 0.025) (**Table 3**).

The relationship between pancreas divisum and rapid progression to chronic pancreatitis in children

Thirty-five children with CP had PD. ERCP was performed in 15 children before progression to CP due to recurrent pancreatitis, including pancreatic duct stent placement or sphincterotomy. In comparison, ERCP treatment delayed the time to progress to CP in symptomatic PD (P = 0.033). Moreover, 28/35 children underwent genetic testing, and 17 cases were accompanied by gene mutations, including 10 cases of *SPINK1* variation and seven cases of *PRSS1* variation. With or without genetic variation, children with ARP accompanied by PD progressed to CP at approximately the same rate (P = 0.887) (**Table 4**).

Discussion

This was a longitudinal retrospective study of 276 children that represented a larger population of well-characterized children with ARP or CP. In terms of age of onset, there were no sex differences between children with ARP and those with CP. The median age at first onset was approximately 5.0 years and 5.8 years for those with APR and CP, respectively. Compared with patients in other countries, patients in China are more likely to develop ARP and CP earlier (10, 11). In our study, approximately 8.1% of children with CP had a family history of pancreatitis, lower than the values reported in other countries, and the INSPPIRE reported that the prevalence of family history of pancreatitis in children with CP is approximately 23.6%, this difference may be related to ethnic differences (10).

The etiology of ARP or CP differs significantly between adults and children, with alcohol consumption and cholelithiasis being the major causes of ARP and CP in adults (12, 13). In this study, congenital bile duct or pancreatic duct structural abnormalities or gene mutations were the common causes of pancreatitis recurrence in children. However, 17.1 and 20.6% had ARP and CP, respectively, of unknown etiologies, the proportion of unknown etiology is similar to other studies on the etiology of recurrent pancreatitis (14). This relatively high proportion may be because some children with ARP or CP with genetic factors did not complete genetic testing or because of some other unknown causes of pancreatitis recurrence.

The number of drug-related risk factors in the etiological analysis of ARP in this study was higher than that in other studies (15, 16), probably because SCMC is one of the largest cancer centers in China, with many hematopathy patients receiving treatment at the center, and because asparaginase is a commonly used chemotherapy drug for acute lymphoblastic leukemia, thus increasing the proportion of cases with drug-induced ARP. Similarly, the number of patients with ARP

TABLE 3 Factors that contribute to the progression of ARP to CP from first onset.

Variables	Univariate model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex	0.860 (0.614, 1.205)	0.381				
Age of onset	1.038 (0.991, 1.087)	0.112	**1.070 (1.003, 1.141)**	**0.039**	**1.079 (1.015, 1.148)**	**0.015**
Family history	**2.159 (1.163, 4.007)**	**0.015**	1.536 (0.790, 2.985)	0.206	1.360 (0.868, 2.132)	0.180
Pancreatic duct obstruction	**1.803 (1.238, 2.627)**	**0.002**	0.761 (0.483, 1.198)	0.238	0.700 (0.359, 1.364)	0.295
Pancreas divisum	**1.679 (1.140, 2.471)**	**0.009**				
Annular pancreas	**2.360 (1.038, 5.364)**	**0.040**				
Genetic variation	**1.670 (1.106, 2.522)**	**0.015**	**1.607 (1.024, 2.522)**	**0.039**		
SPINK1	1.243 (0.835, 1.851)	0.284				
PRSS1	1.434 (0.912, 2.254)	0.118			**1.579 (1.060, 2.352)**	**0.025**

Statistically significant differences are shown in bold. HR, hazard ratio.

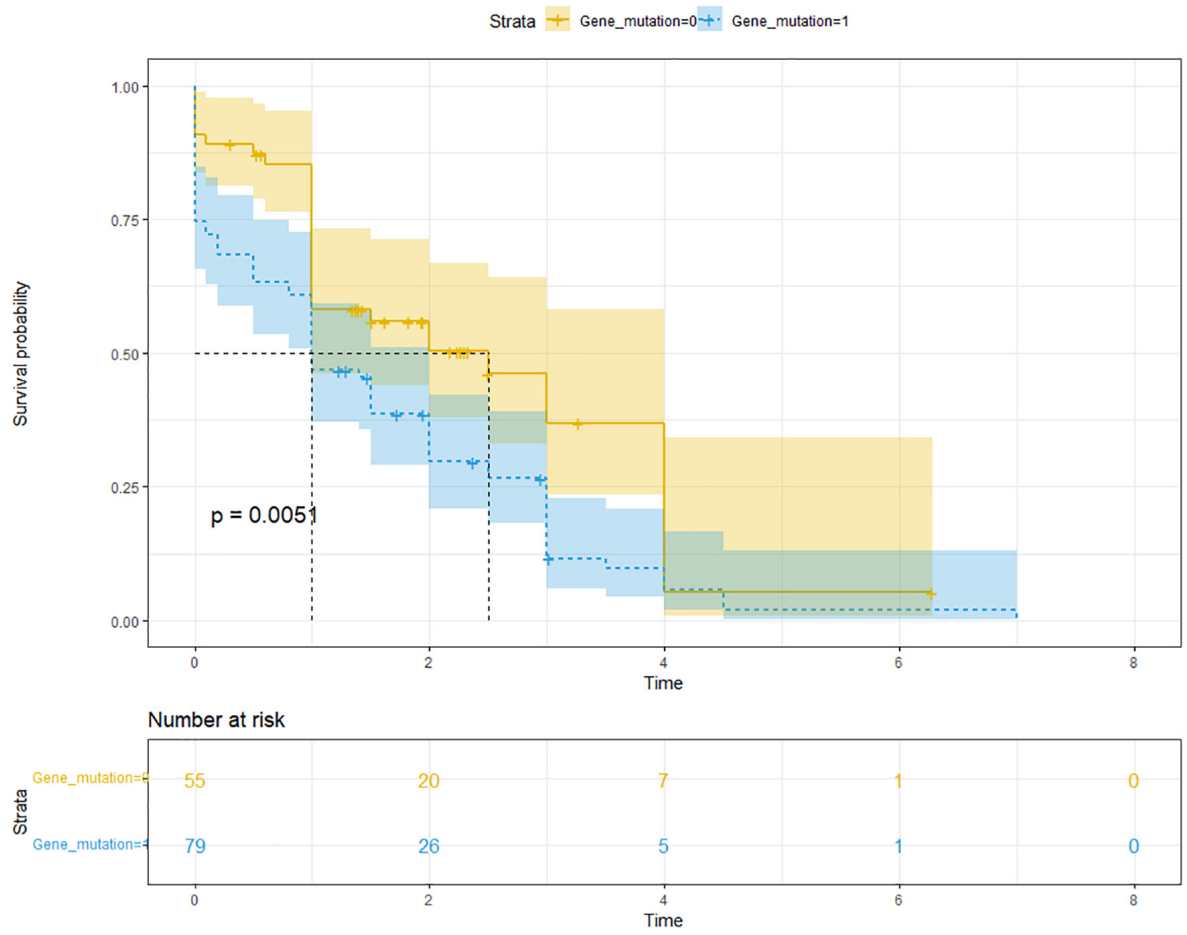

FIGURE 1
Comparison of the Kaplan–Meier curves of CP progression between those with (blue) and without (yellow) gene mutations showed a significantly faster rate of progression from ARP to CP (HR of progression was 1.607; 95% CI: 1.024, 2.522; $P = 0.039$). Median time of progression to CP was 1.0 years for those with gene mutation and 2.5 years for those without gene mutations. HR, hazard ratio; CI, confidence interval.

caused by tumor compression or infiltration increased in the etiology of this study.

Most children with CP have histories of recurrent pancreatitis before diagnosis. In this study, 80.9% of the children with CP had recurrent pancreatitis before the diagnosis of CP. We focused on analyzing the high-risk factors for CP and the risk factors that promote the rapid progression of ARP to CP. This study found that genetic factors are independent risk factors for CP. The gene detection rate of CP in children was 64.8%. The *SPINK1* mutation is the most common in China, especially the C.194 + 2T > C variant, followed by the *PRSS1* mutation, but the *CFTR* mutation is less common. No *CTRC* gene mutations were detected in our study. The gene mutation results of the children in this study were consistent with those of indigenous adults but different from the results in other countries (11). In Japan, the United States, and other countries, *PRSS1* and *CFTR* mutations are more common (17–20).

We further confirmed that genetic mutations are a high-risk factor for CP. Compared with children without gene mutations, children with gene mutations associated with pancreatitis have a higher risk for CP and pancreatitis progression rate, especially

TABLE 4 Relationship between pancreatic division and rapid progression of CP in children.

Variables	*N* (%)	Mean rank	*P*-value
ERCP			**0.033**
Yes	15/35 (42.9)	22.23	
No	20/35 (57.1)	14.83	
Genetic variation			0.887
Yes	17/28 (60.7)	14.68	
No	11/28 (39.3)	14.23	

Statistically significant differences ($P < 0.05$) are shown in bold. ERCP, endoscopic retrograde cholangiopancreatography.

those with *PRSS1* gene mutation. The findings reported by the INSPPIRE were that at least one pancreatitis-related gene mutation was found in 48 and 73% of ARP and CP patients, respectively, and *SPINK1* and *PRSS1* mutations were more closely related to CP, and children with ARP with pathogenic *PRSS1* variants rapidly progress to CP (1, 10). Overall, compared to normal children, previous studies have demonstrated the association of *SPINK1* and *PRSS1* with ARP and CP (7, 11); nonetheless, using children with ARP as a reference in this study, *PRSS1* mutations were more closely associated with CP and pancreatitis progression than *SPINK1* mutations. Another high-risk factor contributing to the recurrence of pancreatitis in children is structural abnormalities of the congenital bile duct or pancreatic duct. Previous analyses have shown that biliary diseases such as biliary obstruction can cause recurrent biliary pancreatitis. It is a common cause of recurrent pancreatitis but not a risk factor for CP in children. Structural abnormalities of the congenital pancreatic duct, especially PD, are independent risk factors for CP. However, whether PD is a high-risk factor for CP remains controversial. The results from the INSPPIRE suggest that PD may be a risk factor for ARP and CP in children, independent of genetic risk factors (21). However, it is also believed that PD alone is not a risk factor for pancreatitis but has synergistic effects with genetic factors, especially CFTR gene mutations, which can promote the development of CP (22, 23). Therefore, in this study, we conducted an independent analysis of this issue and identified PD as a risk factor for CP in children. Children with PD presenting with pancreatitis were more likely to develop CP, but this did not affect the disease's natural history. Moreover, gene mutations and PD do not synergistically promote a faster progression to CP. However, therapeutic ERCP, such as stenting or sphincterotomy to relieve pancreatic duct obstruction, appears to provide benefit in delaying progression to CP in children with PD with recurrent pancreatitis. It would be informative to know what the results in a Chinese population are. This study also found that the age of onset was inversely correlated with the rate of disease progression, which is similar to the result reported by the INSPPIRE (10), which showed that children with ARP with an onset age >6 years progressed to CP faster than children with an onset age <6 years. Regarding the speculation about the cause of this phenomenon, it may be due to the atypical initial symptoms of pancreatic disease in some children, so there is a possibility of delayed diagnosis. Gene mutations are another risk factor for disease progression. Patients with gene mutations progress to CP more quickly after the first onset of pancreatitis.

This study focused on the risk factors for CP and for ARP's progression to CP in a large sample of Chinese children for the first time through a longitudinal study. Some of these study's findings are similar to those from other countries. We also obtained some interesting findings that are quite different from those of other studies. Therefore, this study expands the breadth of existing related research. However, this study had some limitations; it was a retrospective study, and all data were obtained from the SCMC, and some patients came from the pediatric cancer center of SCMC, which may cause inclusion criteria and population bias issues. However, this hospital is the only diagnosis and treatment center for children with chronic pancreatic diseases in China. Therefore, the patients came from many provinces across the country, and the present study's findings should represent the situation across China.

In this study, we recognized that age of onset, family history, abnormal pancreatic duct anatomy, and gene mutations are essential factors to be considered in the etiological analysis of CP. We also identified risk factors associated with these factors in the progression of pancreatic disease. Overall, genetic factors and PD were independent risk factors for CP, while gene mutations were risk factors for disease progression. Therefore, for children with two or more episodes of AP or a first episode AP and family history of pancreatitis, it is recommended to perform genetic testing and imaging of the bile duct and pancreatic duct structure. This can improve our understanding of the etiology, risk factors, and the accuracy of prognostic assessments for CP.

Conclusion

Gene mutations and congenital pancreatic anatomic variants, especially PD, are independent risk factors for CP. Children with *PRSS1* gene mutations have a faster rate of progression to CP; however, PD does not affect the disease progression rate to CP, and ERCP appears to provide a benefit in delaying progression to CP in children with PD with recurrent pancreatitis.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Children's Medical Center. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

ZD and XW contributed substantially to the study's conception and design. JYZ and JQZ contributed to the acquisition or analysis and interpretation of data. YH performed the statistical analysis. JQZ drafted the manuscript or made critical revisions related to the critical intellectual content of the manuscript. All authors have read and approved the final version to be published.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Kumar S, Ooi CY, Werlin S, Abu-El-Haija M, Barth B, Bellin MD, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. *JAMA Pediatr.* (2016) 170:562–9. doi: 10.1001/jamapediatrics.2015.4955

2. Schwarzenberg SJ, Bellin M, Husain SZ, Ahuja M, Barth B, Davis H, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr.* (2015) 166:890–6.e891. doi: 10.1016/j.jpeds.2014.11.019

3. Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology.* (2019) 156:1969–78. doi: 10.1053/j.gastro.2018.12.043

4. Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. *Lancet.* (2020) 396:499–512. doi: 10.1016/S0140-6736(20)31318-0

5. Kichler A, Jang S. Chronic pancreatitis: epidemiology, diagnosis, and management updates. *Drugs.* (2020) 80:1155–68. doi: 10.1007/s40265-020-01360-6

6. Suzuki M, Minowa K, Isayama H, Shimizu T. Acute recurrent and chronic pancreatitis in children. *Pediatr Int.* (2021) 63:137–49. doi: 10.1111/ped.14415

7. Abu-El-Haija M, Valencia CA, Hornung L, Youssef N, Thompson T, Barasa NW, et al. Genetic variants in acute, acute recurrent and chronic pancreatitis affect the progression of disease in children. *Pancreatology.* (2019) 19:535–40. doi: 10.1016/j.pan.2019.05.001

8. Gariepy CE, Heyman MB, Lowe ME, Pohl JF, Werlin SL, Wilschanski M, et al. The causal evaluation of acute recurrent and chronic pancreatitis in children: consensus from the INSPPIRE group. *J Pediatr Gastroenterol Nutr.* (2017) 64:95–103. doi: 10.1097/MPG.0000000000001446

9. Xu YF, Wang YR, Li N, Yao R, Li GQ, Li J, et al. New insights from unbiased panel and whole-exome sequencing in a large Chinese cohort with disorders of sex development. *Eur J Endocrinol.* (2019) 181:311–23. doi: 10.1530/EJE-19-0111

10. Liu QY, Abu-El-Haija M, Husain SZ, Barth B, Bellin M, Fishman DS, et al. Risk factors for rapid progression from acute recurrent to chronic pancreatitis in children: report from INSPPIRE. *J Pediatr Gastroenterol Nutr.* (2019) 69:206–11. doi: 10.1097/MPG.0000000000002405

11. Zou WB, Tang XY, Zhou DZ, Qian YY, Hu LH, Yu FF, et al. SPINK1, PRSS1, CTRC, and CFTR genotypes influence disease onset and clinical outcomes in chronic pancreatitis. *Clin Transl Gastroenterol.* (2018) 9:204. doi: 10.1038/s41424-018-0069-5

12. Ali UA, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol.* (2016) 14:738–46. doi: 10.1016/j.cgh.2015.12.040

13. Bertilsson S, Swärd P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. *Clin Gastroenterol Hepatol.* (2015) 13:1662–9.e3. doi: 10.1016/j.cgh.2015.04.012

14. Sepúlveda EVF, Guerrero-Lozano R. Acute pancreatitis and recurrent acute pancreatitis: an exploration of clinical and etiologic factors and outcomes. *J Pediatr.* (2019) 95:713–9. doi: 10.1016/j.jped.2018.06.011

15. Gariepy CE, Ooi CY, Maqbool A, Ellery KM. Demographics and risk factors for pediatric recurrent acute pancreatitis. *Curr Opin Gastroenterol.* (2021) 37:491–7. doi: 10.1097/MOG.0000000000000764

16. Husain SZ, Morinville V, Pohl J, Abu-El-Haija M, Bellin MD, Freedman S, et al. Toxic-metabolic risk factors in pediatric pancreatitis: recommendations for diagnosis, management, and future research. *J Pediatr Gastroenterol Nutr.* (2016) 62:609–17. doi: 10.1097/MPG.0000000000001035

17. Nabi Z, Talukdar R, Venkata R, Aslam M, Shava U, Reddy DN. Genetic evaluation of children with idiopathic recurrent acute pancreatitis. *Dig Dis Sci.* (2020) 65:3000–5. doi: 10.1007/s10620-019-06026-2

18. Saito N, Suzuki M, Sakurai Y, Nakano S, Naritaka N, Minowa K, et al. Genetic analysis of Japanese children with acute recurrent and chronic pancreatitis. *J Pediatr Gastroenterol Nutr.* (2016) 63:431–6. doi: 10.1097/MPG.0000000000001320

19. Sultan M, Werlin S, Venkatasubramani N. Genetic prevalence and characteristics in children with recurrent pancreatitis. *J Pediatr Gastroenterol Nutr.* (2012) 54:645–50. doi: 10.1097/MPG.0b013e31823f0269

20. Palermo JJ, Lin TK, Hornung L, Valencia CA, Mathur A, Jackson K, et al. Geno-phenotypic analysis of pediatric patients with acute recurrent and chronic pancreatitis. *Pancreas.* (2016) 45:1347–52. doi: 10.1097/MPA.0000000000000655

21. Lin TK, Abu-El-Haija M, Nathan JD, Palermo JP, Barth B, Bellin M, et al. Pancreas divisum in pediatric acute recurrent and chronic pancreatitis: report from INSPPIRE. *J Clin Gastroenterol.* (2019) 53:e232–8. doi: 10.1097/MCG.0000000000001063

22. Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. *Am J Gastroenterol.* (2012) 107:311–7. doi: 10.1038/ajg.2011.424

23. DiMagno MJ, Dimagno EP. Pancreas divisum does not cause pancreatitis, but associates with CFTR mutations. *Am J Gastroenterol.* (2012) 107:318–20. doi: 10.1038/ajg.2011.430

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Central role of the sentinel acute pancreatitis event (SAPE) model in understanding recurrent acute pancreatitis (RAP): Implications for precision medicine

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Traditional approaches to understanding the origins of chronic pancreatitis (CP) and find treatments led to abysmal failure. Thus, no drugs now exists to meet this need. Outdated concepts of the etiopathogenesis of CP have been replaced with new insights and disease models that provide the framework for early detection of the pathogenic pancreatitis process. Application of these principals require a new paradigm in disease definition and management, i.e. personalized / precision medicine. The key is acute pancreatitis (AP) starting with the first (sentinel) acute pancreatitis (AP) event (SAPE). This event sensitizes the pancreas to recurrent acute pancreatitis (RAP) as ongoing stressors drive various inflammatory responses to cause CP. The problem is the complex etiologies of AP and the additional genetic and environmental factors that promote progression to RAP and CP. This paper provides a background on the key conceptual changes that facilitate new approaches and the rationale for using mechanism-specific therapies to prevent RAP and CP.

KEYWORDS

chronic pancreatitis in children, precision medicine, genetics, recurrent acute pancreatitis, CFTR (cystic fibrosis transmembrane conductance regulator), CFTR-related disorders (CFTR-RD), alcohol, smoking

Introduction

There have been very few new treatments approved for the prevention of recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP) in humans. The problem is complex and previously unsolvable, as the historical definitions and models of CP were wrong, and the translation from case-control studies, cohort studies and population-based epidemiology studies to the specific therapeutic needs of individual patients at a specific point of time is,

frankly, impossible. Indeed, after 100 years of pancreatic research since the suggestion by Chiari that pancreatitis was linked to autodigestion of the pancreas by pancreatic digestive enzymes in 1896 (1) the leading experts finally concluded that CP "remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment" (2). This review highlights the fact that the *traditional disease paradigm* required to understand CP was wrong. A more effective approach than the traditional approaches of modern Western Medicine based on the Germ Theory of Disease is the paradigm of Precision Medicine (3, 4).

Traditional CP definitions, diagnostic criteria and etiologic theory

We begin by highlighting three basic problems with the traditional disease paradigm.

Problem 1

The first problem was the traditional pathophysiological definition of CP. The famous Marseille-Rome classification conference of 1989 defined CP as "the presence of chronic inflammatory lesions characterized by the destruction of exocrine parenchyma and fibrosis and at least in the later stages, the destruction of endocrine parenchyma." (5) This is a descriptive-pathologic definition of an advanced inflammatory disease used to distinguish CP from other diseases with similar features of pancreatic inflammation, fibrosis, atrophy, and Type 1 or Type 2 diabetes mellitus. It requires advanced disease features and pathology as a the primary state, but fails to define the essence of the underlying disorder or the unique pathogenic processes.

Problem 2

The second problem was diagnosis. Since tissue pathology is generally not available for diagnosis, the Pancreatic Society of Great Britain and Ireland developed clinically applicable diagnostic criteria for CP during the 1984 Cambridge Conference (6) using imaging findings of *irreversible pancreatic fibrosis* as the defining feature of CP. These descriptive definitions and corresponding diagnostic criteria are useful for clinical documentation of underlying disease, but (a) require the underlying disease to advance to an irreversible stage before it can be diagnosed, and (b) provides no insights into disease mechanisms or targets for early therapy. However, fibrosis alone is not necessary or sufficient for distinguishing CP form other conditions in the differential diagnosis, especially at earlier stages when treatment may still be effective (7).

Problem 3

The third problem was etiology. The primary etiology for human CP was believed to be alcoholism, with alcohol typically associated with 80% of cases (8–11). However, a few studies reported that 50% or more of the cases of CP in adults were idiopathic (11–15). The idiopathic group also increased in overall fraction of CP cases as abdominal imaging technology improved, identifying CP cases at earlier stages. But even with alcoholic etiology, <5% of alcoholics develop CP (16) and animals fed alcohol do not get acute pancreatitis (AP) or CP (17, 18) unless pancreatitis is driven by other factors, such as cerulean in alcohol-drinking animals (19). Thus, the primary "etiology" of CP cannot not be the direct cause.

In summary, at least three fundamental clinical concepts surrounding CP were known problems without clear solutions. This resulted in persistence of two major barriers to treating CP: lack of clarity on the mechanistic process leading from a normal-appearing, completely asymptomatic human to end-stage CP and therapeutic targets of the pathogenic mechanism(s) are needed for effective intervention—especially when the disease is in an early stage to stop progression.

A breakthrough that required a complete paradigm shift in modeling CP

Hereditary pancreatitis (HP) is an autosomal dominant, high-penetrance form of RAP/CP. A study of large families with HP in the Appalachian region of the Eastern United States (20) was used to discover that gain-of-function mutations in the cationic trypsinogen gene (*PRSS1*) could cause HP (21, 22). This discovery implicated genetics as a cause of CP, but also provided a framework for the study of complex, acquired inflammatory disorders. Three of the key observations including: (a) the mutation carriers were 100% normal until they developed an attack of AP, (b) AP sensitized the pancreas in some way so that in most cases RAP followed, and (c) RAP is a driver of CP (23).

SAPE hypothesis

Based on this model we developed the "Sentinel Acute Pancreatitis Event" hypothesis model (24). The hypothesis is that an episode of AP alters the pancreas to make it hypersensitive to RAP. The mechanisms were hypothesized to represents the resolution to an intense inflammatory event that includes residual pro-inflammatory macrophages (e.g. Th1→F0E0Th2) and/or other immune cells throughout the parenchyma, and possibility epigenetic changes to the acinar or duct cells that are potentially pro-inflammatory. Thus, a minor increase in stress or injury that was originally only sufficient to generate

sub-clinical stress signals that were compensated for by normal pancreas defense mechanisms, now triggers RAP and drives CP after the sentinel acute pancreatitis event. If the stress or injury is minimized, then the new lower inflammatory trigger threshold is not exceeded, the non-necrotic pancreas recovers and functions normally.

Evidence supporting the SAPE hypothesis

Alcohol and rats

Our laboratory tested the SAPE hypothesis in an alcohol-consuming rat model. Rats that consumed large amounts of alcohol for months had no pathologic evidence of pancreatitis, even though they did show evidence of mitochondrial stress (25) and neurohormonal compensation for the effects of alcohol (26, 27). Alcohol-consuming rats and rats on similar chow without alcohol were given an episode of AP using cerulean injections (19). After the first episode of AP the histology of the pancreas was similar in alcohol vs. control diet rats. However, after inducing 3 episodes of AP, the alcohol-consuming rats developed severe pancreatic injury, marked infiltration of leukocytes and fibrosis characteristic of CP, whereas the control rats recovered and had minimal pathology. This demonstrated the importance of AP in initiating the process leading to CP that is driven by continued alcohol and RAP, and the fact that alcohol was contributing to this process by altering the type or severity of the immune response in some ways.

GEMMs and RAP

A mechanism for the SAPE hypothesis was recently demonstrated in mice. Using genetically engineered mouse models (GEMMs) Geisz and Sahin-Toth (28) identified *persistently infiltrating macrophages* after the initial acute pancreatitis event and provided supporting evidence that residual inflammatory cells contribute to the mechanism of enhanced injury and more severe inflammatory response during successive episodes of AP or stressors. Thus, after an initial episode of AP, the pancreas is "primed" for RAP by macrophages.

Alcoholic pancreatitis in Japan

Takeyama published an important observational cohort study in Japanese after an episode of AP with a 13–17 year follow-up (29). He observed a high rate of RAP and progression to CP in patients following AP who continued alcohol use, with a reduction in RAP and CP in patients who stopped or significantly reduced drinking. This demonstrates that alcohol drives RAP and CP at high rates in patient *after* an initial episode of AP.

Biliary RAP

The most common cause of AP is impacted gallstones at the sphincter of Oddi beyond the convergence of the common bile duct and the main pancreatic duct. The risk of RAP is very high in these patients, and cholecystectomy (CCY) is recommended as soon as possible, even *during* the sentinel AP admission. Comparing patients with and without CCY suggest (a) the rate of RAP is ∼30%, that (b) is reduce to ∼11% with CCY (30). However, the rate of AP in controls (e.g., the general population) with gallbladders *in situ* was not calculated (i.e., the risk of AP is *only* at a very high level *after* the sentinel acute pancreatitis event).

Hypertriglyceridemic RAP

Hypertriglyceridemia (HTG) is associated with AP (31, 32) and CP (33). The upper limits of normal for serum triglyceride (TG) is 150 mg/dL. The risk of HTG-AP is proportional to the serum lipids (34), yet <10% of patients with persistent TG>2,000 mg/dL for years ever have an episode of AP. In contrast, at least a third of patients with HTG that had one episode of AP rapidly develop RAP (34), indicating hypersensitivity of AP patients to RAP.

PS-cystic fibrosis RAP

An observational study from France in adults with pancreas sufficient cystic fibrosis (PS-CF) found that out of 40 patients followed over their lifetime, 19 (47.5%) had at least one episode of AP, and of the 19 with AP, 15 had RAP (78.9%) (35). This suggest that in adult PS-CF patients, AP occurs in a large minority, but if that have one episode of AP, they are likely to have RAP.

Timing of interventions to prevent RAP

Four examples of common etiologies of AP and RAP were noted above: Alcohol, biliary, HTG and RAP in PS-CF. Note that strong clinical intervention is implemented AFTER the first attach of AP, as AP sensitizes the pancreas to RAP with low-level injury and stress exposure. For example, alcohol drinking and smoking are not strongly discouraged for prevention of AP, but they are strongly discouraged *after* the first attack of alcoholic AP, as patients are now at very high risk of alcoholic RAP and

CP. The same is true for gallstone pancreatitis. While this is the #1 risk factor of AP, surgeons do not take the gallbladder out of all patients in the population to *prevent AP*. Instead, they take the gallbladder out *after* the first episode of AP, recognizing that the patient is NOW at very high risk of RAP. We argue that it is not justified to put patients with high-risk *CFTR* genotypes (including PS-CF) on CFTR-modulators to prevent the first attack of AP. Instead, patients with high-risk *CFTR* genotypes may benefit from CFTR-modulators *after* the sentinel AP attack because they are now at high risk of RAP and CP (36).

Link between RAP and CP

As noted above, the model of RAP to CP is evident in families with hereditary pancreatitis. Yadav et al. conducted a population-based study in Pittsburgh to determine the outcome of patients after their sentinel pancreatitis event (37). They demonstrated that after AP, RAP occurred most common among alcoholics, intermittent with genetic and idiopathic etiologies, and least among gallstone pancreatitis, with the recurrence directly proportional to duration between AP and CCY. These data were replicated by the Dutch Pancreatitis Study Group, with additional risk shown for smoking (38). This RAP→F0E0CP progression was noted in multiple etiologies, consistent with the idea that the pancreas is sensitized to the AP event, not the inciting stressor or type of injury. Thus, the SAPE phenomenon appears to be similar, regardless of etiology.

Mechanistic definition of CP and progressive model of symptom development

The SAPE Model was developed to test the hypothesis the CP requires triggering an acute inflammatory event that resolves, but results in hypersensitivity to RAP and recruits/activates resident tissue immune cells that drive continued inflammation, fibrosis, atrophy and other features of CP. The next problem is to more accurately define the CP syndrome in a mechanistic way so that it could be used for early diagnosis and for the exclusion of other disorders and diseases within the differential diagnosis that have similar features. An international task force was commissioned by the European Pancreas Club to develop a consensus definition of CP, and the following mechanistic definition, in two parts (essence and characteristics), was generated (39).

Mechanistic definition of CP

- *Essence*: Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.
- *Characteristics*: Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia.

This definition recognizes the complex nature of CP, separates risk factors from disease activity markers and disease endpoints, and allows for a rational approach to early diagnosis, classification and prognosis (39).

Next, a progressive CP pathogenesis model was proposed to organize the risk, activities and stage of the CP process (Figure 1) (39).

This model illustrates the concept that CP is the result of progression from no disease (A. At Risk) to pancreatic parenchymal destruction (E). Cases typically start with acute pancreatitis (AP, "sentinel AP event" SAPE) and recurrent AP (RAP) stage B. Damage to acinar and duct cells (C-D), and fibrosis (immune cells), leads to diabetes (islet cells), pain syndromes (nervous system) and dysplasia / pancreatic ductal adenocarcinoma (PDAC). The opportunity to intervene is between stages B and D.

Biomarkers

One of the remaining challenges is to define the biomarkers of disease stage. The first observation is that the progressive model has multiple stages, with unclear transitions between Early CP, Established CP or End-Stage CP. Distinction between stages requires the use of biomarkers to serve as objectively measured characteristics of the underling biological processes. Biomarkers can be clinical features, biochemical analytes, measures of physiologic features or functions, histologic features, imaging studies or other. As multiple cell types are involved in chronic pancreatitis (acinar, duct, islet, immune, nervous, etc.,), biomarkers of each component are needed. Furthermore, criteria on distinctions between stages are yet to be defined.

Risks leading to CP and opportunities for interventions

The mechanistic definition of CP indicates that CP only occurs in patients with "genetic, environmental and/or other risk factors". Multiple "other factors" were noted above (e.g. alcohol, gallstones, genetics [*PRSS1*, *CFTR* variants], and HTG). Based on the evidence surrounding alcohol-associated CP, it appears that a combination of factors may be required to develop AP,

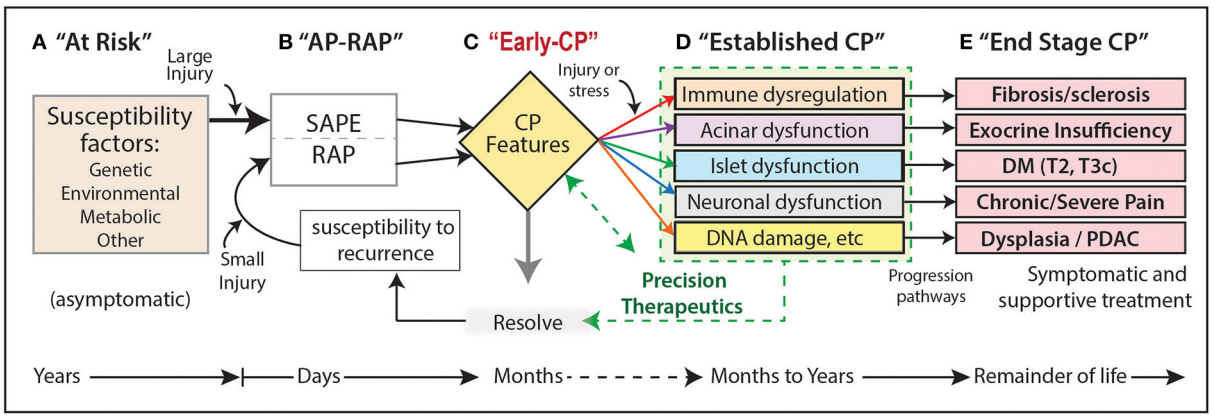

FIGURE 1
(A–E) Progressive CP pathogenesis. Five progressive stages can be defined that persist for days to many years. Each stage may have unique risk factors or stress/injury mechanisms, as well as innate compensatory or protective mechanisms that may be altered or defective in patients who progress. Stage B is a critical driver of the CP pathways as the initial episode of AP (SAPE) lowers the threshold for RAP. CP, chronic pancreatitis; DM, diabetes mellitus; RAP, recurrent acute pancreatitis; SAPE, sentinel acute pancreatitis event; PDAC, pancreatic ductal adenocarcinoma; T2, type II DM; T3c, type IIIc diabetes caused by exocrine pancreas pathology or surgery.

RAP and then CP, with progression occurring only in patients "at risk" at sequential stages.

To understand the risks and mechanisms of disease in individual patients Whitcomb and Etemad developed an organized list of etiologies based on Toxic-metabolic factors (including alcohol, smoking, HTG, hypercalcemia), Idiopathic, Genetic, Autoimmune, Recurrent acute and severe acute pancreatitis, and Obstruction (TIGAR-O) (40), which was updated in 2019 (41). This system was designed to be used within the case report forms (CRF) of the *North American Pancreatitis Study 2* (NAPS2, ClinicalTrials.gov NCT01545167), a prospective observational cohort study of over 1,500 RAP/CP patients and 1,250 controls (33, 42, 43). This study provided many new insights, including demonstrating that less than half of CP subjects are very heavy alcohol users (15, 33, 44), and that there were the high rates of *CFTR* variants in RAP and CP patients (45, 46). The presence of risk factors for RAP/CP also differs dramatically between patients in the UK Biobank (47). These example highlight the importance of comprehensive evaluation of patients and observing the primary and secondary combinations of risk factors that generate pathogenic conditions.

In summary, the key to understanding the risk of RAP and CP is the radical changes to the pancreas after in initial attack of AP (the SAPE). Although the pancreas is hypersensitized to injury or stress signals after SAPE, reducing or elimination the major injury- or stress-inducing factors markedly diminishes the rate of RAP and, by extension, CP. Thus, etiology- and/or pathway-based, targeted interventions are needed for personalized care of patients with inflammatory diseases of the pancreas.

Studies CFTR modulators in RAP

Cystic fibrosis (CF) is a well-defined genetic disorder caused by biallelic mutations in the *CFTR* gene with specific diagnostic criteria (48). Some CF patients have a milder course and rather than suffering a complete destruction of the pancreas *in utero* and infancy to become exocrine pancreatic insufficient (PI), they maintain enough pancreatic function to digest food, i.e., exocrine pancreatic sufficient (PS). The high rate of AP and RAP in PS-CF patients was noted above (35). Studies of CF families and wide availability of *CFTR* genetic testing in various populations reveal that *CFTR* variants are also associated with a wide variety of disorders that do not meet criteria for CF, especially CP (including RAP), bronchiectasis and male infertility (49–51). These single-organ disorders are called CFTR-related diseases (CFTR-RD).

Case series on the use of CFTR modulators in CF patients with RAP

An exciting observation is that patients with PS-CF and RAP often have marked reduction RAP episodes when they are on ivacaftor, a CFTR-potentiator (36, 52–54). These case reports and case series provide compelling evidence that CFTR-modulators (like ivacaftor) may be useful in patients with RAP and early CP when the etiology includes damaging *CFTR* genetic variants (55).

Population-based studies of CFTR modulators in CF patients

The problem of population-based studies is that the "case-control" design limits insights into the true, complex pathophysiologic mechanism of pancreatic disease. For example, 2021 Ramsey, et al. published, "Cystic Fibrosis Transmembrane Conductance Regulator Modulator Use Is Associated With Reduced Pancreatitis Hospitalizations in Patients With Cystic Fibrosis" (56). This study used an administrative database, *MarketScan*, from 2012 to 2018 to evaluate AP hospitalizations and CFTR modulator use among patients with CF. In summary, they found 10,417 patients with CF, including 1,795 who received a CFTR modulator, and classified patients as PS-CF or PI-CF based on pancreatic enzyme replacement therapy (PERT) use. AP was more common in PS-CF than PI-CF (2.9 vs. 0.9%, P = 0.007), and use of CFTR-modulators significantly reduced the frequency of AP events by 67%. However, they estimated that CFTR-modulator use would only reduce AP in PS-CF patients from *10.20 to 3.26 per 1,000 patient-years*. Thus, the justification to use CFTR-modulators in CF patients for the prevention of the initial attack of AP is minimal. However, they did not consider the role of the SAPE model, problems in patient classification using administrative codes, capturing pre-existing AP, a short time frame to capture RAP in this cohort (see below).

There are always limitations to administrative database studies. In this case AP was reported in several patients with pancreatic insufficient CF (PI-CF), highlighting potential classification problems. The incidence of AP in PI-CP should be negligible since these patients have nearly complete loss of trypsin-secreting acinar cells. They used PERT as a surrogate of PI, but PERT is used both for exocrine pancreatic insufficiency (EPI) and pain, bloating, diarrhea and other reasons in pancreatitis patient—especially young ones (57). Thus, many of the PI-CF patients were likely PS-CF with misclassification, reducing the power of the relevant study (i.e., AP in PS-CF).

The etiology of AP in these patients is also unknown. Patients with CF are unlikely to have alcohol-related pancreatitis but have an increased risk of biliary disease and gallstones. Thus, the incidence of AP in the patients using a CFTR-modulator may be artificially increased by gallstone AP, therefore decreasing the estimate of the true effect CFTR-modulators on decreasing AP events.

Another limitation of the database study is that it did not allow the investigators to determine who had AP *before* the 4–6 year observational time frame (e.g. who was already a RAP patient). The study was designed to examine the effect on reducing *the initial attack of AP* in a population with a slightly higher risk of AP than expected in the general population (58, 59), but does not address the primary problem of the very high risk of RAP in patients who had AP. Based on the point above, the study could be framed as a reduction of AP events in 5 patients with RAP.

Finally, the administrative databases included AP events during a short time window. The incidence of AP in the CF population during the study period (~4 years of observation per patient, page 2449–2450) was [22 + 145]/10,417 = 1.6%. The incidence of RAP in RAP patients is 100% (by definition). Of the 8 PS-CF subjects with AP, there were 5 additional attacks (RAP) noted within a 3.9-year observation window. If no individual had more than 2 attacks, then 62.5% were RAP patients—even though the PS-CF patients were on CFTR-modulators 36.5% of the time. Furthermore, not all patients appeared in the database at the same time, and follow-up was limited and variable (median follow-up was 3.9 +/– 2.1 years).

In summary, careful consideration is needed in evaluating the role of medications on RAP and CP based on study design and patient classification. The very strong effect of CFTR modulators reducing RAP rate is shown in case series studies with nearly every patient responding. However, in a retrospective administrative database study, the question that was asked (do CFTR modulators reduce the rate of initial attack of pancreatitis in patients al low individual risk) may not answer more specific patient questions needed to address a precision medicine approach. The SAPE model demonstrates that patients with a previous AP attack are highly susceptible to RAP. And in contrast to expected rates of AP in the CF population (10.2 per 1,000 patient years), *RAP patients develop AP at rates between 250 and 1,000 per 1,000 patient years*, with some patients having 3–4 attacks per year. These are the pancreatitis patients that precision medicine is designed to help.

Other etiologies of CP

CFTR-related pancreatitis represents an illustrative approach to etiology-based disease management using highly targeted therapy. The SAPE provides a clear trigger for immediate evaluation and prevention of RAP. Other areas of need are preventative or therapeutic treatments for CP caused by *PRSS1* gain-of-function mutations, other trypsin-related disorders (e.g., simple and complex genetic variants linked to serine protease inhibitor Kazal-type 1, *SPINK1*, or *Chymotrypsin-C, CTRC*), ER stress-related CP, hypertriglyceridemia recurrent acute pancreatitis and others. It is unclear whether it will be possible to repurpose existing drugs or develop gene-based therapies in the future, but the framework presented here for CFTR-RD is a clear direction toward success.

Conclusions

A transition is required from the old CP disease paradigm to a new paradigm for evidence-based guidance on early identification of patients at risk of RAP and CP. A detailed understanding of the disease risks and stage are needed to determine which mechanism and pathways are pathogenic, and to choose appropriate therapies to prevent RAP and CP. The new Mechanistic Definition of CP, the Progressive Pathogenesis Model and the SAPE phenomenon are critical for designing new intervention studies. These new insights indicate that (a) AP transforms a patient into a high-risk group for RAP and CP, (b) interventions are justified in patients with a history of AP to prevent RAP, (c) evidence from a case series on PS-CF patients with RAP and CFTR-modulators justifies new, scientifically rigorous clinical intervention trials with CFTR-modulators and (d) selecting patients with previous AP or RAP and damaging CFTR variants allows for a well powered study with a limited number of patients based on the high effect size of CFTR-modulators and the high rate of AP events in patients with a history of AP or RAP.

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Conflict of interest

Author DW is a consultant to Nestle', Regeneron and Ariel Precision Medicine. He is a co-founder of Ariel Precision Medicine and may have equity.

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References

1. Chiari H. Ueber selbstverdauung des menschlichen pankreas [Autodigestion of the human pancreas]. *Zeitschrift fur Heilkunde.* (1896) 17:69–96.

2. Steer ML, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med.* (1995) 332:1482–90. doi: 10.1056/NEJM199506013322206

3. Whitcomb DC. What is personalized medicine and what should it replace? *Nat Rev Gastroenterol Hepatol.* (2012) 9:418–24. doi: 10.1038/nrgastro.2012.100

4. Whitcomb DC. Primer on precision medicine for complex chronic disorders. *Clin Transl Gastroenterol.* (2019) 10:e00067. doi: 10.14309/ctg.0000000000000067

5. Sarles H, Bernard JP, Gullo L. Pathogenesis of chronic pancreatitis. *Gut.* (1990) 31:629–32. doi: 10.1136/gut.31.6.629

6. Sarner M, Cotton PB. Classification of pancreatitis. *Gut.* (1984) 25:756–9. doi: 10.1136/gut.25.7.756

7. Whitcomb DC, Shimosegawa T, Chari ST, Forsmark CE, Frulloni L, Garg P, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. *Pancreatology.* (2018) S1424–3903:30113-3. doi: 10.1016/j.pan.2018.05.008

8. Marks IN, Bank S, Louw JH. Chronic pancreatitis in the Western Cape. *Digestion.* (1973) 9:447–53. doi: 10.1159/000197473

9. Sarles H, Cros RC, Bidart JM. A multicenter inquiry into the etiology of pancreatic diseases. *Digestion.* (1979) 19:110–25. doi: 10.1159/000198331

10. Durbec JP, Sarles H. Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreaitis and alcohol, protein and lipid consumption. *Digestion.* (1978) 18:337–50. doi: 10.1159/000198221

11. Pezzilli R. Etiology of chronic pancreatitis: has it changed in the last decade? *World J Gastroenterol.* (2009) 15:4737–40. doi: 10.3748/wjg.15.4737

12. Trapnell JE. Chronic relapsing pancreatitis: a review of 64 cases. *Br J Surg.* (1979) 66:471–5. doi: 10.1002/bjs.1800660706

13. O'Sullivan JN, Nobrega FT, Morlock CG, Brown AL, Jr., Bartholomew LG. Acute and chronic pancreatitis in Rochester Mi. 1940 to 1969. *Gastroenterology.* (1972) 62:373–9. doi: 10.1016/S0016-5085(72)80141-0

14. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology.* (1994) 107:1481–7. doi: 10.1016/0016-5085(94)90553-3

15. Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med.* (2009) 169:1035–45. doi: 10.1001/archinternmed.2009.125

16. Yadav D, Eigenbrodt ML, Briggs MJ, Williams DK, Wiseman EJ. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. *Pancreas.* (2007) 34:390–8. doi: 10.1097/mpa.0b013e318040b332

17. Wilson JS, Korsten MA, Pirola RC. Alcohol-induced pancreatic injury (Part I). Unexplained features and ductular theories of pathogenesis. *Int J Pancreatol.* (1989) 4:109–25. doi: 10.1007/BF02931314

18. Worning H. Etiologic aspects of chronic pancreatitis. Review of current theories and experimental evidence. *Int J Pancreatol.* (1989) 5:1–9.

19. Deng X, Wang L, Elm MS, Gabazadeh D, Diorio GJ, Eagon PK, et al. Chronic alcohol consumption accelerates fibrosis in response to cerulein-induced pancreatitis in rats. *Am J Pathol.* (2005) 166:93–106. doi: 10.1016/S0002-9440(10)62235-3

20. Sossenheimer MJ, Aston CE, Preston RA, Gates LK Jr., Ulrich CD, Martin SP, et al. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype The Midwest Multicenter Pancreatic Study Group (MMPSG). *Am J Gastroenterol.* (1997) 92:1113–6.

21. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet.* (1996) 14:141–5. doi: 10.1038/ng1096-141

22. Gorry MC, Gabbaizedeh D, Furey W, Gates LK Jr., Preston RA, Aston CE, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology.* (1997) 113:1063–8. doi: 10.1053/gast.1997.v113.pm9322498

23. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol.* (2004) 2:252–61. doi: 10.1016/S1542-3565(04)00013-8

24. Whitcomb DC. Hereditary Pancreatitis: new insights into acute and chronic pancreatitis. *Gut.* (1999) 45:317–22. doi: 10.1136/gut.45.3.317

25. Li HS, Zhang JY, Thompson BS, Deng XY, Ford ME, Wood PG, et al. Rat mitochondrial ATP synthase ATP5G3: cloning and upregulation in pancreas after chronic ethanol feeding. *Physiol Genomics.* (2001) 6:91–8. doi: 10.1152/physiolgenomics.2001.6.2.91

26. Deng X, Wood PG, Eagon PK, Whitcomb DC. Chronic alcohol-induced alterations in the pancreatic secretory control mechanisms. *Dig Dis Sci.* (2004) 49:805–19. doi: 10.1023/B:DDAS.0000030093.25897.61

27. Deng X, Wood PG, Eagon PK, Whitcomb DC. Rapid adaptation of pancreatic exocrine function to short term alcohol feeding in rats. *Pancreatology.* (2005) 5:183–95. doi: 10.1159/000085270

28. Geisz A, Sahin-Toth M. Sentinel acute pancreatitis event increases severity of subsequent episodes in mice. *Gastroenterology.* (2021) 161:1692–4. doi: 10.1053/j.gastro.2021.06.013

29. Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. *Clin Gastroenterol Hepatol.* (2009) 7:S15–7. doi: 10.1016/j.cgh.2009.08.022

30. Umans DS, Hallensleben ND, Verdonk RC, Bouwense SAW, Fockens P, van Santvoort HC, et al. Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis. *Br J Surg.* (2020) 107:191–9. doi: 10.1002/bjs.11429

31. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol.* (2014) 48:195–203. doi: 10.1097/01.mcg.0000436438.60145.5a

32. Wang Y, Sternfeld L, Yang F, Rodriguez JA, Ross C, Hayden MR, et al. Enhanced susceptibility to pancreatitis in severe hypertriglyceridemic lipoprotein lipase deficient mice and agonist-like function of pancreatic lipase in pancreatic cells. *Gut.* (2008). doi: 10.1136/gut.2007.146258

33. Conwell DL, Banks PA, Sandhu BS, Sherman S, Al-Kaade S, Gardner TB, et al. Validation of demographics, etiology, and risk factors for chronic pancreatitis in the USA: a report of the North American Pancreas Study (NAPS) Group. *Dig Dis Sci.* (2017) 62:2133–40. doi: 10.1007/s10620-017-4621-z

34. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med.* (2016) 176:1834–42. doi: 10.1001/jamainternmed.2016.6875

35. Gaitch N, Hubert D, Gameiro C, Burgel PR, Houriez F, Martinez B, et al. CFTR and/or pancreatitis susceptibility genes mutations as risk factors of pancreatitis in cystic fibrosis patients? *Pancreatology.* (2016) 16:515–22. doi: 10.1016/j.pan.2016.03.021

36. Akshintala VS, Kamal A, Faghih M, Cutting GR, Cebotaru L, West NE, et al. Cystic fibrosis transmembrane conductance regulator modulators reduce the risk of recurrent acute pancreatitis among adult patients with pancreas sufficient cystic fibrosis. *Pancreatology.* (2019) 19:1023–6. doi: 10.1016/j.pan.2019.09.014

37. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol.* (2012) 107:1096–103. doi: 10.1038/ajg.2012.126

38. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol.* (2016) 14:738–46. doi: 10.1016/j.cgh.2015.12.040

39. Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology.* (2016) 16:218–24. doi: 10.1016/j.pan.2016.02.001

40. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology.* (2001) 120:682–707. doi: 10.1053/gast.2001.22586

41. Whitcomb DC, North American Pancreatitis Study G. Pancreatitis: TIGAR-O version 2 risk/etiology checklist with topic reviews, updates, and use primers. *Clin Transl Gastroenterol.* (2019) 10:e00027. doi: 10.14309/ctg.0000000000000027

42. Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology.* (2008) 8:520–31. doi: 10.1159/000152001

43. Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock JN, Sherman S, et al. Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. *Am J Gastroenterol.* (2016) 111:1488–96. doi: 10.1038/ajg.2016.316

44. Jeon CY, Whitcomb DC, Slivka A, Brand RE, Gelrud A, Tang G, et al. Lifetime drinking history of persons with chronic pancreatitis. *Alcohol Alcohol.* (2019) 54:615–24. doi: 10.1093/alcalc/agz072

45. Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. *Gastroenterology.* (2011) 140:162–71. doi: 10.1053/j.gastro.2010.10.045

46. LaRusch J, Jung J, General IJ, Lewis MD, Park HW, Brand RE, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. *PLoS Genet.* (2014) 10:e1004376. doi: 10.1371/journal.pgen.1004376

47. Spagnolo DM, Greer PJ, Ohlsen CS, Mance S, Ellison M, Breze C, et al. Acute and chronic pancreatitis disease prevalence, classification, and comorbidities: a cohort-study of the UK Biobank. *Clin Transl Gastroenterol.* (2022) 19:e00455. doi: 10.14309/ctg.0000000000000455

48. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr.* (2017) 181S:S4–S15 e1. doi: 10.1016/j.jpeds.2016.09.064

49. Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros.* (2011) 10 Suppl 2:S86–102. doi: 10.1016/S1569-1993(11)60014-3

50. Miller AC, Comellas AP, Hornick DB, Stoltz DA, Cavanaugh JE, Gerke AK, et al. Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. *Proc Natl Acad Sci U S A.* (2020) 117:1621–7. doi: 10.1073/pnas.1914912117

51. Baldwin C, Zerofsky M, Sathe M, Troendle DM, Perito ER. Acute recurrent and chronic pancreatitis as initial manifestations of cystic fibrosis and cystic fibrosis transmembrane conductance regulator-related disorders. *Pancreas.* (2019) 48:888–93. doi: 10.1097/MPA.0000000000001350

52. Carrion A, Borowitz DS, Freedman SD, Siracusa CM, Goralski JL, Hadjiladis D, et al. Reduction of recurrence risk of pancreatitis in cystic fibrosis with ivacaftor: case series. *J Pediatr Gastroenterol Nutr.* (2018) 66:451–4. doi: 10.1097/MPG.0000000000001788

53. Kounis I, Levy P, Rebours V. Ivacaftor CFTR potentiator therapy is efficient for pancreatic manifestations in cystic fibrosis. *Am J Gastroenterol.* (2018) 113:1058–9. doi: 10.1038/s41395-018-0123-7

54. Johns JD, Rowe SM. The effect of CFTR modulators on a cystic fibrosis patient presenting with recurrent pancreatitis in the absence of respiratory symptoms: a case report. *BMC Gastroenterol.* (2019) 19:123. doi: 10.1186/s12876-019-1044-7

55. Hegyi P, Wilschanski M, Muallem S, Lukacs GL, Sahin-Toth M, Uc A, et al. CFTR: a new horizon in the pathomechanism and treatment of pancreatitis. *Rev Physiol Biochem Pharmacol.* (2016) 170:37–66. doi: 10.1007/112_2015_5002

56. Ramsey ML, Gokun Y, Sobotka LA, Wellner MR, Porter K, Kirkby SE, et al. Cystic fibrosis transmembrane conductance regulator modulator use is associated with reduced pancreatitis hospitalizations in patients with cystic fibrosis. *Am J Gastroenterol.* (2021). doi: 10.14309/ajg.0000000000001527

57. Burton F, Alkaade S, Collins D, Muddana V, Slivka A, Brand RE, et al. Use and perceived effectiveness of non-analgesic medical therapies for chronic pancreatitis in the United States. *Aliment Pharmacol Ther.* (2011) 33:149–59. doi: 10.1111/j.1365-2036.2010.04491.x

58. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology.* (2013) 144:1252–61. doi: 10.1053/j.gastro.2013.01.068

59. Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. *Dig Dis Sci.* (2017) 62:1683–91. doi: 10.1007/s10620-017-4510-5

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Hypertriglyceridemia-induced acute pancreatitis in children: A mini-review

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Severe hypertriglyceridemia (HTG) is a known metabolic cause of acute pancreatitis (AP) in pediatric patients. The incidence of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is less well established in pediatric compared to adult patients. Studies in adults suggest that higher risk of AP occurs when triglyceride levels (TG) are >1,000 mg/dL. Most common etiologies for severe HTG in pediatric patients are either from primary hypertriglyceridemia, underlying genetic disorders of lipid and TG metabolism, or secondary hypertriglyceridemia, separate disease or exposure which affects TG metabolism. Most common theories for the pathophysiology of HTG-AP include hydrolysis of TG by pancreatic lipase to free fatty acids leading to endothelial and acinar cell damage and ischemia, as well as hyperviscosity related to increased chylomicrons. Though there are varying reports of HTG-AP severity compared to other causes of AP, a steadily growing body of evidence suggests that HTG-AP can be associated with more severe course and complications. Therapeutic interventions for HTG-AP typically involve inpatient management with dietary restriction, intravenous fluids, and insulin; select patients may require plasmapheresis. Long term interventions generally include dietary modification, weight management, control of secondary causes, and/or antihyperlipidemic medications. Though some therapeutic approaches and algorithms exist for adult patients, evidence-based management guidelines have not been well established for pediatric patients.

KEYWORDS

hypertriglyceridemia, pancreatitis, children, pediatric, triglyceride

Introduction

Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is a recognized but incompletely characterized disease in children and adolescents. Early accounts of an association between severe hypertriglyceridemia (HTG) and pancreatitis date back to the mid-1800's (1). In adults, HTG-AP is one of the most common identified causes of acute pancreatitis (AP) after gallstones and alcohol, accounting for an estimated 1–10% of cases (2–6). The overall annual incidence of AP in children is estimated between 3.6–13.2/100,000 persons per year and increasing, potentially related to increased

awareness/testing vs. true increased incidence (7, 8); however, some reports have found annual incidence of Pediatric AP may be stabilizing (9). Idiopathic AP accounts for as many as 13–37% of pediatric cases, with identified causes including biliary disease 10–30%, medications <25%, and variable incidence of infection, trauma, systemic diseases, metabolic diseases (including HTG-AP), and hereditary causes (10, 11). The incidence of HTG-AP in children is not well quantified, but an estimated 2–7% of AP is secondary to HTG or the category "metabolic causes" (10–13). Published data on pediatric HTG-AP is limited. The purpose of this review is to describe the etiologies, clinical features, acute management, and prevention of HTG-AP and to highlight existing literature and clinical guidelines targeting HTG-AP in pediatric patients.

Etiologies and pathophysiology of hypertriglyceridemia

Primary hypertriglyceridemia

Primary Hypertriglyceridemias typically caused by monogenic or multifactorial defects resulting in dysfunctional triglyceride (TG) synthesis or metabolism. Some of the most common disorders are summarized below (14, 15).

Chylomicronemias

Causes of severe HTG can be divided into monogenic chylomicronemia and multifactorial/polygenic chylomicronemia.

Monogenic chylomicronemia is an autosomal recessive condition also known as familial chylomicronemia syndrome. Mutations in one of five genes, *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1* result in deficiency of lipoprotein lipase (LPL), Apolipoprotein C-II, Apolipoprotein A-V, lipase maturation factor 1, or GPIHBP1, respectively (15). In this condition, chylomicron accumulation results in high fasting TG levels and reduced High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) (16). Recurrent pancreatitis is common (17) due to severe HTG.

As indicated by its name, multifactorial/polygenic chylomicronemia can be caused by multiple factors including heterozygous variants in the aforementioned monogenic chylomicronemia genes or from combination of several TG-raising polymorphisms leading to clinical manifestations similar to monogenic chylomicronemia (15).

Other causes of primary HTG

Causes of less severe HTG can be categorized into three groups: multifactorial/polygenic HTG, combined hyperlipoproteinemia, and dysbetalipoproteinemia.

Multifactorial/polygenic HTG, previously known as familial hypertriglyceridemia, has no currently identified genetic locus. HTG typically manifests in adulthood; however, pediatric expression has increased due to childhood obesity (18–20). This condition results in Very Low-Density Lipoproteins (VLDL) overproduction and impaired catabolism of TG-rich lipoproteins resulting in HTG (14, 21). Typically, patients are asymptomatic with HTG between 250 and 1,000 mg/dL (22).

Combined hyperlipoproteinemia, previously named familial combined hyperlipidemia, has multiple genetic loci and complex pathophysiology with variable expressivity (23, 24). Combined hyperlipoproteinemia is typically characterized by overproduction of VLDL and apolipoprotein B-100, reduction in fatty acid uptake by adipocytes, and decreased clearance of chylomicron remnants (14). These patients may exhibit LDL elevation in addition to HTG (15).

Dysbetalipoproteinemia is caused by a combination of polygenic contributors in addition to apolipoprotein-E mutation (15). This results in abnormal metabolism of chylomicrons, Intermediate Density Lipoprotein, and VLDL remnant particles leading to elevated total cholesterol and TG (25). It is not typically expressed in childhood unless there is secondary exogenous risk (26, 27).

Secondary hypertriglyceridemia

Secondary hypertriglyceridemia results from many diseases, exposures, and underlying risk factors. Blackett et al. report genetic background and developmental factors play a significant role in the risk for secondary HTG (28). Heterozygous relatives of patients with primary dyslipidemias can develop severe dyslipidemia/HTG, further worsened by other factors such as alcohol, obesity, and high-risk medications (29, 30). Features of growth and development such as intrauterine growth restriction, prematurity, childhood obesity, and puberty also increase risks for dyslipidemia and HTG (28).

Type 1 Diabetes and insulin deficiency, at baseline and in extremis such as Diabetic Ketoacidosis (DKA), have known associations with elevated TG and cholesterol which improve with insulin therapy (31–33). Conversely, insulin resistance, in obesity and/or Type 2 Diabetes, can lead to increased serum free fatty acids (FFA) and insulin-stimulated hepatic TG synthesis which increases VLDL and TG levels (34). Additionally, chylomicron production (and resulting HTG) is less susceptible to insulin suppression in insulin resistant patients (35).

Pediatric disorders in other organ systems that have association with HTG include diseases of liver (non-alcoholic fatty liver disease, hepatitis C, type 1 glycogen storage disorder), kidney (nephrosis), endocrine (hypothyroidism, growth hormone deficiency/excess, congenital generalized lipodystrophy), and immune system (human immunodeficiency virus (HIV) lipodystrophy, gammopathies) (28). Additionally,

many medications have known and some unknown mechanisms that lead to HTG including glucocorticoids, L-asparaginase, oral estrogens, retinoids, immune suppressants, protease inhibitors, bile acid sequestrants, loop/thiazide diuretics, beta-blockers, and alcohol (28).

Pathophysiology of hypertriglyceridemia-induced acute pancreatitis

The pathophysiology of HTG-AP is not well characterized. One theory proposed by Havel et al. suggests that pancreatic lipase hydrolyzes excess TG in pancreatic capillary beds leading to high concentration of FFAs; these FFAs aggregate causing damage to acinar and capillary endothelial cells with resulting ischemia, increased acidity, and further FFA toxicity (36, 37); additionally, chylomicrons may increase serum viscosity, further decreasing pancreatic blood flow and adding to ischemic/acidotic environment (36–38).

Clinical definitions and presentation

Diagnosis of pediatric AP requires meeting ≥2 of 3 criteria including: (1) abdominal pain compatible with acute pancreatitis, (2) serum lipase and/or amylase level ≥3 times upper limit of normal, (3) imaging findings consistent with acute pancreatitis (39). HTG-AP frequently presents similarly to other causes of AP; however, certain features in patient history (obesity, alcohol use, diabetes), family history (hyperlipidemia, early cardiac death), physical exam (eruptive or tuberous xanthomas, lipemia retinalis, hepatosplenomegaly), and laboratory evaluation (lipemic or "milky" appearing serum) may raise suspicion for hypertriglyceridemia (2, 40, 41).

Triglyceride levels in pediatric patients are considered "high" at the 95th percentile for age, specifically, TG >100 mg/dL (0–9 years old) or >130 mg/dL (10–19 years old) (42). While fasting TG levels >200–499 mg/dL are defined as higher risk and recommendations are made to consider pharmacotherapy, no further stratification is defined for TG levels >500 mg/dL. Shah et al. combined the Endocrine Society values for adult severe HTG and the Pediatric Expert Panel recommendations to better delineate classification and risk for children with TG ≥500 mg/dL with additional categories for "Very High" (≥ 500-999 mg/dL), "Severe" (≥1,000–1,999), and "Very Severe" (≥2,000 mg/dL) (14, 43). The threshold at which HTG can cause AP is debated. Commonly cited levels are between 1,000–1,772 mg/dL (41, 44) with some reports as low as 500–1,000 mg/dL (45). The risk of AP with TG levels <1,000 mg/dL is not well defined, however, the lifetime risk of AP in severe HTG >1,000 mg/dL has been estimated at ∼5 and 10–20% for very severe HTG >2,000 mg/dL (46).

There are varying reports on the clinical course, severity, and complications in HTG-AP compared to other causes of AP. HTG has been shown to affect severity of AP in animal models (47, 48). *Ex-vivo* studies have demonstrated that triglycerides may play a role in AP-associated respiratory failure (49). Some reports did not find a difference in morbidity and mortality between HTG-AP and other causes of AP (2, 50); however, the threshold for HTG in at least one prospective study was >175 mg/dL, which is lower than typically seen in HTG-AP. Conversely, there have been several studies which demonstrated increase in severity, recurrence, hospital stay, Intensive Care Unit (ICU) care, incidence of pancreatic necrosis, abscess formation/other infection, and renal failure in patients with HTG-AP compared to other causes of AP (51–54). Despite mounting evidence of increased severity in HTG-AP, actual TG level likely does not directly correlate with severity (50, 53).

Treatment of hypertriglyceridemia-induced acute pancreatitis

The treatment goals of HTG-AP are to lower TG levels and prevent recurrence of AP. Patients with HTG >1,000 mg/dL plus AP or abdominal pain (symptomatic HTG) typically require hospital admission for aggressive interventions to minimize the risk of complications (55, 56). For asymptomatic severe HTG (>1,000 mg/dL) without confirmed AP, reasons for hospitalization include uncontrolled diabetes, HTG at a level where AP previously occurred, continued exposure to trigger that can increase TG levels, or pregnancy in third trimester.

Initial management of acute episode

Intravenous fluids and diet

Fluid management recommendations include initial 10–20 ml/kg boluses of lactated ringers or normal saline fluids based on hydration/hemodynamic status followed by continuous intravenous fluids (IVF) at 1.5–2x maintenance rate (57). Current recommendations in both adult and pediatric literature suggest that high-rate IVF and early enteral nutrition (unless contraindicated or not feasible) decrease length of hospital stay and risk of mortality for acute pancreatitis patients (57, 58). In contrast, the first step of therapy for HTG-AP involves dietary restriction/*nil per os* (NPO). Limiting enteral nutrition can decrease production of diet-derived chylomicrons. This also facilitates clearance of already present chylomicrons and reduces TG (59). Once TG levels are <500 mg/dL, patients can gradually increase fat intake to a goal 10–15% of total dietary calories while monitoring TG levels (28, 41, 43).

Insulin

Insulin can increase activation of LPL which increases clearance of chylomicrons and decreases levels of TG (31). Insulin is effective for both HTG and hyperglycemia in diabetic patients (60, 61) but also can be used to treat HTG in non-diabetic patients (62, 63). Euglycemia should be maintained with dextrose fluids in non-diabetic patients. Both intravenous (IV) and subcutaneous dosing have been used successfully (62, 63), but continuous IV Insulin has the benefit of easier titration; though no society guidelines for continuous insulin dosing in HTG patients were found, Schaefer et al. have suggested continuous insulin drip 0.1–0.3 U/kg/hour with dextrose fluids to maintain blood glucose between 140– 80 mg/dL (55). Insulin can reduce TG level up to 40% in the first 24 h (60) and between 50–75% over 2–3 days (64); even further reduction up to 80% in the first 24 h is possible when kept NPO (61). One small ($n = 17$) retrospective pediatric HTG-AP cohort study from Ippisch et al. showed statistically significant difference ($P = 0.0339$) in mean 24-h reduction of TG by 40% with insulin vs. 17% without insulin (65).

Plasmapheresis

In adult HTG-AP, plasmapheresis can effectively reduce TG levels rapidly by 40–70% after a single treatment (40, 66, 67). Multiple case reports demonstrate the utility of plasmapheresis in patients with concomitant severe disease such as DKA or complications of HTG-AP such as acute respiratory distress syndrome (66, 68). The main indications for plasmapheresis include severe HTG-AP with worsening organ dysfunction/multi-organ failure, worsening systemic inflammation, or lactic acidosis (69, 70). Evidence of improvement in clinical outcomes from plasmapheresis varies. Chen et al. (71) did not show a statistical difference in morbidity or mortality between plasmapheresis vs. no plasmapheresis groups, though this was partially attributed to delay in initiation. Plasmapheresis for HTG-AP has relatively fewer published reports in pediatric patients (68, 72). One limitation in pediatric patients is the availability of equipment, protocols, and providers to effectively manage therapeutic plasmapheresis for HTG reduction. If the patient cannot tolerate plasmapheresis or it is not available, providers should strongly consider other interventions, such as continuous insulin even in non-diabetic patients (40).

Heparin

Heparin stimulates LPL release *in vivo* (31) from several extrahepatic tissues such as myocytes, adipose tissues, and macrophages; however, after initial peak in LPL, serum levels rapidly drop likely due to uptake and degradation in the liver (73). Additionally, prolonged use can deplete LPL stores, allowing rebound in TG levels. There has also been some reluctance to use heparin in cases of pancreatic necrosis due to risk of hemorrhage (74). The routine use of heparin in the management of HTG-AP might be limited due to the above features.

After stabilization

For acute HTG-AP, consensus TG treatment goal varies; this may be related to the relative risk at >500 mg/dL (40, 46, 65, 69) vs. absolute risk at >1,000 mg/dL (43, 55, 56) for development of AP and other complications. The decision on when to discontinue higher level interventions and advance diet should be determined based on individual patient factors and feasibility of attaining goal TG level. Certain factors such as excessive post-prandial TG rise in genetic hypertriglyceridemia may warrant goal <500 mg/dL (56), but further evidence for this recommendation is needed. All patients should be counseled on the need for long term interventions including dietary fat restriction, weight management, and exercise. Patients at risk for persistent HTG should be started on oral antihyperlipidemic agents during hospitalization. An algorithm (Figure 1) summarizing pertinent management steps for Acute HTG-AP has been created by adapting various external references (40, 55, 65, 69).

Long-term management/prevention

Screening

The American Academy of Pediatrics (AAP) recommends universal lipid screening for all children between 9–11 and 17–21 years old. Additional screening for dyslipidemia should be considered in any patient 2 years or older with any one of the following: (1) parent, grandparent, aunt/uncle, or sibling with history of a heart attack, angina, stroke, coronary artery bypass/stent/angioplasty, or sudden death in males <55 years and females <65 years. (2) Parent with a total cholesterol ≥240 mg/dL or known dyslipidemia. (3) Patient has diabetes, hypertension, BMI >85th percentile, or smokes cigarettes. (4) Patient has other moderate- or high-risk medical conditions including chronic kidney disease/post-renal transplant, post-orthotopic heart transplant, Kawasaki disease with current or regressed coronary aneurysms, chronic inflammatory disease, HIV, and nephrotic syndrome (42).

Dietary and lifestyle interventions

Management of HTG in the outpatient setting is primarily driven by lifestyle and dietary changes. Per the CHILD-2 diet from the AAP, dietary management of HTG includes reducing

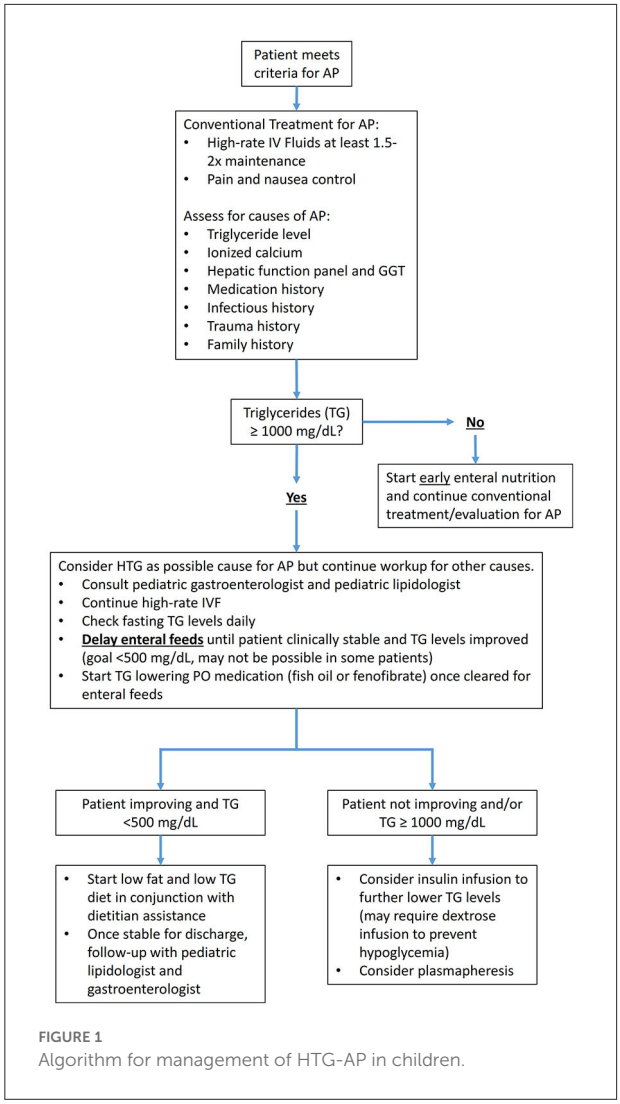

FIGURE 1
Algorithm for management of HTG-AP in children.

the amount of daily calories from fat to 25–30% with ≤7% from saturated fat, limit monounsaturated fat to ∼10%, limit cholesterol intake to <200 mg/d, avoid trans fats, reduce simple carbohydrate such as sugar-sweetened beverages, and increasing dietary fish to raise omega-3 fatty acid intake (42). For severe HTG, daily fat intake should be further decreased to 10–15% of total calories (41, 75).

Attention should be paid to prevent deficiency of essential fatty acids, linoleic acid (LA) and α-linolenic acid (ALA), as well as fat soluble vitamins (28). The minimum recommended intake to prevent essential fatty acid deficiency is ≥10% of total calories from polyunsaturated fats (76) with 2–4% of calories/energy from LA and 0.25–0.5% from ALA (77, 78); however, it is advisable to consult with a clinical dietician to ensure that each patient has their own individualized nutrition plan. Other interventions to manage HTG include increasing physical activity with the most recent guidelines recommending >60 minutes of moderate-to-vigorous physical activity daily for children aged 6–17 years (79–81).

Pharmacotherapy

Several drugs are available to lower TG when diet and lifestyle interventions are insufficient (Table 1). Fibrates and omega-3 fatty acids are the two most common therapies used to treat HTG particularly in the outpatient setting (82, 83). While fibrates are not FDA approved for use in children, they are generally tolerated well and are considered part of the armamentarium in managing significant HTG in children (83).

In adults, fibrates can lower TG levels by 46–62% with isolated hypertriglyceridemia and 24–36% in mixed dyslipidemia (84). There is limited safety data in pediatric patients regarding long term treatment with fibrates both alone and in combination with statins (85, 86). Nevertheless, a review of National Health and Nutrition Examination Survey data from 1999–2006 found that fibrates were the most commonly prescribed TG lowering medication in children with HTG >500 md/dL (87). Additionally, Manlhiot et al. described a statistically significant decrease in TG levels using fibrate therapy in children, though there was no specification of agent or dose (20). One drawback with fibrates is length of time from initiation to clinical effect (63).

Omega-3 fatty acids are frequently used as adjunctive agents for TG management. Adult studies have shown a mean reduction of ∼45% with 4g per day dosing (88). However, some pediatric studies have not shown significant change with either low dose (500–1,000 mg daily) or high dose (3,360 mg daily) of Omega-3 fatty acids (89, 90).

Niacin (Nicotinic Acid) is another medication used in adult patients for TG/cholesterol control. One of the use-limiting adverse effects of niacin is Prostaglandin E2 mediated flushing, which can be improved by taking aspirin prior (84), though aspirin can lead to Reye syndrome in younger children. A study by Colletti et al. showed niacin was effective at reducing total and LDL cholesterol in children but did not lower triglycerides; additionally, reversible adverse effects were seen in 76% of study participants and discontinuation of niacin due to adverse effects occurred in 38% of patients (91). Niacin is no longer routinely recommended for treatment of dyslipidemia due to this side effect profile.

Statins are widely prescribed antihyperlipidemic agents that do have well known utility in pediatric patients (87) and have approval from the Food and Drug Administration for 8–18 year old patients for treating elevated LDL-C or non-HDL-C with HTG and other risk factors (42). However, the efficacy of TG lowering effects from statins can vary (20, 92).

TABLE 1 Summary of pharmacotherapy options for HTG-AP in children.

Medication	Indications	Effects	Comments
Fibrates	Maintenance/Preventive	TG ↓↓ LDL-C ↓ (mild) HDL-C ↑ (mild)	Used off-label in children; monitor for hepatic and muscle side effects.
Omega 3 fatty acids	Maintenance/Preventive	TG ↓ LDL-C - variable ↑/↓ HDL-C - variable ↑/↓	Goal is ∼4 g/day of EPA +DHA; no hepatic or muscle side effects; can be used in combination with statins or fibrates
Statins	Maintenance/Preventive	TG ↓ (mild) LDL-C ↓↓ HDL-C ↑	Not used primarily for TG lowering but can be used if patient has combined TG and LDL-C elevation
Insulin	Acute Severe HTG	TG ↓↓ Glucose ↓↓	See acute treatment section
Heparin	Acute Severe HTG	TG ↓↓ (risk to ↑)	See acute treatment section

Conclusion

Hypertriglyceridemia is a known metabolic cause of acute pancreatitis in adults and increasingly recognized in children. HTG can be associated with primary/genetic causes or secondary causes (insulin dysregulation, medications, and other systemic diseases). TG levels > 1,000 mg/dL are most commonly associated with risk for developing acute pancreatitis, though there may be risk if > 500 mg/dL. Presentation for HTG-AP is similar to other causes of AP, but features such as obesity, diabetes, pregnancy, alcohol/high risk medication use, familial dyslipidemia, or exam findings of HTG may suggest the diagnosis and outcomes may be more severe. Several acute interventions (dietary restriction, insulin, plasmapheresis, heparin) and preventative measures (limiting dietary fat, exercise/weight loss, oral antihyperlipidemic medications) are available, but most outcome data on these interventions and management algorithms are focused on adult patients. For example, early plasmapheresis vs. reserving invasive interventions for severe disease/lack of improvement is currently contested in adult HTG-AP patients, but lower relative availability and evidence-based outcomes for plasmapheresis in pediatric patients presents a notable barrier. Further studies are needed to refine the therapeutic approach to pediatric HTG-AP.

Author contributions

JG, KE, and AT contributed to the conception of review and structure. JG performed the literature review and wrote the first draft of the manuscript. KE and AT contributed additional literature sources for review and content revision. All authors contributed to manuscript revision and approved of submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Speck L. A case of lipidemia. *Arch Verin Wiss Heilkd.* (1865) 1:232.

2. Fortson MR, Freedman SN, Webster PD, 3rd. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol.* (1995) 90: 2134–9.

3. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am.* (1990) 19:783–91. doi: 10.1016/S0889-8553(21)00513-6

4. Athyros VG, Giouleme OI, Nikolaidis NL, Vasiliadis TV, Bouloukos VI, Kontopoulos AG, et al. Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. *J Clin Gastroenterol.* (2002) 34:472–5. doi: 10.1097/00004836-200204000-00020

5. Saligram S, Lo D, Saul M, Yadav D. Analyses of hospital administrative data that use diagnosis codes overestimate the cases of acute pancreatitis. *Clin Gastroenterol Hepatol.* (2012) 10:805–11 e1. doi: 10.1016/j.cgh.2012.03.025

6. Zheng Y, Zhou Z, Li H, Li J, Li A, Ma B, et al. A multicenter study on etiology of acute pancreatitis in Beijing during 5 years. *Pancreas.* (2015) 44:409–14. doi: 10.1097/MPA.0000000000000273

7. Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crameri J, Oliver MR. Changing incidence of acute pancreatitis: 10-year experience at the royal children's hospital, Melbourne. *J Gastroenterol Hepatol.* (2007) 22:1313–6. doi: 10.1111/j.1440-1746.2007.04936.x

8. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an american pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas.* (2010) 39:5–8. doi: 10.1097/MPA.0b013e3181baac47

9. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, et al. Nationwide trends in acute and chronic pancreatitis among privately insured children and non-elderly adults in the United States, 2007-2014. *Gastroenterology.* (2018) 155:469. doi: 10.1053/j.gastro.2018.04.013

10. Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr.* (2011) 52:262–70. doi: 10.1097/MPG.0b013e3182061d75

11. Majbar AA, Cusick E, Johnson P, Lynn RM, Hunt LP, Shield JP. Incidence and clinical associations of childhood acute pancreatitis. *Pediatrics.* (2016) 138:e20161198. doi: 10.1542/peds.2016-1198

12. Alabdulkareem A, Almahmoud T, Al-Tahan H, Javad S, Al Hatlani M. Etiology and clinical characteristics of pediatric acute pancreatitis in Saudi Arabia: a 20-year experience from a single tertiary center. *Int J Pediatr Adolesc Med.* (2018) 5:13–7. doi: 10.1016/j.ijpam.2018.01.001

13. Pohl J, Morinville V, Husain SZ, Uc A. Toxic-metabolic risk factors are uncommon in pediatric chronic pancreatitis. *J Pediatr Gastroenterol Nutr.* (2016) 62:e66–7. doi: 10.1097/MPG.0000000000001156

14. Shah AS, Wilson DP. Primary hypertriglyceridemia in children and adolescents. *J Clin Lipidol.* (2015) 9:S20–8. doi: 10.1016/j.jacl.2015.04.004

15. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. *Eur Heart J.* (2020) 41:99–109c. doi: 10.1093/eurheartj/ehz785

16. Santamarina-Fojo S. The familial chylomicronemia syndrome. *Endocrinol Metab Clin North Am.* (1998) 27:551–67, viii. doi: 10.1016/S0889-8529(05)70025-6

17. Rahalkar AR, Giffen F, Har B, Ho J, Morrison KM, Hill J, et al. Novel *Lpl* mutations associated with lipoprotein lipase deficiency: two case reports and a literature review. *Can J Physiol Pharmacol.* (2009) 87:151–60. doi: 10.1139/Y09-005

18. Bouaziz Abed A, Maaloul I, Mustapha R, Chiha M, Aissa K. [Primary hypertriglyceridemia type Iv : early presentation of a severe case]. *Tunis Med.* (2013) 91:683.

19. Clauss SB, Kwiterovich PO. Genetic disorders of lipoprotein transport in children. *Prog Pediatr Cardiol.* (2003) 17:123–33. doi: 10.1016/S1058-9813(03)00049-3

20. Manlhiot C, Larsson P, Gurofsky RC, Smith RW, Fillingham C, Clarizia NA, et al. Spectrum and management of hypertriglyceridemia among children in clinical practice. *Pediatrics.* (2009) 123:458–65. doi: 10.1542/peds.2008-0367

21. Durrington P. Dyslipidaemia. *Lancet.* (2003) 362:717–31. doi: 10.1016/S0140-6736(03)14234-1

22. Tullu MS, Advirkar AV, Ghildiyal RG, Tambe S. Familial hypertriglyceridemia. *Indian J Pediatr.* (2008) 75:1257–8. doi: 10.1007/s12098-008-0219-y

23. Aouizerat BE, Allayee H, Cantor RM, Davis RC, Lanning CD, Wen PZ, et al. A genome scan for familial combined hyperlipidemia reveals evidence of linkage with a locus on chromosome 11. *Am J Hum Genet.* (1999) 65:397–412. doi: 10.1086/302490

24. Pajukanta P, Nuotio I, Terwilliger JD, Porkka KV, Ylitalo K, Pihlajamaki J, et al. Linkage of familial combined hyperlipidaemia to chromosome 1q21-Q23. *Nat Genet.* (1998) 18:369–73. doi: 10.1038/ng0498-369

25. Blom DJ, Byrnes P, Jones S, Marais AD. Dysbetalipoproteinaemia–clinical and pathophysiological features. *S Afr Med J.* (2002) 92:892–7.

26. Fung M, Hill J, Cook D, Frohlich J. Case series of type Iii hyperlipoproteinemia in children. *BMJ Case Rep.* (2011) 2011:bcr0220113895-bcr. doi: 10.1136/bcr.02.2011.3895

27. Ziemer A, Goring HD. [Severe type Iii hyperlipoproteinemia with unusual lipoprotein phenotype in an adolescent patient]. *Hautarzt.* (1993) 44:538–44.

28. Blackett PR, Wilson DP, McNeal CJ. Secondary hypertriglyceridemia in children and adolescents. *J Clin Lipidol.* (2015) 9:S29–40. doi: 10.1016/j.jacl.2015.04.006

29. Brunzell JD, Schrott HG. The interaction of familial and secondary causes of hypertriglyceridemia: role in pancreatitis. *J Clin Lipidol.* (2012) 6:409–12. doi: 10.1016/j.jacl.2012.06.005

30. Julien P, Vohl MC, Gaudet D, Gagne C, Levesque G, Despres JP, et al. Hyperinsulinemia and abdominal obesity affect the expression of hypertriglyceridemia in heterozygous familial lipoprotein lipase deficiency. *Diabetes.* (1997) 46:2063–8. doi: 10.2337/diabetes.46.12.2063

31. Eckel RH, Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. *N Engl J Med.* (1989) 320:1060–8. doi: 10.1056/NEJM198904203201607

32. Sherwin RS, Tamborlane WV, Genel M, Felig P. Treatment of juvenile-onset diabetes by subcutaneous infusion of insulin with a portable pump. *Diabetes Care.* (1980) 3:301–8. doi: 10.2337/diacare.3.2.301

33. Weidman SW, Ragland JB, Fisher JN Jr, Kitabchi AE, Sabesin SM. Effects of insulin on plasma lipoproteins in diabetic ketoacidosis: evidence for a change in high density lipoprotein composition during treatment. *J Lipid Res.* (1982) 23:171–82. doi: 10.1016/S0022-2275(20)38186-4

34. Tobey TA, Greenfield M, Kraemer F, Reaven GM. Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics, and plasma triglyceride levels in normotriglyceridemic man. *Metabolism.* (1981) 30:165–71. doi: 10.1016/0026-0495(81)90167-0

35. Nogueira JP, Maraninchi M, Beliard S, Padilla N, Duvillard L, Mancini J, et al. Absence of acute inhibitory effect of insulin on chylomicron production in type 2 diabetes. *Arterioscler Thromb Vasc Biol.* (2012) 32:1039–44. doi: 10.1161/ATVBAHA.111.242073

36. Havel RJ. Pathogenesis, differentiation and management of hypertriglyceridemia. *Adv Intern Med.* (1969) 15:117–54.

37. Saharia P, Margolis S, Zuidema GD, Cameron JL. Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. *Surgery.* (1977) 82:60–7.

38. Gan SI, Edwards AL, Symonds CJ, Beck PL. Hypertriglyceridemia-induced pancreatitis: a case-based review. *World J Gastroenterol.* (2006) 12:7197–202. doi: 10.3748/wjg.v12.i44.7197

39. Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. *J Pediatr Gastroenterol Nutr.* (2012) 55:261–5. doi: 10.1097/MPG.0b013e31824f1516

40. Tsuang W, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: presentation and management. *Am J Gastroenterol.* (2009) 104:984–91. doi: 10.1038/ajg.2009.27

41. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ.* (2007) 176:1113–20. doi: 10.1503/cmaj.060963

42. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* (2011) 128(Suppl. 5):S213–56. doi: 10.1542/peds.2009-2107C

43. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* (2012) 97:2969–89. doi: 10.1210/jc.2011-3213

44. Sandhu S, Al-Sarraf A, Taraboanta C, Frohlich J, Francis GA. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: a retrospective cohort study. *Lipids Health Dis.* (2011) 10:157. doi: 10.1186/1476-511X-10-157

45. Zhang XL Li F, Zhen YM Li A, Fang Y. Clinical study of 224 patients with hypertriglyceridemia pancreatitis. *Chin Med J.* (2015) 128:2045–9. doi: 10.4103/0366-6999.161361

46. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol.* (2014) 48:195–203. doi: 10.1097/01.mcg.0000436438.60145.5a

47. Czako L, Szabolcs A, Vajda A, Csati S, Venglovecz V, Rakonczay Z Jr, et al. Hyperlipidemia induced by a cholesterol-rich diet aggravates necrotizing pancreatitis in rats. *Eur J Pharmacol.* (2007) 572:74–81. doi: 10.1016/j.ejphar.2007.05.064

48. Wang YJ, Sun JB Li F, Zhang SW. Hyperlipidemia intensifies cerulein-induced acute pancreatitis associated with activation of protein Kinase C in rats. *World J Gastroenterol.* (2006) 12:2908–13. doi: 10.3748/wjg.v12.i18.2908

49. Kimura W, Mossner J. Role of hypertriglyceridemia in the pathogenesis of experimental acute pancreatitis in rats. *Int J Pancreatol.* (1996) 20:177–84. doi: 10.1007/BF02803766

50. Balachandra S, Virlos IT, King NK, Siriwardana HP, France MW, Siriwardena AK. Hyperlipidaemia and outcome in acute pancreatitis. *Int J Clin Pract.* (2006) 60:156–9. doi: 10.1111/j.1742-1241.2005.00645.x

51. Baranyai T, Terzin V, Vajda A, Wittmann T, Czako L. [Acute pancreatitis caused by hypertriglyceridemia]. *Orv Hetil.* (2010) 151:1869–74. doi: 10.1556/oh.2010.28966

52. Deng LH, Xue P, Xia Q, Yang XN, Wan MH. Effect of admission hypertriglyceridemia on the episodes of severe acute pancreatitis. *World J Gastroenterol.* (2008) 14:4558–61. doi: 10.3748/wjg.14.4558

53. Lloret Linares C, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D, Levy P, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas.* (2008) 37:13–2. doi: 10.1097/MPA.0b013e31816074a1

54. Navarro S, Cubiella J, Feu F, Zambón D, Fernández-Cruz L. Ros E. [Hypertriglyceridemic Acute Pancreatitis. Is Its Clinical Course Different from Lithiasic Acute Pancreatitis?]. *Medicina Clinica.* (2004) 123. doi: 10.1016/s0025-7753(04)74599-6

55. Schaefer EW, Leung A, Kravarusic J, Stone NJ. Management of severe hypertriglyceridemia in the hospital: a review. *J Hosp Med.* (2012) 7:431–8. doi: 10.1002/jhm.995

56. Valaiyapathi B, Ashraf AP. Hospital management of severe hypertriglyceridemia in children. *Curr Pediatr Rev.* (2017) 13:225–31. doi: 10.2174/1573400514666180117092707

57. Abu-El-Haija M, Kumar S, Quiros JA, Balakrishnan K, Barth B, Bitton S, 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. doi: 10.1097/MPG.0000000000001715

58. Ellery KM, Kumar S, Crandall W, Gariepy C. The benefits of early oral nutrition in mild acute pancreatitis. *J Pediatr.* (2017) 191:164–9. doi: 10.1016/j.jpeds.2017.08.032

59. Lopez-Miranda J, Williams C, Lairon D. Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism. *Br J Nutr.* (2007) 98:458–73. doi: 10.1017/S000711450774268X

60. Henderson SR, Maitland R, Mustafa OG, Miell J, Crook MA, Kottegoda SR. Severe hypertriglyceridaemia in type 2 diabetes mellitus: beneficial effect of continuous insulin infusion. *QJM.* (2013) 106:355–9. doi: 10.1093/qjmed/hcs238

61. Thuzar M, Shenoy VV, Malabu UH, Schrale R, Sangla KS. Extreme hypertriglyceridemia managed with insulin. *J Clin Lipidol.* (2014) 8:630–4. doi: 10.1016/j.jacl.2014.09.004

62. Jabbar MA, Zuhri-Yafi MI, Larrea J. Insulin therapy for a non-diabetic patient with severe hypertriglyceridemia. *J Am Coll Nutr.* (1998) 17:458–61. doi: 10.1080/07315724.1998.10718794

63. Mikhail N, Trivedi K, Page C, Wali S, Cope D. Treatment of severe hypertriglyceridemia in nondiabetic patients with insulin. *Am J Emerg Med.* (2005) 23:415–7. doi: 10.1016/j.ajem.2005.02.036

64. Coskun A, Erkan N, Yakan S, Yildirim M, Carti E, Ucar D, et al. Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin. *Prz Gastroenterol.* (2015) 10:18–22. doi: 10.5114/pg.2014.45412

65. Ippisch HM, Alfaro-Cruz L, Fei L, Zou Y, Thompson T, Abu-El-Haija M. Hypertriglyceridemia induced pancreatitis: inpatient management at a single pediatric institution. *Pancreas.* (2020) 49:429–34. doi: 10.1097/MPA.0000000000001505

66. Kohli RS, Bleibel W, Shetty A, Dhanjal U. Plasmapheresis in the treatment of hypertriglyceridemic pancreatitis with ards. *Dig Dis Sci.* (2006) 51:2287–91. doi: 10.1007/s10620-006-9315-x

67. Syed H, Bilusic M, Rhondla C, Tavaria A. Plasmapheresis in the treatment of hypertriglyceridemia-induced pancreatitis: a community hospital's experience. *J Clin Apher.* (2010) 25:229–34. doi: 10.1002/jca.20232

68. Lutfi R, Huang J, Wong HR. Plasmapheresis to treat hypertriglyceridemia in a child with diabetic ketoacidosis and pancreatitis. *Pediatrics.* (2012) 129:e195–8. doi: 10.1542/peds.2011-0217

69. Garg R, Rustagi T. Management of hypertriglyceridemia induced acute pancreatitis. *Biomed Res Int.* (2018) 2018:4721357. doi: 10.1155/2018/4721357

70. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing committee of the american society for apheresis: the seventh special issue. *J Clin Apher.* (2016) 31:149–62. doi: 10.1002/jca.21470

71. Chen JH, Yeh JH, Lai HW, Liao CS. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. *World J Gastroenterol.* (2004) 10:2272–4. doi: 10.3748/wjg.v10.i15.2272

72. Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: a systematic review. *Pancreatology.* (2015) 15:313–20. doi: 10.1016/j.pan.2015.02.010

73. Nasstrom B, Olivecrona G, Olivecrona T, Stegmayr BG. Lipoprotein lipase during continuous heparin infusion: tissue stores become partially depleted. *J Lab Clin Med.* (2001) 138:206–13. doi: 10.1067/mlc.2001.117666

74. Valdivielso P, Ramirez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med.* (2014) 25:689–94. doi: 10.1016/j.ejim.2014.08.008

75. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Jama.* (2001) 285:2486–97. doi: 10.1001/jama.285.19.2486

76. Mogensen K. Essential fatty acid deficiency. *Pract Gastroenterol.* (2017) 41:37–44.

77. Gramlich L, Ireton-Jones C, Miles JM, Morrison M, Pontes-Arruda A. Essential fatty acid requirements and intravenous lipid emulsions. *J Parenter Enteral Nutr.* (2019) 43:697–707. doi: 10.1002/jpen.1537

78. Estes-Doetsch H, Ganzer H, Roberts K, Brody RA. Risk factors and assessment considerations for essential fatty acid deficiency in nonparenterally fed patients using a case example. *Nutrition in Clinical Practice.* (2022) 37:843–51. doi: 10.1002/ncp.10822

79. Graham TE. Exercise, postprandial triacylglyceridemia, and cardiovascular disease risk. *Can J Appl Physiol.* (2004) 29:781–99. doi: 10.1139/h04-051

80. Richardson L, Paulis WD, van Middelkoop M, Koes BW. An overview of national clinical guidelines for the management of childhood obesity in primary care. *Prev Med.* (2013) 57:448–55. doi: 10.1016/j.ypmed.2013.08.010

81. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. *Jama.* (2018) 320:2020–8. doi: 10.1001/jama.2018.14854

82. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 Aha/Acc/Aacvpr/Aapa/Abc/Acpm/Ada/Ags/Apha/Aspc/Nla/Pcna guideline on the management of blood cholesterol. *Circulation.* (2018) 2018:CIR0000000000000625. doi: 10.1016/j.jacc.2018.11.003

83. de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation.* (2019) 139:e603–e34. doi: 10.1161/CIR.0000000000000618

84. Bell DA, Watts GF. Contemporary and novel therapeutic options for hypertriglyceridemia. *Clin Ther.* (2015) 37:2732–50. doi: 10.1016/j.clinthera.2015.08.001

85. Becker M, Staab D, Von Bergman K. Long-term treatment of severe familial hypercholesterolemia in children: effect of sitosterol and bezafibrate. *Pediatrics.* (1992) 89:138–42. doi: 10.1542/peds.89.1.138

86. Wheeler KA, West RJ, Lloyd JK, Barley J. Double blind trial of bezafibrate in familial hypercholesterolaemia. *Arch Dis Child.* (1985) 60:34–7. doi: 10.1136/adc.60.1.34

87. Christian JB, Juneja MX, Meadowcroft AM, Borden S, Lowe KA. Prevalence, characteristics, and risk factors of elevated triglyceride levels in us children. *Clin Pediatr.* (2011) 50:1103–9. doi: 10.1177/0009922811414286

88. Harris WS, Ginsberg HN, Arunakul N, Shachter NS, Windsor SL, Adams M, et al. Safety and efficacy of omacor in severe hypertriglyceridemia. *J Cardiovasc Risk.* (1997) 4:385–91. doi: 10.1097/00043798-199710000-00011

89. Chahal N, Manlhiot C, Wong H, McCrindle BW. Effectiveness of Omega-3 polysaturated fatty acids (Fish Oil) supplementation for treating hypertriglyceridemia in children and adolescents. *Clin Pediatr.* (2014) 53:645–51. doi: 10.1177/0009922814527503

90. de Ferranti SD, Milliren CE, Denhoff ER, Steltz SK, Selamet Tierney ES, Feldman HA, et al. Using high-dose Omega-3 fatty acid supplements to lower triglyceride levels in 10- to 19-year-olds. *Clin Pediatr.* (2014) 53:428–38. doi: 10.1177/0009922814528032

91. Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW. Niacin treatment of hypercholesterolemia in children. *Pediatrics.* (1993) 92:78–82. doi: 10.1542/peds.92.1.78

92. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation.* (2000) 101:207–13. doi: 10.1161/01.CIR.101.2.207

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Development of the human pancreas and its exocrine function

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The pancreas has both endocrine and exocrine function and plays an important role in digestion and glucose control. Understanding the development of the pancreas, grossly and microscopically, and the genetic factors regulating it provides further insight into clinical problems that arise when these processes fail. Animal models of development are known to have inherent issues when understanding human development. Therefore, in this review, we focus on human studies that have reported gross and microscopic development including acinar-, ductal-, and endocrine cells and the neural network. We review the genes and transcription factors involved in organ formation using data from animal models to bridge current understanding where necessary. We describe the development of exocrine function in the fetus and postnatally. A deeper review of the genes involved in pancreatic formation allows us to describe the development of the different groups (proteases, lipids, and amylase) of enzymes during fetal life and postnatally and describe the genetic defects. We discuss the constellation of gross anatomical, as well as microscopic defects that with genetic mutations lead to pancreatic insufficiency and disease states.

KEYWORDS

pancreas, ontogeny, genes, development, prenatal and postnatal of enzyme secretion

Introduction

The pancreas has both endocrine and exocrine functions. The endocrine system consists of multiple peptide hormones that function to regulate blood glucose but also influence exocrine functions (e.g., somatostatin). Its exocrine function involves the secretion of enzymes, bicarbonate, and water to aid in the digestion of nutrients.

There are many unanswered questions related to embryonic pancreatic development. Due to ethical issues, research in human development of the pancreas has been limited and predominantly conducted *via* animal studies.

In this review, we describe the current understanding of the development of the human pancreas, including gross and microscopic anatomy with a focus on exocrine function. In addition, we will describe disease states as the consequence of abnormalities in pancreas development and the genetic

mutations behind them. We will utilize animal models to highlight the possible development of the human pancreas and its implications in disease states.

Intrauterine pancreas development

The foregut endoderm gives rise to the dorsal and ventral pancreatic buds between days 26 and 31 of embryonic development.

Initially, there are two ventral pancreatic buds but the left side regresses. Figure 1 depicts the rotation of the stomach and duodenum starting at week 5 (Figure 1A) which results in the fusion of the two buds with the ventral bud lying posterior by week 6 (Figure 1B). The majority of the organ is derived from the dorsal bud while the ventral bud will give rise to the uncinate process and part of the head of the pancreas (Figure 1C) (1–3).

Pancreatic ducts

The main pain of the pancreatic duct (duct of Wirsung) is formed from the pancreatic duct of the ventral bud and the distal part of the duct of the dorsal bud. The proximal part of the dorsal bud contains an accessory pancreatic duct that opens into the minor duodenal papilla (4, 5). Initially, the ducts of the dorsal and ventral pancreas fuse, followed by partial regression of the dorsal pancreatic duct proximal to the duodenum to form Santorini's canal (6). In some, this will open into the minor papilla, while in others, it will be non-draining or connect with the main duct (6–8). Lack of fusion of the ventral and pancreatic ducts results in pancreatic divisum (9). By the 8th week, the bile tree and main pancreatic duct are joined together at the duodenum (10).

Three variants have been noted in the location of biliary and pancreatic ducts. The most common is when the pancreatic and bile duct joins at variable distances from the duodenum. The second variant includes joining at the duodenal wall and the third variant is when the pancreatic duct and biliary duct open at separate locations in the duodenum. While no particular pathology has been associated, there may be potential for pancreatitis in some individuals with the second and third variants (7, 11). These variations are important during the time of surgery or ERCP (11, 12).

Cellular matrix

Based on animal models the formation of cells that make up the pancreas starts as the epithelium of the buds begins to fold. It is followed by phases of branching, proliferating, and differentiating. The result is grape-like clusters, in which islet cells form clusters to the periphery of acinar and ductal cells (5).

The pancreas is made predominantly of acinar and duct cells, while the islet cells make up 1 to 2% of the pancreas. By the 9th week, the pancreas exists as tubules and clusters of undifferentiated epithelial cells. The tubules continue to grow, followed by lobule formation by the 14th week. Acinar cells with zymogen granules are noted between the 12th and 15th week, and in significant numbers by the 20th week (13). During this phase, the endoplasmic reticulum and Golgi apparatus undergo significant maturation (6). This is followed by progressive growth with a lumen in the center and lobules to the periphery with numerous acini (6).

Pancreatic stellate cells secrete extracellular matrix proteins and seem to have a significant function in the first trimester of human pancreatic development by enhancing differentiation to exocrine cell lineages (14).

Neuronal network

Comparable with the enteric nervous system, an intra-pancreatic nervous system develops to enable a degree of independence of the pancreas from the central nervous system and the gut. The pancreatic ganglia are the nervous integration centers of the pancreatic exocrine and endocrine secretion. Vagal preganglionic, sympathetic postganglionic, sensory, and enteric fibers innervate the fully developed pancreas. Postganglionic nerve fibers surround almost every acinus, forming a periacinar plexus containing cholinergic, noradrenergic, peptidergic, and nitrergic fibers, which terminate at the acinar cells. The autonomic nervous system of the pancreas interacts with ganglionic structures that are randomly scattered throughout the pancreatic parenchyma and represent the intrinsic neural component of the pancreatic nerve supply (15). Neurons and nerve fibers form complexes with endocrine cells, and epithelial cells located in ducts early in the second trimester and include pain fibers from parasympathetic nerves (16). Interestingly, innervation is found most densely at the head of the pancreas and decreases toward the tail (17). The sympathetic system seems to develop during this early fetal period and may have a role in endocrine pancreas development (18). Understanding sympathetic innervation of the exocrine pancreas is in its infancy. Studies seem to demonstrate sympathetic inhibition of blood flow, resulting in decreased exocrine secretion, and therefore indirect effect (19). On the other hand, parasympathetic innervation has a large role in exocrine function, mediated *via* vagal nerve activity, especially in the cephalic phase (20). Gastric, intestinal, and absorbed nutrient phases also appear to have both direct and indirect (*via* vagal nerve) mechanisms of pancreatic enzyme secretion (21). See *Neural Control of the Pancreas | Pancreapedia* for more information.

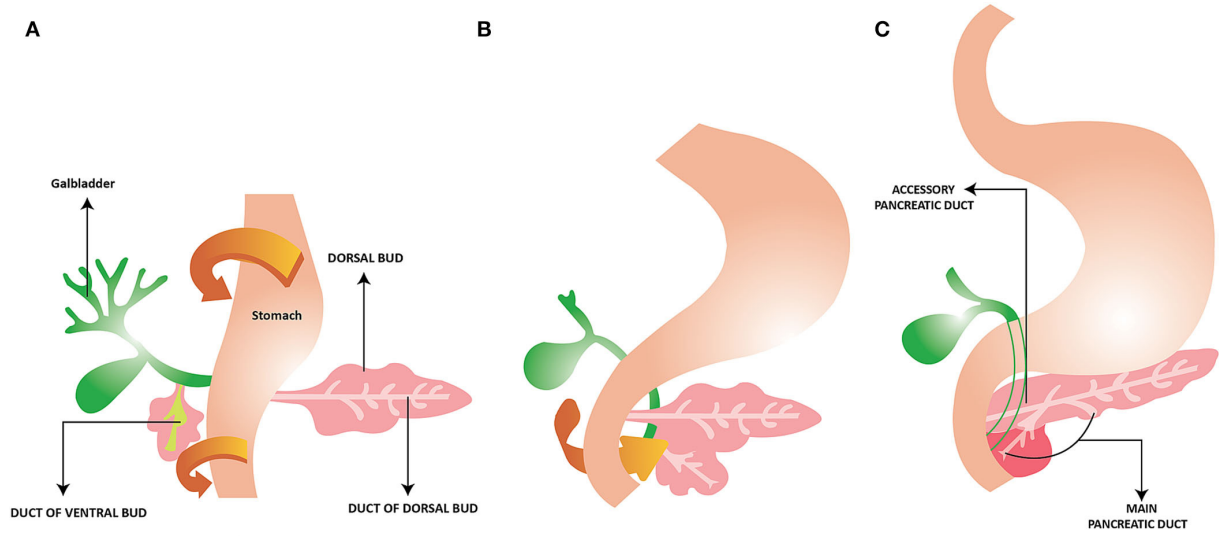

FIGURE 1
Development of the Pancreas. **(A)** Rotation of the ventral bud with the stomach and duodenum to the right. **(B)** The ventral and dorsal bud fuse together. **(C)** The main pancreatic duct exiting via the ventral bud to the duodenum. Ventral bud gives rise to uncinate process and part of the head of the pancreas. The dorsal bud gives rise to the remainder of the pancreas. Reprinted from "Pancreatic Duct Variations and the Risk of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis" Ojo A S. Cureus, 12 (9): e10445. 2020 by Cureus.

Development of exocrine function

The major adult human digestive exocrine pancreatic enzymes include amylase, pancreatic triglyceride lipase (PTL), colipase, trypsinogen, chymotrypsinogen, carboxypeptidase A1 and A2, and elastase. We will discuss the enzymes found in the intrauterine period followed by postnatal development and the maturation process to adult levels of the enzymes.

Intrauterine period

Most of the human pancreas exocrine development is derived from morphological studies. The exocrine tissue comprises acinar cells that secrete digestive enzymes and a duct system that deliver them to the small intestine.

Pancreatic secretory trypsin inhibitor (*PSTI*) or serine protease inhibitor kazal type 1 (*SPINK1*) was first noted by immunohistochemistry at the 8th gestational week (22).

Proteases

Adult human proteases include trypsinogen, chymotrypsinogen, elastase 1, and carboxypeptidase A1 and A2.

Many enzymes, including trypsinogen, chymotrypsinogen, and elastase-1, appear between 14th and 16th weeks of gestation (22–24).

The trypsinogen and chymotrypsinogen appear to be present from 16th weeks gestation and increase until birth (23). Activation of trypsinogen to trypsin requires enterokinase, while chymotrypsinogen requires trypsin for conversion to chymotrypsin (25, 26). Chymotrypsin was present in the 23-week premature infants with levels similar to term infants (27). While initially the development of enterokinase was thought to be around 26th week gestation, the levels of chymotrypsin found by Kolacek et al. suggest this may be slightly earlier (27, 28).

Neonates from 32 weeks gestation to term appear to have 90% to 100% of trypsin levels of children 2 years of age. On the other hand, levels of chymotrypsin is 50-60% and while carboxypeptidase B is 10-25% the level of 2-year-old children, thus showing the development of protease levels over time (Table 1) (29).

Lipases

Pancreatic triglyceride lipase (PTL) is the predominant lipase in human adults. However, other enzymes involved in fat breakdown include colipase and phospholipase A and B.

Lipases such as carboxyl ester lipase and pancreatic lipase-related proteins 1 and 2 (*PLRP*) were present from 14 to 16 weeks gestation (22–24), though *PLRP1* has no known activity (38). The mRNA encoding *PLRP1* and *PLRP2* was present by the 16th week in the human fetal pancreas. In contrast, the mRNA encoding PTL is limited in the fetal pancreas (29), and likely does not start increasing until 41 weeks gestation (24).

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TABLE 1 Ontogeny of common pancreatic enzymes in humans.

Pancreatic enzyme	Prenatal development (Gestational week)	Postnatal activities	Adult level	References
Amylase	39 weeks	<1% of adult values or absent levels until 6 weeks	6 months to 2 years	(22, 29–32)
Pancreatic triglyceride lipase	13–21 weeks	5–10% of adult values	2 years	(29, 33–35)
Trypsin *	14–16 weeks	90–100% of adult values	<1month	(22, 23, 29, 30)
Chymotrypsin*	14–16 weeks	50–60% of adult values	2 years	(22, 23, 29, 30, 36)
Elastase	14–16 weeks	25% of adult values	2 weeks	(22, 37)

*Initially detected as trypsinogen and chymotrypsinogen.

Amylase

Pancreatic amylase (encoded by *AMY2*) is present in adult humans but has not been detected in the fetus, and in fact is at low levels in humans even until 3 months of age (22, 39, 40).

Postnatal maturation of the exocrine function

Digestion of lipid, protein, and carbohydrates in infants relies on the state of the maturation of exocrine pancreatic function. However, diet composition can also affect enzyme production. Infants do not respond to exogenous cholecystokinin (CCK) or secretin well, but the exact maturation time of response of the exocrine pancreas to secretagogues is not well-defined (41, 42). Understanding normal age-based values of pancreatic enzyme activity in duodenal fluid with pancreatic function testing would allow a better understanding of the ontogeny of pancreatic exocrine tissue.

Interestingly, a diet in the form of starch and protein augments the production of α-amylase and trypsin, respectively, but fat does not stimulate the increased lipase levels in infants (36). However, a high protein and low-fat diet stimulates both trypsin and PTL activity (36). After 12 months of age, PTL does appear to be stimulated over baseline activity by meals (29). It may therefore be possible that CCK and secretin more effectively stimulate exocrine function closer to 12 months of age.

Initially, infants have "physiologic" steatorrhea in the first 3 to 6 months postnatally. As previously noted, lipase is at very low levels in the neonatal period. Based on rodent models, *PLRP2* may have a role in triglyceride digestion in newborns (38). Along with *PLRP2*, the presence of colipase has been noted, which based on animal models appears to increase the activity of *PLRP2* (43). Overall, PTL output or the coefficient of fat absorption is 5 to 10% of the adult values (29, 33, 44). In a study by Track et al., the PTL levels at 3 weeks were significantly higher than at 3 days of life and approached that of adult levels (34). However, in the study by Lebenthal et al., the PTL levels were low at birth and 1 month, with a substantial rise by 2 years (Table 1) (29, 30).

Amylase in the acinar cells was not detected until 39 weeks gestational age, and the functional amount of amylase does not arise until the 6th week postnatally (22, 29). In premature infants, amylase activity does not increase after a meal, compared to trypsin, and it is presumed that pancreatic amylase needs are met in the form of salivary amylase and amylase in breastmilk (29, 45). Indeed, it is thought that amylase remains at low levels until 6 months, although isolated amylase deficiency was noted to be frequent till 2 years of age (Table 1) (31, 32). Interestingly, in one cohort, isolated amylase deficiency had been noted beyond 2 years of age with a prevalence of up to 3.5% (32).

Elastase on the other hand is found at low levels at birth in meconium but reaches levels at the lower end of normal within 3 to 4 days in term infants and 2 weeks in preterm infants (Table 1) (37).

The immaturity of exocrine pancreas function is a notable factor in infant's vulnerability to metabolic and nutritional stress (33). Thus, additional non-pancreatic sources of digestion are present. Breast milk can be a source of amylase and bile salt-stimulated lipase. Additionally, brush-border glucoamylase is present in newborns with similar concentrations to that of adults, which may help in the digestion of complex carbohydrates.

Genes involved in the pancreas development

The process for the development of the pancreas and the fetus is based on specific coordination between genetics and the local environment. Much of our understanding of genes and molecular signaling comes from animal studies with the assumption that human development is similar. Table 2 summarizes genes and roles in pancreas development.

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We will discuss some of the genes that are involved in pancreas development and more specifically acinar and ductal cells. For further details, please visit *Development of the Pancreas | Pancreapedia* and work by Jennings et al. (47).

After the initial formation of pancreatic tissue, activation of *Wnt/β-catenin* is required for pancreatic tissue growth, particularly in acinar cells (46). Inhibition of another protein, sonic hedgehog (*SHH*), likely due to the proximity of the notochord, allowed for future expression of pancreas-duodenum homeobox 1 (*PDX1*), also known as insulin promoter factor 1 (IPF1) (47, 52). *PDX1* has been found as early as pancreatic bud formation and continues to be present in all epithelial cells in the embryonic period, and remains in the nuclei of non-endocrine epithelial cells along with the nuclei and cytoplasm of islet cells into adulthood (48).

Acinar cells begin initially as several carboxypeptidase A1 pyramidal cells bud from the pancreatic epithelium, likely representing the proacinar population. Additionally, *GATA4*, basic helix-loop-helix transcription factor (*MIST1*), and pancreatic secretory trypsin inhibitor are also expressed (1). However, the seminal work by Jennings et al. (56) suggests forkhead box protein A2 (*FOXA2*), and SRY-related homeobox 9 (*SOX9)* are other predominant transcription factors that define cell types. In particular, *SOX9* and *FOXA2* are present in ductal cells, while *GATA4* is present in acinar cells from the second trimester onward (56). *SOX9* has been noted in dorsal and ventral buds from day 32 with higher levels found in later embryonic stages days 44 to 52 (60). Other cellular markers of ductal cells include cytokeratin 19 (CK19) and CD133. CD133 is found in fetal duct-like cells, while CK19 is widely expressed in fetal pancreatic epithelial cells and continues as a ductal cell marker in adults (48, 65).

Notch signaling interacts with recombination signal binding protein for immunoglobulin kappa J region (*RBPJ*) to downregulate neurogenin-3 (*NEUROG3*) expression *via* hairy and enhancer of split-1 (*HES1*) (66). NEUROG3 is involved in endocrine commitment. *HES1* along with pancreas-associated transcription factor 1a (*PTF1a*) promotes acinar development (5).

As previously noted, *PTF1a* is important in the development of acinar cells. This is a class B basic helix-loop-helix (bHLH) transcription factor, which appears to be conserved across species. In animal models, the development of pancreatic buds includes *PTF1a* along with *PDX1* expression (67). However, further development of the pancreas includes an enhancer that binds to the active form of *PTF1a* and *RBPJ* to regulate *PTF1a* expression in acinar cells (68). Over time RBPJ is replaced with RBJPL which in complex with PTF1A and other class A bHLH forms PTF1-L and drives downstream regulators of digestive enzymes (53, 69, 70).

Structural abnormalities in pancreas development

Detailed description of developmental abnormalities that are associated with pancreatitis are outside the scope of this review. For completeness we describe them in brief.

Pancreatic divisum

Pancreatic divisum is the most common abnormality related to ductal fusion and drainage. It occurs in up to 10% of individuals (9). The lack of pancreas fusion results in drainage of the dorsal part of the pancreas *via* the minor papilla, while the ventral portion drains the head of the pancreas, uncinate process, and biliary tree into the major duct (71). It remains unclear if this anomaly increases the risk of recurrent pancreatitis and chronic pancreatitis.

Annular pancreas

The annular pancreas is a rare cause of pancreatitis and duodenal obstruction, typically with non-bilious emesis (72). It results in a thin band of pancreatic tissue surrounding the second part of the duodenum. It is hypothesized that the two ventral buds remain and fuse with the dorsal bud to create the ring (4). This may be the result of abnormal hedgehog signaling (5). Within the annular pancreas, there are six further classifications of type of annular pancreas depending on ductal drainage, including the main duct, minor duct, and common bile duct (73, 74).

Pancreatobiliary malformation

Anomalous pancreaticobiliary junction results from the joining of bile and pancreatic ducts outside the duodenal wall. It is believed that dysplasia and misarrangement of the bile and ventral pancreatic duct around the time of ventral pancreas formation results in pancreaticobiliary malformation (PBM) (75, 76). Typically, the end of the common bile duct is surrounded by the papillary sphincter, regulating bile flow while preventing reflux of pancreatic juices (77). However, with PBM, the sphincter is more distal (more than 15 mm) to the junction of the bile and pancreatic duct. As a result, bile and pancreatic juices may reflux into the other respective ducts, resulting in inflammation, bile duct dilation, pancreatitis, bile duct, and gallbladder cancer (78, 79).

It is further divided into three types, bile duct, pancreatic duct, and complex type, based on each joining at an acute angle.

TABLE 2 Transcription factors and cell signaling involved in human pancreas development.

GENE	ROLE	References
Wnt/ β-catenin	Inhibition in endoderm allows for pancreas and liver development. Later activation is required for cellular growth, specifically acinar cells	(46)
PDX1	Important in early pancreas formation, is found in multipotent progenitor cells as well as ductal and endocrine cells. Mutations have been associated with pancreatic agenesis as well as MODY	(47–51)
Sonic Hedgehog (SHH)	Signaling from notochord decreases activity of Shh, allowing *PDX1* expression	(47, 52)
PTF1A	Has a role along with *PDX1* in pancreas development and formation, as well as a crucial role in acinar cell development	(53–55)
GATA4	Transcription factor involved in early dorsal and ventral pancreatic bud formation. Later is found in progenitor and peripheral Tip cells, and finally acinar cells Association with neonatal diabetes and possible exocrine insufficiency	(56, 57)
NEUROG3	Appears to be present by 8 weeks, and disappears by 35 weeks, and is important in endocrine islet cell formation	(58, 59)
SOX9	Transcription factor in determining cell types and is uniformly present in ductal cells. Additionally has a role in ventral and dorsal bud formation. Mutation results in multiple systemic abnormalities, including pancreatic hypoplasia	(56, 60)
HNF1B	Involved in pancreas formation and ductal cell lineage early on in embryogenesis. Mutations have been associated with pancreas agenesis and MODY	(61–64)

Reflux into the biliary system is thought to result in a higher risk for congenital choledochal cyst, and, in particular, type Ia, Ic, and IV-A are associated with PBM (80). The biliary system is particularly susceptible as the pressure in the pancreatic duct is generally higher (81).

Ansa pancreatica

The **ansa pancreatica** is a rare type of anatomical variation of the pancreatic duct. It is a communication between the main pancreatic duct (of Wirsung) and the accessory pancreatic duct (of Santorini). Ansa pancreatica has been considered a predisposing factor in patients with idiopathic acute pancreatitis (82).

Genetic diseases with compromised exocrine function

The most common genetic disorder resulting in exocrine pancreatic insufficiency include Cystic fibrosis (>90%), followed by Schwachman-diamond, Johanson-Blizzard, Pearson's bone marrow, pancreatic agenesis/hypoplasia, isolated enzyme deficiencies, and genetic or metabolic causes of pancreatitis (83). These will be discussed here in brief for completeness.

Cystic fibrosis

Cystic fibrosis transmembrane conductance regulator (*CFTR*) is found in ductal epithelial cells and is involved in HCO^3 - and Cl^- transport between the membranes along with water (84). Impaired movement of the ions, and fluid, results in increased viscosity and obstruction of the lumen (85). It is hypothesized that pancreatic insults begin in utero and progress after birth to affect all ducts resulting in pancreatic insufficiency (86). Pancreatic insufficiency occurs in 85% of this population, with a high prevalence among those with homozygous mutations for Δ*508* (83).

Schwachman-diamond syndrome

Schwachman-Diamond syndrome is an autosomal recessive disorder with bone marrow involvement, skeletal abnormalities, and pancreatic insufficiency with variable penetrance (87). Mutations predominantly on chromosome 7 seem to be responsible, but with a spectrum of homozygous and compound heterozygous mutations (88, 89). It has been identified in 90% of individuals with this syndrome and the protein produced by the gene appears to affect ribosome function and may reduce protein production (90). Biopsies of the pancreas have shown that the duct and islet cell functions are preserved; however, acini are replaced by adipose tissue (91). Interestingly, over time, it seems that patients regain some function, and 40% to 60% have sufficient exocrine function (92).

Johanson-Blizzard syndrome

Johanson-Blizzard syndrome is an autosomal recessive disorder with a defect in the *UBR1* gene on Chromosome 15 (15q14–21.1) (93). E3 Ubiquitin ligase UBR1 is involved in the breakdown of intracellular pathways, thus mutations in this affect appropriate protein recycling (94). The typical clinical features are exocrine pancreatic insufficiency, hypoplasia/aplasia of the alae nasi, congenital scalp defects, and growth retardation (95, 96). Zenker et al. reported that individuals with this syndrome did not express *UBR1* and had intrauterine-onset destructive pancreatitis with secondary replacement of acinar cells with adipose tissue resulting in pancreatic insufficiency (93, 97, 98).

Pearson syndrome

Pearson syndrome is characterized by the bone marrow with vacuolization of erythroid and myeloid precursors, and sideroblasts, along with pancreatic insufficiency and it was initially reported by Pearson (99). It was later confirmed that this syndrome is the result of mitochondrial DNA deletion, affecting protein-coding and tRNA genes and therefore mitochondrial structure and function (100, 101). However, the prevalence of pancreatic insufficiency varies, likely due to variation in mitochondrial DNA deletions (100, 102–104).

Pancreatic agenesis

Agenesis of the dorsal pancreas can have non-specific findings, including abdominal pain, and often requires imaging findings such as CT to show a lack of pancreatic tissue (105). Several transcription factors have been implicated in pancreas malformation and agenesis, these include *PDX1*, Hepatocyte nuclear factor (*HNF1B*), *PTF1A*, and *SOX9*. A case report described a homozygous point deletion mutation in *PDX1* resulting in pancreatic agenesis with resulting exocrine and endocrine insufficiency (106). While complete agenesis of the pancreas is incompatible with life, case reports have noted variations in ventral and dorsal agenesis ranging from partial to complete (107, 108).

HNF1B mutations have led to the absence of part of the head, body, and tail of the pancreas, suggesting a role for *HNF1B* in dorsal pancreas formation (61–63). Another key regulator, particularly of exocrine function, *PTF1A*, has been implicated in pancreatic and cerebellar agenesis (54). Mutations in downstream enhancers of *PTF1A* have also been noted with isolated pancreatic agenesis (55). Finally, *SOX9* has a role in multiple tissues, and particularly the pancreas through much of its formation. Mutation in one gene results in developmental abnormalities of skeletal, reproductive, and other organs such as pancreas hypoplasia (56, 60).

Pancreatitis

SPINK1 is responsible for inhibiting prematurely activated trypsin in the pancreas. Mutations in the gene have resulted in variations in pathology ranging from increased risk of pancreatitis and exocrine pancreatic insufficiency to inconsistent implications in pancreatic disease (109, 110). Overall, it does appear that the gene is implicated in the earlier cause of pancreatitis and has more pancreatic insufficiency than normal cohorts (111). Indeed, case reports have described exocrine pancreatic insufficiency in infants (112).

Cationic trypsinogen (*PRSS1*), anionic trypsinogen (PRSS2), and mesotrypsin (*PRSS3*) are forms of trypsinogen with PRSS1 being the dominant one (104). A hereditary pancreatitis is a rare form of chronic pancreatitis resulting from a mutation in *PRSS1*, which is autosomal dominant with high penetrance and risk of pancreatic adenocarcinoma (113, 114). Episodes of pancreatitis have been noted to be bimodal with peaks around 6 years and 18 years of age, but with variability in pancreatic exocrine function deficiency, though this was often based on clinical symptoms or stool testing (113, 115, 116).

Carboxypeptidases are metalloproteases that play a role in the digestion of proteins and peptides by hydrolyzing C-terminal peptide bonds (117). Following trypsinogen, carboxypeptidase A1 (*CPA1*) is the next most common protein excreted in pancreatic fluid (118). Among a cohort of German individuals, *CPA1* variants were noted to be a risk factor for chronic pancreatitis. Although the mechanism is uncertain, the authors propose misfolding with subsequent stress in the endoplasmic reticulum as a cause (119).

Chymotrypsinogen C variants (*CTRC*) is a calcium-dependent serine protease that is important in cationic trypsinogen activation and trypsin degradation (120, 121). Within the pancreas, however, it appears that it has a role in trypsinogen degradation (121, 122). Therefore, mutations result in loss of function and have been associated with early pancreatitis and chronic pancreatitis in pediatrics (123, 124).

Maturity onset diabetes of the young (MODY)

Mutations in transcription factors previously noted in the development of the pancreas have been implicated in anatomical variants as well as in endocrine issues, namely, MODY. HNF1B and PDX1 are two that have been implicated (49, 50, 62, 125).

Additionally, deficiency in carboxyl ester lipase (CEL) resulted in another form of MODY. CEL, also referred to as bile salt-dependent lipase (BSDL), is one of the four lipases involved in hydrolyses of dietary fat, fat-soluble vitamins, and more specifically cholesterol esters (126). The combined endoscopic pancreatic stimulation test and MRI have shown severely reduced acinar function, along with low pancreas volume with increased lipomatosis in cases of MODY (127, 128).

Future directions

Knowledge of gene expression and the role of transcription factors allow for further research into stem cell therapy. Current research in both the endocrine and exocrine function was conducted on animal models, though with human pluripotent stem cells (hPSCs). Pluripotent stem cells can be obtained from embryonic cells or can be induced from adult somatic cells, such as fibroblasts or ductal epithelium. Ethical issues are likely to be a big barrier to the use of embryonic cells. Thus, understanding of factors required to convert somatic cells to pluripotent stem cells and then into pancreatic cell lines will hold promise for future. Studies so far seem to show promise in de-differentiating somatic cells-induced pluripotent stem cells (iPSC) and then differentiating into pancreatic progenitor cells (129, 130). In fact, clinical studies are underway in Type 1 diabetes mellitus and the new technologies hold promise in those with exocrine pancreatic dysfunction, particularly in those with chronic pancreatitis requiring islet cell transfer.

There are many answered questions in the human development of the pancreas. How does autonomic innervation, including sympathetic and parasympathetic innervation, develop in the embryo, including when does stimulation such as cephalic input begin? Likewise, a better understanding of innervation by pain fibers may help target therapy.

As current tests for exocrine pancreatic insufficiency include the use of CCK and secretin stimulation, and understanding the maturational process and when the pancreas responds are important.

The use of whole exome sequencing has been increasing with increased access to technology. How certain variants affect exocrine function, and therefore digestion, absorption, and growth will likely provide useful clinical information.

Conclusion

This review shows a framework for the development of the human pancreas including both gross and microanatomy. Pancreas organogenesis is a stepwise process regulated by a complex network of signaling and transcriptional events, that start with the early endoderm toward pancreatic fate. Many crucial players in this process have been identified, including signaling pathways, genes, regulatory elements, and transcription factors. Much of the work is based on the static evaluation of embryonic and fetal specimens that were available due to ethical issues. While gene expressions and transcription factors involved in pancreas formation have been reported, further understanding of cell-to-cell interaction, including those with stellate cells is necessary. It is possible that with a better understanding of iPSC conversion into various pancreatic cell lineages will help understand better the interaction between these cell types along with gene expression and transcription factor production. Molecular understanding of pancreas formation holds exciting promise for future therapies in both the endocrine and exocrine arms.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Pan FC, Brissova M. Pancreas development in humans. *Curr Opin Endocrinol Diabetes Obes.* (2014) 21:77–82. doi: 10.1097/MED.0000000000000047

2. O'Rahilly R, Müller F. Developmental stages in human embryos: revised and new measurements. *Cells Tissues Organs.* (2010) 192:73–84. doi: 10.1159/000289817

3. Gittes GK. Developmental biology of the pancreas: a comprehensive review. *Dev Biol.* (2009) 326:4–35. doi: 10.1016/j.ydbio.2008.10.024

4. Moore KL, Persaud TVN, Torchia MG. Alimentary system. In: *The Developing Human- Clinically Oriented Embryology*. 11th ed. Amsterdam: Elsevier Publishing Company (2018). p. 193–221.

5. Schoenwolf G, Bleyl S, Brauer P, Francis-West P. Development of the gastrointestinal tract. In: *Larsen's Human Embryology*. 6th ed. Amsterdam: Elsevier Publishing Company. (2020).

6. Adda G, Hannoun L, Loygue J. Development of the human pancreas: variations and pathology. A tentative classification. *Anat Clin.* (1984) 5:275–83. doi: 10.1007/BF01798752

7. Millbourn E. On the excretory ducts of the pancreas in man, with special reference to their relations to each other, to the common bile duct and to the duodenum. *Acta Anat.* (1950) 9:1–34. doi: 10.1159/000140426

8. Türkvatan A, Erden A, Türkoglu MA, Yener Ö. Congenital variants and anomalies of the pancreas and pancreatic duct: imaging by magnetic resonance cholangiopancreaticography and multidetector computed tomography. *Korean J Radiol.* (2013) 14:905–13. doi: 10.3348/kjr.2013.14.6.905

9. Agha FP, Williams KD. Pancreas divisum: incidence, detection, and clinical significance. *Am J Gastroenterol.* (1987) 82:315–20.

10. Wong KC, Lister J. Human fetal development of the hepato-pancreatic duct junction–a possible explanation of congenital dilatation of the biliary tract. *J Pediatr Surg.* (1981) 16:139–45. doi: 10.1016/S0022-3468(81)80340-5

11. Aljiffry M, Abbas M, Wazzan MAM, Abduljabbar AH, Aloufi S, Aljahdli E. Biliary anatomy and pancreatic duct variations: a cross-sectional study. *Saudi J Gastroenterol.* (2020) 26:188–93. doi: 10.4103/sjg.SJG_573_19

12. Chavalitdhamrong D, Draganov PV. Unexpected anomaly of the common bile duct and pancreatic duct. *World J Clin Cases.* (2014) 2:36–8. doi: 10.12998/wjcc.v2.i2.36

13. Laitio M, Lev R, Orlic D. The developing human fetal pancreas: an ultrastructural and histochemical study with special reference to exocrine cells. *J Anatomy*. (1974) 117(Pt 3):619–34.

14. Li J, Chen B, Fellows GF, Goodyer CG, Wang R. Activation of pancreatic stellate cells is beneficial for exocrine but not endocrine cell differentiation in the developing human pancreas. *Front Cell Develop Biol.* (2021) 9:4276. doi: 10.3389/fcell.2021.694276

15. Kiba T. Relationships between the autonomic nervous system and the pancreas including regulation of regeneration and apoptosis: recent developments. *Pancreas.* (2004) 29:e51–8. doi: 10.1097/00006676-200408000-00019

16. Krivova Y, Proshchina A, Barabanov V, Leonova O, Saveliev S. Structure of neuro-endocrine and neuro-epithelial interactions in human foetal pancreas. *Tissue Cell.* (2016) 48:567–76. doi: 10.1016/j.tice.2016.10.005

17. Amella C, Cappello F, Kahl P, Fritsch H, Lozanoff S, Sergi C. Spatial and temporal dynamics of innervation during the development of fetal human pancreas. *Neuroscience.* (2008) 154:1477–87. doi: 10.1016/j.neuroscience.2008.04.050

18. Krivova YS, Proshchina AE, Otlyga DA, Leonova OG, Saveliev SV. Prenatal development of sympathetic innervation of the human pancreas. *Ann Anat.* (2022) 240:151880. doi: 10.1016/j.aanat.2021.151880

19. Love JA Yi E, Smith TG. Autonomic pathways regulating pancreatic exocrine secretion. *Auton Neurosci.* (2007) 133:19–34. doi: 10.1016/j.autneu.2006.10.001

20. DiMagno EP. Regulation of interdigestive gastrointestinal motility and secretion. *Digestion.* (1997) 58 Suppl 1:53–5. doi: 10.1159/000201527

21. Chandra R, Liddle R. *Regulation of Pancreatic Secretion. Pancreapedia: Exocrine Pancreas Knowledge Base* (2015). doi: 10.3998/panc.2015.38

22. Fukayama M, Ogawa M, Hayashi Y, Koike M. Development of human pancreas. Immunohistochemical study of fetal pancreatic secretory proteins. *Differentiation.* (1986) 31:127–33. doi: 10.1111/j.1432-0436.1986.tb00393.x

23. Carrère J, Figarella-Branger D, Senegas-Balas F, Figarella C, Guy-Crotte O. Immunohistochemical study of secretory proteins in the developing human exocrine pancreas. *Differentiation.* (1992) 51:55–60. doi: 10.1111/j.1432-0436.1992.tb00680.x

24. Yang Y, Sanchez D, Figarella C, Lowe ME. Discoordinate expression of pancreatic lipase and two related proteins in the human fetal pancreas. *Pediatr Res.* (2000) 47:184–8. doi: 10.1203/00006450-200002000-00006

25. Hermon-Taylor J, Perrin J, Grant DA, Appleyard A, Bubel M, Magee AI. Immunofluorescent localisation of enterokinase in human small intestine. *Gut.* (1977) 18:259–65. doi: 10.1136/gut.18.4.259

26. McClure WO, Edelman GM. Fluorescent probes for conformational states of proteins. The activation of chymotrypsinogen. *Biochemistry.* (1967) 6:567–72. doi: 10.1021/bi00854a026

27. Kolacek S, Puntis JW, Lloyd DR, Brown GA, Booth IW. Ontogeny of pancreatic exocrine function. *Arch Dis Child.* (1990) 65:178–81. doi: 10.1136/adc.65.2.178

28. Antonowicz I, Lebenthal E. Developmental pattern of small intestinal enterokinase and disaccharidase activities in the human fetus. *Gastroenterology.* (1977) 72:1299–303. doi: 10.1016/S0016-5085(77)80031-0

29. Lebenthal E, Lee PC. Development of functional responses in human exocrine pancreas. *Pediatrics.* (1980) 66:556–60. doi: 10.1542/peds.66.4.556

30. McClean P, Weaver LT. Ontogeny of human pancreatic exocrine function. *Arch Dis Child.* (1993) 68(1 Spec No):62–5. doi: 10.1136/adc.68.1_Spec_No.62

31. Hadorn B, Zoppi G, Shmerling DH, Prader A, McIntyre I, Anderson CM. Quantitative assessment of exocrine pancreatic function in infants and children. *J Pediatr.* (1968) 73:39–50. doi: 10.1016/S0022-3476(68)80037-X

32. Hopson P, Patel S, Bornstein J, Mehta D, Horvath K. Isolated amylase deficiency in children and its clinical implication. *J Pediatr Gastroenterol Nutr.* (2019) 68:854–60. doi: 10.1097/MPG.0000000000002317

33. Stormon MO, Durie PR. Pathophysiologic basis of exocrine pancreatic dysfunction in childhood. *J Pediatr Gastroenterol Nutr.* (2002) 35:8–21. doi: 10.1097/00005176-200207000-00004

34. Track NS, Creutzfeldt C, Bokermann M. Enzymatic, functional and ultrastructural development of the exocrine pancreas—II. The human pancreas. *Comp Biochem Physiol A Comp Physiol.* (1975) 51:95–100. doi: 10.1016/0300-9629(75)90419-3

35. Moriscot C, Renaud W, Carrère J, Figarella-Branger D, Figarella C, Guy-Crotte O. Developmental gene expression of trypsinogen and lipase in human fetal pancreas. *J Pediatr Gastroenterol Nutr.* (1997) 24:63–7. doi: 10.1097/00005176-199701000-00015

36. Zoppi G, Andreotti G, Pajno-Ferrara F, Njai DM, Gaburro D. Exocrine pancreas function in premature and full term neonates. *Pediatr Res.* (1972) 6:880–6. doi: 10.1203/00006450-197212000-00005

37. Kori M, Maayan-Metzger A, Shamir R, Sirota L, Dinari G. Faecal elastase 1 levels in premature and full term infants. *Arch Dis Child Fetal Neonatal Ed.* (2003) 88:F106–8. doi: 10.1136/fn.88.2.F106

38. Lowe ME. The triglyceride lipases of the pancreas. *J Lipid Res.* (2002) 43:2007–16. doi: 10.1194/jlr.R200012-JLR200

39. Skude G. Sources of the serum isoamylases and their normal range of variation with age. *Scand J Gastroenterol.* (1975) 10:577–84. doi: 10.1080/00365521.1975.12097015

40. Skude G. Electrophoretic separation, detection, and variation of amylase isoenzymes. *Scand J Clin Lab Invest.* (1975) 35:41–7. doi: 10.3109/00365517509068003

41. Dumont Y, Larose L, Poirier G, Morisset J. Modulation of pancreatic muscarinic receptors by weaning. *Life Sci.* (1982) 30:253–7. doi: 10.1016/0024-3205(82)90506-9

42. Leung YK, Lee PC, Lebenthal E. Maturation of cholecystokinin receptors in pancreatic acini of rats. *Am J Physiol.* (1986) 250:G594–7. doi: 10.1152/ajpgi.1986.250.5.G594

43. D'Agostino D, Lowe ME. Pancreatic lipase-related protein 2 is the major colipase-dependent pancreatic lipase in suckling mice. *J Nutr.* (2004) 134:132–4. doi: 10.1093/jn/134.1.132

44. Fomon SJ, Ziegler EE, Thomas LN, Jensen RL, Filer LJ Jr. Excretion of fat by normal full-term infants fed various milks and formulas. *Am J Clin Nutr.* (1970) 23:1299–313. doi: 10.1093/ajcn/23.10.1299

45. Borgstrom B, Lindquist B, Lundh G. Enzyme concentration and absorption of protein and glucose in duodenum of premature infants. *AMA J Dis Child.* (1960) 99:338–43. doi: 10.1001/archpedi.1960.02070030340010

46. Murtaugh LC. The what, where, when and how of Wnt/β-catenin signaling in pancreas development. *Organogenesis.* (2008) 4:81–6. doi: 10.4161/org.4.2.5853

47. Jennings RE, Berry AA, Strutt JP, Gerrard DT, Hanley NA. Human pancreas development. *Development.* (2015) 142:3126–37. doi: 10.1242/dev.120063

48. Piper K, Brickwood S, Turnpenny LW, Cameron IT, Ball SG, Wilson DI, et al. Beta cell differentiation during early human pancreas development. *J Endocrinol.* (2004) 181:11–23. doi: 10.1677/joe.0.1810011

49. Shih DQ, Stoffel M. Molecular etiologies of MODY and other early-onset forms of diabetes. *Curr Diab Rep.* (2002) 2:125–34. doi: 10.1007/s11892-002-0071-9

50. Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat Genet.* (1997) 17:138–9. doi: 10.1038/ng1097-138

51. Stoffers DA, Thomas MK, Habener JF. Homeodomain protein IDX-1: a master regulator of pancreas development and insulin gene expression. *Trends Endocrinol Metab.* (1997) 8:145–51. doi: 10.1016/S1043-2760(97)00008-8

52. Hebrok M, Kim SK, Melton DA. Notochord repression of endodermal Sonic hedgehog permits pancreas development. *Genes Dev.* (1998) 12:1705–13. doi: 10.1101/gad.12.11.1705

53. Krapp A, Knöfler M, Ledermann B, Bürki K, Berney C, Zoerkler N, et al. The bHLH protein PTF1-p48 is essential for the formation of the exocrine and the correct spatial organization of the endocrine pancreas. *Genes Dev.* (1998) 12:3752–63. doi: 10.1101/gad.12.23.3752

54. Sellick GS, Barker KT, Stolte-Dijkstra I, Fleischmann C, Coleman RJ, Garrett C, et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat Genet.* (2004) 36:1301–5. doi: 10.1038/ng1475

55. Weedon MN, Cebola I, Patch AM, Flanagan SE, De Franco E, Caswell R, et al. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet.* (2014) 46:61–4. doi: 10.1038/ng.2826

56. Jennings RE, Berry AA, Kirkwood-Wilson R, Roberts NA, Hearn T, Salisbury RJ, et al. Development of the human pancreas from foregut to endocrine commitment. *Diabetes.* (2013) 62:3514–22. doi: 10.2337/db12-1479

57. Shaw-Smith C, De Franco E, Lango Allen H, Batlle M, Flanagan SE, Borowiec M, et al. GATA4 mutations are a cause of neonatal and childhood-onset diabetes. *Diabetes.* (2014) 63:2888–94. doi: 10.2337/db14-0061

58. Murtaugh LC. Pancreas and beta-cell development: from the actual to the possible. *Development.* (2007) 134:427–38. doi: 10.1242/dev.02770

59. Salisbury RJ, Blaylock J, Berry AA, Jennings RE, De Krijger R, Piper Hanley K, et al. The window period of NEUROGENIN3 during human gestation. *Islets.* (2014) 6:e954436. doi: 10.4161/19382014.2014.954436

60. Piper K, Ball SG, Keeling JW, Mansoor S, Wilson DI, Hanley NA. Novel SOX9 expression during human pancreas development correlates to abnormalities in Campomelic dysplasia. *Mech Dev.* (2002) 116:223–6. doi: 10.1016/S0925-4773(02)00145-4

61. Haldorsen IS, Vesterhus M, Raeder H, Jensen DK, Søvik O, Molven A, et al. Lack of pancreatic body and tail in HNF1B mutation carriers. *Diabet Med.* (2008) 25:782–7. doi: 10.1111/j.1464-5491.2008.02460.x

62. Haumaitre C, Fabre M, Cormier S, Baumann C, Delezoide AL, Cereghini S. Severe pancreas hypoplasia and multicystic renal dysplasia in two human fetuses carrying novel HNF1beta/MODY5 mutations. *Hum Mol Genet.* (2006) 15:2363–75. doi: 10.1093/hmg/ddl161

63. El-Khairi R, Vallier L. The role of hepatocyte nuclear factor 1β in disease and development. *Diabetes Obes Metab.* (2016) 18 Suppl 1:23–32. doi: 10.1111/dom.12715

64. Solar M, Cardalda C, Houbracken I, Martín M, Maestro MA, De Medts N, et al. Pancreatic exocrine duct cells give rise to insulin-producing beta cells during embryogenesis but not after birth. *Dev Cell.* (2009) 17:849–60. doi: 10.1016/j.devcel.2009.11.003

65. Ramond C, Beydag-Tasöz BS, Azad A, van de Bunt M, Petersen MBK, Beer NL, et al. Understanding human fetal pancreas development using subpopulation sorting, RNA sequencing and single-cell profiling. *Development.* (2018) 145:5480. doi: 10.1242/dev.165480

66. Puri S, Hebrok M. Cellular plasticity within the pancreas—lessons learned from development. *Dev Cell.* (2010) 18:342–56. doi: 10.1016/j.devcel.2010.02.005

67. Hald J, Sprinkel AE, Ray M, Serup P, Wright C, Madsen OD. Generation and characterization of Ptf1a antiserum and localization of Ptf1a in relation to Nkx6.1 and Pdx1 during the earliest stages of mouse pancreas development. *J Histochem Soc.* (2008) 56:587–95. doi: 10.1369/jhc.2008.950675

68. Masui T, Long Q, Beres TM, Magnuson MA, MacDonald RJ. Early pancreatic development requires the vertebrate suppressor of hairless (RBPJ) in the PTF1 bHLH complex. *Genes Dev.* (2007) 21:2629–43. doi: 10.1101/gad.1575207

69. Masui T, Swift GH, Hale MA, Meredith DM, Johnson JE, Macdonald RJ. Transcriptional autoregulation controls pancreatic Ptf1a expression during development and adulthood. *Mol Cell Biol.* (2008) 28:5458–68. doi: 10.1128/MCB.00549-08

70. Holmstrom SR, Deering T, Swift GH, Poelwijk FJ, Mangelsdorf DJ, Kliewer SA, et al. LRH-1 and PTF1-L coregulate an exocrine pancreas-specific transcriptional network for digestive function. *Genes Dev.* (2011) 25:1674–9. doi: 10.1101/gad.16860911

71. Mortelé KJ, Rocha TC, Streeter JL, Taylor AJ. Multimodality imaging of pancreatic and biliary congenital anomalies. *Radiographics.* (2006) 26:715–31. doi: 10.1148/rg.263055164

72. Ravitch MM, Woods AC Jr. Annular pancreas. *Ann Surg.* (1950) 132:1116–27. doi: 10.1097/00000658-195012000-00011

73. Cunha JE, de Lima MS, Jukemura J, Penteado S, Jureidini R, Patzina RA, et al. Unusual clinical presentation of annular pancreas in the adult. *Pancreatol J Int Assoc Pancreatol (IAP).* (2005) 5:81–5. doi: 10.1159/000084493

74. Yogi Y, Shibue T, Hashimoto S. Annular pancreas detected in adults, diagnosed by endoscopic retrograde cholangiopancreatography: report of four cases. *Gastroenterol Jpn.* (1987) 22:92–9. doi: 10.1007/BF02806340

75. Kamisawa T, Ando H, Suyama M, Shimada M, Morine Y, Shimada H. Japanese clinical practice guidelines for pancreaticobiliary maljunction. *J Gastroenterol.* (2012) 47:731–59. doi: 10.1007/s00535-012-0611-2

76. Matsumoto Y, Fujii H, Itakura J, Mogaki M, Matsuda M, Morozumi A, et al. Pancreaticobiliary maljunction: etiologic concepts based on radiologic aspects. *Gastrointest Endosc.* (2001) 53:614–9. doi: 10.1067/mge.2001.113920

77. Boyden EA. The anatomy of the choledochoduodenal junction in man. *Surg Gynecol Obstet.* (1957) 104:641–52.

78. Ishibashi H, Shimada M, Kamisawa T, Fujii H, Hamada Y, Kubota M, et al. Japanese clinical practice guidelines for congenital biliary dilatation. *J Hepatobiliary Pancreat Sci.* (2017) 24:1–16. doi: 10.1002/jhbp.415

79. Kamisawa T, Takuma K, Anjiki H, Egawa N, Kurata M, Honda G, et al. Pancreaticobiliary maljunction. *Clin Gastroenterol Hepatol.* (2009) 7:S84–8. doi: 10.1016/j.cgh.2009.08.024

80. Todani T. Congenital choledochal dilatation: classification, clinical features, and long-term results. *J Hepatobiliary Pancreat Surg.* (1997) 4:276–82. doi: 10.1007/BF02489025

81. Csendes A, Kruse A, Funch-Jensen P, Oster MJ, Ornsholt J, Amdrup E. Pressure measurements in the biliary and pancreatic duct systems in controls and in patients with gallstones, previous cholecystectomy, or common bile duct stones. *Gastroenterology.* (1979) 77:1203–10. doi: 10.1016/0016-5085(79)90158-6

82. Jarrar MS, Khenissi A, Ghrissi R, Hamila F, Letaief R. Ansa pancreatica: an anatomic variation and a rare cause of acute pancreatitis. *Surg Radiol Anat.* (2013) 35:745–8. doi: 10.1007/s00276-013-1103-7

83. Durie PR. Inherited causes of exocrine pancreatic dysfunction. *Can J Gastroenterol.* (1997) 11:145–52. doi: 10.1155/1997/137618

84. Liu F, Zhang Z, Csanády L, Gadsby DC, Chen J. Molecular structure of the human CFTR ion channel. *Cell.* (2017) 169:85–95. doi: 10.1016/j.cell.2017.02.024

85. Kopelman H, Corey M, Gaskin K, Durie P, Weizman Z, Forstner G. Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. *Gastroenterology.* (1988) 95:349–55. doi: 10.1016/0016-5085(88)90490-8

86. Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med.* (2013) 3:a009746. doi: 10.1101/cshperspect.a009746

87. Goobie S, Popovic M, Morrison J, Ellis L, Ginzberg H, Boocock GR, et al. Shwachman-Diamond syndrome with exocrine pancreatic dysfunction and bone marrow failure maps to the centromeric region of chromosome 7. *Am J Hum Genet.* (2001) 68:1048–54. doi: 10.1086/319505

88. Andolina JR, Morrison CB, Thompson AA, Chaudhury S, Mack AK, Proytcheva M, et al. Shwachman-Diamond syndrome: diarrhea, no longer required? *J Pediatr Hematol Oncol.* (2013) 35:486–9. doi: 10.1097/MPH.0b013e3182667c13

89. Hashmi SK, Allen C, Klaassen R, Fernandez CV, Yanofsky R, Shereck E, et al. Comparative analysis of Shwachman-Diamond syndrome to other inherited bone marrow failure syndromes and genotype-phenotype correlation. *Clin Genet.* (2011) 79:448–58. doi: 10.1111/j.1399-0004.2010.01468.x

90. Wong CC, Traynor D, Basse N, Kay RR, Warren AJ. Defective ribosome assembly in Shwachman-Diamond syndrome. *Blood.* (2011) 118:4305–12. doi: 10.1182/blood-2011-06-353938

91. Rothbaum R, Perrault J, Vlachos A, Cipolli M, Alter BP, Burroughs S, et al. Shwachman-Diamond syndrome: report from an international conference. *J Pediatr.* (2002) 141:266–70. doi: 10.1067/mpd.2002.125850

92. Cipolli M. Shwachman-Diamond syndrome: clinical phenotypes. *Pancreatol J Int Assoc Pancreatol (IAP).* (2001) 1:543–8. doi: 10.1159/000055858

93. Zenker M, Mayerle J, Lerch MM, Tagariello A, Zerres K, Durie PR, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet.* (2005) 37:1345–50. doi: 10.1038/ng1681

94. Sukalo M, Fiedler A, Guzmán C, Spranger S, Addor MC, McHeik JN, et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. *Hum Mutat.* (2014) 35:521–31. doi: 10.1002/humu.22538

95. Almashraki N, Abdulnabee MZ, Sukalo M, Alrajoudi A, Sharafadeen I, Zenker M. Johanson-Blizzard syndrome. *World J Gastroenterol.* (2011) 17:4247–50. doi: 10.3748/wjg.v17.i37.4247

96. Johanson A, Blizzard R, A. syndrome of congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. *J Pediatr.* (1971) 79:982–7. doi: 10.1016/S0022-3476(71)80194-4

97. Daentl DL, Frías JL, Gilbert EF, Opitz JM. The Johanson-Blizzard syndrome: case report and autopsy findings. *Am J Med Genet.* (1979) 3:129–35. doi: 10.1002/ajmg.1320030203

98. Moeschler JB, Polak MJ, Jenkins JJ III, Amato RS. The Johanson-Blizzard syndrome: a second report of full autopsy findings. *Am J Med Gen.* (1987) 26:133–8. doi: 10.1002/ajmg.1320260120

99. Pearson HA, Lobel JS, Kocoshis SA, Naiman JL, Windmiller J, Lammi AT, et al. A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. *J Pediatr.* (1979) 95:976–84. doi: 10.1016/S0022-3476(79)80286-3

100. Rotig A, Colonna M, Bonnefont JP, Blanche S, Fischer A, Saudubray JM, et al. Mitochondrial DNA deletion in Pearson's marrow/pancreas syndrome. *Lancet.* (1989) 1:902–3. doi: 10.1016/S0140-6736(89)92897-3

101. Khasawneh R, Alsokhni H, Alzghoul B, Momani A, Abualsheikh N, Kamal N, et al. A novel mitochondrial DNA deletion in patient with Pearson syndrome. *Med Arch.* (2018) 72:148–50. doi: 10.5455/medarh.2018.72.148-150

102. Broomfield A, Sweeney MG, Woodward CE, Fratter C, Morris AM, Leonard JV, et al. Paediatric single mitochondrial DNA deletion disorders: an overlapping spectrum of disease. *J Inherit Metab Dis.* (2015) 38:445–57. doi: 10.1007/s10545-014-9778-4

103. Farruggia P, Di Cataldo A, Pinto RM, Palmisani E, Macaluso A, Valvo LL, et al. Pearson syndrome: a retrospective cohort study from the marrow failure study group of a IEOP (Associazione Italiana Emato-Oncologia Pediatrica). *JIMD Rep.* (2016) 26:37–43. doi: 10.1007/8904_2015_470

104. Whitcomb DC, Lowe ME. Genetic disorders of the pancreas and pancreatic disorders of childhood. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease - 2 Volume Set: Pathophysiology, Diagnosis, Management*. 11th ed. Amsterdam: Elsevier (2020). p. 862–92.

105. Güçlü M, Serin E, Ulucan S, Kul K, Ozer B, Gümürdülü Y, et al. Agenesis of the dorsal pancreas in a patient with recurrent acute pancreatitis: case report and review. *Gastrointest Endosc.* (2004) 60:472–5. doi: 10.1016/S0016-5107(04)01733-X

106. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. *Nat Genet.* (1997) 15:106–10. doi: 10.1038/ng0197-106

107. Mei W, Cao F, Li F. Two cases of agenesis of the dorsal pancreas and a review of the literature. *BMC Gastroenterol.* (2020) 20:94. doi: 10.1186/s12876-020-01245-8

108. Valiyeva S, Romano L, Schietroma M, Carlei F, Giuliani A. Partial agenesis of dorsal pancreas. Report of two cases. *Int J Surg Case Rep.* (2020) 77s(Suppl):S17–20. doi: 10.1016/j.ijscr.2020.10.029

109. Drenth JP, te Morsche R, Jansen JB. Mutations in serine protease inhibitor Kazal type 1 are strongly associated with chronic pancreatitis. *Gut.* (2002) 50:687–92. doi: 10.1136/gut.50.5.687

110. Midha S, Khajuria R, Shastri S, Kabra M, Garg PK. Idiopathic chronic pancreatitis in India: phenotypic characterisation and strong genetic susceptibility due to SPINK1 and CFTR gene mutations. *Gut.* (2010) 59:800–7. doi: 10.1136/gut.2009.191239

111. Muller N, Sarantitis I, Rouanet M, de Mestier L, Halloran C, Greenhalf W, et al. Natural history of SPINK1 germline mutation related-pancreatitis. *EBioMed.* (2019) 48:581–91. doi: 10.1016/j.ebiom.2019.09.032

112. Venet T, Masson E, Talbotec C, Billiemaz K, Touraine R, Gay C, et al. Severe infantile isolated exocrine pancreatic insufficiency caused by the complete functional loss of the SPINK1 gene. *Hum Mutat.* (2017) 38:1660–5. doi: 10.1002/humu.23343

113. Rebours V, Boutron-Ruault MC, Schnee M, Férec C, Le Maréchal C, Hentic O, et al. The natural history of hereditary pancreatitis: a national series. *Gut.* (2009) 58:97–103. doi: 10.1136/gut.2008.149179

114. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet.* (1996) 14:141–5. doi: 10.1038/ng1096-141

115. Keim V, Bauer N, Teich N, Simon P, Lerch MM, Mössner J. Clinical characterization of patients with hereditary pancreatitis and mutations in the cationic trypsinogen gene. *Am J Med.* (2001) 111:622–6. doi: 10.1016/S0002-9343(01)00958-5

116. Sossenheimer MJ, Aston CE, Preston RA, Gates LK Jr, Ulrich CD, Martin SP, et al. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype the midwest multicenter pancreatic study group (MMPSG). *Am J Gastroenterol.* (1997) 92:1113–6.

117. Vendrell J, Querol E, Avilés FX. Metallocarboxypeptidases and their protein inhibitors. Structure, function and biomedical properties. *Biochim Biophys Acta.* (2000) 1477:284–98. doi: 10.1016/S0167-4838(99)00280-0

118. Scheele G, Bartelt D, Bieger W. Characterization of human exocrine pancreatic proteins by two-dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis. *Gastroenterology.* (1981) 80:461–73. doi: 10.1016/0016-5085(81)90007-X

119. Witt H, Beer S, Rosendahl J, Chen JM, Chandak GR, Masamune A, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. *Nat Genet.* (2013) 45:1216–20. doi: 10.1038/ng.2730

120. Nemoda Z, Sahin-Tóth M. Chymotrypsin C (caldecrin) stimulates autoactivation of human cationic trypsinogen. *J Biol Chem.* (2006) 281:11879–86. doi: 10.1074/jbc.M600124200

121. Zhou J, Sahin-Tóth M. Chymotrypsin C mutations in chronic pancreatitis. *J Gastroenterol Hepatol.* (2011) 26:1238–46. doi: 10.1111/j.1440-1746.2011.06791.x

122. Rinderknecht H, Adham NF, Renner IG, Carmack C. A possible zymogen self-destruct mechanism preventing pancreatic autodigestion. *Int J Pancreatol.* (1988) 3:33–44. doi: 10.1007/BF02788221

123. Giefer MJ, Lowe ME, Werlin SL, Zimmerman B, Wilschanski M, Troendle D, et al. Early-onset acute recurrent and chronic pancreatitis is associated with PRSS1 or CTRC gene mutations. *J Pediatr.* (2017) 186:95–100. doi: 10.1016/j.jpeds.2017.03.063

124. Grabarczyk AM, Oracz G, Wertheim-Tysarowska K, Kujko AA, Wejnarska K, Kolodziejczyk E, et al. Chymotrypsinogen C genetic variants, including c.180TT, are strongly associated with chronic pancreatitis in pediatric patients. *J Pediatr Gastroenterol Nutr.* (2017) 65:652–7. doi: 10.1097/MPG.0000000000001767

125. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet.* (1997) 17:384–5. doi: 10.1038/ng1297-384

126. Johansson BB, Fjeld K, El Jellas K, Gravdal A, Dalva M, Tjora E, et al. The role of the carboxyl ester lipase (CEL) gene in pancreatic disease. *Pancreatol J Int Assoc Pancreatol (IAP).* (2018) 18:12–9. doi: 10.1016/j.pan.2017.12.001

127. Raeder H, Haldorsen IS, Ersland L, Grüner R, Taxt T, Søvik O, et al. Pancreatic lipomatosis is a structural marker in nondiabetic children with mutations in carboxyl-ester lipase. *Diabetes.* (2007) 56:444–9. doi: 10.2337/db06-0859

128. Tjora E, Wathle G, Engjom T, Erchinger F, Molven A, Aksnes L, et al. Severe pancreatic dysfunction but compensated nutritional status in monogenic pancreatic disease caused by carboxyl-ester lipase mutations. *Pancreas.* (2013) 42:1078–84. doi: 10.1097/MPA.0b013e3182920e9c

129. Ito K, Matsuura K, Mihara Y, Sakamoto Y, Hasegawa K, Kokudo N, et al. Delivery of pancreatic digestive enzymes into the gastrointestinal tract by pancreatic exocrine tissue transplant. *Sci Rep.* (2019) 9:5922. doi: 10.1038/s41598-019-42362-z

130. Chen S, Du K, Zou C. Current progress in stem cell therapy for type 1 diabetes mellitus. *Stem Cell Res Ther.* (2020) 11:275. doi: 10.1186/s13287-020-01793-6

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Admission risk factors and predictors of moderate or severe pediatric acute pancreatitis: A systematic review and meta-analysis

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Introduction: Pediatric acute pancreatitis (PAP) has an increasing incidence and is now estimated to be almost as common as in adults. Up to 30% of patients with PAP will develop moderate or severe disease course (M/SPAP), characterized by organ failure, local or systemic complications. There is still no consensus regarding on-admission severity prediction in these patients. Our aim was to conduct a systematic review and meta-analysis of available predictive score systems and parameters, and differences between on-admission parameters in mild and M/SPAP.

Methods: We conducted a systematic search on the 14th February, 2022 in MEDLINE, Embase and CENTRAL. We performed random-effects meta-analysis of on-admission differences between mild and M/SPAP in laboratory parameters, etiology, demographic factors, etc. calculating risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) and created forest plots. For the meta-analysis of predictive score systems, we generated hierarchical summary receiver operating characteristic curves using a bivariate model. Chi-squared tests were performed and I^2 values calculated to assess statistical heterogeneity.

Results: We included 44 studies – mostly retrospective cohorts – in our review. Among predictive score systems examined by at least 5 studies, the modified Glasgow scale had the highest specificity (91.5% for values ≥3), and the Pediatric Acute Pancreatitis Severity score the highest sensitivity (63.1% for values ≥3). The performance of other proposed score systems and values were summarized. Traumatic (RR: 1.70 95% CI: 1.09–2.67) and drug–induced (RR: 1.33 95% CI: 0.98–1.87) etiologies were associated with a higher rate of M/SPAP, while anatomical (RR: 0.6195% CI: 0.38–0.96) and biliary (RR: 0.72 95% CI: 0.53–0.99) PAP tended to be less severe.

Discussion: Many predictive score systems were proposed to assess the possibility of M/SPAP course. The most commonly used ones exhibit good

specificity, but subpar sensitivity. Our systematic review provides a rigorous overview of predictive options assessed thus far, that can serve as a basis for future improvement of scores *via* the addition of parameters with a better observed sensitivity: e.g., lipase exceeding 7-times the upper threshold, hemoglobin, etc. The addition of etiological factors is another possibility, as they can herald a more severe disease course.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=307271, PROSPERO, identifier: CRD42022307271.

KEYWORDS

pediatric pancreatitis, severity, predictive factors, on-admission, meta-analysis

Introduction

While in the adult emergency department, acute pancreatitis is a common differential diagnostic concern (1), pediatric acute pancreatitis (PAP) is a less frequently sought diagnosis, mostly because it was for long regarded as a rarely presenting disorder. On the contrary, the last few decades' publications report its increasing incidence, now estimated to be 3-13/100,000/year, which approaches the 13-45/100,000/year incidence seen in adults (2–7). While this trend might reflect a true increase in incidence, there is no doubt that the increasing diagnostic awareness (pancreatic enzyme measurement) greatly contributes (5, 8). Either way, more and more patients with PAP are discovered and hospitalized in need of adequate treatment.

As of yet, however, there are no known specific therapeutic options in PAP. The management of these patients is based on pain control, intravenous fluid replacement, adequate nutrition, monitoring complications and intensive care if necessary (9). Fortunately, as opposed to adults, where 15–30% of patients have a moderate disease course and 10–20% severe, with up to 40% mortality (10–12), PAP usually has a more benign course, with only 20–30% of cases being classified as moderate or severe (M/SPAP) in the majority of pediatric studies (see Table 1). Thus, only around every fourth or fifth pediatric patient will develop local complications, even less organ failure. But the low number of M/SPAP (especially together with the lower diagnostic awareness still persisting in many centers) can lead to the delayed recognition of these children. Great emphasis should be placed on their early identification, in order for a prompt response and transfer to the intensive care unit (ICU) if necessary.

There are multiple proposed score systems that aim to predict which patients will develop M/SPAP. Those most widely examined are the modified Glasgow criteria (56), the Ranson criteria (57) and the Pediatric Acute Pancreatitis Severity (PAPS) score (21), all mainly based on laboratory parameters determined within the first 48 h. But many others are tested and proposed, involving variables such as blood urea nitrogen (BUN), white blood cell count (WBC), albumin, hemoglobin, among else (23, 50, 52). Still, there is no single pediatric-specific predictive value or score system that can be recommended (9). What is more, there are no comprehensive systematic reviews assessing the association between factors determinable on-admission and PAP severity.

Our aim was to perform a systematic review and meta-analysis of available predictive score systems and on-admission differences between severity groups in order to summarize the existing data and possibly shed light on the early identification of these patients.

Materials and methods

Protocol and reporting

The pre-study protocol was registered with PROSPERO, under the registration number: CRD42022307271. No deviations were made from the previously registered protocol. The findings are reported in this article according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (58).

Eligibility criteria

Studies were considered eligible regardless of study design (interventional and observational, retro- and prospective) in case they included at least 10 participants with PAP and presented data on any on-admission factors (any, e.g., demographic, symptom-related, laboratory values, imaging results, etc.) in different severity groups of the disease. Severity definitions used by the individual studies were accepted, but studies using different classifications were only pooled together if these classifications were comparable. In the end, almost all studies used severity classification systems based on the development on local complications

TABLE 1 Characteristics of included studies.

Study identifier	Country	Population description	n PAP	Age (years)	Female %	Severity criteria	Non-mild (%)
Abu-El-Haija (13)	USA	First PAP	165	DIAP: 13.7 (7.5–15.8); non–DIAP: 13.5 (10.0–15.9)	52.7	NASPGHAN	20.0
Antunes (14)	Portugal	PAP	37	NA	59.5	revised Atlanta	24.3
Berney (15)	Italy	PAP	24	10.8 (1–15)†	57.1	OF, ICU	20.8
Bierma et al. (16)	Australia, Netherlands	PAP	175	12.5 (9.2–15.6)	48.6	OF, ICU, local complications, need for pancreatic surgery, death	28.6
Birimberg-Schwartz (17)	Canada	First PAP	223	11 ± 4.8	50.2	NASPGHAN	16.1
Boskovic (18)	Serbia	First PAP	36	10.1 ± 4.7	58.3	revised Atlanta	44.4
Chang et al. (19)	Taiwan	First PAP	180	8.2 (0.2–17)	56.1	Atlanta	28.3
Coffey et al. (20) derivation cohort	Australia	PAP	73	11.6 (8.0–13.7)	37.0	OF, ICU, local complications, need for pancreatic surgery, death	34.2
Coffey et al. (20) validation cohort	Australia	PAP	58	15.1 (11.2–17.2)	60.3	OF, ICU, local complications, need for pancreatic surgery, death	24.1
DeBanto et al. (21) criterion group	USA	PAP ≤ 16 years	202	8.9 ± 1.1	NA	OF, local complications, need for pancreatic surgery, death	19.8
DeBanto et al. (21) validation group	USA	PAP ≤ 16 years	99	9.4 ± 1.5	NA	OF, local complications, need for pancreatic surgery, death	12.1
Fabre et al. (22)	France	First PAP	48	10.8 (2.1–19.5)†	47.9	Atlanta	27.1
Farrel et al. (23)	USA	First PAP	73	NA	64.4	NASPGHAN	30.1
Farrel et al. (23) derivation cohort	USA	First PAP	46	13.7 (9.1–16.2)	47.8	NASPGHAN	21.7
Farrel et al. (23) validation cohort	USA	First PAP	25	14.2 (11.1–17.3)	48.0	NASPGHAN	24.0
Fonseca Sepúlveda (24)	Colombia	PAP	130	11.4 ± 3.8	62.3	Atlanta	29.2
Galai et al. (25)	Israel	PAP ≥ 6 month follow–up	117	13.2 (7.0–15.9)	52.1	revised Atlanta	12.8
Guerrero-Lozano (26)	Colombia	PAP	30	NA	NA	revised Atlanta	NA
Hao (27)	China	PAP	159	6.2 ± 3.3	46.2	revised Atlanta	53.5
Hashimoto et al. (28)	Japan	PAP	37	6 (5–12)	59.5	OF, local complications, need for pancreatic surgery, death	56.8
Hornung (29)	USA	First PAP	176	NA	NA	NASPGHAN	22.2
Izquierdo et al. (30)	Colombia	PAP, CECT within 48h	30	10.5 ± 3.5	73.3	OF, local complications, need for pancreatic surgery, death	33.3
Izquierdo et al. (30)	Colombia	PAP	130	mild: 12 (7–17); M/SPAP: 11 (3–18)	62.3	OF, local complications, need for pancreatic surgery, death	29.2
Kandula (31)	USA	First PAP, ≤ 3 years	87	1.7 (0–2.9)†	48.3	OF, local complications, death	3.8
Kaur et al. (32)	India	PAP	134	11.9% <5; 34.3% 5–10; 40.3% 10–15; 13.4% 15–20	NA	NASPGHAN	42.5
APPLE (33–38)	mostly Hungary	PAP	45	11.7 (3–18)†	48.9	revised Atlanta	13.3

(Continued)

TABLE 1 (Continued)

Study identifier	Country	Population description	n PAP	Age (years)	Female %	Severity criteria	Non-mild (%)
Lautz et al. (39)	USA	PAP	211	10.9 ± 4.9	47.9	OF, local complications, need for pancreatic surgery, death	26.5
Li (40)	China	First PAP, CECT on admission	107	9.3 (2.1–15.3)	45.8	revised Atlanta	25.2
Mehta (41)	USA	PAP	121	12.1 ± 4.6	60.3	NA	17.4
Nauka et al. (42)	USA	PAP	79	14 (9.5–16)	41.8	NASPGHAN	21.5
Orkin (43)	USA	First PAP ≤ 21 years	114	NA	NA	NA	NA
Parian (44)	Philippines	PAP	28	11.5 ± 4.1	NA	NA	NA
Pezzili et al. (45)	Italy	PAP	50	10.5 (2–17)†	50.0	Atlanta	18.0
Sag (46)	Turkey	First PAP	63	9.6 ± 4.8	50.8	NASPGHAN	46.0
Sánchez-Ramírez (47)	Mexico	PAP	55	10.5 ± 1.6	49.1	NA	NA
Suzuki et al. (48) criterion group	Japan	PAP (but 2–fold enzyme elevation)	145	7.3 (0.8–17)‡	60.7	OF, local complications, need for pancreatic surgery, death	6.9
Suzuki et al. (49) validation group	Japan	PAP (but 2–fold enzyme elevation)	131	7.7 ± 4.3	51.9	revised Atlanta	9.9
Szabo et al. (50) derivation group	USA	PAP ≤ 21 years	284	12.7 ± 4.9	50.0	ICU, local complications, respiratory complications (OF, oedema, pleural effusion), need for pancreatic surgery, death	19.0
Szabo et al. (50) validation group	USA	PAP ≤ 21 years	165	12.9 ± 5.2	58.2		NA
Thavamani et al. (51)	USA	PAP ≤ 21 years (CP excluded)	39,805	15.2 ± 4.7	59.2	revised Atlanta	4.0
Vitale et al. (52)	USA	First PAP ≤ 21 years	118	mild: 13.5 (10.2–15.9); M/SPAP: 13.8 (7.9–15.9)	47.5	NASPGHAN	18.6
Walker et al. (53)	UK	First PAP	59	13 (0.1–17)†	50.9	revised Atlanta	37.3
Wetherill (54)	UK	First PAP	37	14 (4–17)†	48.7	OF, local complications	35.1
Zheng et al. (55)	China	PAP	111	8.2 ± 3.3	53.2	NASPGHAN	13.5

Age is given as mean ± standard deviation, or median (interquartile range), unless otherwise indicated. †, median (range); ‡, mean (range). In the severity criteria column; most commonly "NASPGHAN" (2017 North American Society for Pediatric Gastroenterology; Hepatology; and Nutrition Pancreas Committee criteria); "Atlanta" (1992 Atlanta classification) and "revised Atlanta" (2012 revision of the Atlanta classification) are given; if not; the factors are provided based on which cases were classified as non-mild. CECT, contrast-enhanced computed tomography; CP, chronic pancreatitis; DIAP, drug-induced acute pancreatitis; h, hours; ICU, intensive care unit admission; M/SPAP, moderate or severe pediatric acute pancreatitis; n, total number; NA, not available; OF, organ failure; PAP, pediatric acute pancreatitis.

and organ failure (sometimes supplemented with ICU admission), the two most common ones being the revised Atlanta classification (59) and the 2017 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) criteria (60). These both form severity categories based on complications, according to the same principle: patients with organ failure lasting 48 h or more are categorized as severe; with transient (<48 h) organ failure, or local complications (acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection or walled-off necrosis) or systemic complications (i.e., exacerbation of comorbidity), moderate; with none of the above, mild. Few older studies used the original Atlanta classification, which separates mild and severe pancreatitis, the latter mostly covering the moderate and severe disease courses in the newer classifications (61).

Our initial plan was to also compare severe and non-severe cases, but due to the low number of severe cases in the identified studies, data was rarely presented separately for these patients, thus only mild vs. M/SPAP comparison could be performed. Factors collected within 48 h of admission were accepted to be "on-admission." Acute pancreatitis was defined as the presence of at least two of the following three criteria: abdominal pain; elevation in serum amylase or lipase reaching at least three-times the upper limit of the normal threshold; characteristic imaging findings.

The PECO (Population-Exposure-Control-Outcome) framework of our systematic review and eligible studies were:

P: PAP (≤18 years old).
E&C: any on-admission factor (demographic, laboratory, imaging, etc.).

O: PAP severity (mild, moderate, severe, non-mild, non-severe).

Systematic search and selection

A systematic search was conducted on the 14th February, 2020 in MEDLINE (*via* PubMed), EMBASE and CENTRAL with the following search key: "acute AND (pediatric OR pediatric OR children) AND pancreatitis AND (severe OR mild OR severity)." No restrictions were imposed on the search. Search results were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA) and selected according to a predefined set of criteria by two independent reviewers. In case of any disagreements, an independent third reviewer made the decision to include the study. The selection process was visualized using a PRISMA flow diagram.

Data extraction

Data was extracted from eligible articles into a standardized Excel sheet and validated by an independent second reviewer (KO). The collected data included items related to study characteristics, the investigated study population, any exposures and controls investigated and outcomes (severity criteria used, number with mild, moderate and severe disease) as detailed in the pre-study protocol. In case of multiple reports of the same outcome in overlapping populations, the higher patient number was favored.

Statistical analysis

For any on-admission factor examined in a comparable manner by at least three articles, we conducted a meta-analysis using a random-effects model. To estimate the between study heterogeneity we applied the Restricted maximum-likelihood estimation in case of continuous outcomes and the Mantel-Hanszel method with the Paule-Mandel estimator in case of dichotomous outcomes. We calculated pooled risk ratios (RR) for dichotomous and mean differences (MD) for continuous variables with 95% confidence intervals (CI), and visualized the results using forest plots. To quantify existing statistical heterogeneity, we performed Chi² tests (using a $p < 0.1$ to indicate statistically significant heterogeneity), and calculated I^2 values (0 to 40%: might not be important; 30 to 60%: may represent moderate heterogeneity; 50 to 90%: may represent substantial heterogeneity; 75 to 100% considerable heterogeneity). It should be pointed out that in the case of several laboratory variables (serum lipase, amylase, C-reactive protein (CRP), BUN and creatinine) more than half of the data had to be converted from medians with interquartile ranges to means with standard deviations using the default setting of the metacont function (62), in order to perform meta-analytical calculations.

In case predictive variables or score systems were reported in a way that the number of true and false negatives and positives were ascertainable in a sufficient number of studies, a random effects meta-analysis was performed and a hierarchical summary receiver operating characteristic (HSROC) curve was computed with a 95% confidence region and a 95% prediction region, using a bivariate model (63). Although this method is currently deemed most valid in case of a low number of studies, its results might be more limited below 10 studies, which was not achieved in our paper (64). In case of at least 10 studies for a given analysis, we created and visually assessed funnel plots and performed Egger's test to assess the possibility of publication bias.

All calculations were be performed using R: A language and environment for statistical computing [R version 4.1.2, "mada" and "meta" packages, R Core Team (65), Vienna, Austria].

Risk of bias

To assess the risk of bias in the included studies, we used the Quality in Prognostic Studies (QUIPS) tool, as recommended by the Cochrane Collaboration (66). Two independent reviewers conducted the assessment (MFJ and KO).

Results

Study selection

The systematic search retrieved 1,917 records, of which 44 studies, reported on by 69 records were found eligible for inclusion. The selection process is visualized on Figure 1.

Characteristics of included studies

Among the 44 included studies, most were retrospective cohort studies, with the exception of three prospective studies (13, 52, 67) and two that were in part prospective (23, 29). Studies either examined all PAP patients, or excluded recurrent episodes. As explained in the 'Methods' section of this manuscript, almost all studies used the 2017 NASPGHAN or the revised Atlanta classification or a comparable method for forming severity categories. In the majority of studies, 70–80% of cases were classified as mild. Study report citations can be found in our Supplementary Table 1.

Synthesis of results

Primary outcome

Predictive score systems, predictive parameters

We were able to perform meta-analytical calculations for the three most widely examined predictive score systems:

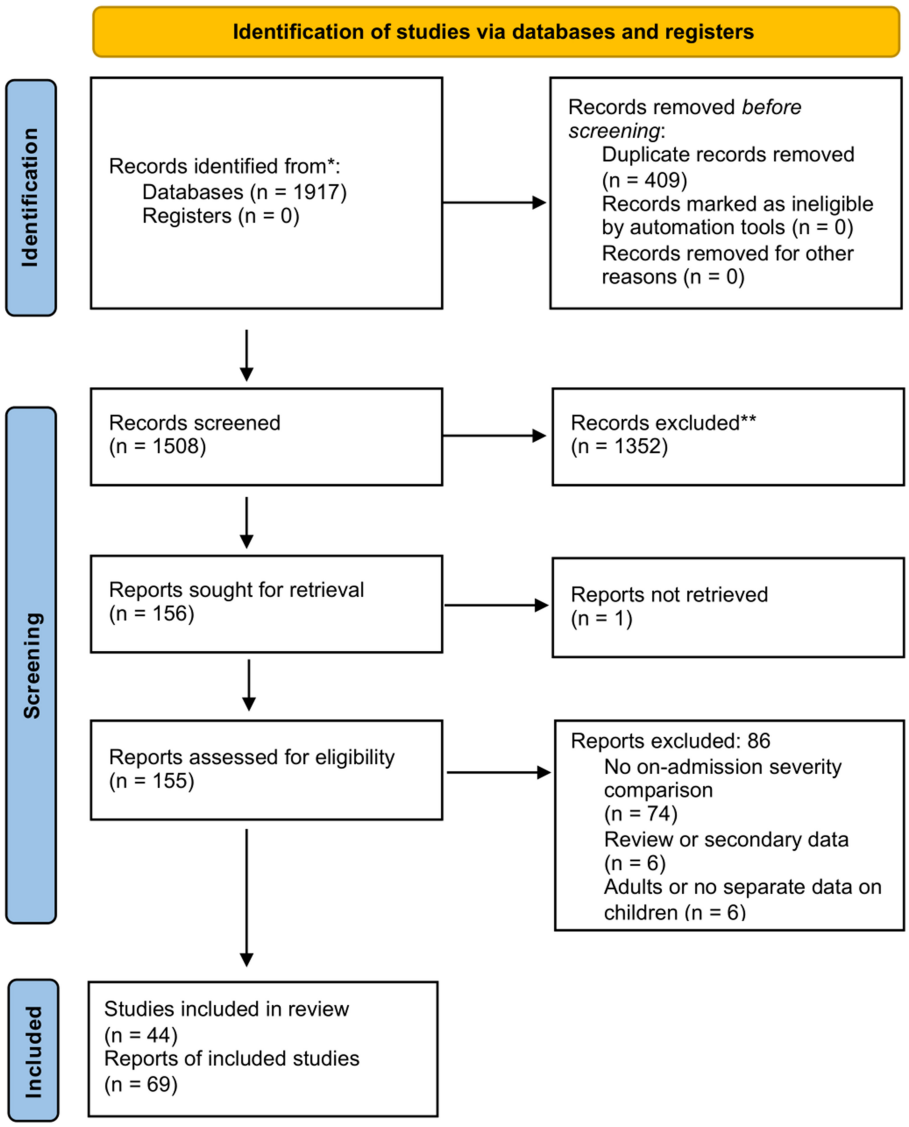

FIGURE 1
PRISMA flow diagram. The selection of reports is visualized. *n*: number.

the modified Glasgow criteria, the Ranson criteria and the PAPS score. The produced HSROC curves, AUC values of these systems, their sensitivity and specificity for predicting M/SPAP with a score of 3 or higher are presented on Figure 2, additional summary estimates can be found in the Supplementary Figures 1–6. AUC values could also be pooled from three studies for the modified Glasgow score: 0.76 (95% CI: 0.61–0.92) (Supplementary Figure 7).

Other prognostic scores and parameters for which information was available on predictive performance measures, but not enough data was provided to conduct meta-analytical calculations are narratively summarized in Table 2.

Secondary outcomes

Demographic factors, previous pancreatitis

We were able to perform quantitative syntheses for differences in age and previous PAP. We found no statistically significant difference in the age of onset between patients with mild and M/SPAP. There was a tendency of younger onset in the M/SPAP group, MD: 1.08 years younger (95% CI: 2.21 years younger to 0.05 years older; $I^2 = 72.5\%$, $p < 0.001$; Supplementary Figure 8). While also no statistically significant difference was found between genders, there was a tendency of less M/SAP cases among females (RR: 0.87, 95% CI: 0.73–1.03; $I^2 = 0\%$, $p = 0.808$; Supplementary Figure 9).

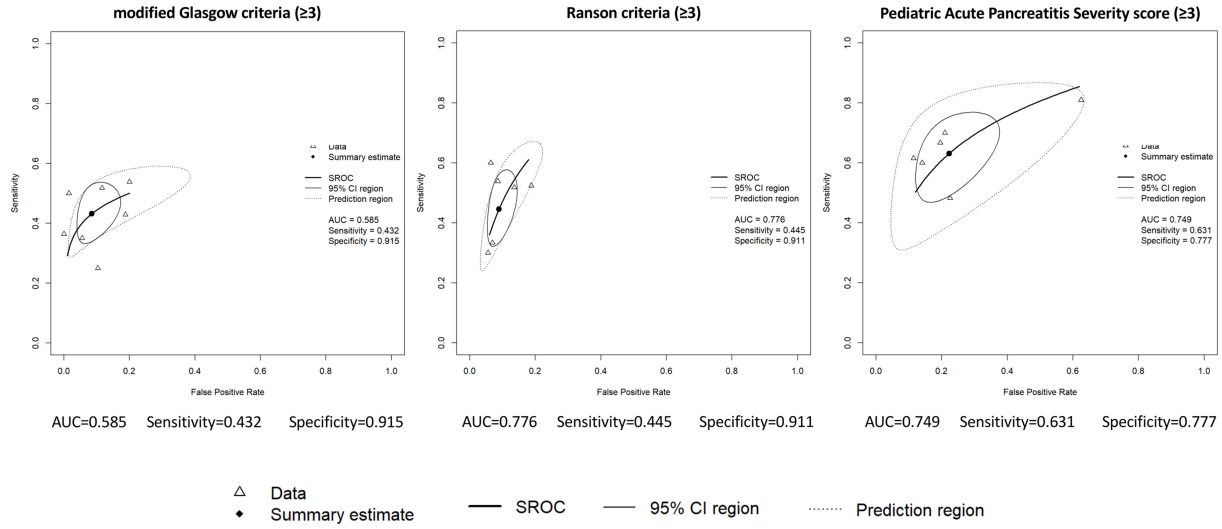

FIGURE 2
Hierarchical summary receiver operating characteristic (HSROC) curves. Data are presented for the following predictive score systems: modified Glasgow criteria, Ranson criteria, Pediatric Acute Pancreatitis Severity score. The values used as cut-off for indicating a moderate or severe disease are given in brackets. Triangles represent data obtained from individual studies, rectangles represent the summary estimates, bold solid line the summary receiver operating curve, solid line the 95% CI region, dotted line the prediction region. AUC, area under the curve; CI, confidence interval; SROC, summary receiver operating characteristic curve.

We found a history of previous PAP to be associated with an increased rate of M/SPAP (RR: 1.64, 95% CI: 1.21–2.23; $I^2 = 0\%$, $p = 0.446$; Supplementary Figure 10).

Multiple studies reported on weight differences between mild and M/SPAP, although in altering ways, rendering meta-analytical calculations unfeasible. Generally speaking, most studies noted no significant differences between groups. Of note, Thavamani 2021 analyzed an inpatient database in the United States covering a high number of patients and found both undernutrition and obesity to be associated with increasing PAP severity (51).

Etiology

We were able to perform quantitative syntheses assessing the risk of M/SPAP for the following etiologies or risk factors: abdominal trauma, anatomical malformations, associated drugs, biliary obstruction, idiopathic PAP, infective PAP, PAP following endoscopic retrograde cholangiopancreatography (ERCP). PAP related to anatomical malformation or biliary obstruction was associated with a lower likelihood of M/SPAP, while the proportion of M/SPAP was higher next to drug-induced or traumatic etiologies. Effects are summarized on Figure 3. The individual forest plots for these comparisons can be found in the Supplementary Figures 11–17.

Metabolic, systemic and genetic etiologies were also reported on by multiple studies, but their definitions were either substantially different or unascertainable, so meta-analyses were not performed for these etiological factors. Even though patient numbers were usually low for these etiologies in most studies, there was a tendency of more M/SPAP cases in patients with underlying PAP-associated systemic diseases, and no such tendency was seen with metabolic causes and genetic or familial cases (16, 19–21, 48).

Differences in laboratory parameters

We were able to perform quantitative syntheses for the following on-admission serum laboratory parameters: lipase, amylase, WBC count, lactate dehydrogenase (LDH), CRP, glucose, BUN, albumin, aspartate transaminase (AST) and creatinine (Supplementary Figures 18–27).

M/SPAP was associated with significantly higher on-admission WBC (+4.86 G/L, 95% CI: +3.14 – +5.17 G/L; $I^2 = 58.9\%$, $p = 0.013$), LDH (+876.8 U/L, 95% CI: +25.4 – +1,728.1 U/L; $I^2 = 73.0\%$, $p = 0.011$), CRP (+15.2 mg/L, 95% CI: +9.1 – +21.3 mg/L; $I^2 = 10.7\%$, $p = 0.347$), glucose (+0.73 mmol/L, 95% CI: +0.28 – +1.17 mmol/L; $I^2 = 0.0\%$, $p = 0.617$) and BUN (+0.96 mmol/L, 95% CI: +0.02 – +1.91 mmol/L; $I^2 = 78.5\%$, $p = 0.003$). There was a tendency of higher lipase (+426.4 U/L, 95% CI: −244.3 – +1097.1 U/L; $I^2 = 74.3\%$, $p < 0.001$) and amylase (+125.2 U/L, 95% CI: −76.1 – +326.4 U/L; $I^2 = 62.2\%$, $p = 0.021$) values and lower albumin (−3.34 g/L, 95% CI: −8.20 – +1.52 g/L; $I^2 = 81.1\%$, $p = 0.013$) on admission. No difference was found between mild and M/SPAP in on-admission AST (−11.3 U/L, 95% CI: −194.8 – +172.2 U/L; $I^2 = 97.3\%$, $p < 0.001$) and creatinine (+0.48 μmol/L, 95% CI: −4.35 – +5.30 μmol/L; $I^2 = 0.0\%$, $p = 0.528$).

TABLE 2 Summary of predictive performance parameters presented by the included studies.

Predictive score/factor	Studies (ref)	Assessed within:	AUC	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Computed Tomography Severity Index (CTSI)	3 (27–29)	48 h	0.64–0.90	score ≥ 4	50–81	78–86	61–71	**98–99**
Pediatric JPN score	2 (31, 32)	48 h		score ≥ 3	80–83	**96–98**	62–77	50–90
Lipase + WBC + albumin	1 (17)	24 h	0.76–0.77	best performance	68	71		
Hemoglobin <13 g/dL and/or BUN ≥12.5 mg/dL	1 (33)	24 h		1 or both present	81.5	64.1		**89.3**
Lipase >7xULN and Ca trough ≤ 2.15 mmol/L	1 (36)	48 h		both present	46	**89**	65	79
Lipase	4 (17, 34–36)	24 h	0.61–0.80	≥ 7xULN	**82–94**	23–56		
	1 (36)	48 h		50% decrease on day 2	73	54	46	79
				≥ 7xULN + 50% decrease day 2	67	79		
Amylase	1 (34)	24 h	0.70	≥ 3xULN	62.5	80.0		
Hemoglobin	1 (34)	24 h	0.70	≥ 143 g/L	**85.7**	43.5		
WBC	2 (17, 37)	24 h	0.59–0.63					
	1 (38)	48 h	0.79	>17 G/L	68.2	81.1	68.2	81.1
CRP	2 (37, 39)	24 h	0.73–0.39	>27.5 mg/L	68.2	81.1		
	1 (38)	48 h	**0.92**	>108 mg/L	**91.0**	83.8		
Albumin	2 (17, 37)	24 h	0.71–0.80					
	2 (38, 40)	48 h	**0.85**	<34 g/L	**91.0**	75.7	69.0	**93.3**
				<28 g/L	41.0	**90.4**	80.0	62.2
BUN	2 (16, 18)	24 h	0.73–0.75	≥13 mg/dL	63–68	73–81	52–72	**84–91**
	1 (40)	48 h		≥20 mg/dL	48.8	**85.0**	63.6	75.5
Calcium	2 (36, 40)	48 h		<2.1 mmol/L	47.6	81.1	60.6	71.7
				trough ≤ 2.15 mmol/L	59	81	60	80
Dyspnoea	1 (40)	48 h		present	23.5	**98.4**	**85.7**	76.5
Pleural effusion	1 (40)	48 h		present	49.0	**95.3**	80.6	82.5

The left column indicates the factor, combination of factors or group of factors examined. The second column presents the number of enrolled studies presenting data on said factor, with their references. When data is not presented as a single value, but instead with a dash, that indicates the range of values observed by the available studies. Predictive values indicating good performance (using an arbitrary threshold of 0.85) appear in bold to ease overview. AUC, area under the curve; BUN, blood urea nitrogen; CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; ULN, upper limit of normal; WBC, white blood cell count.

The narrative review of other laboratory parameters not eligible for quantitative synthesis was beyond the scope of our paper.

Additional outcomes, prediction of severe cases

Izquierdo 2018 and Lautz 2011 performed retrospective reviews of patients with PAP who had CT investigations on admission (within 48 and 72 h, respectively). While Lautz 2011 found the presence of necrosis to be significantly associated with PAP severity (42.3% vs. 10.5% M/SPAP in those with and without necrosis, $p = 0.002$), in the work by Izquierdo et al. only parenchymal necrosis >30% showed such an association (39, 68). Galai et al. and Pezzili et al. reported on symptom duration, which was not significantly different between groups in their cohorts (25, 45). In Nauka 2019, systemic inflammatory response syndrome (SIRS) on admission was significantly

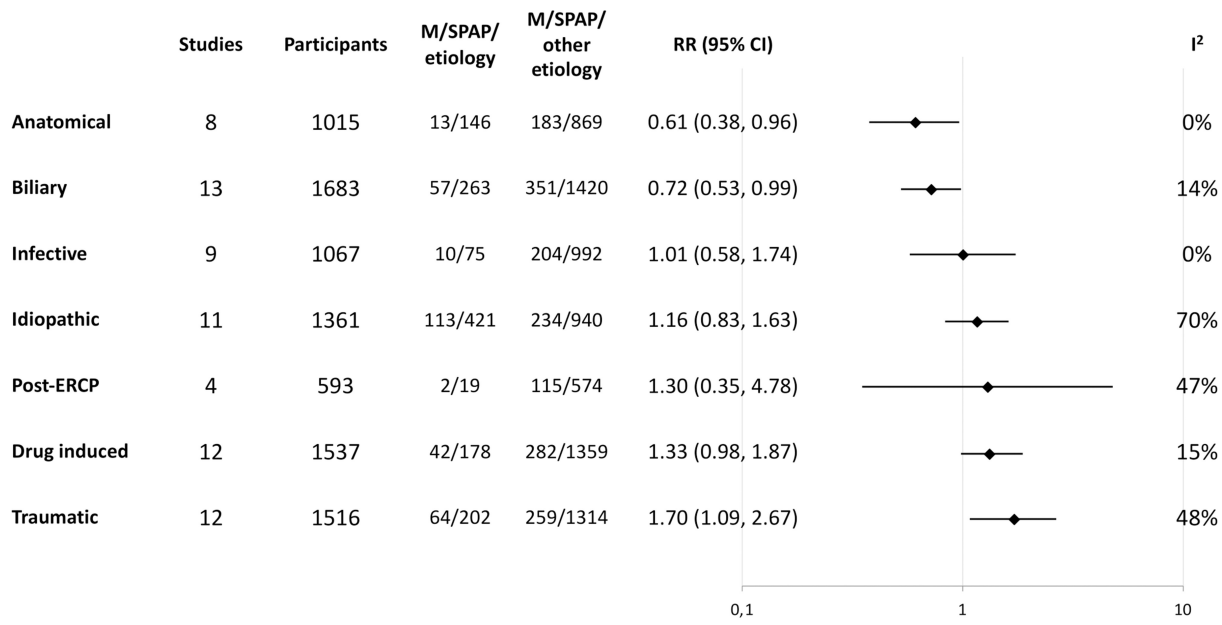

FIGURE 3
Summary of moderate or severe disease course risk with different etiologies. Random-effect meta-analysis results are summarized for the etiological factors and ordered according to effect size. The "Studies" and "Participants" columns indicate the total number of studies and participants in the meta-analysis, while the next two columns indicate the number of events (moderate or severe course) in those with the analyzed etiology and those without. CI, confidence interval; M/SPAP, moderate or severe pediatric acute pancreatitis; RR, risk ratio.

associated with M/SPAP (odds ratio: 3.23, 95% CI: 1.01–9.78, $p = 0.038$) (42).

Only three studies presented detailed data on admission differences between patients with severe and non-severe PAP. In Hao 2018, previous PAP was significantly associated with severe disease course. Mehta and colleagues found an opposite tendency: none of their five severe cases had previous episodes vs. 51 and 63% of mild and moderate cases. In Li 2018, patients with severe PAP had significantly higher WBC, neutrophil count and CRP on admission, as well as a significantly higher CTSI score.

Risk of bias

Risk of bias assessment results, separated according to above results subsections, are available in the Supplementary Figures 28–30.

Discussion

In this systematic review and meta-analysis we assessed the association between on admission factors and the severity of acute pancreatitis in the pediatric age group. Due to the nature of the available studies we were able to compare the on-admission presentation of mild and M/SPAP. Although the definitions of M/SPAP minimally varied in the included studies, it generally represents patients who developed local or systemic complications or organ failure.

Our main finding and the foremost merit of our paper is the meta-analysis of the most commonly used severity prediction score systems and the rigorous narrative review and summary of other examined and proposed variables and scores for PAP severity prediction.

The most widely explored severity prediction scores were the modified Glasgow criteria, the Ranson criteria and the PAPS score. The modified Glasgow and Ranson criteria, initially developed for adult-onset acute pancreatitis demonstrated good specificity for predicting M/SPAP (both around 91–93%), but subpar sensitivity (43 and 45%, respectively). In 2002, DeBanto and colleagues developed the pediatric specific PAPS score largely based on these two criteria, also arguing that sensitivity and NPV are more important in this case, so that no severe cases are missed (21). They were able to achieve an improvement in sensitivity in their cohort (67–70%), with lower specificity (79–81%). But overall, the meta-analysis of six studies examining the PAPS score in a comparable manner found more modest predictive metrics: a sensitivity of 63% and a specificity of 78%. To conclude, none of the above scoring systems have an acceptable sensitivity for predicting M/SPAP. As DeBanto and colleagues phrased it, this would be crucial, since the rationale is that all or almost all patients with M/SPAP should be identified so we can know when to be more vigilant.

But all is not lost – there are several other parameters that were examined (some of them even in multicentric settings and

in multiple studies) that were reported to have acceptable or good sensitivity for predicting M/SPAP. Suzuki et al. modified the adult JPN scoring system to fit the pediatric age group and supplemented it with the age and weight thresholds used in PAPS score (69). In their criterion and validation groups they achieved good sensitivity (80–83%) and exceptional specificity (96–98%). Although very promising, as no other studies (be it dependent or independent) have further examined this score, the results should be handled with care. Multiple studies examined the severity predictive ability of lipase, a parameter not included in any of the mentioned score systems: its elevation above seven-times the ULN within 24 h showed a sensitivity of 82–94% in three separate studies. Hemoglobin is also not included in any of the above scores and it was not significantly different between groups in many of the cohorts. A possible reason behind this is that both its elevation and decrease are observed to predict M/SPAP – as Coffey et al. hypothesized, due to hypovolemia and due to hemorrhage –, with good sensitivity, albeit in few studies (20). Walker and colleagues also demonstrated good sensitivity for albumin < 34 g/L and CRP > 108 mg/L within 24 h, although more modest CRP elevation showed poor sensitivity in another study. These parameters could either serve as an adjunct to the predictive scores with good specificity, or be used to develop new score systems with the goal of utilizing a single one that is optimal in all its predictive metrics.

There is also something to be said for the simplification of these scores. The modified Glasgow, Ranson, PAPS and JPN scores all rely on numerous parameters (all >8) some of which are expensive or difficult to assess (e.g., fluid sequestration, collecting arterial blood sample for partial oxygen tension) or unnecessarily invasive to children. And it should be pointed out that – although later extensively validated – the original Ranson criteria was developed on a modest 100 patients, involving all 11 objective parameters that correlated with serious illness or death (70). This later served as a basis for the Glasgow score, adapted with minimal modifications to the pediatric population in the form of the PAPS score. So there is no saying, that a less complicated set of parameters could not replace these existing combinations. Another important drawback, is that all four scores include parameters taken 48 h after admission, when on admission or within 24 h would clearly be preferable. While there are numerous promising simpler score system alternatives, as highlighted in the appropriate part of our "Results" section, these are rarely validated by other (especially independent) studies (although there are exceptions of course), and they usually fall short of the modified Glasgow and Ranson in terms of specificity and lipase $>$ seven-times the ULN in terms of sensitivity.

Another key detail is that the existing and proposed scores are almost entirely based on laboratory parameters. The only non-laboratory parameter in the Ranson score and its derivates is age, which was transposed to be <7 years or <23 kilograms in the PAPS and pediatric JPN scores. DeBanto and colleagues introduced these cut-offs to define a lower limit of physiological reserves. In our meta-analysis, we found no significant age difference between mild and M/SPAP, which indicates that a simple threshold cannot be used, either because there is no age difference, or because multiple severity peaks exist. As Thavamani and colleagues found in their large-scale analysis, both undernutrition and obesity are associated with increased PAP severity (51).

There are a handful of studies that look to imaging results in the prediction of M/SPAP. The CTSI is based on the characterization of the inflammation and necrosis *via* contrast enhanced computed tomography (CECT). This method is established among adults, predicting severe pancreatitis with an around 86% sensitivity and 71% specificity, when performed within 48–72 h of admission (71). While some authors argue that performing a CECT should be a part of the routine evaluation of patients with pancreatitis, guidelines still do not recommend it, due to fiscal reasons, radiation and the existence of useful predictive scores (72–74). Availability and especially radiation are even greater concerns in a pediatric setting, thus the routine use of the CTSI is unlikely. Still, retrospective studies evaluated its performance in PAP, finding an around 80% specificity and conflicting results for sensitivity (22, 28, 39). It should be pointed out, that a retrospective approach is even more limited in this case, since the proportion of patients with PAP and available CECT results is low. An alternative could be ultrasound based severity prediction, which, although not routinely used, had some promising results in adults (75), but is yet to be examined in children.

Aside from laboratory and imaging results, not much else is taken into account in the available literature. Etiological factors for example – in our meta-analysis, traumatic and drug-induced etiologies were associated with a higher rate of M/SPAP, while a higher rate of mild cases was seen in children with anatomical malformations or PAP of a biliary origin. We also found a history of previous PAP to be associated with M/SPAP. These parameters could serve as promising additions to future score systems.

Strengths and limitations

Perhaps the biggest strength of our work is that we do not know of any previous systematic review and meta-analysis in the topic. Another major strength is that we did not restrict our eligibility in terms of the factors assessed on admission – any that were detailed in the identified publications were reviewed, including demographic, etiological, laboratory, imaging symptom-related, etc. We also performed a meta-analysis of available predictive score systems that were examined in different publications with varying diagnostic metrics, thus we are able to give an estimation of their true predictive capabilities.

Among limitations, it should be stated that almost all studies were retrospective and this can influence some of our results: e.g., the performance of predictive systems or the availability of

laboratory measurements might differ in a prospective setting. Since only three full-text articles were stated to be prospective, that didn't allow for the performance of subgroup analysis of only prospective studies. Another limitation is that – most likely due to the low number of severe cases – no severe vs. non-severe comparisons could be made. As disclosed in the "Statistical analysis" section of the manuscript, continuous data frequently had to be converted to means, which is limited in case of most laboratory variables, since these do not follow a normal distribution in PAP. Low patient numbers, such as in the case of infective and post-ERCP etiologies should also be noted, since it can reduce our confidence in these findings.

Conclusions

None of the available scoring systems provide acceptable sensitivity and specificity for predicting which patients with pediatric pancreatitis will develop a moderate or severe disease course. The Ranson and modified Glasgow scores have the best specificity, but their sensitivity is subpar. Parameters such as lipase exceeding seven times the ULN could be used as an adjunct or added to future score systems to improve sensitivity, which is crucial in this case. Future scores should also strive for simplification and using only factors assessed on-admission or within 24 h. Non-laboratory parameters are rarely investigated, conversely, our analysis suggests that factors such as etiology and previous pancreatitis show an association with PAP severity. Major limitations of the current state of predictive score development are the retrospective study design, modest patient numbers and frequent non-validation of proposed scores by fellow researchers, which can only be improved by multi-center collaborative studies.

Implications

...for practice: The Ranson and modified Glasgow scores provide the best specificity and lipase values > seven-times the ULN the best sensitivity for predicting which patients with PAP will develop complications. These patients should be monitored closely in order for prompt treatment initiation.

...for research: Our systematic review can serve as a basis for future predictive score system development. We highlight the importance of simplicity, using on-admission parameters and reaching this goal via forming international collaborations and investigating prospectively.

Author contributions

Authorship was based on the criteria proposed by International Committee of Medical Journal Editors (ICMJE). MJ, AP, and AN drafted the conception of the work. MJ and KO conducted the data acquisition. ZS the data analysis. MJ and AP wrote the manuscript. All authors contributed to the interpretation of the data. All authors revised the manuscript critically for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. Natesan S, Lee J, Volkamer H, Thoureen T. Evidence-based medicine approach to abdominal pain. *Emerg Med Clin North Am.* (2016) 34:165–90. doi: 10.1016/j.emc.2015.12.008

2. Uc A, Husain SZ. Pancreatitis in children. *Gastroenterology.* (2019) 156:1969–78. doi: 10.1053/j.gastro.2018.12.043

3. Lopez MJ. The changing incidence of acute pancreatitis in children: a single-institution perspective. *J Pediatr.* (2002) 140:622–4. doi: 10.1067/mpd.2002.123880

4. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, et al. Nationwide trends in acute and chronic pancreatitis among privately insured children and non-elderly adults in the United States,

2007-2014. *Gastroenterology*. (2018) 155:469-78.e1. doi: 10.1053/j.gastro.2018.04.013

5. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas.* (2010) 39:5–8. doi: 10.1097/MPA.0b013e3181baac47

6. Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crameri J, Oliver MR. Changing incidence of acute pancreatitis: 10-year experience at the Royal Children's Hospital, Melbourne. *J Gastroenterol Hepatol.* (2007) 22:1313–6. doi: 10.1111/j.1440-1746.2007.04936.x

7. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology.* (2013) 144:1252–61. doi: 10.1053/j.gastro.2013.01.068

8. Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr.* (2011) 52:262–70. doi: 10.1097/MPG.0b013e3182061d75

9. Párniczky A, Abu-El-Haija M, Husain S, Lowe M, Oracz G, Sahin-Tóth M, et al. EPC/HPSG evidence-based guidelines for the management of pediatric pancreatitis. *Pancreatology.* (2018) 18:146–60. doi: 10.1016/j.pan.2018.01.001

10. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. *Lancet.* (2020) 396:726–34. doi: 10.1016/S0140-6736(20)31310-6

11. Párniczky A, Kui B, Szentesi A, Balázs A, Szucs Á, Mosztbacher D, et al. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. *PLoS ONE.* (2016) 11:e0165309. doi: 10.1371/journal.pone.0165309

12. Portelli M, Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management. *Hepatobiliary Pancreat Dis Int.* (2017) 16:155–9. doi: 10.1016/S1499-3872(16)60163-7

13. Abu-El-Haija M, Hornung L, Lin TK, Nathan JD, Thompson T, Vitale DS, et al. Drug induced pancreatitis is the leading known cause of first attack acute pancreatitis in children. *Pancreatology.* (2020) 20:1103–08. doi: 10.1016/j.pan.2020.07.008

14. Antunes H, Nascimento J, Mesquita A, Correia-Pinto J. Acute pancreatitis in children: a tertiary hospital report. *Scand J Gastroenterol.* (2014) 49:642–7.

15. Berney T, Belli D, Bugmann P, Beghetti M, Morel P, LeCoultre C. Influence of severe underlying pathology and hypovolemic shock on the development of acute pancreatitis in children. *J Pediatr Surg.* (1996) 31:1256–61.

16. Bierma MJ, Coffey MJ, Nightingale S, van Rheenen PF, Ooi CY. Predicting severe acute pancreatitis in children based on serum lipase and calcium: a multicentre retrospective cohort study. *Pancreatology.* (2016) 16:529–34. doi: 10.1016/j.pan.2016.04.005

17. Birimberg-Schwartz L, Rajiwate S, Dupuis A, Gonska T. Pediatric acute pancreatitis: changes in management and disease outcomes over 16 years. *Pancreas.* (2021) 50:341–6.

18. Boskovic A, Pasic S, Soldatovic I, Milinic N, Stankovic I. The role of D-dimer in prediction of the course and outcome in pediatric acute pancreatitis. *Pancreatology.* (2014) 14:330–4.

19. Chang YJ, Chao HC, Kong MS, Hsia SH, Lai MW, Yan DC. Acute pancreatitis in children. *Acta Paediatr.* (2011) 100:740–4. doi: 10.1111/j.1651-2227.2011.02158.x

20. Coffey MJ, Nightingale S, Ooi CY. Serum lipase as an early predictor of severity in pediatric acute pancreatitis. *J Pediatr Gastroenterol Nutr.* (2013) 56:602–8. doi: 10.1097/MPG.0b013e31828b36d8

21. DeBanto JR, Goday PS, Pedroso MR, Iftikhar R, Fazel A, Nayyar S, et al. Acute pancreatitis in children. *Am J Gastroenterol.* (2002) 97:1726–31. doi: 10.1111/j.1572-0241.2002.05833.x

22. Fabre A, Petit P, Gaudart J, Mas E, Vial J, Olives JP, et al. Severity scores in children with acute pancreatitis. *J Pediatr Gastroenterol Nutr.* (2012) 55:266–7. doi: 10.1097/MPG.0b013e318254c1c7

23. Farrell PR, Hornung L, Farmer P, DesPain AW, Kim E, Pearman R, et al. Who's at Risk? A Prognostic model for severity prediction in pediatric acute pancreatitis. *J Pediatr Gastroenterol Nutr.* (2020) 71:536–42. doi: 10.1097/MPG.0000000000002807

24. Fonseca Sepúlveda EV, Guerrero-Lozano R. Acute pancreatitis and recurrent acute pancreatitis: an exploration of clinical and etiologic factors and outcomes. *J Pediatr (Rio J).* (2019) 95:713–9.

25. Galai T, Cohen S, Yerushalmy-Feler A, Weintraub Y, Moran-Lev H, Amir AZ. Young age predicts acute pancreatitis severity in children. *J Pediatr Gastroenterol Nutr.* (2019) 68:720–6. doi: 10.1097/MPG.0000000000002294

26. Guerrero-Lozano R, Izquierdo Y, Fonseca V, Moreno LA, Montoya R. Utility of tomographic classifications in predicting unfavorable outcomes in children with acute pancreatitis. *J Pediatr Gastroenterol Nutr.* (2017) 65:S333–S4.

27. Hao F, Guo H, Luo Q, Guo C. Disease progression of acute pancreatitis in pediatric patients. *J Surg Res.* (2016) 202:422–7.

28. Hashimoto N, Yotani N, Michihata N, Tang J, Sakai H, Ishiguro A. Efficacy of pediatric acute pancreatitis scores at a Japanese tertiary center. *Pediatr Int.* (2016) 58:224–8. doi: 10.1111/ped.12774

29. Hornung LN, Farrell PR, Farmer P, Serrette A, Lin TK, Nathan JD, et al. BUN change from admission and levels at 24-48 hours are significant predictors of severity in pediatric acute pancreatitis. *Pancreas.* (2019) 48:1445.

30. Izquierdo YE, Fonseca EV, Moreno L, Montoya RD, Guerrero R. Multivariate model for the prediction of severity of acute pancreatitis in children. *J Pediatr Gastroenterol Nutr.* (2018) 66:949–52. doi: 10.1097/MPG.0000000000001983

31. Kandula L, Lowe ME. Etiology and outcome of acute pancreatitis in infants and toddlers. *J Pediatr.* (2008) 152:106–10.

32. Kaur J, Wadhwa N. Jeena S. Classifying pediatric acute pancreatitis into mild, moderately severe and severe! *J Pediatr Gastroenterol Nutr.* (2018) 66:242. doi: 10.1097/MPG.0000000000002005

33. Lásztity N, Mosztbacher D, Juhász FM, Kaán K, Tokodi I, Tészás A, et al. Clinical signs of severity and therapeutic intervention in pediatric acute pancreatitis-data from APPLE multicentre, observational clinical trial. *J Pediatr Gastroenterol Nutr.* (2019) 68:212.

34. Lásztity N, Mosztbacher D, Toth AZ, Demcsak A, Tokodi I, Czelecz J, et al. Clinical signs of severity and therapeutic intervention in pediatric acute pancreatitis e prospective multicenter nation-wide cohort. *Pancreatology.* (2018) 18:S20–S1.

35. Martonosi AR, Mosztbacher D, Juhász MF, Tokodi I, Tészás A, Gárdos L, et al. Diabetic ketoacidosis worsen the outcome of AP in childhood - preliminary results of APPLE (Analysis of Pediatric Pancreatitis) prospectice, multicentric, observational clinical trial. *Pancreatology.* (2019) 19:S90–S1.

36. Parniczky A, Lásztity N, Mosztbacher D, Tóth A, Szucs D, Vass N, et al. Pediatric pancreatitis: Multicentre prospective data collection and analysis by the hungarian pancreatic study group. *Pancreatology.* (2015) 15:S65.

37. Párniczky A, Németh BC, Mosztbacher D, Szentesi A. Abu-el Haija M, Pienar C, et al. Explore the childhood onset pancreatitis with the support of APPLE (analysis of pediatric pancreatitis) multicenter, observational, clinical trial. *J Pediatr Gastroenterol Nutr.* (2019) 68:223–4.

38. Párniczky A, Németh BC, Mosztbacher D, Tóth AZ, Lásztity N, Abu-El-Haija M, et al. Explore the childhood onset pancreatitis with the support of APPLE (Analysis of Pediatric Pancreatitis) multicenter, observational, clinical trial. *Pancreas.* (2019) 48:1506.

39. Lautz TB, Turkel G, Radhakrishnan J, Wyers M, Chin AC. Utility of the computed tomography severity index (Balthazar score) in children with acute pancreatitis. *J Pediatr Surg.* (2012) 47:1185–91. doi: 10.1016/j.jpedsurg.2012.03.023

40. Li W, Luo S, Zhu Y, Shu M, Wen Y, Wang Z, et al. Concordance of the balthazar grade and the revised atlanta classification: proposing a modified balthazar grade to predict the severity of acute pancreatitis in pediatric population. *Pancreas.* (2018) 47:1312–6.

41. Mehta M, Baldwin C, Sathe M, Troendle D. Severe pancreatitis is rare in pediatric patients: Results from a retrospective review. *J Pediatr Gastroenterol Nutr.* (2018) 67:S255.

42. Nauka PC, Weinstein TA, Dolinger MT, Miller JM, Kohn N, Bitton S, et al. Validation of lipase and systemic inflammatory response syndrome as prognostic indicators in pediatric acute pancreatitis: a retrospective analysis. *J Pediatr Gastroenterol Nutr.* (2019) 68:389–93. doi: 10.1097/MPG.0000000000002217

43. Orkin SH, Lin TK, Fei L, Nathan JD, Thompson T, Abu-El-Haija M. Serum amylase and lipase patterns in pediatric acute pancreatitis diagnosis: Is serum amylase really needed? *Gastroenterol.* (2017) 152:S435.

44. Parian E, Tan M, Urtula R, Nolasco ME. Clinical profile and outcome of acute pancreatitis in children admitted in philippine children's medical center. *Gut.* (2019) 68:A15.

45. Pezzilli R, Morselli-Labate AM, Castellano E, Barbera C, Corrao S, Di Prima L, et al. Acute pancreatitis in children. An Italian multicentre study. *Dig Liver Dis.* (2002) 34:343–8. doi: 10.1016/S1590-8658(02)80128-1

46. Sag E, Akbulut UE, Comert HSY, Ozdogan EB, Karahan SC, Cakir M. Acute pancreatitis in children: Single center experince over 10-year period. *J Pediatr Gastroenterol Nutr.* (2017) 64:251.

47. Sánchez-Ramírez CA, Larrosa-Haro A, Flores-Martínez S, Sánchez-Corona J, Villa-Gómez A, Macías-Rosales R. Acute and recurrent pancreatitis in children: etiological factors. *Acta Paediatr.* (2007) 96:534–7.

48. Suzuki M, Saito N, Naritaka N, Nakano S, Minowa K, Honda Y, et al. Scoring system for the prediction of severe acute pancreatitis in children. *Pediatr Int.* (2015) 57:113–8. doi: 10.1111/ped.12449

49. Suzuki M, Saito N, Minowa K, Kagimoto S, Shimizu T. Validation of severity assessment for acute pancreatitis in children. *Pediatr Int.* (2017) 59:1127–8. doi: 10.1111/ped.13356

50. Szabo FK, Hornung L, Oparaji JA, Alhosh R, Husain SZ, Liu QY, et al. A prognostic tool to predict severe acute pancreatitis in pediatrics. *Pancreatology.* (2016) 16:358–64. doi: 10.1016/j.pan.2016.03.002

51. Thavamani A, Umapathi KK, Sferra TJ, Sankararaman S. Undernutrition and obesity are associated with adverse clinical outcomes in hospitalized children and adolescents with acute pancreatitis. *Nutrients.* (2021) 13:1–10. doi: 10.3390/nu13010043

52. Vitale DS, Hornung L, Lin TK, Nathan JD, Prasad S, Thompson T, et al. Blood urea nitrogen elevation is a marker for pediatric severe acute pancreatitis. *Pancreas.* (2019) 48:363–6. doi: 10.1097/MPA.0000000000001265

53. Walker H, Melling J, Jones M, Melling CV. C-reactive protein accurately predicts severity of acute pancreatitis in children. *J Pediatr Surg.* (2021) 57:759–64. doi: 10.1093/bjs/znab259.680

54. Wetherill C, Melling J, Jones M. C-reactive protein accurately predicts severity of acute pancreatitis in children. *Pancreatol.* (2013) 13:e84.

55. Zheng W, Zhang L, Long G, Chen B, Shu X, Jiang M. Amalgamation of systemic inflammatory response syndrome score with C-reactive protein level in evaluating acute pancreatitis severity in children. *Scand J Gastroenterol.* (2018) 53:755–9. doi: 10.1080/00365521.2018.1459825

56. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut.* (1984) 25:1340–6. doi: 10.1136/gut.25.12.1340

57. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet.* (1974) 139:69–81.

58. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

59. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* (2013) 62:102–11. doi: 10.1136/gutjnl-2012-302779

60. Abu-El-Haija M, Kumar S, Szabo F, Werlin S, Conwell D, Banks P, et al. Classification of Acute Pancreatitis in the Pediatric Population: Clinical Report From the NASPGHAN Pancreas Committee. *J Pediatr Gastroenterol Nutr.* (2017) 64:984–90. doi: 10.1097/MPG.0000000000001583

61. Acute Pancreatitis A. Ga, September 11 through 13, 1992. *Arch Surg.* (1993) 128:586–90. doi: 10.1001/archsurg.1993.01420170122019

62. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health.* (2019) 22:153–60. doi: 10.1136/ebmental-2019-300117

63. Doebler P, Holling H. Meta-analysis of diagnostic accuracy with mada. *R Packag.* (2015) 1:15. Available online at: https://cran.r-project.org/web/packages/mada/vignettes/mada.pdf

64. Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. *Stat Methods Med Res.* (2017) 26:1896–911. doi: 10.1177/0962280215592269

65. R Core Team. (2021). Available online at: https://cran.r-project.org/doc/FAQ/R-FAQ.html#Citing-R

66. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3.* Cochrane (2022).

67. Farrell PR, Jones EK, Hornung L, Thompson T, Patel J, Lin TK, et al. Cytokine profile elevations on admission can determine risks of severe acute pancreatitis in children. *J Pediatr.* (2021) 238:33–41.e4. doi: 10.1016/j.jpeds.2021.07.015

68. Izquierdo YE, Fonseca EV, Moreno L, Montoya RD, Guerrero Lozano R. Utility of CT classifications to predict unfavorable outcomes in children with acute pancreatitis. *Pediatr Radiol.* (2018) 48:954–61. doi: 10.1007/s00247-018-4101-4

69. Suzuki M, Fujii T, Takahiro K, Ohtsuka Y, Nagata S, Shimizu T. Scoring system for the severity of acute pancreatitis in children. *Pancreas.* (2008) 37:222–3. doi: 10.1097/MPA.0b013e31816618e1

70. Ranson JH, Rifkind KM, Turner JW. Prognostic signs and non-operative peritoneal lavage in acute pancreatitis. *Surg Gynecol Obstet.* (1976) 143:209–19.

71. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol.* (2010) 105:435–41. doi: 10.1038/ajg.2009.622

72. Lankisch PG, Struckmann K, Assmus C, Lehnick D, Maisonneuve P, Lowenfels AB. Do we need a computed tomography examination in all patients with acute pancreatitis within 72 h after admission to hospital for the detection of pancreatic necrosis? *Scand J Gastroenterol.* (2001) 36:432–6. doi: 10.1080/003655201300051351

73. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology.* (2013) 13:e1-15. doi: 10.1016/j.pan.2013.07.063

74. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol.* (2013) 108:1400-16. doi: 10.1038/ajg.2013.218

75. Lu Q, Zhong Y, Wen XR, Huang ZW, Fan YT, Xia Q, et al. Can contrast-enhanced ultrasound evaluate the severity of acute pancreatitis? *Dig Dis Sci.* (2011) 56:1578–84. doi: 10.1007/s10620-010-1460-6

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Assessment of exocrine pancreatic function in children and adolescents with direct and indirect testing

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The exocrine pancreas plays an important role in digestion. Understanding of the physiology and regulation of exocrine function provides insight into disease processes and basis of functional testing. Specifically, exocrine pancreatic insufficiency (EPI) can cause maldigestion and thus a proper assessment of exocrine pancreatic function is important. There are indirect and direct methods for evaluating pancreatic function. Indirect methods are varied and include stool, serum, urine, and breath tests. Fecal elastase is a commonly used indirect test today. Direct methods involve stimulated release of pancreatic fluid that is collected from the duodenum and analyzed for enzyme activity. The most used direct test today is the endoscopic pancreatic function test. Indirect pancreatic function testing is limited in identifying cases of mild to moderate EPI, and as such in these cases, direct testing has higher sensitivity and specificity in diagnosing EPI. This review provides a comprehensive guide to indirect and direct pancreatic function tests as well as an in-depth look at exocrine pancreatic function including anatomy, physiology, and regulatory mechanisms.

KEYWORDS

pancreas, exocrine function, acinar cells, duct cells, indirect pancreatic function test, direct pancreatic function test

Introduction

The exocrine pancreas plays a crucial role in digestion and as such, its function is crucial in pediatric population where growth and development are reliant upon adequate nutrition. The objective of this article is to provide a comprehensive review of the exocrine pancreas and discuss options to evaluate its function.

Anatomy of the pancreas

The pancreas consists of 5 different parts, the head, uncinate process, neck, body, and tail. The head and uncinate process located near the portal vein, superior

mesenteric vein, and superior mesenteric artery. This may be a possible explanation why severe acute pancreatitis can be seen with systemic inflammatory reactions.

The pancreas has both exocrine and endocrine functions. The exocrine pancreas encompasses roughly 85% of the pancreatic mass where 10% of the gland is accounted for by extracellular matrix, 4% by blood vessels and the major ducts, and only 2% of the gland is comprised of endocrine tissue (1). The exocrine and endocrine functions are coordinated to allow a regulatory feedback system for digestive enzyme and hormone secretion. Specifically, the blood flow from the endocrine pancreas enters the capillaries of the exocrine tissue before entering the general circulation, and in the exocrine tissue, there are insulin receptors that are involved in regulation of digestive enzyme synthesis (2–4).

The exocrine pancreas is composed of **acinus** (a collection of about 40 acinar cells) and its **draining ducts** (5). The centro-acinar cell functions as an extension of the ductal epithelium into the acinus and provides progenitor cells important for pancreatic regeneration (6, 7). The **acinar cells** synthesize digestive enzymes (lipases, amylase, and proteases) to be stored in zymogen granules and then secreted (enzyme-containing zymogen granules fuse with the apical cell membrane surface) (8). The ductules drain into interlobular (intercalated) ducts and then into the main pancreatic ductal system.

Thanks to its highly developed endoplasmic reticulum (ER) system, the acinar cell of the exocrine pancreas has one of the highest protein synthesis rates among mammalian organ (9, 10). The ER is also a major storage site for intracellular calcium, which, when released into the cytoplasm, is a mediator for secretion of stored digestive enzymes into the pancreatic ductal system (11).

Another cell type known for its role in pathologic states is the **pancreatic stellate cell** that has a role in pancreatic fibrosis (12, 13). They are found around the acinar and ductular structures as well as the islets of Langerhans. In chronic pancreatitis the stellate cell is transformed into a proliferating myofibroblast cell type that synthesizes and secretes extracellular matrix proteins, proinflammatory cytokines and growth factors (14).

Physiology and regulation of pancreatic secretion

The adult pancreas secretes up to 2500 ml of colorless, odorless, alkaline, isosmotic pancreatic fluid. The flow and concentration of this fluid is highly regulated. The flow rate increases from an average rate of 0.2 or 0.3 ml/min in the resting (interdigestive) state to 4.0 ml/min during postprandial stimulation (15). The ratio of the different enzymes released is adjusted to the composition of digested food. For example, a carbohydrate-rich diet results in an increase in synthesis of amylase and a decrease in chymotrypsinogen (16), while a lipid-rich diet enhances lipase synthesis (17).

Electrolyte secretion

The principal compounds secreted by the exocrine pancreas are water, sodium, potassium, chloride, and bicarbonate. The osmolality of pancreatic juice is independent of flow rate.

Secretin is the main stimulant of electrolyte secretion from ductal and centroacinar cells. Secretin was the first hormone ever discovered at the beginning of 20th century (18). Secretin is released from enteroendocrine S cells in the duodenal mucosa when the pH of the lumen is less than 4.5 (19). Binding of secretin to its receptor activates adenylate cyclase, resulting in the generation of cyclic adenosine monophosphate (cAMP), which acts as the intracellular messenger. The duct cells and centroacinar cells contain carbonic anhydrase, which is important for their ability to secrete bicarbonate (20).

Presence of bicarbonate secretion in the proximal pancreatic ducts is largely mediated by a chloride and bicarbonate exchange transporter. In distal ducts, the luminal bicarbonate concentration is already high, and thus the bicarbonate secretion is mediated by bicarbonate conductance *via* the cystic fibrosis transmembrane conductance regulator (CFTR) (21). The secreted bicarbonate acts to buffer the acidic fluid entering the duodenum from the stomach and brings this fluid pH to the optimal level for pancreatic enzyme function.

The concentration of bicarbonate secreted can vary based upon the secretory rate of the pancreas. In resting state, the chloride concentration is high in the pancreatic fluid. Alternatively in an active state following secretin stimulation, the bicarbonate concentration is significantly increased. Bicarbonate concentration thus serves as a great marker for pancreatic function, and in testing discussed in detail later, a bicarbonate level lower than 80 mEq/L it is considered abnormal (22, 23).

Pancreatic enzyme secretion

The acinar cells release pancreatic enzymes from their zymogen granules into the lumen of the acinus, and these proteins combine with the water and bicarbonate secretions of the centroacinar and duct cells.

The exocrine secretion has significant reserve capacity. DiMagno et al. (24) investigated this by plotting lipase output and fecal fat excretion in patients with EPI. They reported that fecal fat excretion was increased when the lipase output fell below 10%. Later they found that maldigestion and malabsorption do not occur until the digestive enzyme secretion (when stimulated by CCK) is reduced to 5% to 10% of normal values (25).

Stimulation of pancreatic enzyme secretion

Pancreatic enzyme secretion is stimulated both by neural and humoral mechanisms.

Neural mechanisms

Direct vagal and regional reflexes stimulate pancreatic enzyme secretion. The vagal stimulation activates the cholinergic, muscarinic receptors (M3) with resultant generation of intracellular cyclic guanosine monophosphase (cGMP). The vagus-mediated cephalic phase of pancreatic secretion in humans and experimental animals results in pancreatic fluid that is low-volume with high enzyme concentration.

Distention at the gastric antrum elicits pancreatic enzyme secretion by activation of a vago-vagal reflex called the antro-pancreatic reflex (26). The antro-pancreatic reflex is an important component of the gastric phase of pancreatic secretion (27).

Humoral mechanisms

Cholecystokinin (CCK) is the major humoral mediator of enzyme secretion during the intestinal phase. Specifically, the presence of fat and protein products in the intestine will trigger release of CCK-releasing peptide that then act on CCK containing cells (I-cells) to release CCK (28).

In addition to CCK, other peptide hormones (e.g., secretin, neurotensin) and neurocrine agents (e.g., GRP, PACAP) can stimulate enzyme secretion (29). However, as mentioned above, secretin has cental role in stimulating electrolyte and bicarbonate secretion.

The effect of CCK is mediated *via* a specific receptor (CCK-A receptor) that can be found on acinar cells, intrapancreatic neurons, and cholinergic afferent neurons. In humans, pancreatic enzyme secretion in response to CCK stimulation or food is inhibited by atropine and somatostatin (30–32). This suggest that CCK's action on the pancreas is dependent on cholinergic mechanism.

Several other peptides including PACAP, GRP, and neurotensin can also act to stimulate pancreatic enzyme secretion (29). However, the extent to which these peptides play a role pancreatic enzyme secretion in humans is not well known.

Enzyme secretion products

Amylase

Pancreatic **amylase is secreted in its active form.** Amylase acts to break down starch and glycogen to glucose, maltose, maltotriose, and dextrins. The 2–9 glucose units are further breaking down by the small intestinal brush border enzymes. These simple sugars are then absorbed *via* the active transport mechanisms along the brush border of the intestinal epithelial cells.

Proteases

Proteins are first hydrolyzed into peptides in the stomach. These peptides then go on to the intestine and stimulate release of CCK-releasing peptide, CCK, and secretin, which then stimulate the pancreas to secrete enzymes and bicarbonate into the intestine.

The proteolytic enzymes include **trypsinogen, elastase,** and **carboxypeptidase A and B**. They are **secreted as proenzymes** that require activation. Trypsinogen is converted to its active form trypsin, by another enzyme, **enterokinase**, which is produced by the duodenal mucosal cells (33). Trypsin, in turn, activates the other proteolytic enzymes. Together, these enzymes cleave bonds between amino acids, so that they can be actively transported into the intestinal epithelial cells for absorption.

To prevent activation of these enzymes while in the pancreas, the acinar cells produce a trypsinogen inhibitor. A failure to express this trypsinogen inhibitor, pancreatic secretory trypsin inhibitor (PSTI), also known as serine protease inhibitor Kazal type 1 (SPINK1), is a known cause of familial pancreatitis.

Pancreatic lipases

The **pancreatic lipase** acts to break down triglycerides. Unlike the proteases discussed above, lipase is secreted in an active form. **Colipase** is also secreted by the pancreas and acts to enhance activity of lipase by binding to it and changing its molecular configuration.

Phospholipase A2 is secreted by the pancreas as a proenzyme and requires activation by trypsin. Phospholipase A2 hydrolyzes phospholipids.

Carboxylic ester hydrolase and cholesterol esterase act to break down lipid substrates, such as esters of cholesterol, fat-soluble vitamins, and triglycerides. These can then be then packaged into micelles for transport into the intestinal epithelial cells.

The diminished or absent lipase secretion leads to steatorrhea, one of the main clinical symptoms of exocrine pancreatic insufficiency. In our diet, fats are mainly long-chain triglycerides that are broken down into two fatty acids and one beta monoglyceride by the pancreatic lipase.

Pancreatic lipase is degraded when the luminal pH drops <4, therefore diseases that result in acidic intraluminal environments (pancreatic duct cell dysfunction, excessive gastric acid section, etc.) can inhibit fat digestion. This is the main reason that pancreatic enzyme replacement preparations have enteric coated granules.

Gastric lipase is a non-pancreatic lipase that acts to hydrolyze fats; however, it cannot fully compensate for the absence of pancreatic lipase. Infants rely upon other enzymes secreted from the pancreas (pancreatic triglyceride lipase (PTL)-related protein 2, and bile salt-stimulated lipase (BSSL)) that act in conjunction with gastric lipase to achieve efficient fat absorption (34). Interestingly, BSSL is also present in human milk, which facilitates fat absorption and growth in breast-fed infants. **Table 1** lists the enzymes and their substrates and products.

Inhibition of pancreatic secretion

Inhibition of exocrine pancreatic secretion occurs through several mechanisms. Somatostatin, pancreatic polypeptide (PP), peptide YY (PYY), neuropeptide Y pancreastatin, and glucagon are all peptides that inhibit secretion indirectly through the activation of inhibitory intrapancreatic neurons. Somatostatin is produced by the delta cells in islets of Langerhans and it exerts an inhibitory effect on amino acid uptake as well as enzyme and bicarbonate secretion (32, 35).

Feedback regulation

Feedback regulation was studied in human and animals by first noting that when pancreatic fluid was diverted from the intestine an increase in pancreatic fluid secretion occurred (36). This augmented enzyme secretion occurred secondary to a rise in circulating CCK (37).

TABLE 1 Summary of the enzymes produced by the acinar cells and their actions.

Enzyme	Substrate	Products
Carbohydrate digestion		
Amylase (active)	Starch, glycogen	Glucose, maltose, maltotriose, dextrins
Protein digestion		
Endopeptidases		
Trypsinogen (inactive)	Cleave bonds between amino acids in proteins	Amino acids, dipeptides
Chymotrypsinogen (inactive)		
Proelastase (inactive)		
Exopeptidases		
Procarboxypeptidase A&B (inactive)	Cleave amino acids from the end of the peptides	Amino acids
Carboxypeptidase A&B (active)		
Fat digestion		
Lipase (active)	Triglycerides	Fatty acids, B-monoglycerides
Phospholipase A2 (inactive)	Phospholipids	
Cholesterol esterase	Neutral lipids	

Alternatively, the increase in CCK and pancreatic fluid secretion into the intestine is inhibited by presence of trypsin in the intestine as well as other digestive enzymes (38). This feedback is accomplished *via* the CCK-releasing peptide in such that with the absence of peptides, CCK-releasing factor will be inactivated by trypsin and thus CCK secretion is decreased (28).

Phases of exocrine secretion

Interdigestive secretion

There is fluid secretion in the fasting (interdigestive) stage that is cyclic and follows the pattern of the migrating myoelectric complex (MMC) (39, 40). This pattern occurs every 60 to 120 min, with bursts of enzyme and bicarbonate secretions being released. Also, there is bile secreted from the gallbladder following partial gallbladder contraction during phases of the MMC. This provides a housekeeping function by cleaning the debris from the small intestine. This process involves the cholinergic nervous system and the hormones motilin and pancreatic polypeptide (39, 40).

Digestive secretion

Cephalic phase

Cephalic phase is mediated by the vagus nerve. In humans, the cephalic phase was identified in studies utilizing a sham feeding method by which the participant would chew food and spit it out. One study (41) indicated that this sham feeding stimulated pancreatic enzyme secretion that rose to about 90% at its maximum, and bicarbonate was also secreted. Atropine suppressed basal trypsin output and essentially abolished the response to sham feeding (42). This suggests that acetylcholine is a major neurotransmitter involved in mediating cephalic phase of pancreatic secretion (39). Among the hormones, gastrin-releasing peptide (GRP) is released from the pancreas upon vagal stimulation and may mediate enzyme secretion (43).

Gastric phase

Gastric phase is initiated by gastric distention by meals. This phase results in secretion of pancreatic enzymes with little effect on the secretion of water and bicarbonate. In studies mimicking gastric distention (fundus or antrum) with a balloon, a resultant low-volume enzyme-rich secretion was obtained through a gastropancreatic vago-vagal reflex (44). Output of gastric contents into the duodenum (gastric chyme with peptides and fatty acids) also act as stimulus at the level of the intestinal mucosa and begins the intestinal phase of pancreatic secretion through neural and hormonal mechanisms. Thus, the rate of gastric emptying can play an important role in pancreatic secretion. As such surgery that

alters emptying can often lead to augmented signaling and mixing of gastric and pancreatic fluids.

Intestinal phase

Intestinal phase is mediated by entero-pancreatic vago-vagal reflexes and various hormones. This phase starts when chyme enters the small intestine from the stomach. Specifically, the chyme consists of hydrogen ions, fatty acids, amino acids, and peptides, and these have roles in the intestinal phase of pancreatic section (45). Of the amino acids, phenylalanine, valine, methionine, and tryptophan are known to cause a more robust pancreatic secretory response (46).

Ductal secretion is initiated by hydrogen ions, creating a low pH environment (pH below 4.5) that triggers secretin release from enteroendocrine S cells (19).

The magnitude of stimulation of the pancreas varies not only by the type of nutrients but also by the site of delivery of the nutrients (47). Elemental diet causes less pancreatic enzyme secretion compared to a standard meal, and delivery of nutrients to the jejunum causes less pancreatic secretion than delivery to the duodenum (47).

Vago-vagal reflexes were found to play a role in pancreatic enzyme and bicarbonate secretion. Particularly studies with vagotomy led to low intestinal loads of amino acids and fatty acids, and studies with atropine led to lower physiologic concentrations of CCK (48, 49).

Assessment of exocrine function

Since the 1940s there have been many tests developed to assess the exocrine pancreatic function. They Include tests that can assess the function of a single enzyme from the stool, serum, urine, or by breath test (indirect tests) and ones that assess the activity of several digestive enzymes from stimulated pancreatic fluid (direct functional tests). The main indications of the exocrine function assessments are listed in **Table 2**.

TABLE 2 Indications for the assessment of exocrine pancreatic function.

Signs or symptoms concerning for EPI
Failure to thrive
Steatorrhea
Chronic diarrhea
Chronic abdominal pain
Abdominal bloating
Borborygmi
Fat soluble vitamin deficiencies
Genetic syndromes associated with EPI
Cystic fibrosis
Shwachman-Diamond syndrome
Johanson Blizzard syndrome
Pearson syndrome
Assess PERT
Non-compliance with treatment
Measure PERT dose adjustment

PERT, pancreatic enzyme replacement therapy.

Development of enzyme secretions

It is important to understand the intrauterine and postnatal development of enzyme secretion for the accurate interpretation of the functional test results.

Intrauterine development of amylase, lipase, and trypsinogen secretion does not occur at the same time (50, 51). Trypsinogen and chymotrypsinogen were found to be present around 14 to 16 weeks, followed by lipase first appearing by 21 weeks of gestation. Lipase is uniformly present by postnatal age of 15 days (50). Amylase detection is postnatally and occurs much later than all other enzymes. Lebenthal and Lee et al. reported that infants at 30 days old have no detectable amylase activity in duodenal fluid; however, children at around 2 years of age had normal adult level of amylase activity (52, 53).

This postnatal appearance of amylase and lipase in infants may not cause symptoms in breast-fed infants as breast milk has significant amylase (54) and bile salt–dependent lipase in breast milk (contributes to lipid digestion in infants) (55).

There are case reports of isolated lipase/colipase deficiency, detected by duodenal fluid aspiration in children with clinical presentation of greasy stools (56–62). Additionally, isolated amylase deficiency was identified in a large retrospective pediatric database of endoscopic pancreatic function testing (ePFT) (63). An error in mRNA processing or protein secretion was suggested by Mehta et al. in a reported pediatric case with isolated amylase deficiency diagnosed after repeated ePFTs (20 and 33 months of age), despite detecting normal pancreatic amylase messenger RNA by reverse-transcriptase polymerase chain reaction in the duodenal fluid (64). Understanding of isolated pancreatic enzyme deficiencies as pathologic or physiologic is overall limited and represents area for future research.

Indirect exocrine function tests

Indirect function tests are based upon the function of a single enzyme. They measure individual pancreatic enzymes or their substrate byproducts from stool, serum, or breath samples. The examples of these tests are fecal fat, steatocrit, fecal elastase (FE-1), stool chymotrypsin, serum markers, and the ^{13}C-mixed triglyceride breath test. Each indirect test has

its own inherent limitations; however, they all share a common limitation of poor sensitivity and specificity in detecting mild to moderate EPI.

Stool based tests

Fecal elastase test

Fecal elastase (FE-1) is the most widely used indirect screening test for EPI. The basis of this tests that the elastase is resistant to hydrolysis by bacterial proteases and it remains stable in room temperature (65). A small stool sample is adequate for the test. The other advantage is that pancreatic enzyme replacement therapy (PERT) does not interfere with the result. Therefore, discontinuation of PERT is not necessary when performing the FE-1 test (66).

FE-1 has been well studied in pancreatic exocrine dysfunction associated with chronic pancreatitis, cystic fibrosis, diabetes, and celiac disease (67–70). The normal result is >200 mg/g of dry stool. A level <200 mg/g indicates EPI, and <100 mg/g correlates well with steatorrhea (71). Khan et al. proposed a method of staging EPI (into mild, moderate, and severe) based upon value of FE-1 combined with presence of symptoms and fat soluble vitamin deficiency (72).

It is important to note that large volume liquid stool can dilute the fecal elastase and provide inaccurate results, therefore for the correct analysis the stool sample should be lyophilized, and dry weight should be uses for calculations (73).

Diet is not suggested to have an large impact on FE-1 testing, however Walkowiak et al. reported that in pancreatic sufficient patients with normal range FE-1, a short term vegan diet did lower their FE-1 suggesting possible adaptation of pancreatic proteases to low protein high fiber diet (74).

The sensitivity of the FE-1 in children with CF is between 86% and 100% (71, 75, 76). In a meta-analysis, FE-1 of <200 mgc/g was found to have an overall pooled sensitivity of 77% and specificity of 88% in detecting EPI (77). As expected, the accuracy of FE-1 increases in cases of severe EPI (sensitivity of 97%) and alternatively decreases in cases of isolated deficiency or mild EPI (sensitivity 49%).

Although the FE-1 can only detect EPI reliably in the severe range, it remains more sensitive than fecal fat testing. Isolated enzyme deficiencies are not detected by FE-1, for example, steatorrhea secondary to isolated lipase or colipase deficiency (78).

Stool fat content measurement

Assessment of fecal fat is a standard method to detect fat malabsorption. The causes of fat malabsorption are varied, and as such, a positive test is neither specific nor sensitive to exocrine pancreatic dysfunction. It is an indirect assessment of lipase activities of the pancreas. This test measures the fraction of fat in the stool after initiating a standard fat containing diet. However, this procedure is not specific for lipase activity as there are other non-pancreatic etiologies of the abnormal fecal fat detection. These include gut mucosal injury (e.g., celiac disease), small bowel bacterial overgrowth, short bowel syndrome, Crohn disease, and even liver disease with cholestasis (79, 80). In patients with cystic fibrosis (CF) without pancreatic insufficiency, fat malabsorption can occur due to gastric hypersecretion or an abnormal gastrointestinal motility (81). In a study in patients with Shwachman-Diamond syndrome (SDS) and CF, steatorrhea developed when lipase fell below 2% or colipase fell below 1% (82) and as such that are clear cases here fecal fat testing would likely be positive.

Fecal fat testing is a cumbersome test for the patient and laboratory to perform; thus, has fallen out of favor as first line testing in many clinical settings. The test includes all stool collection for 72 h while the total fat intake (100 g/day) is standardized starting 3 days before and during the full 3 days of collection (83). Then the ratio of stool fat content compared to total fat intake is calculated. Typically, a level of >7 g/day is defined as malabsorption (79). It is a time-consuming test, although there is a report that 24-hour collections are adequate (84). It is important to store the collected fat in a refrigerator, otherwise the bacteria in stool will start fermenting the fat and fat content may decrease.

It is well known that the fat absorption ratio is age dependent. In children that are younger than 6 months of age, the reference values are >85%, and above that age, reference values are >93% to 95% (85, 86).

The classical method for stool fat analysis was quantitative testing *via* the Van de Kamer method. However, the near-infrared reflectance analysis simplified the quantification, and this correlates well with the classical Van de Kamer method (87, 88). The qualitative stool fat test is based on the use of Sudan stain of the stool and microscopic analysis of fat droplets and results are reported in a graded fashion (1 + normal; 2 + slight increase; and 3 + definite increase) (89). Qualitative analysis is lacking in its ability to separate normal from mild or inconsequential cases of steatorrhea.

The coefficient of fat absorption is another measure obtained with fecal fat testing. A value <90% is defined as insufficient, the calculation is: (fat ingestion – fat excretion)/fat ingestion) × 100(%). However, Erchinger et al. reported that for the diagnosis of fat malabsorption, the additional evaluation to calculate the ratio of fat absorption did not provide additional information compared to fecal fat content (90).

Steatocrit

Steatocrit is a fast and easily performed screening test for fat malabsorption. Recall that fat malabsorption has pancreatic and non-pancreatic etiologies, thus a positive steatocrit is not

specific to pancreatic insufficiency. This test includes the collection of stools that is then homogenized and an aliquot of sample transferred to hematocrit tube and centrifuged at 12,000 rpm for 15 min. The ratio of the fat layer to the total sample length is assessed. After the test introduction in infants in 1981 (91) this simple, cheap and rapid test became popular. However, it has poor sensitivity and specificity compared with the 72-hour stool fat collection. Tran et al. reported that the sensitivity of the test can be improved *via* acidification of the stool sample prior to centrifugation (acid steatocrit test) (92, 93).

Stool chymotrypsin

Chymotrypsin in stool is detected by a photometric assay test (93). Unlike elastase, chymotrypsin is prone to proteolytic degradation and can limit the availability and handling of the test. Another limitation is that the test cannot differentiate human chymotrypsin from the chymotrypsin found in PERT (94). Thus, PERT must be stopped at least 3 days before the test. When compared to ^{13}C mixed triglyceride breath testing and FE-1, fecal chymotrypsin had the lowest sensitivity and specificity at 56% and 82%, respectively (95). The test's main advantage can be that it allows assessing compliance to PERT.

Urine based test

Pancreolauryl test

The substrate for the pancreaolauryl test is dilaurate (lauric acid, a 12-carbon atom chain fatty acid, and a component of triglycerides that comprises about half of the fatty-acid content in coconut milk) combined with fluorescein. Pancreatic lipase releases the fluorescein that is then absorbed and can be measured in the urine (96) and blood (97). Later the test was modified by adding mannitol to correct for changes in intestinal permeability that could affect absorption and skew the test results (98). The results are reported as a fluorescein/mannitol ratio. However, when compared with FE-1 test, the pancreolauryl test was less accurate (99).

Serum tests

Serum testing for EPI has fallen out of favor for reasons discussed below, however understanding of these tests in relation to other pancreatic diseases and in monitoring secondary effects of EPI are important.

Amylase and lipase, are present in the blood stream due in part to physiologic release or leaking of these from the acinar cells into the systemic circulation. Thus, pancreatic disease states with inflammation can lead to elevation of these. Alternatively, atrophy or significant loss of pancreatic tissue can cause a decrease in amylase and lipase.

In the 1980s, serum IRT was found to have sensitivity and specificity in diagnosing severe cases of EPI, in which a result of less than 20 ng/ml was consistent with pancreatic steatorrhea, compared with levels higher than 20 ng/ml in those without steatorrhea (100). Interestingly around that time, IRT was recognized in dried blood spots in neonates found to have cystic fibrosis and was later adopted into the newborn screening. Adoption of serum IRT for EPI fell out of favor due to the significant limitations in age reported by Durie et al. (101) and the advent of other more specific pancreatic function tests. Thus, outside of neonatal screening, IRT is no longer used clinically for assessment of exocrine pancreatic function.

Other serum tests associated with downstream effects of EPI include decreased serum levels of fat-soluble vitamins, apolipoproteins, total cholesterol, magnesium, retinol-binding protein, calcium, zinc, selenium, and carotene (102). It was reported that patients with EPI are at risk for vitamin E deficiency (103, 104), that can lead to neurological symptoms, highlighting the importance of these adjunctive serum tests in detecting complications in EPI. Additional tests may include hemoglobin, albumin, prealbumin, and HbA1c, as well as diminished bone density, all of which can be abnormal in the setting of untreated EPI (105).

Breath test

^{13}C mixed triglyceride breath test

The ^{13}C is a natural nonradioactive form of the carbon. The test measures ^{13}C–CO_2, which is one of the breakdown products of digested triglycerides (106). This test is based on the function of lipase, however, like the fecal fat assay, the ^{13}C-mixed triglyceride breath test is a test of fat maldigestion and is not specific to EPI.

The ^{13}C mixed triglyceride breath test was first described by Vantrappen et al. in 1989 (107). The test utilizes a ^{13}C-labelled mixed triglyceride [1,3-distearyl,2 (carboxyl-13C) octanoyl glycerol] substrate that is consumed with a meal, typically butter (or similar fat) on toast. This fat is then hydrolyzed by the pancreatic lipase (and/or other non-pancreatic fat digestion processes) and the ^{13}C-labelled octanoate, an 8-carbon medium-chain fatty acid, is absorbed in the blood and metabolized by the liver and the ^{13}C-labelled CO_2 appears in the expired air of the patient. The$^{13}CO_2$ is detected in breath samples at various time points throughout a 5–6-hour study. The result of the test is expressed as percentage of ^{13}C cumulative recovery over the testing period, with values in normal subjects being between 20%–40% of cumulative recovery (106). The $^{13}CO_2$ is measured by mass spectrometry or near-infrared analysis.

The amount of ^{13}C-labelled CO_2 is an indirect measure of pancreatic lipase activity, although as mentioned above, there

may be other non-pancreatic diseases influencing the result. The main advantage of the ^{13}C-mixed triglyceride breath test is in its ability to assess the efficacy of PERT. The limitations of the test are that there is a wide variability in the amount of expired ^{13}C-labelled CO_2, and these values can fluctuate with activity level, gastric emptying rate, liver disease, intestinal diseases that affect absorption, lung disease, and endogenous CO_2 production (108–110). The breath test is also difficult to perform in infants and young children.

The 13C-mixed triglyceride breath test is widely published (111–114), however, currently it is only available in a few countries in Europe and in Australia.

Direct (stimulatory) exocrine function tests

Direct pancreatic function tests measure enzyme activity in pancreatic secretions. They are stimulated tests with either secretagogues (Secretin/CCK) or meal (Lundh test). They allow to assess the activity all the main pancreatic enzymes and provide option for other analyses of the collected fluids.

Direct pancreatic function test with secretagogue (secretin, cholecystokinin [CCK] administration is considered the gold standard to assess exocrine pancreatic function. In 1948, the first direct pancreatic function test was published (115). It used a specific double lumen tube to collect fluid samples from the duodenum (Dreiling tube) following simulation with secretagogue. Later a meal-based stimulation "Lundh meal test" was developed. This was then followed by the development of the endoscopic stimulation test in the 20th century. The advantages and disadvantages and clinical utility of the different tests are summarized in **Table 3**.

Dreiling tube test

The Dreiling tube method (115) was considered a gold standard for the assessment of exocrine pancreatic function.

TABLE 3 Summary of the advantages, disadvantages, and clinical value of the different tests.

Test	Description	Advantages	Disadvantages	Clinical indications
Direct (stimulatory) tests to assess all enzymes				
Secretin	Measurements of resting duodenal enzyme activity in the first 10 min and bicarbonate secretion 15–60 min after IV secretin	Provide the most sensitive and specific measurements of exocrine pancreatic function (ePFT and Dreiling tube methods)	Require duodenal intubation and intravenous administration of hormones; not widely available	Detection of mild, moderate, or severe exocrine pancreatic dysfunction
Cholecystokinin	Measurements of duodenal outputs of amylase, trypsin, chymotrypsin. and lipase after IV administration			
Secretin and cholecystokinin	Measurements of volume, bicarbonate and enzymes activities after IV secretin and cholecystokinin}			
Meal-stimulated test				
Lundh test meal	Measurement of duodenal enzyme activities after oral ingestion of a test meal	Does not require IV administration of hormones	Requires duodenal intubation, a test meal, and normal anatomy, including small intestinal mucosa; not widely available	Detection of moderate or severe exocrine pancreatic dysfunction when a direct test cannot be done (i.e., limited availability of test)
Indirect (non-stimulated) tests to assess a single enzyme function				
Fecal fat	Measurement of fat in the stool after ingesting meals with a known amount of fat	Provides a quantitative measurement of steatorrhea	Requires sufficient dietary fat intake and collection of stool; only detects severe pancreatic dysfunction	Detection of severe exocrine pancreatic dysfunction and steatorrhea
Fecal chymotrypsin and Fecal elastase 1	Measurement of chymotrypsin or elastase 1 in the stool	Do not require IVs, tubes, or administration of oral substrates	Insensitive for detecting mild or moderate dysfunction	Detection of severe exocrine pancreatic dysfunction
Fluorescein dilaurate	Oral ingestion of fluorescein dilaurate with a meal, followed by measurements of fluorescein in urine or blood	Provide simple measurements for severe pancreatic dysfunction	Do not detect mild or moderate dysfunction; results may be abnormal in patients with small intestinal mucosal disease	Detection of severe exocrine pancreatic dysfunction
^{13}C-Mixed Triglyceride Breath Test	It is consumed with a meal. Expired $^{13}CO_2$ collected and measured by by mass spectrometry or near-infrared analysis	For the patients is an easy and convenient test	Requires special substrate and equipment and 5-6 h of breath collection. The result influenced by the intestinal function and liver metabolism	Detection of moderate and severe exocrine pancreatic dysfunction.

Although the test is considered highly sensitive and specific (22, 116–122), the Dreiling tube collection method has inherent limitations.

The process of collection *via* the Dreiling tube starts with placement of an oro-duodenal tube (guided by fluoroscopy), baseline fluid is collected, then sequential administration of secretin and CCK and collection of the outcoming pancreatic fluid *via* aspiration of duodenal contents at varying time points. The volume of aspirate, pH, bicarbonate concentration, total protein concentration, and pancreatic enzyme activity are recorded. Amylase, trypsin, chymotrypsin, and lipase all can all be assayed and are reported as total enzyme output determined by the volume of fluid collected.

Multiple factors can influence the results of this test including mixing of gastric acid with intestinal fluid, inaccurate measure of "total volume" as the duodenal tube cannot reliably aspirate all secreted fluid, and dislocation of the tube (123).

The Dreiling tube collection method is invasive, impractical, difficult for patients to complete, and radiation exposure associated with verification of tube positioning, and can be time consuming to perform. Protocols for specimen collection in the publications are variable and the duration of the tests vary from 45 min to 150 min (124–127). In children specifically, this method of collection has never gained favor. Instead, many turn to non-invasive indirect testing such as fecal elastase.

Lundh meal test

Another measurement of pancreatic function is the meal-based Lundh test (126). In this test, patients are asked to ingest a 300-mL liquid meal composed of dried milk, vegetable oil and dextrose (6% fat, 5% protein and 15% carbohydrate). This is then followed with the aspiration of fluid from the duodenum *via* a nasoduodenal tube, and measurement of enzyme activities. This is a physiological test that utilizes different phases of the meal (cephalic, gastric and intestinal), the effect of the meal on small intestinal sensory process, release of the secretin and CCK and the whole neurohumoral systems (vagal effects) and the pancreas responses to the neurohumoral system. Jensen et al. found significant correlation in lipase and bicarbonate concentrations between endoscopic secretin stimulation test and the Lundh test in 23 healthy volunteers (128).

Endoscopic pancreatic function test (ePFT)

Method of fluid collection and analysis

The test is performed during a standard pediatric upper gastrointestinal endoscopy. Before endoscopic intubation, secretin or CCK is administered intravenously. For accurate collection of pancreatic fluid, the endoscope is positioned close to the ampulla of Vater and an aspiration catheter inserted through the biopsy channel (**Figure 1**) and with light suction is utilized. Pancreatic fluid secretion typically starts 3 to 4 min after the secretin administration, and the optimal collection time is within 10 min from the time of secretin injection.

There is a known dilutional effect of enzyme activities by ductal cell secretions if the fluid is collected beyond 10 min

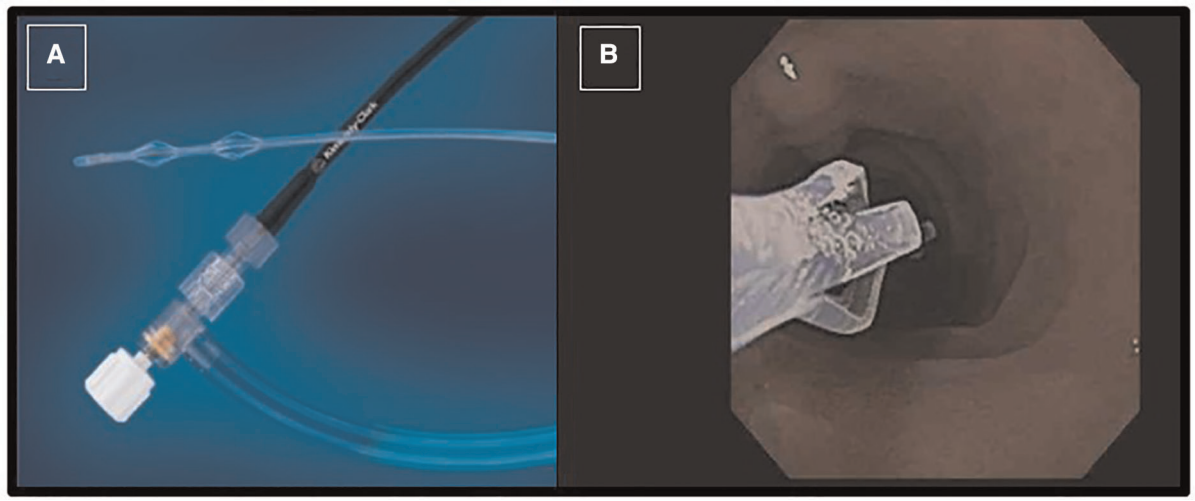

FIGURE 1
Picture of the collection catheter passed through endoscope working channel (A); the tip of catheter is seen in the duodenum close to the ampulla of vater (B).

(129). Interpretation of the test results should be based on the sample with the highest (peak) enzyme activities (129, 130). However, the fluid secreted after 10 min reflects the effect of the secretin on the ductal cell function that is measured by bicarbonate concentration. In healthy subjects an increase in bicarbonate >80 mmol/L indicates normal function (123).

The fluid collected is measured for pH, protein content, and enzyme activity (amylase, lipase, trypsin, chymotrypsin, and elastase). The pH in the protein content of the fluid is utilized to assess the quality of the sample, in which a pH of less than 7 suggests possible contamination of gastric fluid and a low-protein would indicate dilution with duodenal fluid (131). **Table 5** lists factors that can affect the result of the ePFT.

History and rationale of the ePFT

The first endoscopic fluid collection was reported in 1979 (130, 132). The first pediatric study comparing the Dreiling test with ePFT was reported by Madrazo et al. (133). Since then, multiple adult and a few pediatric papers (129, 133–135) have been published. In adults this test is most used to assess bicarbonate secretion that is an indicator of the ductal cell damage in chronic pancreatitis (CP). In contrast, in children the main role of this test is to determine the acinar cell enzyme secretion. The ePFT is more practical and efficient option for direct testing then the Dreiling and the Lundh tests to assess both the ductal and acinar cell functions.

The basis to assess acinar secretion is that secretin washes out the enzyme concentrated fluid that is present in the ducts prior to stimulation with secretagogue (interdigestive fluid). The interdigestive fluid in the pancreatic ducts has significant enzyme activity. This was found in several studies evaluating basal enzyme secretion was roughly 20% of the total pancreatic enzyme capacity, indicating that this basal secretion is adequate to prevent malabsorption and steatorrhea seen when pancreatic enzyme activity is <10% (136–138). Hence any dysfunction in enzyme secretion can be detected regardless of whether it is generalized insufficiency or an isolated enzyme deficiency.

Comparison of ePFT and dreiling tube method

The fluid collected in ePFT is analyzed and reported as peak enzyme activity in unit/ml/min (139). Alternatively, the Dreiling tube method reports the test results as total enzyme output by multiplying the enzyme activity and the volume of fluid collected.

The first pediatric study comparing the Dreiling tube and ePFT reported comparable results (133). Conwell et al. also compared the two collection methods in healthy adults and in patients with chronic pancreatitis using CCK infusion and reported that the ePFT was equivalent to the Dreiling tube collection (123). They also analyzed the safety and cost of the two tests which found that ePFT was safer, shorter in duration, and less costly ($1,890 vs. $2,659). The smaller fluid volume collected by ePFT reproduced the classic acinar and duct cell secretory profiles after hormonal stimulation (123, 137, 140). Based on these studies, ePFT was found to be a useful method for the assessment of pancreatic duct cell function (141, 142).

In conclusion, ePFT is comparable to the Dreiling tube method but offers several advantages over the Dreiling method. ePFT is less time consuming, does not result in patient's discomfort as performed during sedation, and eliminates need for radiation exposure. The limitations of ePFT include lack of uniformly accepted protocol, and requirement of anesthesia to perform (143). See list of advantages and limitations to ePFT in **Table 4**.

ePFT for acinar function in children

Following the first pediatric study in 1991 (133), Del Rosario et al. conducted a study in that one group of children received IV bolus of both CCK and secretin, while the second group received placebo after the administration of secretin and found no statistical difference in mean lipase level (129). The other important message of this study was that the peak enzyme values at the 5- and 10-minutes collections were similar in both groups, but the 15-minute specimens had significantly less enzyme activities due to dilution effect, and as such the optimal timing of collection was identified (129).

Another ePFT study in children, reported during the time of secretin shortage, compared secretin and CCK alone and in combination. It found that CCK was acceptable to be used alone for pancreatic enzyme measurements in the absence of commercially available secretin (135).

In 2016 a larger study with 508 ePFTs in children reported peak enzyme activities at 5 min that was then followed by a decrease activity over time (144). Additionally, they found discordance between ePFT and FE-1 testing in 165 children (144).

TABLE 4 Advantages and limitations of the ePFT.

Advantages of ePFT	Limitations of ePFT
•It allows assessing acinar and duct function combined with endoscopy. •It is significantly shorter than the traditional tube collection method. •Technically easy to perform and it is a safe procedure without patient's discomfort. •Enzyme measurements allow diagnosing isolated and generalized enzyme deficiencies in children. •It is helpful in the workup of malabsorptive diarrhea or poor weight gain.	•It can be performed only during anesthesia. •It slightly prolongs the duration of EGD assesses peak enzyme activities and not the total secretory capacity of pancreas. •Certain drugs used for anesthesia my influence the composition of the collected fluid.

EGD, esophago-gastro-duodenoscopy; ePFT, endoscopic pancreatic function test.

TABLE 5 Factors that have an effect on the results of ePFT (modified from (125).

	Factor	Effect
Substrate supply	Kwashiorkor and marasmus	Reduced stimulated enzyme output
	Protein repletion in kwashiorkor	Restored depressed pancreatic function
	Starch added to infant formula	Enhanced pancreatic α-amylase secretion
	Carbohydrate-rich diet in adults	No influence on amylase secretion
	Protein increase in infant formula	Augmented trypsin and lipase production
	Vegan diet	Decrease in the median of fecal elastase and chymotrypsin output
Celiac disease	Gluten in undiagnosed celiac patients	Temporary pancreatic dysfunction in 22.7% of newly diagnosed children
Ibd*	New or relapsed cases	Up to 40% had abnormal EPI
Drugs	Morphine	Increased bicarbonate and decreased protein secretion after 60 min
	Diazepam with hyoscine butylbromide	Reduced trypsin secretion
	Atropine	Decreased both basal and secretin-stimulated bicarbonate secretion
	Terbutaline	Inhibitory effect on the water and bicarbonate secretion
	Midazolam and meperidine	Did not affect the peak bicarbonate concentration or total bicarbonate output
Technique	Gastric acid contamination - low pH	Decreases pH below the pH optimum of enzymes and dilutes pancreatic fluid resulting in falsely low enzyme activity. Low pH also can denatures enzymes, especially lipase
	Collection of the fluid initially present in the duodenum	Duodenal secretions mixed with pancreatic fluid resulting falsely low enzyme activities
	Low protein	May result in unreliable enzyme assays
	Late collection	Due to increased water output the peak enzyme concentration per ml fluid can be falsely low (Figure 2)
	Bloody fluid	Mucosal injury resulting in blood contamination that influences the assays
	Single specimen	May result in low test sensitivity and specificity
Sample handling	Unfrozen specimen sent to the lab	It results in abnormally low enzyme activities

IBD, inflammatory bowel disease.

Up to now, the largest pediatric study included 1913 children and young adults summarized the experience with ePFT (secretin stimulated, collection time between 4 and 10 min) and determined that the test had high reproducibility, repeatability, and clinical validity (145). Additionally, by adding ePFT to standard upper gastrointestinal endoscopy when there was a suspicion of malabsorption, the diagnostic yield increased by 36.9% (145).

ePFT for ductal function test in children (single center data)

A method used at Arnold Palmer Hospital for Children, includes performing longer duration pancreatic fluid collection (45 min) after IV secretin administration in children where duct dysfunction was suspected. Those who had abnormal test result had genetic tests ordered. Figure 2 shows three cases with normal function and three abnormal test results with the genetic tests results added (125).

ePFT for ductal function in adults

After IV secretin administration, high bicarbonate secretion continues for a longer duration. Many adult studies used a 60 min collection time to assess ductal function and this subsequently led to longer anesthesia time.

A prospective ePFT study in patients (>16 years) with cystic fibrosis and healthy normal subjects administered the secretin 25 min before the endoscope insertion and collected the pancreatic fluid between 30 and 45 min (134) that significantly shorter than the 60 min test. The ePFT differentiated pancreatic-sufficient and insufficient patients with a sensitivity of 100% and specificity of 88%. Based on this study the 15 min collection was found to be sufficient to diagnose duct cell dysfunction. When CCK administration was added to secretin during ePFT it did not improve the accuracy of diagnosing EPI in adults with chronic pancreatitis (146). A similar conclusion was reported in pediatrics (135).

Figure 3 illustrates when the ePFT can be used for acinar and duct cell function assessment by using IV secretin administration.

Imaging modalities to assess pancreatic exocrine function

Imaging studies are important in evaluation of anatomy of the pancreas as it relates to its function and thus should be utilized in assessing causes of exocrine pancreatic dysfunction. Of all imaging studies available, the secretin enhanced MRI (s-MRI) is the only one that can highlight functionality of the exocrine pancreas by evaluating fluid secretion.

Imaging studies can detect chronic pancreatitis typically when >50% of the gland is fibrotic (147). Thus, when it comes to assessing early stages of chronic pancreatitis in children with negative imaging studies, the combination of ePFT and endoscopic ultrasound should be considered (148). Additionally, identifying early stages of chronic pancreatitis utilizing these methods may also lead to improved outcomes with total pancreatectomy with autologous islet cell transplant (149).

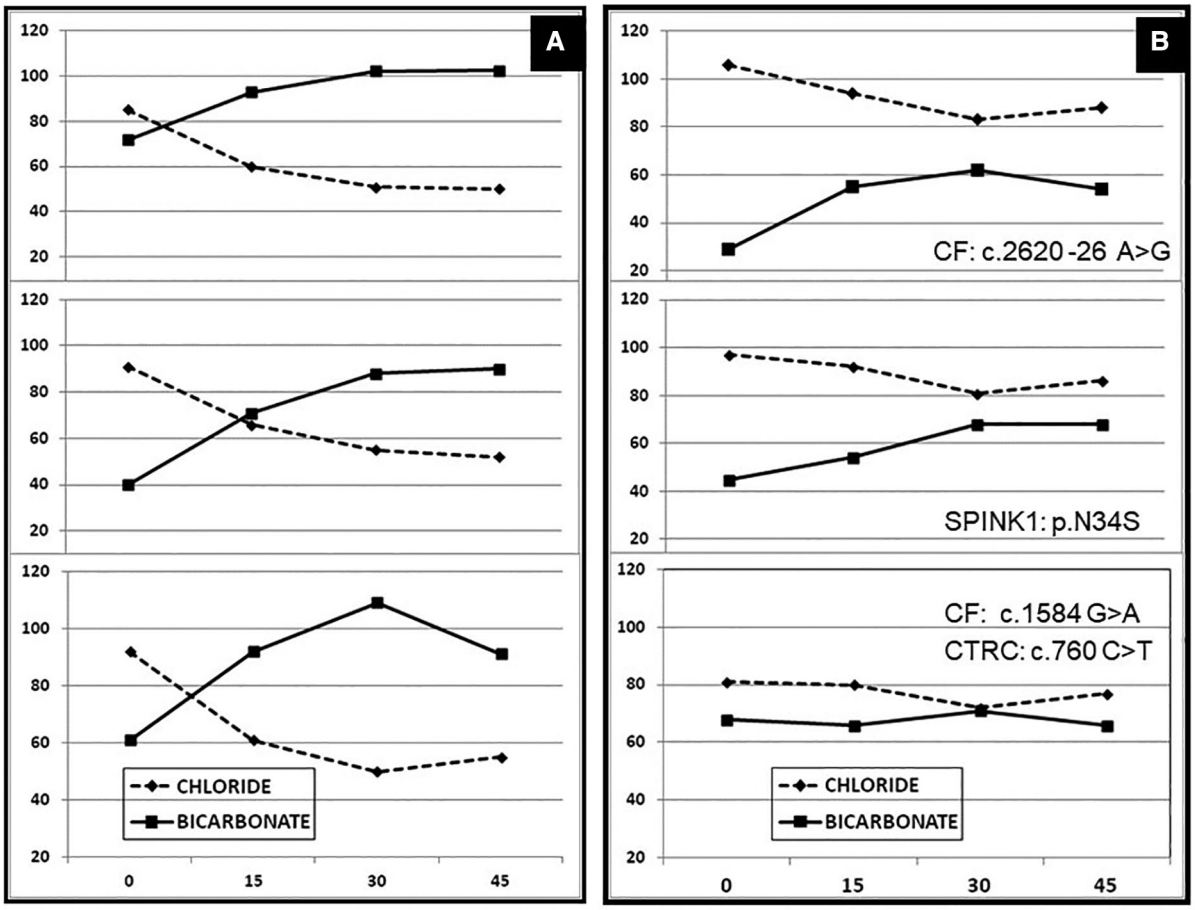

FIGURE 2
Ductal function assessment with bicarbonate concentration from prolonged ePFT with fluid collection up to 45 min. (A) Normal tests with the bicarbonate concentration is above 80 mmol/L. (B) Abnormal tests in patients with genetic abnormalities in three patients when the bicarbonate never reached the 80 mmol/L [adapted from Horvath, K. et al. (125)].

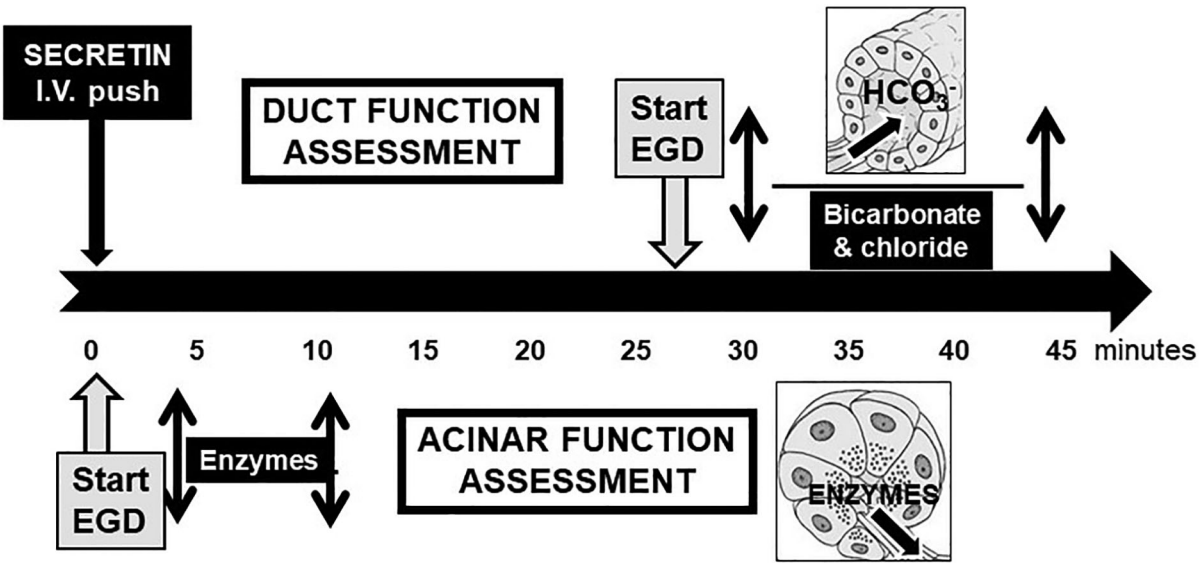

FIGURE 3
This flowchart shows the optimal time of fluid collection for acinar and ductal function after IV push administration of secretin [modified from Engjom, T. et al. (134)].

Ultrasound

Usually, ultrasound is the initial imaging modality in any suspected pancreatic disease as it can assess the size of pancreas, presence of peripancreatic fluid, the size and irregularity of the main duct and the presence of calcifications. Its sensitivity is 50% to 80% in adults (150).

Magnetic resonance cholangio-pancreatography (MRCP)

It is the test of choice as it is more sensitive, does not require radiation and can image ducts as small as 1 mm (151) and enables to detect biliary stones and anatomical variants, such as pancreas divisum. Visualization of the pancreatic ducts are enhanced by the administration of secretin, which induces fluid secretion (152), this is the secretin-MRI (s-MRI).

The s-MRI is potentially a useful method to assess exocrine function by measuring the volume of the secreted fluid. Madzak et al. evaluated s-MRI in patients with CF and healthy patients (mean age 21 years) and found that CF patients with EPI had lower diffusion coefficient before secretin in the pancreatic head and lower secreted bowel fluid volumes ($P = 0.035$) (153). The s-MRI was also studied in pediatric population by Trout et al. who measured the secreted fluid in 50 healthy children and reported an association between the secreted volume and body surface area. They concluded that a secreted volume <43 ml or a secretion rate <2.3 ml/min (5th percentile values) can be considered abnormal in children (154).

Endoscopic ultrasonography (EUS)

Endoscopic ultrasound involves the use of a specialized endoscopic device with ultrasound capability. Given that it is performed during endoscopy, it is considered an invasive technique and it is highly operator dependent (155). It provides highly accurate images of pancreatic ducts and parenchyma. When utilized in children, EUS can be both diagnostic and therapeutic. For example, imaging of the pancreas with EUS followed by an EUS-guided fine needle aspiration or biopsy can be useful in the diagnosis of idiopathic fibrosing pancreatitis or autoimmune pancreatitis (156). Additionally, microlithiasis can be identified by EUS as a possible contributor to acute recurrent pancreatitis in children (156). As a therapeutic modality, it can be used for the internal drainage of pancreatic pseudocysts as a complication of acute pancreatitis.

The role of EUS in evaluating the exocrine function of the pancreas was studied prospectively in 128 adult patients with EUS criteria of chronic pancreatitis and it was compared with the ^{13}C-Mixed triglyceride breath test. They found that diagnosis of EPI increased linearly with the number of EUS criteria, and that the presence of intraductal calcifications, hyperechogenic foci with shadowing, and dilation of the main pancreatic duct were significantly and independently associated with EPI (157).

Conclusions and future directions

In conclusion, accurate assessment of pancreatic function is essential in children with clinical concerns for maldigestion and malabsorption. EPI can be caused by several etiologies including developmental delays in enzyme maturation, isolated deficiencies, genetic disorders, and chronic pancreatitis. These can be easily missed as symptoms of EPI are often non-specific. Therefore, early diagnosis and treatment are important for improved outcomes in children.

Many studies showed that indirect measures of pancreatic function are unable to detect mild and moderate exocrine dysfunctions. Among the indirect non-stimulatory tests, FE-1 is the mostly used and most convenient test but its sensitivity and specificity is low compared with the direct function tests.

Although the Dreiling tube test was considered "the gold standard" for direct pancreatic function testing in the past, it is an unacceptable means of studying pancreatic exocrine function in children. ePFT is now the preferred method as it is technically easy to perform during upper gastrointestinal endoscopy, shorter in duration, and has comparable value with the Dreiling tube method.

The ePFT can be performed when routine endoscopy is obtained for investigation in children who are suspected of having malnutrition secondary to pancreatic exocrine dysfunction. It can detect both isolated and generalized deficiencies even if they are mild or moderate degree deficiencies. Like the "gold standard" Dreiling tube test collection, there is no uniformly accepted protocol for the ePFT. Although based on the pancreatic physiology fluid collection between 4 and 10 min reliable to assess the acinar cell function.

A multicenter study is needed for the standardization of ePFT in large number of children undergoing ePFT utilizing a single and uniform protocol.

Author contributions

All authors equally contributed to the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Fisher WE, Andersen DK, Windsor JA, Saluja AK, Brunicardi FC. Pancreas. In: FC Brunicard, chief editor. *Schwartz principles of surgery*, 10th ed. New York: McGraw Hill Education (2015). Chapter 33.

2. Ballian N, Brunicardi FC. Islet vasculature as a regulator of endocrine pancreas function. *World J Surg.* (2007) 31(4):705–14. doi: 10.1007/s00268-006-0719-8

3. Korc M, Iwamoto Y, Sankaran H, Williams JA, Goldfine ID. Insulin action in pancreatic acini from streptozotocin-treated rats. I. Stimulation of protein synthesis. *Am J Physiol.* (1981) 240(1):G56–62. doi: 10.1152/ajpcell.1981.240.1.C56

4. Sankaran H, Iwamoto Y, Korc M, Williams JA, Goldfine ID. Insulin action in pancreatic acini from streptozotocin-treated rats. II. Binding of 125I-insulin to receptors. *Am J Physiol.* (1981) 240(1):G63–8. doi: 10.1152/ajpgi.1981.240.1.G63

5. Motta PM, Macchiarelli G, Nottola SA, Correr S. Histology of the exocrine pancreas. *Microsc Res Tech.* (1997) 37(5-6):384–98. doi: 10.1002/(SICI)1097-0029(19970601)37:5/6<384::AID-JEMT3>3.0.CO;2-E

6. Beer RL, Parsons MJ, Rovira M. Centroacinar cells: at the center of pancreas regeneration. *Dev Biol.* (2016) 413(1):8–15. doi: 10.1016/j.ydbio.2016.02.027

7. Delaspre F, Beer RL, Rovira M, Huang W, Wang G, Gee S, et al. Centroacinar cells are progenitors that contribute to endocrine pancreas regeneration. *Diabetes.* (2015) 64(10):3499–509. doi: 10.2337/db15-0153

8. O'Konski MS, Pandol SJ. Effects of caerulein on the apical cytoskeleton of the pancreatic acinar cell. *J Clin Invest.* (1990) 86(5):1649–57. doi: 10.1172/JCI114887

9. Konturek JW, Gabryelewicz A, Kulesza E, Konturek SJ, Domschke W. Cholecystokinin (CCK) in the amino acid uptake and enzyme protein secretion by the pancreas in humans. *Int J Pancreatol.* (1995) 17(1):55–61. doi: 10.1007/BF02788359

10. Case RM. Synthesis, intracellular transport and discharge of exportable proteins in the pancreatic acinar cell and other cells. *Biol Rev Camb Philos Soc.* (1978) 53(2):211–354. doi: 10.1111/j.1469-185X.1978.tb01437.x

11. Petersen OH, Tepikin AV. Polarized calcium signaling in exocrine gland cells. *Annu Rev Physiol.* (2008) 70:273–99. doi: 10.1146/annurev.physiol.70.113006.100618

12. Cyriac J, Mahadevan P, Augustine P, Ramesh H, Koshy A. Stellate cell activation in tropical calcific pancreatitis compared to alcoholic pancreatitis, adenocarcinoma of pancreas and Normal pancreas. *JOP.* (2012) 13(4):376–86. doi: 10.6092/1590-8577/552

13. Li J, Chen B, Fellows GF, Goodyer CG, Wang R. Activation of pancreatic stellate cells is beneficial for exocrine but not endocrine cell differentiation in the developing human pancreas. *Front Cell Dev Biol.* (2021) 9:694276. doi: 10.3389/fcell.2021.694276

14. Omary MB, Lugea A, Lowe AW, Pandol SJ. The pancreatic stellate cell: a star on the rise in pancreatic diseases. *J Clin Invest.* (2007) 117(1):50–9. doi: 10.1172/JCI30082

15. Pandol SJ. *The exocrine pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences (2010). Colloquium series on integrated systems physiology: from molecule to function to disease Morgan & Claypool Life Sciences; #14. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54128/ doi: 10.4199/C00026ED1V01Y201102ISP014

16. Brannon PM. Adaptation of the exocrine pancreas to diet. *Annu Rev Nutr.* (1990) 10:85–105. doi: 10.1146/annurev.nu.10.070190.000505

17. Birk RZ, Brannon PM. Regulation of pancreatic lipase by dietary medium chain triglycerides in the weanling rat. *Pediatr Res.* (2004) 55(6):921–6. doi: 10.1203/01.PDR.0000127430.04127.4F

18. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. *J Physiol.* (1902) 28(5):325–53. doi: 10.1113/jphysiol.1902.sp000920

19. Chey WY, Konturek SJ. Plasma secretion and pancreatic secretion in response to liver extract meal with varied pH and exogenous secretin in the dog. *J Physiol.* (1982) 324:263–72. doi: 10.1113/jphysiol.1982.sp014111

20. Steward MC, Ishiguro H, Case RM. Mechanisms of bicarbonate secretion in the pancreatic duct. *Annu Rev Physiol.* (2005) 67:377–409. doi: 10.1146/annurev.physiol.67.031103.153247

21. Ishiguro H, Yamamoto A, Nakakuki M, Yi L, Ishiguro M, Yamaguchi M, et al. Physiology and pathophysiology of bicarbonate secretion by pancreatic duct epithelium. *Nagoya J Med Sci.* (2012) 74(1-2):1–18. PMID: 22515107; PMCID: PMC4831246

22. Stevens T, Parsi MA. Update on endoscopic pancreatic function testing. *World J Gastroenterol.* (2011) 17(35):3957–61. doi: 10.3748/wjg.v17.i35.3957

23. Wu B, Conwell DL. The endoscopic pancreatic function test. *Am J Gastroenterol.* (2009) 104(10):2381–3. doi: 10.1038/ajg.2008.181

24. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med.* (1973) 288(16):813–5. doi: 10.1056/NEJM197304192881603

25. DiMagno MJ, DiMagno EP. Chronic pancreatitis. *Curr Opin Gastroenterol.* (2011) 27(5):452–9. doi: 10.1097/MOG.0b013e328349e333

26. Johnson CD, Devaux MA, Treffot MJ, Sarles H. The cephalogastric phase of the pancreatic response to food in the dog. *Pancreas.* (1991) 6(2):190–6. doi: 10.1097/00006676-199103000-00010

27. Furukawa N, Okada H. Effects of antral distension on pancreatic exocrine secretion in dogs: evidence for a short reflex. *Jpn J Physiol.* (1987) 37(4):671–85. doi: 10.2170/jjphysiol.37.671

28. Spannagel AW, Green GM, Guan D, Liddle RA, Faull K, Reeve Jr JR. Purification and characterization of a luminal cholecystokinin-releasing factor from rat intestinal secretion. *Proc Natl Acad Sci U S A.* (1996) 93(9):4415–20. doi: 10.1073/pnas.93.9.4415

29. Wheeler S, Eardley JE, McNulty KF, Sutcliffe CP, Morrison JD. An investigation into the relative merits of pituitary adenylate cyclase-activating polypeptide (PACAP-27) and vasoactive intestinal polypeptide as vagal neurotransmitters in exocrine pancreas of rats. *Exp Physiol.* (1997) 82(4):729–47. doi: 10.1113/expphysiol.1997.sp004061

30. Chey WY, Chang TM. Neural control of the release and action of secretin. *J Physiol Pharmacol.* (2003) 54(Suppl 4):105–12. PMID: 15075453

31. Gullo L, Biliotti G, Pezzilli R, Di Stefano M, Ancona D. Effect of octreotide (SMS 201-995) on meal-stimulated pancreatic secretion in three patients with external pancreatic fistula. *Am J Gastroenterol.* (1991) 86(7):892–4. PMID: 2058634

32. Gullo L, Pezzilli R, Barbara L. Effect of somatostatin on plasma amino acid uptake by human pancreas. *Gastroenterology.* (1989) 97(3):732–6. doi: 10.1016/0016-5085(89)90645-8

33. Hermon-Taylor J, Perrin J, Grant DA, Appleyard A, Bubel M, Magee AI. Immunofluorescent localisation of enterokinase in human small intestine. *Gut.* (1977) 18(4):259–65. doi: 10.1136/gut.18.4.259

34. Lindquist S, Hernell O. Lipid digestion and absorption in early life: an update. *Curr Opin Clin Nutr Metab Care.* (2010) 13(3):314–20. doi: 10.1097/MCO.0b013e328337bbf0

35. Gullo L. The effect of neurotensin on pure pancreatic secretion in man. *Scand J Gastroenterol.* (1987) 22(3):343–8. doi: 10.3109/00365528709078602

36. Green GM, Lyman RL. Feedback regulation of pancreatic enzyme secretion as a mechanism for trypsin inhibitor-induced hypersecretion in rats. *Proc Soc Exp Biol Med.* (1972) 140(1):6–12. doi: 10.3181/00379727-140-36384

37. Louie DS, May D, Miller P, Owyang C. Cholecystokinin mediates feedback regulation of pancreatic enzyme secretion in rats. *Am J Physiol.* (1986) 250(2 Pt 1):G252–9. doi: 10.1152/ajpgi.1986.250.2.G252

38. Walkowiak J, Witmanowski H, Strzykala K, Bychowiec B, Songin T, Borski K, et al. Inhibition of endogenous pancreatic enzyme secretion by oral pancreatic enzyme treatment. *Eur J Clin Invest.* (2003) 33(1):65–9. doi: 10.1046/j.1365-2362.2003.01077.x

39. Dominguez-Munoz JE, Bregulla M, Nelson DK, Glasbrenner B, Sauerbruch T, Malfertheiner P. Independent cycles of exocrine pancreatic secretion, hormones and gastroduodenal motility in healthy fasting humans: reassessment of a complex partnership. *Neurogastroenterol Motil*. (1998) 10(1):27–34. doi: 10.1046/j.1365-2982.1998.00084.x

40. Zimmerman DW, Sarr MG, Smith CD, Nicholson CP, Dalton RR, Barr D, et al. Cyclic interdigestive pancreatic exocrine secretion: is it mediated by neural or hormonal mechanisms? *Gastroenterology*. (1992) 102(4 Pt 1):1378–84. doi: 10.1016/0016-5085(92)90779-X

41. Anagnostides A, Chadwick VS, Selden AC, Maton PN. Sham feeding and pancreatic secretion. Evidence for direct vagal stimulation of enzyme output. *Gastroenterology*. (1984) 87(1):109–14. doi: 10.1016/0016-5085(84)90132-X

42. Katschinski M, Steinicke C, Reinshagen M, Dahmen G, Beglinger C, Arnold R, et al. Gastrointestinal motor and secretory responses to cholinergic stimulation in humans. Differential modulation by muscarinic and cholecystokinin receptor blockade. *Eur J Clin Invest*. (1995) 25(2):113–22. doi: 10.1111/j.1365-2362.1995.tb01535.x

43. Holst JJ, Knuhtsen S, Nielsen OV. Role of gastrin-releasing peptide in neural control of pancreatic exocrine secretion. *Pancreas*. (1989) 4(5):581–6. doi: 10.1097/00006676-198910000-00009

44. Kreiss C, Schwizer W, Erlacher U, Borovicka J, Lochner-Kuery C, Muller R, et al. Role of antrum in regulation of pancreaticobiliary secretion in humans. *Am J Physiol*. (1996) 270(5 Pt 1):G844–51. doi: 10.1152/ajpgi.1996.270.5.G844

45. Liddle RA, Goldfine ID, Rosen MS, Taplitz RA, Williams JA. Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J Clin Invest*. (1985) 75(4):1144–52. doi: 10.1172/JCI111809

46. Go VL, Hofmann AF, Summerskill WH. Pancreozymin bioassay in man based on pancreatic enzyme secretion: potency of specific amino acids and other digestive products. *J Clin Invest*. (1970) 49(8):1558–64. doi: 10.1172/JCI106373

47. Kaushik N, Pietraszewski M, Holst JJ, O'Keefe SJ. Enteral feeding without pancreatic stimulation. *Pancreas*. (2005) 31(4):353–9. doi: 10.1097/01.mpa.0000183374.11919.e5

48. Adler G, Reinshagen M, Koop I, Goke B, Schafmayer A, Rovati LC, et al. Differential effects of atropine and a cholecystokinin receptor antagonist on pancreatic secretion. *Gastroenterology*. (1989) 96(4):1158–64. doi: 10.1016/0016-5085(89)91636-3

49. Bozkurt T, Adler G, Koop I, Arnold R. Effect of atropine on intestinal phase of pancreatic secretion in man. *Digestion*. (1988) 41(2):108–15. doi: 10.1159/000199739

50. Carrere J, Figarella-Branger D, Senegas-Balas F, Figarella C, Guy-Crotte O. Immunohistochemical study of secretory proteins in the developing human exocrine pancreas. *Differentiation*. (1992) 51(1):55–60. doi: 10.1111/j.1432-0436.1992.tb00680.x

51. Fukayama M, Ogawa M, Hayashi Y, Koike M. Development of human pancreas. Immunohistochemical study of fetal pancreatic secretory proteins. *Differentiation*. (1986) 31(2):127–33. doi: 10.1111/j.1432-0436.1986.tb00393.x

52. Lebenthal E, Lee PC. Development of functional responses in human exocrine pancreas. *Pediatrics*. (1980) 66(4):556–60. doi: 10.1542/peds.66.4.556

53. Hadorn B, Zoppi G, Shmerling DH, Prader A. Quantitative assessment of exocrine pancreatic function in infants and children. *Bibl Paediatr*. (1967) 86:255–8. PMID: 6054636

54. Lonnerdal B. Nutritional and physiologic significance of human milk proteins. *Am J Clin Nutr*. (2003) 77(6):1537S–43S. doi: 10.1093/ajcn/77.6.1537S

55. Freed LM, York CM, Hamosh P, Mehta NR, Hamosh M. Bile salt-stimulated lipase of human milk: characteristics of the enzyme in the milk of mothers of premature and full-term infants. *J Pediatr Gastroenterol Nutr*. (1987) 6(4):598–604. doi: 10.1097/00005176-198707000-00019

56. Figarella C, Negri GA, Sarles H. Presence of colipase in a congenital pancreatic lipase deficiency. *Biochim Biophys Acta*. (1972) 280(1):205–11. doi: 10.1016/0005-2760(72)90227-5

57. Figarella C, De Caro A, Leupold D, Poley JR. Congenital pancreatic lipase deficiency. *J Pediatr*. (1980) 96(3 Pt 1):412–6. doi: 10.1016/S0022-3476(80)80683-4

58. Hildebrand H, Borgstrom B, Bekassy A, Erlanson-Albertsson C, Helin I. Isolated co-lipase deficiency in two brothers. *Gut*. (1982) 23(3):243–6. doi: 10.1136/gut.23.3.243

59. Behar DM, Basel-Vanagaite L, Glaser F, Kaplan M, Tzur S, Magal N, et al. Identification of a novel mutation in the PNLIP gene in two brothers with congenital pancreatic lipase deficiency. *J Lipid Res*. (2014) 55(2):307–12. doi: 10.1194/jlr.P041103

60. Ligumsky M, Granot E, Branski D, Stankiewicz H, Goldstein R. Isolated lipase and colipase deficiency in two brothers. *Gut*. (1990) 31(12):1416–8. doi: 10.1136/gut.31.12.1416

61. Muller DP, McCollum JP, Trompeter RS, Harries JT. Proceedings: studies on the mechanism of fat absorption in congenital isolated lipase deficiency. *Gut*. (1975) 16(10):838. PMID: 1205319

62. Sheldon W. Congenital pancreatic lipase deficiency. *Arch Dis Child*. (1964) 39:268–71. doi: 10.1136/adc.39.205.268

63. Hopson P, Patel S, Bornstein J, Mehta D, Horvath K. Isolated amylase deficiency in children and its clinical implication. *J Pediatr Gastroenterol Nutr*. (2019) 68(6):854–60. doi: 10.1097/MPG.0000000000002317

64. Mehta DI, Wang HH, Akins RE, Wang L, Proujansky R. Isolated pancreatic amylase deficiency: probable error in maturation. *J Pediatr*. (2000) 136(6):844–6. doi: 10.1016/S0022-3476(00)96936-1

65. Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut*. (1996) 39(4):580–6. doi: 10.1136/gut.39.4.580

66. Sziegoleit A, Krause E, Klor HU, Kanacher L, Linder D. Elastase 1 and chymotrypsin B in pancreatic juice and feces. *Clin Biochem*. (1989) 22(2):85–9. doi: 10.1016/S0009-9120(89)80003-7

67. Katschinski M, Schirra J, Bross A, Goke B, Arnold R. Duodenal secretion and fecal excretion of pancreatic elastase-1 in healthy humans and patients with chronic pancreatitis. *Pancreas*. (1997) 15(2):191–200. doi: 10.1097/00006676-199708000-00012

68. Walkowiak J, Lisowska A, Przyslawski J, Grzymislawski M, Krawczynski M, Herzig KH. Faecal elastase-1 test is superior to faecal lipase test in the assessment of exocrine pancreatic function in cystic fibrosis. *Acta Paediatr*. (2004) 93(8):1042–5. doi: 10.1111/j.1651-2227.2004.tb02715.x

69. Philippe MF, Benabadji S, Barbot-Trystram L, Vadrot D, Boitard C, Larger E. Pancreatic volume and endocrine and exocrine functions in patients with diabetes. *Pancreas*. (2011) 40(3):359–63. doi: 10.1097/MPA.0b013e3182072032

70. Carroccio A, Verghi F, Santini B, Lucidi V, Iacono G, Cavataio F, et al. Diagnostic accuracy of fecal elastase 1 assay in patients with pancreatic maldigestion or intestinal malabsorption: a collaborative study of the Italian society of pediatric gastroenterology and hepatology. *Dig Dis Sci*. (2001) 46(6):1335–42. doi: 10.1023/A:1010687918252

71. Walkowiak J, Sands D, Nowakowska A, Piotrowski R, Zybert K, Herzig KH, et al. Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations. *J Pediatr Gastroenterol Nutr*. (2005) 40(2):199–201. doi: 10.1097/00005176-200502000-00022

72. Khan A, Vege SS, Dudeja V, Chari ST. Staging exocrine pancreatic dysfunction. *Pancreatology*. (2022) 22(1):168–72. doi: 10.1016/j.pan.2021.11.005

73. Fischer B, Hoh S, Wehler M, Hahn EG, Schneider HT. Faecal elastase-1: lyophilization of stool samples prevents false low results in diarrhoea. *Scand J Gastroenterol*. (2001) 36(7):771–4. doi: 10.1080/003655201300192058

74. Walkowiak J, Madry E, Lisowska A, Szaflarska-Poplawska A, Grzymislawski M, Stankowiak-Kulpa H, et al. Adaptive changes of pancreatic protease secretion to a short-term vegan diet: influence of reduced intake and modification of protein. *Br J Nutr*. (2012) 107(2):272–6. doi: 10.1017/S0007114511002923

75. Phillips IJ, Rowe DJ, Dewar P, Connett GJ. Faecal elastase 1: a marker of exocrine pancreatic insufficiency in cystic fibrosis. *Ann Clin Biochem*. (1999) 36(Pt 6):739–42. doi: 10.1177/000456329903600606

76. Walkowiak J, Cichy WK, Herzig KH. Comparison of fecal elastase-1 determination with the secretin-cholecystokinin test in patients with cystic fibrosis. *Scand J Gastroenterol*. (1999) 34(2):202–7. doi: 10.1080/00365529950173104

77. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2018) 16(8):1220–8.e4. doi: 10.1016/j.cgh.2018.01.027

78. Wali PD, Loveridge-Lenza B, He Z, Horvath K. Comparison of fecal elastase-1 and pancreatic function testing in children. *J Pediatr Gastroenterol Nutr*. (2012) 54(2):277–80. doi: 10.1097/MPG.0b013e31820b0227

79. Fine KD, Fordtran JS. The effect of diarrhea on fecal fat excretion. *Gastroenterology*. (1992) 102(6):1936–9. doi: 10.1016/0016-5085(92)90316-Q

80. Glasgow JF, Hamilton JR, Sass-Kortsak A. Fat absorption in congenital obstructive liver disease. *Arch Dis Child*. (1973) 48(8):601–7. doi: 10.1136/adc.48.8.601

81. Littlewood JM, Wolfe SP. Control of malabsorption in cystic fibrosis. *Paediatr Drugs*. (2000) 2(3):205–22. doi: 10.2165/00128072-200002030-00005

82. Gaskin KJ, Durie PR, Lee L, Hill R, Forstner GG. Colipase and lipase secretion in childhood-onset pancreatic insufficiency. Delineation of patients with steatorrhea secondary to relative colipase deficiency. *Gastroenterology*. (1984) 86(1):1–7. doi: 10.1016/0016-5085(84)90582-1

83. Thompson JB, Su CK, Ringrose RE, Welsh JD. Fecal triglycerides. II. Digestive versus absorptive steatorrhea. *J Lab Clin Med*. (1969) 73(3):521–30. PMID: 5766197

84. Caras S, Boyd D, Zipfel L, Sander-Struckmeier S. Evaluation of stool collections to measure efficacy of PERT in subjects with exocrine pancreatic insufficiency. *J Pediatr Gastroenterol Nutr*. (2011) 53(6):634–40. doi: 10.1097/MPG.0b013e3182281c38

85. Fomon SJ, Ziegler EE, Thomas LN, Jensen RL, Filer Jr LJ. Excretion of fat by Normal full-term infants fed various milks and formulas. *Am J Clin Nutr*. (1970) 23(10):1299–313. doi: 10.1093/ajcn/23.10.1299

86. Rings EH, Minich DM, Vonk RJ, Stellaard F, Fetter WP, Verkade HJ. Functional development of fat absorption in term and preterm neonates strongly correlates with ability to absorb long-chain fatty acids from intestinal lumen. *Pediatr Res*. (2002) 51(1):57–63. doi: 10.1203/00006450-200201000-00011

87. Koumantakis G, Radcliff FJ. Estimating fat in feces by near-infrared reflectance spectroscopy. *Clin Chem*. (1987) 33(4):502–6. doi: 10.1093/clinchem/33.4.502

88. Stein J, Purschian B, Zeuzem S, Lembcke B, Caspary WF. Quantification of fecal carbohydrates by near-infrared reflectance analysis. *Clin Chem*. (1996) 42 (2):309–12. doi: 10.1093/clinchem/42.2.309

89. Drummey GD, Benson Jr JA, Jones CM. Microscopical examination of the stool for steatorrhea. *N Engl J Med*. (1961) 264:85–7. doi: 10.1056/NEJM196101122640207

90. Erchinger F, Engjom T, Jurmy P, Tjora E, Gilja OH, Dimcevski G. Fecal fat analyses in chronic pancreatitis importance of fat ingestion before stool collection. *PLoS One*. (2017) 12(1):e0169993. doi: 10.1371/journal.pone.0169993

91. Phuapradit P, Narang A, Mendonca P, Harris DA, Baum JD. The steatocrit: a simple method for estimating stool fat content in newborn infants. *Arch Dis Child*. (1981) 56(9):725–7. doi: 10.1136/adc.56.9.725

92. Tran M, Forget P, Van den Neucker A, Strik J, van Kreel B, Kuijten R. The acid steatocrit: a much improved method. *J Pediatr Gastroenterol Nutr*. (1994) 19 (3):299–303. doi: 10.1097/00005176-199410000-00007

93. Kaspar P, Moller G, Wahlefeld A. New photometric assay for chymotrypsin in stool. *Clin Chem*. (1984) 30(11):1753–7. doi: 10.1093/clinchem/30.11.1753

94. Stein J, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. *Clin Chem*. (1996) 42(2):222–6. doi: 10.1093/clinchem/42.2.222

95. Loser C, Brauer C, Aygen S, Hennemann O, Folsch UR. Comparative clinical evaluation of the 13C-mixed triglyceride breath test as an indirect pancreatic function test. *Scand J Gastroenterol*. (1998) 33(3):327–34. doi: 10.1080/00365529850170946

96. Boyd EJ, Cumming JG, Cuschieri A, Wood RA, Wormsley KG. Prospective comparison of the fluorescein-dilaurate test with the secretin-cholecystokinin test for pancreatic exocrine function. *J Clin Pathol*. (1982) 35(11):1240–3. doi: 10.1136/jcp.35.11.1240

97. Malfertheiner P, Buchler M, Muller A, Ditschuneit H. The fluorescein dilaurate serum test following metoclopramide and secretin stimulation for evaluating pancreatic function. Contribution to the diagnosis of chronic pancreatitis. *Z Gastroenterol*. (1987) 25(4):225–32. PMID: 3590900

98. Green MR, Austin S, Weaver LT. Dual marker one day pancreolauryl test. *Arch Dis Child*. (1993) 68(5):649–52. doi: 10.1136/adc.68.5.649

99. Elphick DA, Kapur K. Comparing the urinary pancreolauryl ratio and faecal elastase-1 as indicators of pancreatic insufficiency in clinical practice. *Pancreatology*. (2005) 5(2-3):196–200. doi: 10.1159/000085271

100. Moore DJ, Forstner GG, Largman C, Cleghorn GJ, Wong SS, Durie PR. Serum immunoreactive cationic trypsinogen: a useful indicator of severe exocrine dysfunction in the paediatric patient without cystic fibrosis. *Gut*. (1986) 27(11):1362–8. doi: 10.1136/gut.27.11.1362

101. Durie PR, Forstner GG, Gaskin KJ, Moore DJ, Cleghorn GJ, Wong SS, et al. Age-related alterations of immunoreactive pancreatic cationic trypsinogen in sera from cystic fibrosis patients with and without pancreatic insufficiency. *Pediatr Res*. (1986) 20(3):209–13. doi: 10.1203/00006450-198603000-00002

102. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. (2013) 19(42):7258–66. doi: 10.3748/wjg.v19.i42.7258

103. Nakamura T, Takebe K, Imamura K, Tando Y, Yamada N, Arai Y, et al. Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). *Acta Gastroenterol Belg*. (1996) 59(1):10–4. PMID: 8686411

104. Dutta SK, Bustin MP, Russell RM, Costa BS. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. *Ann Intern Med*. (1982) 97(4):549–52. doi: 10.7326/0003-4819-97-4-549

105. Lindkvist B, Dominguez-Munoz JE, Luaces-Regueira M, Castineiras-Alvarino M, Nieto-Garcia L, Iglesias-Garcia J. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology*. (2012) 12(4):305–10. doi: 10.1016/j.pan.2012.04.006

106. Weaver LT, Amarri S, Swart GR. 13C Mixed triglyceride breath test. *Gut*. (1998) 43(Suppl 3):S13–9. doi: 10.1136/gut.43.2008.S13

107. Vantrappen GR, Rutgeerts PJ, Ghoos YF, Hiele MI. Mixed triglyceride breath test: a noninvasive test of pancreatic lipase activity in the duodenum. *Gastroenterology*. (1989) 96(4):1126–34. doi: 10.1016/0016-5085(89)91632-6

108. Kalivianakis M, Verkade HJ, Stellaard F, van der Were M, Elzinga H, Vonk RJ. The 13C-mixed triglyceride breath test in healthy adults: determinants of the 13CO2 response. *Eur J Clin Invest*. (1997) 27(5):434–42. doi: 10.1046/j.1365-2362.1997.1310678.x

109. Kalivianakis M, Minich DM, Bijleveld CM, van Aalderen WM, Stellaard F, Laseur M, et al. Fat malabsorption in cystic fibrosis patients receiving enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids. *Am J Clin Nutr*. (1999) 69(1):127–34. doi: 10.1093/ajcn/69.1.127

110. Kalivianakis M, Elstrodt J, Havinga R, Kuipers F, Stellaard F, Sauer PJ, et al. Validation in an animal model of the carbon 13-labeled mixed triglyceride breath test for the detection of intestinal fat malabsorption. *J Pediatr*. (1999) 135 (4):444–50. doi: 10.1016/S0022-3476(99)70166-6

111. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol*. (2011) 26(Suppl 2):12–6. doi: 10.1111/j.1440-1746.2010.06600.x

112. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. *Best Pract Res Clin Gastroenterol*. (2010) 24(3):337–47. doi: 10.1016/j.bpg.2010.03.006

113. van Dijk-van Aalst K, Van Den Driessche M, van Der Schoor S, Schiffelers S, van't Westeinde T, Ghoos Y, et al. 13C Mixed triglyceride breath test: a noninvasive method to assess lipase activity in children. *J Pediatr Gastroenterol Nutr*. (2001) 32(5):579–85. doi: 10.1097/00005176-200105000-00017

114. Amarri S, Harding M, Coward WA, Evans TJ, Weaver LT. 13Carbon Mixed triglyceride breath test and pancreatic enzyme supplementation in cystic fibrosis. *Arch Dis Child*. (1997) 76(4):349–51. doi: 10.1136/adc.76.4.349

115. Dreiling DA, Hollander F. Studies in pancreatic function; preliminary series of clinical studies with the secretin test. *Gastroenterology*. (1948) 11(5):714–29. PMID: 18100241

116. Bornman PC, Botha JF, Ramos JM, Smith MD, Van der Merwe S, Watermeyer GA, et al. Guideline for the diagnosis and treatment of chronic pancreatitis. *S Afr Med J*. (2010) 100(12 Pt 2):845–60. doi: 10.7196/SAMJ.4530

117. Conwell DL, Banks PA. Chronic pancreatitis. *Curr Opin Gastroenterol*. (2008) 24(5):586–90. doi: 10.1097/MOG.0b013e32830b10fb

118. Dominguez Munoz JE. Diagnosis of chronic pancreatitis: functional testing. *Best Pract Res Clin Gastroenterol*. (2010) 24(3):233–41. doi: 10.1016/j.bpg.2010.03.008

119. Keller J, Aghdassi AA, Lerch MM, Mayerle JV, Layer P. Tests of pancreatic exocrine function - clinical significance in pancreatic and non-pancreatic disorders. *Best Pract Res Clin Gastroenterol*. (2009) 23(3):425–39. doi: 10.1016/j.bpg.2009.02.013

120. Lankisch PG. Function tests in the diagnosis of chronic pancreatitis. Critical evaluation. *Int J Pancreatol*. (1993) 14(1):9–20. doi: 10.1007/BF02795225

121. Lieb 2nd JG, Draganov PV. Pancreatic function testing: here to stay for the 21st century. *World J Gastroenterol*. (2008) 14(20):3149–58. doi: 10.3748/wjg.14.3149

122. Sternby B, Nilsson A, Melin T, Borgstrom B. Pancreatic lipolytic enzymes in human duodenal contents. Radioimmunoassay compared with enzyme activity. *Scand J Gastroenterol*. (1991) 26(8):859–66. doi: 10.3109/00365529109037023

123. Conwell DL, Zuccaro Jr. G, Vargo JJ, Morrow JB, Obuchowski N, Dumot JA, et al. An endoscopic pancreatic function test with cholecystokinin-octapeptide for the diagnosis of chronic pancreatitis. *Clin Gastroenterol Hepatol*. (2003) 1 (3):189–94. doi: 10.1016/S1542-3565(03)70035-4

124. Carroccio A, Iacono G, Montalto G, Cavataio F, Di Marco C, Balsamo V, et al. Exocrine pancreatic function in children with coeliac disease before and after a gluten free diet. *Gut*. (1991) 32(7):796–9. doi: 10.1136/gut.32.7.796

125. Horvath K, Mehta DI, Hill ID. Assessment of exocrine pancreatic function during endoscopy in children. *J Pediatr Gastroenterol Nutr*. (2019) 68(6):768–76. doi: 10.1097/MPG.0000000000002230

126. Lundh G. Pancreatic exocrine function in neoplastic and inflammatory disease; a simple and reliable new test. *Gastroenterology*. (1962) 42:275–80. doi: 10.1016/S0016-5085(62)80025-0

127. Barbezat GO, Hansen JD. The exocrine pancreas and protein-calorie malnutrition. *Pediatrics*. (1968) 42(1):77–92. doi: 10.1542/peds.42.1.77

128. Jensen NM, Larsen S. A rapid, endoscopic exocrine pancreatic function test and the lundh test: a comparative study. *Pancreatology*. (2008) 8(6):617–24. doi: 10.1159/000161013

129. Del Rosario MA, Fitzgerald JF, Gupta SK, Croffie JM. Direct measurement of pancreatic enzymes after stimulation with secretin versus secretin plus cholecystokinin. *J Pediatr Gastroenterol Nutr*. (2000) 31(1):28–32. doi: 10.1097/00005176-200007000-00008

130. Gabert VM, Jensen MS. A comparison of two methods to measure amylase, lipase, trypsin, and chymotrypsin activity and the effect of freezing and thawing on enzyme activities in pancreatic juice. *Pancreas*. (1997) 15(2):183–90. doi: 10.1097/00006676-199708000-00011

131. Xiao Z, Lopez R, Parsi MA, Dodig M, Stevens T. Comparison of autoanalyzer and back titration for measurement of bicarbonate concentration in endoscopically collected pancreatic fluid. *Pancreas*. (2011) 40(2):237–41. doi: 10.1097/MPA.0b013e3181f82aa3

132. Denyer ME, Cotton PB. Pure pancreatic juice studies in Normal subjects and patients with chronic pancreatitis. *Gut*. (1979) 20(2):89–97. doi: 10.1136/gut.20.2.89

133. Madrazo-de la Garza JA, Gotthold M, Lu RB, Hill ID, Lebenthal E. A new direct pancreatic function test in pediatrics. *J Pediatr Gastroenterol Nutr*. (1991) 12 (3):356–60. doi: 10.1097/00005176-199104000-00012

134. Engjom T, Erchinger F, Laerum BN, Tjora E, Aksnes L, Gilja OH, et al. Diagnostic accuracy of a short endoscopic secretin test in patients with cystic fibrosis. *Pancreas*. (2015) 44(8):1266–72. doi: 10.1097/MPA.0000000000000425

135. Pfefferkorn MD, Fitzgerald JF, Croffie JM, Gupta SK, Caffrey HM. Direct measurement of pancreatic enzymes: a comparison of secretagogues. *Dig Dis Sci*. (2002) 47(10):2211–6. doi: 10.1023/A:1020127025489

136. Regan PT, Go VL, DiMagno EP. Comparison of the effects of cholecystokinin and cholecystokinin octapeptide on pancreatic secretion, gallbladder contraction, and plasma pancreatic polypeptide in man. *J Lab Clin Med*. (1980) 96(4):743–8. PMID: 7419959

137. Conwell DL, Zuccaro G, Morrow JB, Van Lente F, O'Laughlin C, Vargo JJ, et al. Analysis of duodenal drainage fluid after cholecystokinin (CCK) stimulation in healthy volunteers. *Pancreas*. (2002) 25(4):350–4. doi: 10.1097/00006676-200211000-00005

138. Liddle RA. Regulation of pancreatic secretion. In: LR Johnson, editors. *Physiology of the gastrointestinal tract*. 4th ed. Elsevier Academic Press (2006). Chapter 55. p. 1397–436.

139. Schibli S, Corey M, Gaskin KJ, Ellis L, Durie PR. Towards the ideal quantitative pancreatic function test: analysis of test variables that influence validity. *Clin Gastroenterol Hepatol*. (2006) 4(1):90–7. doi: 10.1016/S1542-3565(05)00852-9

140. Stevens T, Conwell DL, Zuccaro G, Van Lente F, Khandwala F, Purich E, et al. Electrolyte composition of endoscopically collected duodenal drainage fluid after synthetic porcine secretin stimulation in healthy subjects. *Gastrointest Endosc*. (2004) 60(3):351–5. doi: 10.1016/S0016-5107(04)01809-7

141. Forsmark CE. The early diagnosis of chronic pancreatitis. *Clin Gastroenterol Hepatol*. (2008) 6(12):1291–3. doi: 10.1016/j.cgh.2008.08.008

142. Pollack BJ, Grendell JH. Where have all the dreiling tubes gone? *Am J Gastroenterol*. (2006) 101(2):356–9. doi: 10.1111/j.1572-0241.2006.00398.x

143. Patel N, Sellers ZM, Grover A, Liu QY, Maqbool A, Morinville VD, et al. Endoscopic pancreatic function testing (ePFT) in children: a position paper from the NASPGHAN pancreas committee. *J Pediatr Gastroenterol Nutr*. (2021) 72 (1):144–50. doi: 10.1097/MPG.0000000000002931

144. Alfaro Cruz L, Parniczky A, Mayhew A, Hornung LN, Lin TK, Palermo JJ, et al. Utility of direct pancreatic function testing in children. *Pancreas*. (2017) 46 (2):177–82. doi: 10.1097/MPA.0000000000000724

145. Mehta DI, He Z, Bornstein J, Molle-Rios Z, Conwell DL, Horvath K. Report on the short endoscopic exocrine pancreatic function test in children and young adults. *Pancreas*. (2020) 49(5):642–9. doi: 10.1097/MPA.0000000000001540

146. Law R, Lopez R, Costanzo A, Parsi MA, Stevens T. Endoscopic pancreatic function test using combined secretin and cholecystokinin stimulation for the evaluation of chronic pancreatitis. *Gastrointest Endosc*. (2012) 75(4):764–8. doi: 10.1016/j.gie.2011.11.011

147. Taylor CJ, Chen K, Horvath K, Hughes D, Lowe ME, Mehta D, et al. ESPGHAN And NASPGHAN report on the assessment of exocrine pancreatic function and pancreatitis in children. *J Pediatr Gastroenterol Nutr*. (2015) 61 (1):144–53. doi: 10.1097/MPG.0000000000000830

148. Pelley JR, Gordon SR, Gardner TB. Abnormal duodenal [HCO3-] following secretin stimulation develops sooner than endocrine insufficiency in minimal change chronic pancreatitis. *Pancreas*. (2012) 41(3):481–4. doi: 10.1097/MPA.0b013e31823a4c33

149. Chinnakotla S, Bellin MD, Schwarzenberg SJ, Radosevich DM, Cook M, Dunn TB, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. *Ann Surg*. (2014) 260(1):56–64. doi: 10.1097/SLA.0000000000000569

150. Nydegger A, Couper RT, Oliver MR. Childhood pancreatitis. *J Gastroenterol Hepatol*. (2006) 21(3):499–509. doi: 10.1111/j.1440-1746.2006.04246.x

151. Tipnis NA, Werlin SL. The use of magnetic resonance cholangiopancreatography in children. *Curr Gastroenterol Rep*. (2007) 9 (3):225–9. doi: 10.1007/s11894-007-0023-2

152. Manfredi R, Lucidi V, Gui B, Brizi MG, Vecchioli A, Maresca G, et al. Idiopathic chronic pancreatitis in children: mR cholangiopancreatography after secretin administration. *Radiology*. (2002) 224(3):675–82. doi: 10.1148/radiol.2243011085

153. Madzak A, Engjom T, Wathle GK, Olesen SS, Tjora E, Njolstad PR, et al. Secretin-stimulated MRI assessment of exocrine pancreatic function in patients with cystic fibrosis and healthy controls. *Abdom Radiol (NY)*. (2017) 42 (3):890–9. doi: 10.1007/s00261-016-0972-8

154. Trout AT, Serai SD, Fei L, Sun Q, Abu-El-Haija M. Prospective assessment of Normal pancreatic secretory function measured by MRI in a cohort of healthy children. *Am J Gastroenterol*. (2018) 113(9):1385. doi: 10.1038/s41395-018-0190-9

155. Darge K, Anupindi S. Pancreatitis and the role of US, MRCP and ERCP. *Pediatr Radiol*. (2009) 39(Suppl 2):S153–7. doi: 10.1007/s00247-009-1145-5

156. Neff LP, Mishra G, Fortunato JE, Laudadio J, Petty JK. Microlithiasis, endoscopic ultrasound, and children: not just little gallstones in little adults. *J Pediatr Surg*. (2011) 46(3):462–6. doi: 10.1016/j.jpedsurg.2010.09.007

157. Dominguez-Munoz JE, Alvarez-Castro A, Larino-Noia J, Nieto L, Iglesias-Garcia J. Endoscopic ultrasonography of the pancreas as an indirect method to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. *Pancreas*. (2012) 41(5):724–8. doi: 10.1097/MPA.0b013e31823b5978

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Solid pancreatic masses in children: A review of current evidence and clinical challenges

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Pancreatic tumors in children are infrequently encountered in clinical practice. Their non-specific clinical presentation and overlapping imaging characteristics often make an accurate preoperative diagnosis difficult. Tumors are categorized as epithelial or non-epithelial, with epithelial tumors further classified as tumors of the exocrine or endocrine pancreas. Although both are tumors of the exocrine pancreas, solid pseudopapillary neoplasm is the most prevalent solid pancreatic tumor in children, while pancreatoblastoma is the most common malignant tumor. Insulinoma is the most common pediatric pancreatic tumor of the endocrine pancreas. Malignant tumors require a complete, often radical, surgical resection. However, pancreatic parenchyma-sparing surgical procedures are utilized for benign tumors and low-grade malignancy to preserve gland function. This review will discuss the epidemiology, pathophysiology, clinical and diagnostic characteristics, and management options associated with both common and rare solid pancreatic masses in children. We will also discuss current challenges encountered in their evaluation and treatment.

KEYWORDS

pancreas, pediatrics, child, neoplasms, general surgery, surgical oncology

Introduction

Pancreatic tumors are rare in children. An age-adjusted annual incidence of 0.19 cases per million pediatric population has been estimated in North America (1). Research and evidence-based protocols are, therefore, limited. Often, pediatric pancreatic tumors are difficult to differentiate due to their overlap in non-specific clinical presentation and diagnostic imaging characteristics. In general, pancreatic tumors most commonly diagnosed in children tend to be well-circumscribed lesions without invasiveness. Additionally, in contrast to adults, children and adolescents with malignant pancreatic tumors tend to have disease which is amenable to surgical resection and longer expected survival.

According to the 2019 World Health Organization (WHO) definition, pancreatic tumors can be divided into three categories including benign epithelial tumors, malignant epithelial tumors, and neuroendocrine tumors, with an additional group of rare non-epithelial tumors (2). Epithelial tumors may also be categorized as tumors of the exocrine or endocrine pancreas, with exocrine tumors being of acinar, ductal, or unknown cell origin (3) (**Table 1**). This review discusses the epidemiology, pathophysiology, clinical and diagnostic characteristics, and management options associated with solid pancreatic masses in the pediatric population. We also discuss the challenge of differentiating autoimmune pancreatitis from pancreatic malignancy, as well as the approach to parenchyma preservation during resection of pancreatic masses.

Pancreatoblastoma

Epidemiology

The most common malignant pancreatic neoplasm in children is pancreatoblastoma (PBL), which accounts for 25% of solid pancreatic masses in the first 10 years of life (4). Nonetheless, PBLs are rare with a recent systematic review identifying 81 pediatric cases since 1980 (5). PBLs are typically diagnosed in the first decade of life, with the median age being 4–5 years old (3, 6–8), although there are several cases reported in older children and adults (9–12). Boys are more affected than girls.(3, 8, 13, 14). PBL has been shown to have an association with Beckwith-Wiedemann syndrome, with a prevalence up to 50% in patients diagnosed (15, 16). One case has also been reported with concurrent familial adenomatous polyposis (FAP) (15, 17). PBL is an embryonal tumor originating from pluripotent pancreatic stem cells during the gestational development of foregut structures (7, 18–20). Its molecular pathogenesis has similarities to that of hepatoblastoma, with abnormalities in the adenomatous polyposis coli (APC)/beta-catenin pathway and chromosome 11p. This may explain its reported association with FAP and suggests that PBL could be an extracolonic manifestation of the disease (15–17).

Gross pathology and histology

Tumors are generally located in the head or body of the pancreas (5, 15). They are soft, circumscribed, and large (5 cm–20 cm in size). They are also frequently either partially or fully encapsulated. On cut surface, lesions are tan, lobulated, and separated by thick fibrous bands with associated hemorrhage and necrosis. Cystic changes may be appreciated, especially in patients with Beckwith-Wiedemann syndrome, in which specimens are often completely cystic (3, 15). PBLs are acinar neoplasms, and their microscopic features consist mostly of epithelial monomorphic polygonal cells arranged in a solid, trabecular, or acinar pattern with frequent mitoses. Squamoid nests or corpuscles are characteristic and may be scattered throughout the tumor, however, these features may not be identified on a small biopsy. Squamous corpuscles are characterized by clusters of polygonal cells or whorled spindle cells, with or without central keratinization and expression of epithelial membrane antigen and LEF1 on immunohistochemical staining (3, 8, 15, 21–23) (**Figures 1A,B**). PBL demonstrates positive immunostaining for markers of acinar differentiation such as trypsin, chymotrypsin, and Bcl10, though positivity for neuroendocrine markers, such as chromogranin and synaptophysin, and alpha-fetoprotein (AFP)-positive cells have also been identified (15, 21). Beta-catenin staining may also be noted, predominantly within squamoid corpuscles and in a subset of background neoplastic cells. If present, stroma is often hypercellular, containing spindle-shaped cells (8, 15).

Clinical presentation and imaging characteristics

Patients with PBL are usually asymptomatic but will have a large palpable abdominal mass (3, 24–26). When present, symptoms are non-specific and include abdominal pain, anorexia, weight loss, vomiting, diarrhea, and fatigue (3, 7, 24, 25). Jaundice is usually not present (3, 7). AFP levels are a reliable tumor marker in 70%–80% of patients and has been shown to correlate with tumor size (5, 8, 15, 18). When elevated, serum AFP may be used in disease surveillance due to evidence of its reduction after treatment and elevation in disease recurrence (18, 27, 28).

PBL may be large on presentation, making it difficult to identify its origin within the pancreas. It may appear to compress nearby structures, and local invasion may not be identified until operation. Due to the soft nature of the tumor, biliary compression is rare, though reports of arterial encasement have been published. Locoregional assessment is performed using ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). An abdominal US is often the first modality performed in patients with non-specific symptoms and typically demonstrates a large, solitary lesion with mixed echogenicity and multiple lobulations of solid and cystic components. Cyst-dominant tumors will be more hypoechoic with hyperechoic septae (8, 16). Ultrasound is not adequate to assess the locoregional extent of disease. For this, CT or MRI are required. On multi-phase CT imaging, PBL will demonstrate heterogeneous enhancement, specifically in the septae, as well as both solid and cystic components. Calcifications may also be present in clusters or in a curvilinear distribution. On MRI, T1-weighted imaging characteristically demonstrates a well-circumscribed mass with

TABLE 1 Solid pancreatic tumors diagnosed in children with associated clinical characteristics.

Tumor type	Cell origin; category	Mean age of children affected (years)	Size at diagnosis (cm)	Overall Prognosis
Epithelial tumors				
Acinar cell carcinoma	Acinar cell; exocrine	Rare	10–11	5-year survival rates of up to 50% for localized disease with R0 resection
Pancreatic ductal adenocarcinoma	Ductal cell; exocrine	Rare; 1% occur in patients under 20	2–3	15-year survival rate of 23% in children
Pancreatic neuroendocrine tumor *Insulinoma most common*	Endocrine cell (*beta cell); endocrine	*4.9% found in children 10–19; 0.9% found in children 0–9	*∼2 cm	15-year survival rates of 50% across pancreatic neuroendocrine tumors overall
Pancreatoblastoma	Acinar cell; exocrine	4–5	5–20	5-year overall survival rates >70% with R0 resection and no metastatic disease
Solid pseudopapillary neoplasm	Unknown; exocrine	13–14	5–7 (range <0.5–20)	10-year survival rates >95% with R0 resection even in presence of metastatic disease
Non-epithelial tumors				
Dermoid cyst		Rare	8–12	Benign; good prognosis
Inflammatory myofibroblastic tumor		Rare (range 6 months – 15 years)	1.5–15	Good; low-grade malignancy with no recurrences after complete surgical resection
Kaposiform Hemangioendothelioma		Infancy and early childhood	>8 with KMP	Mortality rate 12%–24%; often with KMP
Lymphatic malformation		Rare	3–20	Benign; good prognosis
Pancreatic Ewing sarcoma		18.2 (range 2–37)	3.2–22	Overall (pancreatic and extra-pancreatic) 5-year survival of 55%–65% with localized disease and multimodal approach
Pancreatic primary lymphoma		10.3 (range 3–16)	5–6	Good; 15 patients - all alive after 56 months follow-up with IC and/or surgery

KMP, Kasabach-Merritt phenomenon; IC: immunochemotherapy.
*Statistics for insulinoma.

low-intermediate signal intensity, while T2-weighted imaging demonstrates necrotic and hemorrhagic components with high signal intensity (3, 8) (**Figure 2**). Endoscopic ultrasound (EUS) can be used to further characterize the tumor, evaluate vascular components, and obtain tissue for diagnostic purposes.

When PBL is locally invasive, it appears as a mass with poorly circumscribed borders and may occupy peripancreatic tissues or adjacent organs. There are also limited reports of biliary and vascular invasion (8, 24). Metastasis on initial evaluation has been reported in 17%–35% of patients, with lymph nodes and liver being the most common locations (7, 29). To assess for metastatic disease, cross-sectional imaging of the abdomen with contrast-enhanced CT and/or MRI are necessary in addition to a chest CT (16).

Due to the lack of a specific staging system for PBL, an evidence-based classification has been suggested by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) group (16). The system, which is based on clinical and pathologic features, was created using the results of initial operation among 20 children with PBL from 2000 through 2009 in Italy, France, Germany, Great Britain, and Poland. Stage I is compatible with a completely excised tumor and an R0 resection with no evidence of pathologic lymph nodes. Stage II includes grossly resected tumors with suspected residual (R1) disease or completely resected tumors (R0) with positive lymph node(s) also completely resected. Stage III tumors are resected or biopsied with gross residual disease (R2) regardless of lymph node status. Lastly, stage IV indicates presence of metastatic disease (16, 18).

Treatment

The most effective and mainstay treatment of PBL is complete surgical resection. It is also the most important prognostic factor, with 5-year overall survival rates of >70% reported in patients without metastases who underwent R0 resection (6, 18). In 81 pediatric cases of PBL, most patients underwent pancreaticoduodenectomy (PD; Whipple procedure) (44.1%), followed by spleen-preserving distal pancreatectomy (DP) (26.5%), central pancreatectomy (11.8%), tumor enucleation (11.8%), and DP with splenectomy (5.8%) (5). Neoadjuvant chemotherapy may be required in cases of metastases or local invasion to allow for complete surgical resection. Often, after establishing a tissue-confirmed diagnosis of PBL, cisplatin and doxorubicin are administered for 4–6 cycles (6, 8, 18, 30). Although substantial tumor regression has been reported in 50%–73%

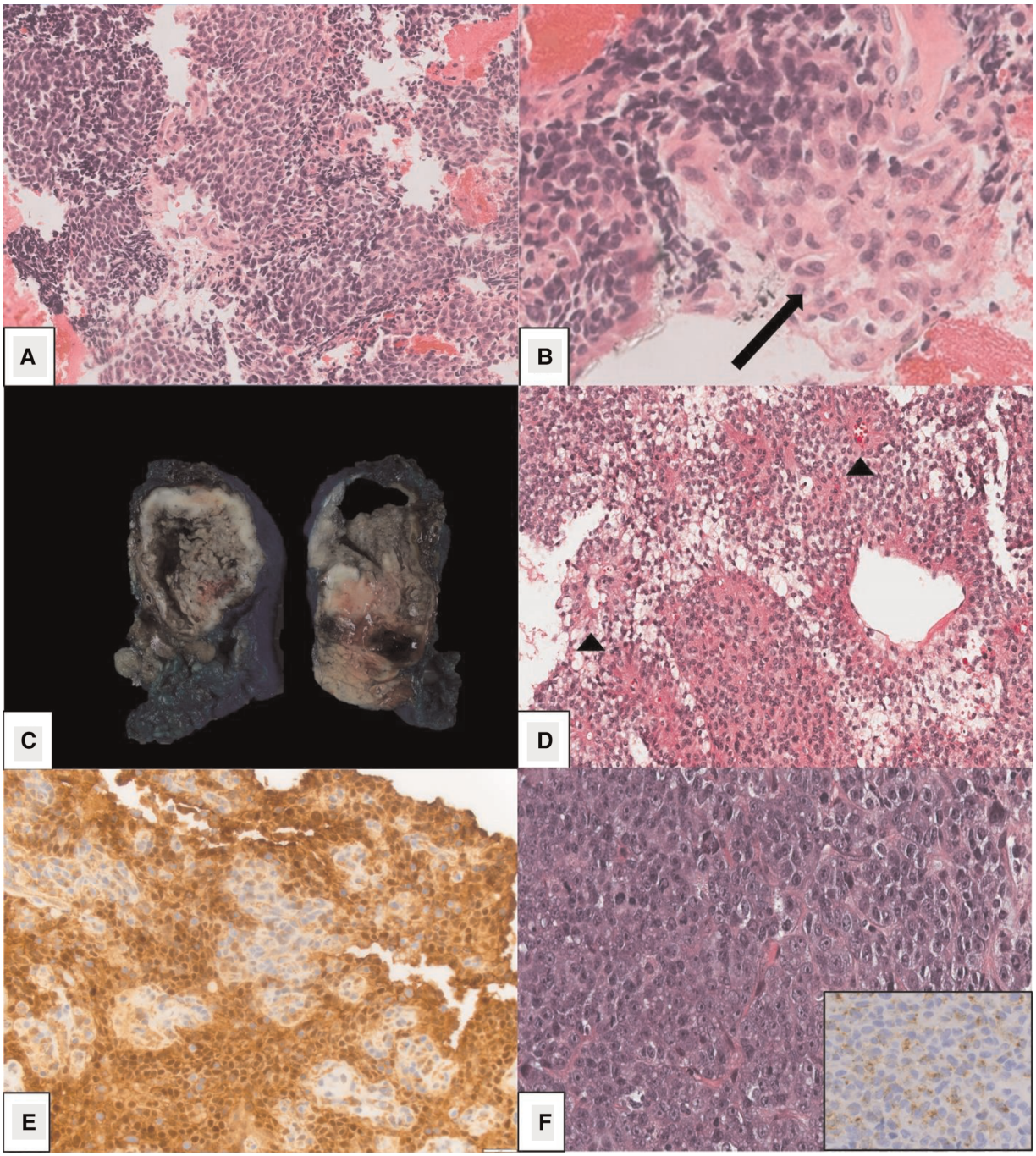

FIGURE 1
Histopathology. (**A-B**) Pancreatoblastoma characterized by rounded cells with eosinophilic cytoplasm and diagnostic squamoid corpuscles (arrow, B) [Picture courtesy: Kathleen Byrnes, MD, Washington University in St. Louis, MO]. (**C-E**) Solid pseudopapillary neoplasm demonstrating a solid and cystic cut-surface (**C**), pseudopapillary structures with central vascular cores (**D**) and nuclear beta-catenin positivity by immunohistochemistry (**E**). (**F**) Acinar cell carcinoma demonstrating a high-grade malignancy composed of round to oval cells with moderate granular amphophilic cytoplasm, prominent nucleoli and positive trypsin immunohistochemistry.

of patients undergoing neoadjuvant chemotherapy, the benefits of adjuvant chemotherapy are less clear and often utilized when surgery is incomplete (R1 or R2) or to prevent relapse (8, 16, 27–29). Radiation therapy may also be considered for incomplete surgical resection; however, clinical benefits are also currently unknown (5, 28).

Historically, 30%–60% of patients were expected to experience relapse of PBL, although more recent reports have

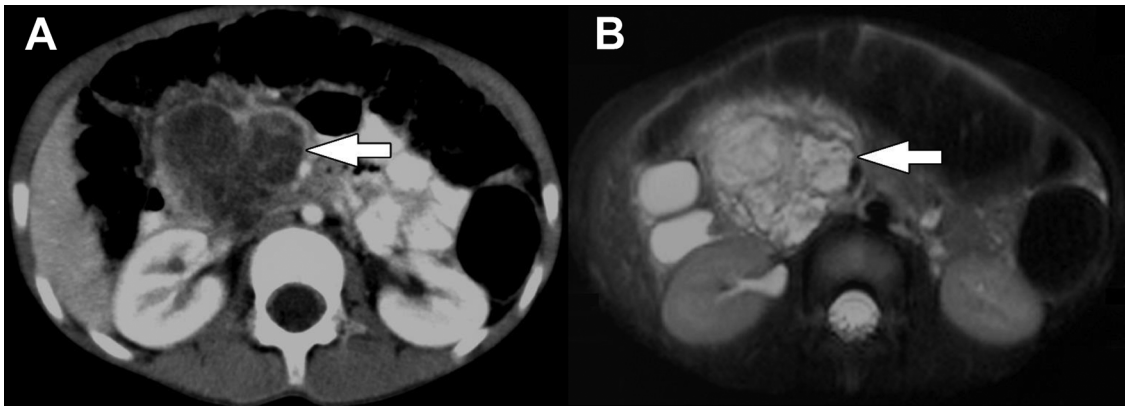

FIGURE 2
Pancreatoblastoma. (A) Axial CT of the abdomen obtained in the portal venous phase following intravenous contrast material administration shows a heterogeneously hypoenhancing mass arising from the head and neck of the pancreas (arrow). (B) T2-weighted fat-saturated MRI in the same patient shows the mass (arrow) to be heterogeneously hyperintense with the appearance of internal complexity.

suggested a much lower occurrence (14.7%) (5, 6, 16). In relapsed disease with metastases to the liver, prognosis is poor and management strategies are not well-defined (6). A recent meta-analysis demonstrated that surgical resection was again fundamental in successfully managing local relapse or metastases, whether *via* metastectomy or ablation (6). Three case reports were also identified in which patients with relapsing multicentric metastases to the liver were managed with liver transplantation (3 remained alive, 1 with a third recurrence). Authors also concluded that second-line chemotherapy with ifosfamide, etoposide, and a platin derivative with or without an anthracycline appeared most beneficial in making tumors amenable to a salvage resection (6). There are no established protocols in place for surveillance of PBL after treatment; however, long-term follow up is highly recommended due to the risk for recurrence. According to the classification proposed by the EXPeRT group, patients with stage II and III disease should have follow-up with imaging (CT or MRI) every 3 months in years 1 and 2 after treatment, every 4 months in year 3, every 6 months in year 4, and annually thereafter (16).

Solid pseudopapillary neoplasm

Epidemiology

Solid pseudopapillary neoplasm (SPN) is an exocrine pancreatic neoplasm which was first characterized in 1959 by Virginia Frantz (31). Over 700 cases have now been documented in English literature, and another 550 cases have been documented in Chinese literature. Approximately 22% to 53% have been reported in the pediatric population (3, 8, 32–35). Most are diagnosed in adolescent and young females in their 2nd or 3rd decade of life. Reports have demonstrated a mean age of 21.9 years at diagnosis overall and 13–14 years among pediatric populations (30, 33, 36). The cellular origin of SPN remains unknown, however, it is thought to arise from embryonal pancreatic pluripotent cells due to consistent negative staining for mucin, enzymes, and hormones (8, 37, 38).

Gross pathology and histology

There is debate regarding the tumor's most common location, and although they can occur throughout the pancreas, a majority are described in the pancreatic tail (36, 39). There have also been isolated reports of extrapancreatic SPN occurring in the mesocolon, omentum, ovary, and retroperitoneum (40–45). Tumors range in size from <0.5 cm up to 20 cm, although most average 5 cm–7 cm in diameter (30, 33, 36, 38, 46, 47). Fortunately, SPN is a slow-growing, indolent tumor of low malignant potential (7%–16%) (3, 48). They are often solitary and ovoid, with those larger in size being sharply circumscribed and surrounded by a fibrous capsule (3, 8, 34, 49). Their cut surface can be heterogenous with soft and friable solid areas, cystic/hemorrhagic areas and necrosis (3, 49, 50) (**Figure 1C**). Their composition can range from solid to entirely cystic, although smaller lesions are usually solid, less circumscribed, and unencapsulated (34). Calcifications may also be present, most often within the capsule (3). Larger tumors with an increased solid composition have been associated with an increased risk of malignancy and recurrence (8, 48). More aggressive tumors also seem to arise in males and demonstrate infiltrative growth patterns. Although largely sporadic, there have been familial cases reported which also demonstrate more aggressive behavior (8, 37, 51).

Microscopically, SPNs are variably composed of solid and cystic elements with interspersed hemorrhage. The most distinctive characteristic is the presence of pseudopapillae, which are composed of central hyalinized fibrovasacular cores and surrounding layers of discohesive epithelial cells whose nuclei tend to be located away from the central fibrovascular cores (**Figure 1D**). Solid areas are composed of sheets of polygonal epithelial cells with clear, eosinophilic to foamy/vacuolated cytoplasm surrounded by delicate microvasculature (3, 34, 52). Nuclear grooves and extracellular hyaline globules may be frequently noted. Immunohistochemistry is a reliable diagnostic adjunct in diagnosing SPN as they can have overlapping radiographic characteristics with pancreatic pseudocysts, acinar cell carcinoma (ACC), mucinous neoplasms, and pancreatic neuroendocrine tumors (NET) (46). SPNs are characterized by diffuse nuclear beta-catenin and LEF-1 expression in addition to cytoplasmic CD10 expression (22) (**Figure 1E**). They are frequently positive for synaptophysin, and less frequently for S-100. SPNs lack chromogranin expression, which helps in its distinction from pancreatic NETs, in addition to the above markers (39, 46, 47, 49, 53, 54). Almost all SPN tumors demonstrate nuclear expression of beta-catenin due to an inherent mutation in the *β-catenin* gene which results in abnormal protein expression (47). Progesterone and estrogen receptors have also been identified on tumor cells, which has been proposed as an explanation for the tumor's predilection for females, although evidence is inconsistent (19, 32, 38, 52, 55). Tamoxifen has, therefore, been considered a potential therapeutic agent, although its effects are unknown (32).

Clinical presentation and imaging characteristics

Due to the slow-growing nature of SPNs, they often go undiagnosed until reaching significant size, on average >8 cm. However, a small proportion of patients are incidentally diagnosed (46, 49). Abdominal pain is the most common symptom at presentation, and some patients may have a palpable mass or abdominal fullness (33, 34). Jaundice is less frequent but may occur if the tumor is located in the head of the pancreas causing biliary obstruction (37). AFP, CEA, and CA 19–9 are typically normal (30, 46, 47).

US of the abdomen will typically demonstrate a well-demarcated mass with varying degrees of heterogeneity based on tumor composition, with hyperechoic and hypoechoic areas. The fibrous capsule may also be visualized (49, 56). CT will also demonstrate these findings with a hypoattenuating, or less frequently, a contrast-enhancing capsule (3, 57). Due to their large size, tumors frequently compress adjacent structures but are unlikely to be invasive. However, invasive features may be poorly identifiable on imaging, often appearing well-demarcated (58, 59). The internal structure of SPNs is complex, with varying amounts of echogenic solid components and hypoechoic cystic areas of hemorrhage. However, the fibrous capsule and internal hemorrhage are the most distinguishing features of SPN compared to other pancreatic tumors (34, 35, 44, 49, 60, 61) (**Figure 3**). Internal septae and peripheral intratumor calcifications have also been described in up to one-third of cases (52, 59). Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging characteristically demonstrates more intense FDG uptake compared to other pancreatic tumors, specifically in the hypermetabolic peripheral capsule, while cystic and necrotic areas have poor uptake (8, 62).

The presence of SPN's characteristic internal hemorrhage is best demonstrated on MRI imaging (**Figure 3**). T1-weighted images show high intensity signal in areas of hemorrhage, while solid portions appear iso- or hypotense, and the fibrous capsule appears hypointense. T2-weighted images may demonstrate a dark, fibrous rim, with solid regions appearing hyperintense, and hemorrhagic areas are more variable in signal intensity. On dynamic contrast-enhanced MRI imaging, tumors have been described as having minimal enhancement in the early arterial phase with a gradual increase in later phases (61). SPNs are generally avascular in composition, pushing vessels to the periphery (57, 59).

Treatment

Like PBL, complete surgical resection also the standard treatment of SPN. Long-term prognosis is excellent, with 10-year survival rates >95% after adequate surgical resection, even in the presence of distant metastases or disease recurrence (34, 38, 52, 63–68). SPN metastases are most frequently to the liver, lymph nodes, and peritoneum. Although metastatic disease is rare at diagnosis in pediatric patients (<10%), it is described in up to 19.5% of adults (3, 33, 34, 48, 69). Operation often includes a DP for tumors in the body or tail of the pancreas, with splenic salvage if possible, or a PD for tumors located in the pancreatic head. Operation should concomitantly include removal of any metastatic disease amenable to resection, and tumor debulking is considered beneficial even in the setting of incomplete primary or metastatic resection (14, 34, 36–38, 69, 70). Enucleation and biopsy should be avoided, as this has led to inadequate resection margins and subsequent recurrence (8, 37, 48).

There have been reports of successful and unsuccessful use of adjuvant chemotherapy for unresectable disease. However, it is not frequently administered due to the lack of evidence-based protocols (30, 71, 72). Radiotherapy has also been suggested as a potential adjunct for unresectable disease because tumors have demonstrated radiosensitivity in multiple cases (73–75). Finally, transarterial catheter embolization (TACE) has been attempted in patients with multiple metastases, although outcomes are not well understood (76). There are currently no specific guidelines

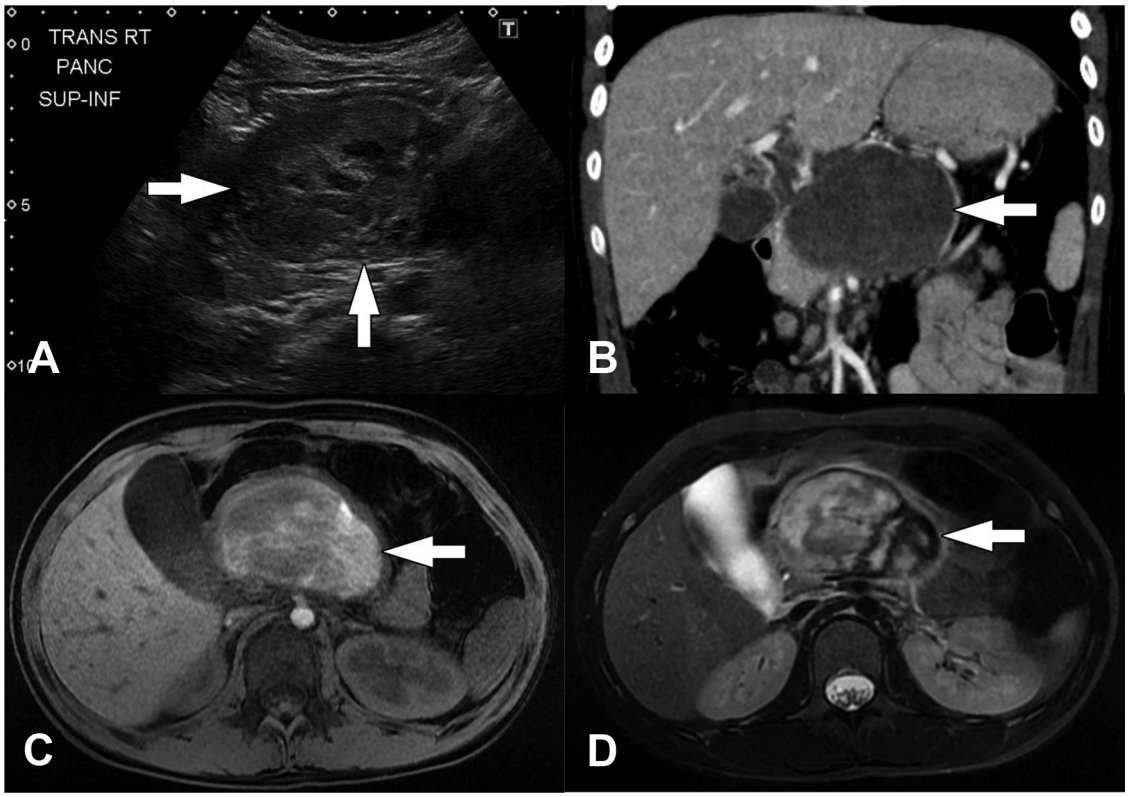

FIGURE 3
Solid pseudopapillary neoplasm. (A) Transverse image from initial transabdominal ultrasound shows a heterogeneous mass (arrows) in the expected location of the pancreas. (B) Coronal reformatted image from subsequently performed CT of the abdomen obtained in the portal venous phase following intravenous contrast material administration shows a heterogeneously hypoattenuating mass arising from the body of the pancreas (arrow). Subtle enhancing septations/material are visible within the mass. (C) Axial T1-weighted and (D) axial T2-weighted images from subsequently performed MRI show the mass in the body of the pancreas (arrows). The mass is internally heterogeneously T1-weighted and T2-weighted hyperintense with prominent peripheral T2-weighted hypointensity. These signal characteristics suggest the presence of internal hemorrhage.

established for surveillance of SPN after surgery (77, 78). However, long-term follow up is important, especially in patients with aggressive features on pathology, and because overall rates of recurrence approach 10% with tumor relapse developing more than 10 years after initial treatment in some patients (30, 38, 69, 70). In the setting of recurrence, repeat surgical resection and tumor debulking is required (33, 46, 72, 79).

Ductal adenocarcinoma

Epidemiology

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant pancreatic neoplasm in adults but is exceedingly uncommon in children. PDAC is rarely seen in patients under 40 years of age, and less than 1% of cases occur in patients under 20 years old (15, 80–82). In patients younger than 20, most are males (1, 15). Most PDACs diagnosed in younger patients are often linked to hereditary syndromes (15). When arising in patients with a strong family history, they are considered familial pancreatic cancers (FPC), of which 20% have *BRCA2* mutations (83–85). Other associated genetic mutations include *p16/CDKNA* (familial atypical multiple mole melanoma syndrome), *ATM* (telangiectatic ataxia), *PRSS1* or *SPINK1* (hereditary pancreatitis), *STK11/LKB1* (Peutz-Jeghers syndrome, and *MLH1/PMS1/PMS2/MSH2/MSH6* (Lynch syndrome) (15, 83, 85, 86). Common somatic mutations also occur in the *KRAS* oncogene (90%) and tumor suppressor genes *p16*, *TP53*, and *SMAD4* (87, 88). In addition to gene mutations, other known risk factors for PDAC are smoking, chronic pancreatitis, and high dietary fat intake (15, 89).

Gross pathology and histology

PDACs occur most frequently in the pancreatic head, while one-third are found in the pancreatic tail (15). Tumors are solid, firm, and yellow or gray in color. They are poorly demarcated, and typically smaller at diagnosis (2 cm–3 cm). PDACs

histologically contain duct-like and tubular components comprised of columnar or mucus-secreting cuboidal cells irregularly infiltrating background pancreas with characteristic perineural invasion (15). Immunohistochemical stains are non-specific, and markers expressed include cytokeratins (7, 8, 18, 19 and 20), EMA, CEA, and CA 19–9/CA125/DUPAN-2 (90, 91) and mucin markers *MUC1, MUC3, MUC4*, and *MUC5AC* (92). In 10 patients younger than 40 years old, PDAC tumors expressed cytoplasmic *MUC1* expression in 90% (80). Loss of nuclear *SMAD4* and *p16* expression has been also widely documented in a subset of tumors (88).

Clinical presentation and imaging characteristics

Unlike other pancreatic tumors diagnosed in children, PDAC characteristically causes obstructive jaundice due to invasion within the head of the pancreas and subsequent biliary tract obstruction. Also seen are weight loss, back pain, and new-onset diabetes (15, 82). On diagnostic imaging, PDAC presents similarly in adults and in younger patients, although a study by Ivy et al. demonstrated poorer differentiation and higher prevalence of metastases at the time of diagnosis in younger patients (81, 93, 94).

Overall, imaging is non-specific, with tumors varying in size with heterogeneous imaging features. Lesions may be occult by US or may appear echogenic relative to background pancreas. By CT scanning, PDAC is characteristically hypoenhancing relative to normal pancreatic tissue. MRI imaging typically demonstrates a hypointense mass on T1-weighted imaging with variable T2 signal (**Figure 4**). It is common for PDAC to invade adjacent structures and vasculature, specifically the biliary and pancreatic ducts, which causes ductal dilatation and the "double duct sign" on imaging (3, 8).

Treatment

Unfortunately, greater than 50% of the reported PDACs in children are metastatic on presentation, mostly to the liver (1, 95). Like PBL and SPN, complete surgical resection is most curative in both children and adults, although only 10%–20% of PDACs are amenable to resection (82). Disease-free survival has been extended in adults using modified FOLFIRINOX (folinic acid, fluorouracil, irinotecan hydrochloride, oxaliplatin), and this regimen has also been used effectively in a small number of pediatric cases (8). Regardless, PDAC carries a poor prognosis for survival even in young patients. Published reports have demonstrated a 5-year survival rate of 4% in patients <40 years old and a 15-year survival rate of 23% in children (80, 81).

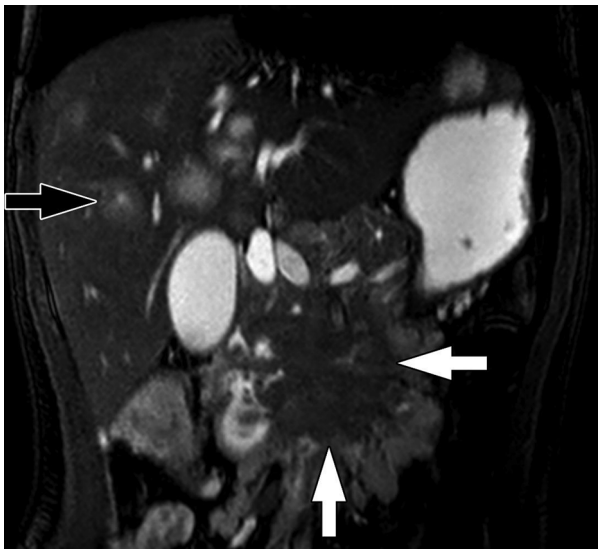

FIGURE 4
Pancreatic ductal adenocarcinoma. Coronal T2-weighted fat-saturated MRI of the abdomen shows a hypointense infiltrative mass involving the head and uncinate process of the pancreas (white arrows). There are additionally ill-defined hyperintense metastases in the liver (one indicated by the black arrow).

Acinar cell carcinoma

Epidemiology

Acinar cell carcinoma (ACC) accounts for just 2% of all pancreas neoplasms, most often diagnosed in adult men at an average age of 58 years old (96). They rarely occur in children, with 26 pediatric cases reported, although they remain more predominant than pediatric PDAC (96–100). The more common genetic alterations have been identified in *BRCA1, BRCA2, ATM, PALB2,* and *MSH2*. Chromosomal rearrangements in *BRAF* and *RAF1* have also been identified in one-fourth of ACCs (101).

Gross pathology and histology

ACCs are found throughout the pancreas and are often large at the time of diagnosis, averaging 10 cm–11 cm in size. On gross section, they are tan to red, and fleshy. Some demonstrate areas of necrosis, hemorrhage, or cystic degeneration. They are frequently well-circumscribed and can be partially or circumferentially encapsulated (15, 96). ACCs often grow and displace adjacent structures, which is demonstrated microscopically by neoplastic cells extending as lobules through the peripheral capsule into parenchyma, vasculature, and nerves (96). On microscopic pathology, multiple growth patterns are seen – acinar, solid, glandular, and trabecular – although acinar and solid patterns are

the most common. The cells often have granular and eosinophilic cytoplasm whose nuclei have a prominent nucleolus. A key distinguishing feature in comparison to PBL is that ACCs lack both squamoid corpuscles and differentiated mesenchyme (3). ACC also has scant fibrous stroma, which can help differentiate it from PDAC (8). They often stain positive for trypsin, chymotrypsin, and BCL10 on immunohistochemistry (100, 102) (**Figure 1F**).

Clinical presentation and imaging characteristics

Similar to most pancreatic tumors, ACC presents with non-specific gastrointestinal symptoms (abdominal pain, emesis, and diarrhea), although weight loss may also occur (96). Unique to ACC is that 10%–15% of patients may develop lipase hypersecretion syndrome. This causes large amounts of lipase to be released into the bloodstream, exceeding 10,000 U/dl in some cases, and leads to subcutaneous fat necrosis, eosinophilia, and polyarthralgia (103, 104). Most frequently, this is seen in the setting of very large primary tumors or metastatic disease (98). Lipase may also be elevated outside of lipase hypersecretion syndrome, and AFP elevation has been reported in younger patients (98, 105, 106).

On US, tumors are usually hypoechoic and are variably defined. CT typically demonstrates a well-demarcated exophytic (on the basis of size) mass with partial or complete encapsulation (**Figure 5**). Tumors are characterized by internal heterogeneity and may have central hypoattenuation/hypoenhancement corresponding to necrosis. One-third of tumors will demonstrate calcifications located centrally or peripherally. ACCs show greater contrast enhancement than PDACs, but less than normal pancreatic tissue. Tumors smaller in size demonstrate more homogeneous enhancement, while larger tumors demonstrate enhancement of their solid components in the periphery (3, 107). MRI findings are less described for ACC but in 2 patients, T1-weighted imaging showed hyperintense signal in one mass and a central mixed signal in the other. Both were hyperintense to pancreatic tissue on T2-weighted images (107). Although the appearance of ACC on imaging can resemble PBL and SPN due to their large size and characteristic central necrosis, PBL and SPN are much more common in children (3).

Treatment

ACC is an aggressive tumor with >50% of patients having metastatic disease on presentation, most commonly to liver and lymph nodes (97, 98). Complete surgical resection with or without the addition of chemotherapy has been shown to provide the best outcomes. Previous results demonstrate 5-year survival rates of 36% in patients with resected disease, compared to 10% in patients who did not undergo resection (108). Although more dismal than most pancreatic tumors, ACC does have a better prognosis than PDAC (96). Fortunately, more recent studies have demonstrated 5-year survival rates of up to 50% for localized disease, compared to older studies which suggested 5-year survival of 6% (108–110). For unresectable disease, only a very small number of patients who received chemotherapy and/or radiation experienced a significant response (104, 109).

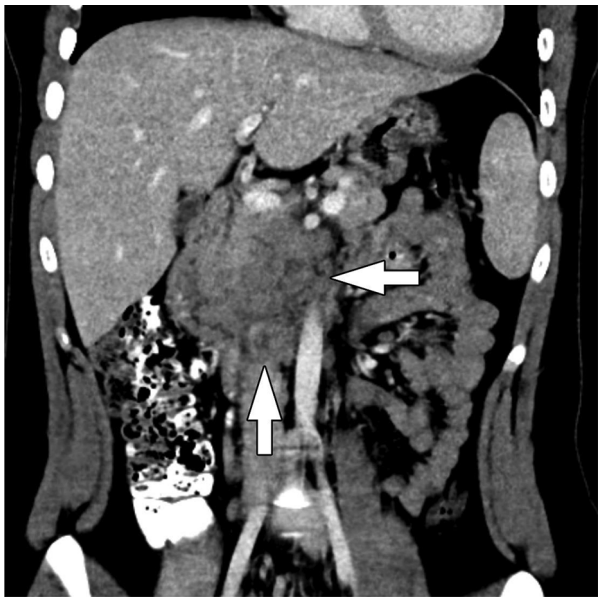

FIGURE 5
Acinar cell carcinoma. Coronal CT of the abdomen obtained in the portal venous phase following intravenous contrast material administration shows an infiltrative, hypoenhancing mass involving the head and uncinate process of the pancreas with adjacent conglomerate pathologic lymph node enlargement (arrows).

Neuroendocrine tumors

Epidemiology

Pancreatic neuroendocrine tumors (NET), also known as islet cell tumors, account for 2% of all pancreatic neoplasms and 5%–10% of all pediatric pancreatic tumors (111, 112). These tumors derive from pancreatic islet cells and are frequently distinguished as well-differentiated, benign adenomas or poorly differentiated, metastatic carcinomas (3, 113). In children, 90% of pancreatic NETs are benign. The overall mean age at diagnosis in all pancreatic NETs is 47 years old, and most pediatric cases are diagnosed in older children (3). Genetic predispositions may also be present, specifically in pediatric cases, with approximately 5% of

pancreatic NETs being associated with multiple endocrine neoplasia type 1 (MEN-1). Genetic associations are also seen in Von-Hippel Lindau (VHL) disease, neurofibromatosis type 1 (NF-1), and tuberous sclerosis complex (TSC) (114, 115). Another important distinction made in pancreatic NETs is whether the tumor is functioning, which means active hormones are secreted by islet cells to produce clinical symptoms, or it is non-functioning/clinically silent (3). In children, the most common pancreatic NETs are insulinomas and gastrinomas (3).

Insulinoma

Derived from beta cells, insulinomas peak in incidence between 40 and 60 years old (113). Although they remain the most common pediatric pancreatic NET, they rarely occur before age 15, with 4.9% being found in children aged 10–19 years old and just 0.9% found in 0–9 year olds (116, 117). Patients with MEN-1 are diagnosed at a mean age of 27 years old, which is 20 years younger than patients without the genetic association (117). Insulinomas are found primarily in the pancreas, although some reports of primary extrapancreatic lesions in the duodenum, ileum, lung, cervix, and ovary have been made (118–123). Due to uncontrolled insulin secretion, insulinomas are associated with clinical symptoms of fasting hypoglycemia, palpitations, perspiration, tremors and even seizure. Persistent hyperinsulinemic hypoglycemia (PHH) may occur, causing mental confusion, fatigue, weakness, and seizures and resolves with the administration of glucose (113). In younger children, these classic symptoms may instead present as behavioral changes, seizures, and coma. Unfortunately, untreated persistent hypoglycemia may lead to lasting neurologic effects (14). Most insulinomas are benign, solitary lesions which are small in size (~2 cm) (123, 124). However, of the 10% which are malignant, tumors are often greater than 2 cm in size, and one-third of patients are reported to have metastatic disease at the time of presentation (124, 125).

Gastrinoma

Gastrinomas are derived from gastrin-secreting G cells. Their peak incidence is from 48 to 55 years old, and as seen in insulinomas, children 5–15 years old are rarely affected (14, 113). They are most commonly located within the gastrinoma triangle, which is comprised of the head of the pancreas, the first and second portions of the duodenum, and the porta hepatis (14, 113). Tumors are typically solitary, though when multiple gastrinomas are present, Zollinger-Ellison syndrome (ZES) should be considered. Clinically, they cause hypersecretion of hydrochloric acid in the stomach, leading to peptic ulcer disease, gastroesophageal reflux disease (GERD), and most commonly, diarrhea. However, these symptoms may be less pronounced than those seen with hyperinsulinemia, and an accurate diagnosis may be delayed (113, 126). In contrast to insulinomas, gastrinomas are larger, with a mean size of 4.2 cm at presentation, and 60% demonstrate malignancy (14, 127).

Other functioning and non-functioning pancreatic NETs

Other functioning and non-functioning pancreatic NETs are either rare or unreported in the pediatric population (3). Glucagonomas are derived from alpha cells and commonly occur in the distal pancreas. Often, they are malignant (60%–70%) and larger in size, averaging 7.2 cm (14, 128). When clinically evident, glucagon secretion may cause a skin rash called necrolytic migratory erythema, which is seen in up to 80% of patients. Glucose intolerance, weight loss, depression, and the tendency to develop deep venous thrombosis may also be seen (129). Somatostatinomas derive from D cells. Patients may present with symptoms of cholelithiasis, steatorrhea, diabetes mellitus (DM), and hypochlorhydria due to the repressive nature of the somatostatin hormone (14, 130). Thus far, there have been no reports of pancreatic glucagonoma or somatostatinoma in children (3, 131). Another uncommon functional pancreatic neuroendocrine tumor is VIPoma, which is composed of D1 cells, secretes vasoactive intestinal peptide (VIP), and causes large volume diarrhea, hypokalemia, and achlorhydria. Most frequently, pediatric cases of VIPoma are not reported in the pancreas (125).

Non-functioning pancreatic NETs are hormonally inactive or clinically silent, often causing a more delayed diagnosis in comparison to symptomatic, functioning tumors. Mean age at presentation is 70 years old, with most tumors averaging 2 cm–5 cm in size and demonstrating malignant features. When symptoms are present, they are typically due to local invasion and mass effect (3). Nearly 10% demonstrate no immunohistochemical staining for pancreatic hormones, although others express glucagon, pancreatic polypeptide (PP), somatostatin, serotonin, and/or calcitonin. Without a hormonal syndrome, they are not considered functioning pancreatic NETs (14, 98, 132).

Gross pathology and histology

Pancreatic NETs are typically round and well-demarcated, with a consistency ranging from soft to firm. Histology of pancreatic NETs is also variable, often with sheets of monomorphic cells which are arranged in a trabecular, acinar, pseudoglandular or solid pattern (3). Nuclei are often round-oval with speckled chromatin. Immunohistochemistry is extremely helpful in establishing the neuroendocrine properties of pancreatic NETs, especially chromogranin, synaptophysin and CD56. Grading is often determined using the World Health Organization's classification which is based on mitotic rate and Ki-67 proliferation (133, 134).

Imaging characteristics

Most pancreatic NETs are insulinomas and are typically small, homogenous, and well-circumscribed on imaging. Gastrinomas and other functioning and non-functioning pancreatic NETs may be larger and more heterogeneous (126, 127). On US, insulinomas are typically round and hypoechoic, possibly with a hyperechoic rim, while larger pancreatic NETs may demonstrate cystic areas or calcifications (127). Multi-phasic CT or MRI are the standard imaging modalities used to diagnose pancreatic NETs (135, 136). Pancreatic NETs characteristically show homogeneous, hyperintense enhancement on CT or MRI following contrast administration (137) (**Figures 6**, 7). Larger, malignant pancreatic NETs are often heterogeneous with non-enhancing cystic components and solid enhancing components located at the periphery (127). On MRI, lesions are usually hypointense on T1 weighted imaging and hyperintense on T2 weighted imaging (8, 138).

As with other pancreatic tumors which are being evaluated for potential enucleation, EUS may be utilized if CT and/or MRI are not diagnostic (139). It has been shown to be highly accurate in endocrine tumor localization; however some studies have also demonstrated that EUS is more operator-dependent, significantly affecting accurate detection (140–143). Additional imaging adjuncts like angiography, transhepatic portal venous sampling, intra-arterial calcium-stimulated venous sampling, and somatostatin receptor scintigraphy have also been utilized for pancreatic NET localization in hormonally active tumors, although these remain less sensitive than CT and MRI (3, 135–137, 144–146). Somatostatin receptor scintigraphy can be helpful for when tumors express somatostatin receptors, which occurs in 60%–70% of insulinomas (3). Indium-111 (^{111}In) octreotide SPECT/CT has been replaced by [^{68}Ga]-DOTA-TATE PET/CT, as the newer somatostatin analogue (^{68}Ga-DOTA-tyrosine^{3}-octreotide) has shown higher detection rates, while remaining low in toxicity and radiation exposure (147).

Treatment

Typically, complete surgical resection is performed to obtain curative treatment for pancreatic NETs. Tumors in the pancreatic head will be resected with a PD, while those more

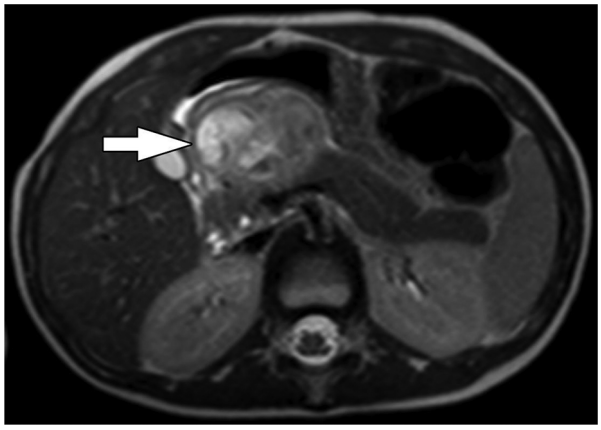

FIGURE 7
Pancreatic NET. Axial T2-weighted MRI shows a heterogeneously hyperintense exophytic mass arising from the neck of the pancreas (arrow). The upstream pancreatic body and tail are Normal and there is no duct dilation to suggest duct obstruction.

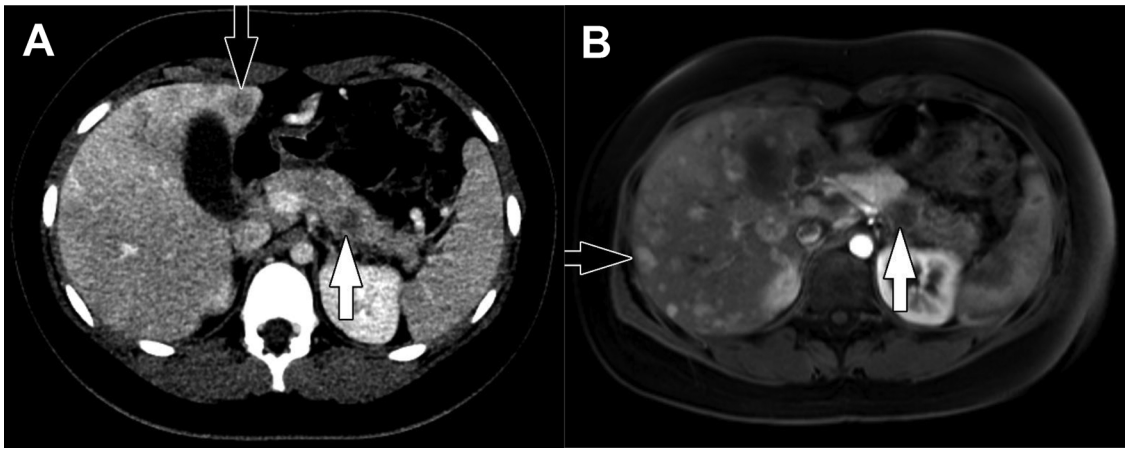

FIGURE 6
Insulinoma. (A) Axial CT of the abdomen obtained in the portal venous phase following intravenous contrast material administration shows a hypoenhancing mass in the body of the pancreas (white arrow) with multiple hypoenhancing liver metastases (one indicated by the black arrow). Characteristically, neuroendocrine tumors hyperenhance in the arterial phase following contrast administration but hypoenhancing lesions do occur. (B) Axial T1-weighted fat-saturated post-contrast MRI obtained in the arterial phase shows the pancreatic tumor (white arrow) to be hypoenhancing while the multiple liver metastases (one indicated by the black arrow) are hyperenhacing. The tail of the pancreas upstream of the tumor is hypoenhancing due to obstructive pancreatitis related to the tumor.

distal in the pancreas will undergo a DP; however, gland-preserving procedures like duodenum-preserving pancreatic head resection (DPPHR), central pancreatectomy, and tumor enucleation are also performed based on the function of the pancreatic NET, its size, and its benign vs. malignant characteristics (36, 148). Enucleation may be especially useful for benign pancreatic NETs like insulinoma because it provides desirable outcomes even when margins are positive. Some functioning pancreatic NETs may also require symptom control prior to resection, typically with octreotide (149). Providers may consider observation and active surveillance in small non-functioning tumors, as just 6% have been identified as malignant in previous reports, although evidence remains limited especially in pediatric patients (148). In the presence of unresectable, locally advanced, or metastatic disease, chemotherapy (a combination of temozolomide-capecitabine, everolimus, or sunitinib) or radionuclide therapy with lutetium-177 (^{111}Lu)-DOTA-TATE may be used (150). Like [^{68}Ga]-DOTA-TATE for tumor localization, [^{111}Lu]-DOTA-TATE targets the somatostatin receptor for therapy. Prognosis varies based on tumor type, histology, and risk for malignancy. Although most benign insulinomas are cured by surgical resection, the median survival of patients with metastatic disease is <2 years (117, 151). Gastrinomas without metastatic disease have a 10-year survival rate of 90%–100%, while most other functioning pancreatic NETs have a 5-year survival rate of less than 50% due to tumors often being advanced at diagnosis (152, 153). In children specifically, reports have demonstrated 15-year survival rates of 50% across pancreatic NETs overall (1).

Non-epithelial tumors

Pancreatic Ewing sarcoma

Pancreatic Ewing sarcoma (formerly, primitive neuroectodermal tumor), accounts for just 0.3% of pancreatic neoplasms (154). Typically, they are an aggressive tumor affecting bone, but nearly 30 pancreatic Ewing sarcomas have been reported in patients under 25 years old (155, 156). Mean age at diagnosis is 18.2 years, and there is no sexual predominance (156). The characteristic genetic translocation involves the *EWSR1* gene on chromosome 22q12 (155) and has been recognized in several reported cases of pancreatic Ewing sarcoma. However, Ewing sarcomas can also demonstrate rearrangements involving the *FUS* gene (157). Over two-thirds of pancreatic Ewing sarcomas are diagnosed within the pancreatic head, ranging in size from 3.2 to 22 cm. Histological characteristics include clusters or nests of small, round blue cells with scant cytoplasm to moderate amounts of clear to eosinophilic cytoplasm. Cells express the product of the *MIC2* gene, which is confirmed by strong diffuse membranous positivity for CD99 on immunohistochemistry (156). NKX2.2 is a nuclear immunohistochemical stain that is also helpful in diagnosis (158).

Abdominal pain is the most common symptom at presentation, followed by jaundice and nausea. Although the tumor can reach significant size, its growth is expansive vs. invasive, causing less obstructive jaundice than expected (156). On imaging, lesions are poorly defined, with cystic or necrotic areas, and heterogeneous enhancement. CT imaging demonstrates a mass hypo- or isointense to normal pancreatic tissue, and MRI imaging demonstrates an iso- or hyperintense mass on T2-weighted imaging. The tumor is also metabolically avid on FDG CT/PET imaging (3, 8).

Complete surgical resection, frequently in combination with chemotherapy (cisplatin, doxorubicin, and high-dose methotrexate), produces the best patient outcomes due to the aggressive nature of pancreatic Ewing sarcoma (159). In cases in which complete resection is not possible, radiation may help control some disease progression (156). Overall pancreatic and extra-pancreatic 5-year survival outcomes are 55%–65% with localized disease and a multimodal approach (160).

Lymphoma (non-Hodgkin's, Burkitt)

Lymphomas involving the pancreas are extremely rare and may originate from distant lymph nodes, tumor extension from peripancreatic lymphadenopathy, or as primary pancreatic lymphoma (PPL). PPL accounts for less than 2% of extra-nodal lymphomas and occurs most frequently in men in their 5th or 6th decade of life. In children, the average age at diagnosis is 10.3 years, ranging from 3 to 16 years old (161). A majority are non-Hodgkin's lymphoma of B-cell type, specifically, Burkitt lymphoma and diffuse large B-cell lymphoma (162). Non-Hodgkin's lymphoma is also thought to be the most common pediatric pancreatic tumor of non-epithelial origin. A previous study demonstrated that one-third of pediatric patients with non-Hodgkin's lymphoma were found to have pancreatic involvement at autopsy (163). Often, it is distinguished from other tumor types by its large, multiple nodal masses; however, Burkitt lymphoma may present as a solitary lesion, multiple masses, or diffuse infiltration, mimicking acute pancreatitis (162, 163). Overall, PPL tumors in children average 5 cm–6 cm in size at diagnosis, and have a predilection for the pancreatic head (161). Histologically, cells have large lymphocytic nuclei, prominent nucleoli, and background necrosis (162).

Commonly, patients present with abdominal pain, fevers, night sweats, weight loss, and jaundice. In patients with bulky disease in the pancreatic head, gastric outlet and duodenal obstruction may also occur (162). On US, disease appears hypoechoic relative to normal pancreas. CT imaging demonstrates either focal or homogeneous enlargement of the

pancreas and patchy hypoenhancement (**Figure 8**). MRI will similarly show hypoenhancement of tumor involved parenchyma or lymph nodes (3). Lymphoma is optimally staged by FDG CT/PET which shows intense avidity (162).

Standard treatment of PPL is chemotherapy, which not only controls symptoms but provides long-term tumor resolution. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are frequently used, with the addition of rituximab for diffuse large B-cell lymphoma due to improved response rates. Surgery is reserved for patients with biliary obstruction, gastric or duodenal obstruction, or when the diagnosis is unclear (162). After immunochemotherapy and/or surgery, 15 pediatric patients with follow-up data reported were all alive and had reached complete remission at a median follow up of 56 months (161).

Lymphatic malformations (lymphangioma)

Pancreatic lymphangiomas, or lymphatic malformations (LM), account for just 0.2% of pancreatic lesions and less than 1% of LMs overall (164–166). Sixty cases have been reported in the literature thus far (167, 168). They are reported across all ages and are more common among women (166). LMs are often congenital masses which develop due to lymphatic obstruction during gestation. If located within the pancreatic parenchyma, adjacent to the gland, or connected by a pedicle, they are considered to originate from the pancreas (169). They are typically slow growing, benign, and occur throughout the pancreas, with sizes ranging from 3 cm to 20 cm (166). Pathologically, pancreatic LMs are multicystic masses with a thin, fibrous capsule. Their micro- and macrocystic regions contain serosanguinous or chylous fluid (3). Histology reveals endothelial cells lining the cyst walls, smooth muscle, collagenous connective tissue and scattered lymphoid aggregates (166).

Most patients with pancreatic LMs are asymptomatic and diagnosed by incidental imaging findings, while others may endorse non-specific gastrointestinal symptoms due to mass effect. Acute presentations have also been reported related to pedicle torsion and rupture (170). On imaging, lesions are characteristically trans-spatial and can either appear as well-defined cystic lesions or more infiltrative fluid collections. Fluid content is characteristically simple (by US and CT) and hyperintense on T2-weighted MRI (**Figure 9**). Lesions complicated by hemorrhage may have more complex fluid content. A thin capsule and fine internal septations may be apparent and generally enhance following contrast administration. Microcystic regions will appear more solid and enhancing (171). Although imaging is useful, differentiating LMs from other cystic pancreatic lesions and pancreatic or peripancreatic fluid collections can be difficult, and EUS with fine needle aspiration/biopsy and histologic evaluation are often necessary to confirm the diagnosis (166).

Although benign, complete surgical resection is often indicated due to the tumor infiltrating adjacent organs, growing and causing mass effect, or leakage of lymphatic fluid. This may require simple excision of the lesion or larger pancreatic resections (172). However, in asymptomatic patients without local invasion, surveillance imaging is considered appropriate (166).

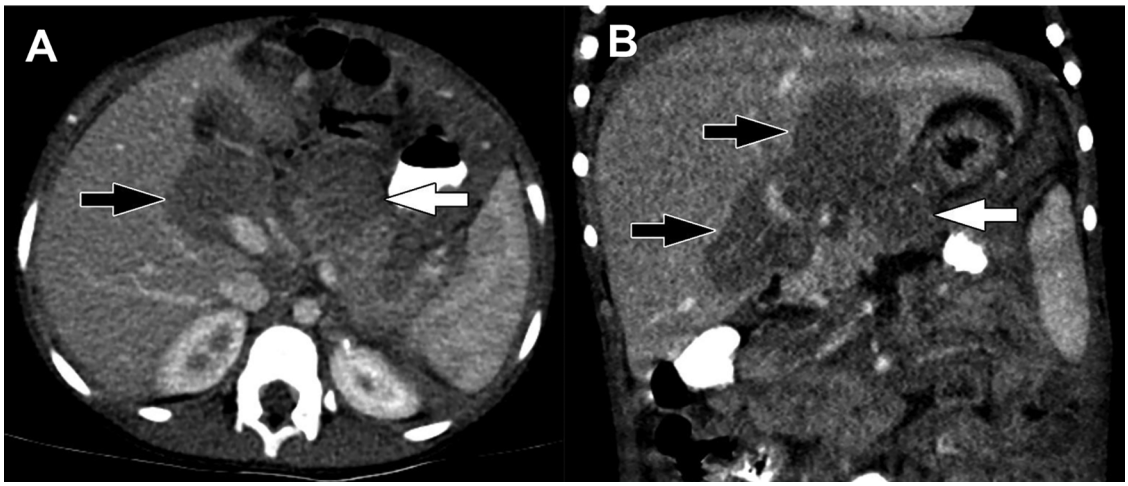

FIGURE 8
Burkitt lymphoma. (**A**) Axial and (**B**) Coronal reformatted images from a CT of the abdomen obtained in the portal venous phase following intravenous contrast material administration show hypoenhancing masses in the pancreas (white arrows) and porta hepatis (black arrows). Multiorgan involvement and infiltrative growth are highly suggestive of Burkitt lymphoma.

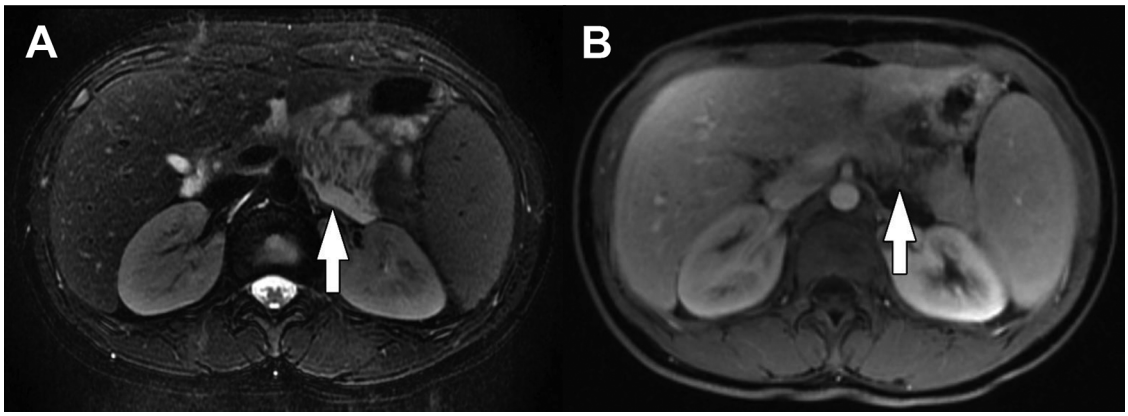

FIGURE 9
Lymphatic malformation. (A) Axial T2-weighted fat-saturated MRI and (B) Axial T1-weighted fat-saturated post-contrast MRI show an infiltrative lesion involving the body of the pancreas (arrows). The lesion is T2-weighted hyperintense reflecting fluid content without enhancement following contrast administration. Transspatial involvement is characteristic of a lymphatic malformation.

Kaposiform hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is an infiltrative vascular tumor known for its aggressive nature and occurrence during infancy or early childhood (173). Although the tumor is most frequently cutaneous in origin, rare occurrences have been reported in the pancreas. It has been estimated to affect less than 1 in 100,000 children, with less than 10 pediatric cases documented in the literature (173–177). Histologically, it is composed of infiltrating nodules, sheets of spindled endothelial cells, and slit-like vascular channels. Microthrombi and hemosiderin deposits are also seen (178). Immunohistochemistry is positive for lymphatic endothelial markers but negative for glucose transporter protein type 1 (Glut1), which distinguishes KHE from infantile hemangioma (174, 177, 179).

Presenting symptoms are typically related to obstructive jaundice and increasing abdominal distention (174, 176). A key clinical feature of KHE is its association with Kasabach-Merritt phenomenon (KMP), which occurs in up to 70% of patients. Tumors with this association are typically >8 cm in size (180). The phenomenon is characterized by consumptive coagulopathy, hemolytic anemia, and thrombocytopenia. In these patients, platelet transfusions should be avoided as they can cause painful engorgement of the lesion (177, 178). KHE often appears as a homogenous soft tissue mass on US, while CT and MRI show a poorly defined mass with infiltration of surrounding tissues and heterogenous contrast enhancement (175).

Although complete surgical resection is ideal, the infiltrative growth pattern of KHE often makes this difficult, requiring excision and adjuvant chemotherapy. Sirolimus, vincristine, interferon, steroids, aspirin, and ticlopidine have been used in clinical practice but with varying outcomes of treatment (175, 176, 181). Mortality rates of 12%–24% have been reported, and typically occurs in patients with KMP (180).

Dermoid cyst

Dermoid cysts of the pancreas, also known as mature teratomas, are benign and extremely rare, with just 35 known cases reported in the literature. Just 8 of those patients were children (182, 183). Due to their development at the time of neural groove closure, extragonadal dermoid cysts are most often found along the midline, although a majority of pancreatic dermoid cysts are found in the pancreatic head. They are often large, reported from 8 cm–12 cm in size. Cysts are composed of tissue from all three germ layers and are a combination of cystic and solid structures such as teeth, hair, cartilage, and dermal contents (3, 183).

In pediatric cases, the most common presenting symptom is vomiting; however, abdominal pain and back pain may also occur. A pre-operative diagnosis can be challenging, and the pathognomonic finding of fat/fluid or hair/fluid levels only occurs in a small number of pancreatic cases (184). Adjunctive EUS has also been used for diagnosis, but tumor appearance varies across reports (185). On CT imaging, cysts are round and well-circumscribed. They are very hypodense and heterogenous, with varying cystic and solid ratios depending on their composition (3, 183, 184). In most cases, simple excision of the pancreatic dermoid cyst is performed, although they sometimes require a DP, or less commonly, a PD (183).

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumors (IMT) are rare mesenchymal tumors of unknown origin most commonly occurring in the lungs of children and adolescents (186). However, they have also been described in the head/neck, liver, pancreas, thyroid, and genitourinary tract (187–191).

There have been 14 reported cases of pancreatic IMT in children, ranging from ages 6 months to 15 years old, but with a mean age at diagnosis overall of 42 years. Pancreatic IMTs are low-grade, slow-growing solid tumors located in the head or tail of the pancreas (186, 192). Microscopically they demonstrate myofibroblastic spindle cells with varying proportions of plasma cells, mast cells, eosinophils, lymphocytes, and histiocytes (193). Nearly 50% of IMTs demonstrate rearrangements in *ALK* gene, while rearrangements involving *ROS1*, *PDGFRβ*, *RET* and *NTRK* have been reported in the *ALK*-negative subset. With the identification of gene rearrangements novel targeted therapies are an option for unresectable tumors (194).

Clinical symptoms are frequently non-specific, though obstructive jaundice may occur in the setting of a pancreatic head lesion (186). Spontaneous splenic rupture has also been reported secondary to the obstruction and congestion of splenic vessels by a pancreatic tail IMT (195). By US, lesions are characteristically hypoechoic. By CT, the imaging appearance of IMTs is variable with lesions appearing hypo- or hyperenhancing with or without calcifications and necrosis. On MRI, IMTs are typically hyperintense on T2-weighted images, and on FDG PET/CT, some tumors are hypermetabolic (8) (**Figure 10**). IMTs have a favorable prognosis after complete surgical resection, with no reported recurrence in these patients. Radical resection is often performed, although enucleation has recently been reported, resulting in current disease-free survival (186). Radiation, chemotherapy, and corticosteroid therapy have been implemented in patients with unresectable disease or findings of malignant pathology after resection (196–198).

Current challenges in management

Distinguishing autoimmune pancreatitis from pancreatic carcinoma

Epidemiology, histopathology, clinical presentation, and imaging characteristics

Autoimmune pancreatitis (AIP) was first recognized in 1961, although a more detailed description of its histopathology was reported in 1991 (199, 200). There are currently two main types (Type 1 and Type 2) acknowledged in clinical practice and within the literature. This may or may not present as a focal pancreatic mass; however, it often causes obstructive jaundice and chronic pancreatitis (201). Studies in Japan have suggested an incidence of 1.4 per 100,000 people and found that 5%–6% of patients with chronic pancreatitis had the underlying etiology of AIP (202). In children, evidence is limited to case reports and case series, although a study in 2017 identified 48 pediatric patients in the literature and from multiple pediatric databases. Cases were diagnosed in children 2 to 17 years old, with a mean age of 13 years (203).

Type 1 AIP, known as lymphoplasmacytic sclerosing pancreatitis (LPSP), is associated with elevation of serum immunoglobulin G4 (IgG4) (201). There are also associations with extrapancreatic IgG4 disease, including Sjogren's syndrome, primary sclerosing cholangitis, inflammatory bowel disease (IBD), and rheumatoid arthritis (RA) (204). Solitary or multiple extrapancreatic fibro-inflammatory lesions may be present, and have been reported in nearly every organ system (204). Males are two times more likely to develop Type I AIP, and although all age groups are affected, it occurs most commonly in 50–60 year olds (15). On histology, it is characterized by lymphoplasmacytic infiltration of smaller interlobular pancreatic ducts, obliterative phlebitis, and peri-ductal and venous fibrosis, which mostly affects the adipose tissue within the pancreas (15, 162). In the setting of obstructive jaundice, the diagnosis of Type I AIP can often be established with a serum elevation of IgG4 greater than 135 mg/dl, which may differentiate the lesion from a more concerning PDAC (205). An elevated plasma cell ratio of IgG4 to IgG greater than 40% and immunohistochemical staining with increased positivity of IgG4 cells (>10 cells per high-power field) may also be present (179, 206, 207). In children, elevated serum IgG4 is less useful, with only 22% of patients having been reported to have IgG4 levels above the upper limit of normal (203). Mayo Clinic also put forth the HISORt criteria, which identifies five cardinal features of Type I AIP for definitive diagnosis. These features include: 1) histology suggesting lymphoplasmacytic infiltrate with storiform fibrosis, 2) imaging demonstrating a diffusely enlarged pancreas, 3) serology demonstrating elevated IgG4 levels, 4) extrapancreatic organ involvement, and 5) disease response to steroid therapy (208, 209).

Type 2 AIP, known as idiopathic duct-centric pancreatitis (IDCP), has a more elusive diagnosis due to the absence of elevated serum IgG4. In the United States, Type 2 accounts for 20 to 40% of AIP cases (202). IBD is typically the only autoimmune association and is seen in close to 30% of patients. Compared to Type 1 AIP, younger patients are more affected by Type 2, with a mean age of 43 years at diagnosis. Although periductal lymphoplasmacytic infiltrates are also present, these are typically devoid of IgG4 plasma cells. In addition, the extent of fibrosis and phlebitis is less, and there is presence of neutrophilic infiltrates of the ductal epithelium and lumen (referred to as granulocytic epithelial lesions) (15, 179, 207). Often, the definitive diagnosis of Type 2 AIP is established by histopathology review of specimens from patients undergoing surgical resection for presumed malignant disease. Otherwise, accurate diagnosis requires the use of a thorough patient history, cross-sectional imaging, endoscopic imaging, and serology (162).

Although the variants of AIP have different histopathology, their clinical and radiologic characteristics overlap with one

another, as well as with concerning solid pancreatic tumors. When AIP affects the pancreatic head, strictures are formed in the distal common bile duct causing obstructive jaundice. Therefore, patients will present with painless jaundice as well as weight loss, abdominal pain, and glucose intolerance, which is similar to the presentation of PDAC. Children with AIP most commonly present with abdominal pain (90%), followed by obstructive jaundice (42%), and weight loss (29%) (203).

While the diagnosis of AIP has proven to be challenging, fewer cases are being identified on surgical pathology, likely indicating that AIP is commonly being diagnosed without surgical resection (162). US may first be the first modality to suggest AIP, demonstrating a hypoechoic, enlarged pancreas or mass-like lesion in the pancreas (8, 203). Classically, CT and MRI imaging demonstrate a diffusely enlarged pancreas, described as being "sausage-shaped" with a smooth outline due to the absence of pancreatic clefts (up to 50%–70% of adults); however, focal and multifocal enlargement may also be seen (8, 162, 210). Although Type 1 and Type 2 AIP appear similar on imaging, Type 2 disease is often more focal (85%). Delayed enhancement is demonstrated in the presence of underlying pancreatic fibrosis, and a hypoattenuating halo is present due to associated fluid, phlegmon, or fibrosis (211). MR cholangiopancreatography (MRCP) displays long strictures (defined as >1/3 the length of the main pancreatic duct), multiple strictures, or segmental/focal narrowing. Endoscopic retrograde cholangiopancreatography (ERCP) has the ability to identify characteristic ductal changes seen in AIP; however, its use is often therapeutic in cases of ductal obstruction (202). In children, cross-sectional imaging demonstrates focal gland enlargement in a slight majority of patients (52%). MRCP imaging demonstrates main pancreatic duct irregularity in 63% of patients, common bile duct (CBD) stricture/tapering in 54%, CBD dilatation in 52%, and a hypoattenuating halo in 16% (203). EUS is more commonly utilized now in diagnosis of AIP in children with high sensitivity, and it also allows biopsy of the lesion with FNA or core biopsy to allow tissue diagnosis.

Distinguishing autoimmune pancreatitis from pancreatic malignancy

Similarities between AIP and pancreatic carcinoma on imaging findings have led to unnecessary radical pancreatic resections in patients with AIP (15). In a study of patients in Japan undergoing PD for a pancreatic head mass from 1992 to 2005, 4% of patients were found to have AIP (202). Key characteristics seen on CT and MRCP imaging which may delineate AIP from PDAC include focal stricture or narrowing and a "capsule-like halo" with delayed enhancement (8, 210). PDAC is more frequently associated with significant pancreatic ductal dilatation and a hyperdense rim on non-contrast imaging. Importantly, focal pancreatitis in the setting of AIP can also produce both upstream pancreatic ductal dilation and CBD dilation, producing a "double duct sign" (**Figure 11**). Also important to recognize is that AIP may respond to a short course of corticosteroid treatment, while PDAC will not (202).

PET imaging is not advantageous in differentiating PDAC from AIP due to diffuse and intense uptake of FDG in areas of pancreatic inflammation. However, if extrapancreatic organs associated with Type 1 AIP have avid FDG uptake, this may help guide a diagnosis (202). In contrast, EUS with tissue biopsy has been shown to be especially beneficial in providing a definitive diagnosis of AIP. EUS findings include an enlarged pancreas with echogenic interlobular septa and a narrowing in the main pancreatic duct. To obtain a tissue diagnosis of AIP, EUS fine-needle aspiration may be performed. With advances in spring-loaded biopsy needles with rapid motion, adequate samples have been reported in up to 80% of cases (212). Accuracy using EUS Tru-Cut needle

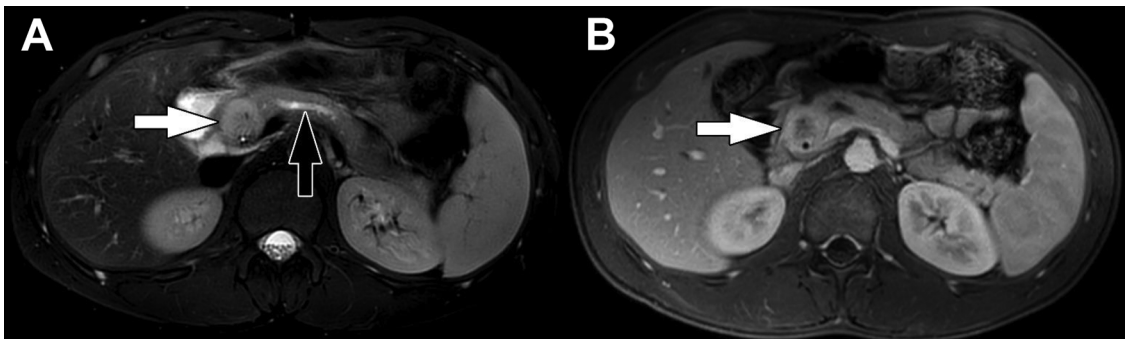

FIGURE 10
Inflammatory myofibroblastic tumor. (A) Axial T2-weighted fat-saturated MRI and (B) Axial T1-weighted fat-saturated post-contrast MRI show a mass in the head of the pancreas (white arrows). The mass is heterogeneously T2-weighted hyperintense with heterogenous enhancement following contrast administration. Lack of central enhancement suggests necrosis. There is associated dilation of the upstream pancreatic duct (black arrow) due to obstruction by the mass.

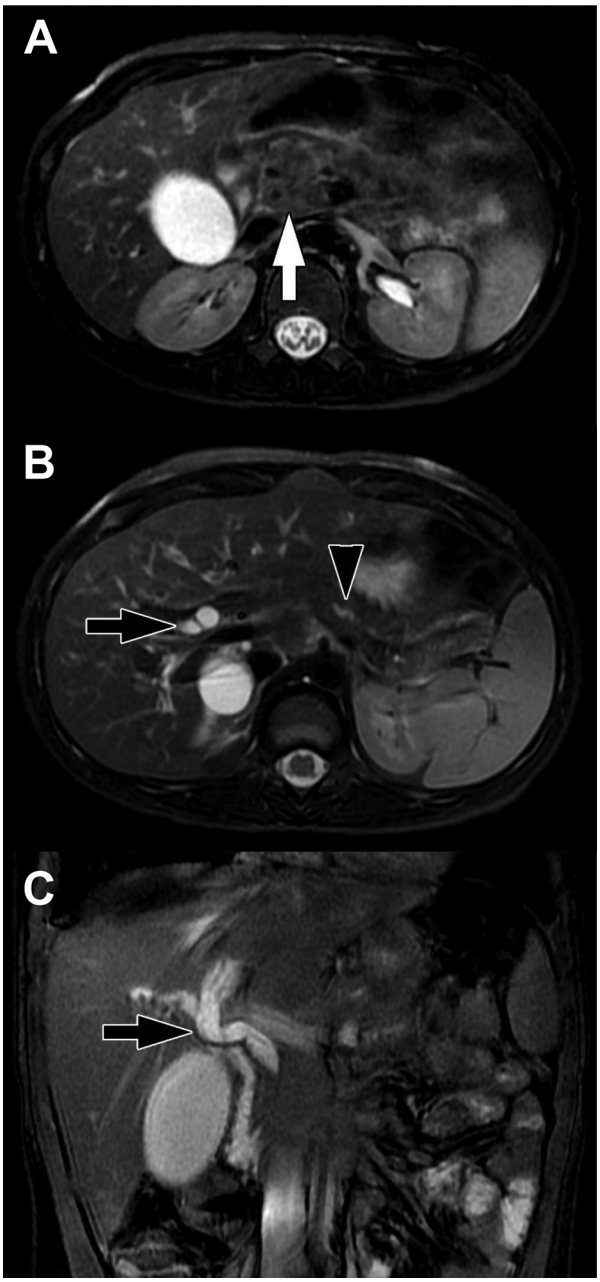

FIGURE 11
Focal pancreatitis. (**A**) Axial T2-weighted fat-saturated MFI shows heterogenous enlargement of the head of the pancreas (arrow). There is no substantial peripancreatic inflammation. (**B**) Axial T2-weighted fat-saturated MRI more cephalad in the same patient shows upstream bile duct dilation (black arrow) and dilation of the pancreatic duct (black arrowhead) due to obstruction by the process in the head of the pancreas. (**C**) Coronal balanced MRI in the same patient shows the extent of dilation of the bile ducts. The double duct sign of dilated pancreatic and bile ducts raises suspicion for a mass in the head of the pancreas.

biopsy is even higher (85%), although technically more challenging. Algorithms have suggested the attempt at EUS fine-needle biopsy first, and if results are negative for PDAC in a case of presumed AIP, EUS Tru-Cut needle biopsy should be secondarily performed (213).

Treatment

The main goals of treatment in AIP are relief of symptoms and pancreatic tissue preservation. High-dose corticosteroids are the most common and successful treatment in cases of AIP, with therapeutic responses seen on imaging as early as 2 weeks (15). Typically, resolution of pancreatic inflammation, swelling, and surrounding fluid/phlegmon occurs. However, pancreatic fibrosis is long-lasting and may result in endocrine and exocrine insufficiency requiring pancreatic enzyme replacement therapy. Relapsing disease has also been reported in up to 53% of patients after steroid treatment and taper, although is more common in Type 1 AIP (60%) than Type 2 (5%) (214, 215). In a cohort of 48 pediatric patients with AIP, most were treated with steroids (60%), followed by biliary and/or pancreatic stenting (17%), partial pancreatectomy (6%), PD (4%), and choledochoduodenostomy (2%), while 17% were clinically monitored. Twenty-one percent of children experienced AIP relapse and 16% experienced exocrine insufficiency requiring enzyme replacement (203). In steroid-resistant or relapsing disease, immunomodulators and rituximab have been utilized (216). A response to steroid therapy is one of the cardinal features in the diagnosis of AIP, and failure of symptom or imaging resolution requires a prompt investigation for alternative diagnoses.

Parenchyma-sparing resection: how much is enough?

Approaches to resection

When approaching pancreatic resection in pediatric patients, two key determinants guide operative planning: tumor type and tumor location. Oncologic and radical resection remains the standard of care for malignant tumors, however, parenchyma-sparing procedures have gained interest for the treatment of benign or low-grade tumors (217). Masses and tumors located in the pancreatic head often require pancreaticoduodenectomy with or without pylorus-preservation, or duodenum-preserving pancreatic head resection (DPPHR). Total pancreatectomy may rarely be required to achieve negative surgical margins. Lesions in the pancreatic body/tail are frequently resected with a distal pancreatectomy. However, central pancreatectomy has been described in masses limited to the pancreatic neck and proximal body, and enucleation may be performed for smaller benign tumors.

Although relatively uncommon, pancreatic surgery in pediatric patients has been shown to be safe and effective, especially when performed by experienced surgeons (218–222). When feasible, laparoscopic pancreatic resections have also demonstrated similar outcomes and decreased morbidity (223,

224). In studies of pediatric patients undergoing pancreatic resection for tumors, cohorts are relatively small with heterogeneous pathology. In a study of 46 children undergoing pancreatic operations, 10 patients with SPN mostly underwent DP, followed by PD, and central pancreatectomy. Two patients with PBL underwent total pancreatectomy and PD, and three patients with desmoid tumors of the pancreas underwent DP. Four patients underwent either DP or PD for pancreatic NET resection (218). Like findings in this particular study, the literature demonstrates low surgery-related mortality rates overall (219–221).

Radical resection remains the gold standard for malignant disease

Pancreatic tumors requiring PD in children and adolescents are uncommon (219, 225). Also known as a Whipple operation, the procedure involves resection of the pancreatic head, duodenum, and distal bile duct, resulting in removal of up to 50% of the gland (**Figure 12**) (226). Historically, an antrectomy is performed with duodenal resection; however, the pylorus may be preserved (pylorus-preserving) by dividing the proximal duodenum and creating a duodenojejunostomy reconstruction. One of the biggest concerns after PD are the rates of endocrine and exocrine dysfunction, which may occur in up to 50% of patients (226). The removal of the duodenum, proximal jejunum, and pancreatic head eliminates important metabolic and hormonal signaling centers of the gastrointestinal tract. This leads to impairment of endocrine function in the form of new-onset diabetes mellitus (DM) and impairment of exocrine function requiring pancreatic enzyme replacement therapy (227).

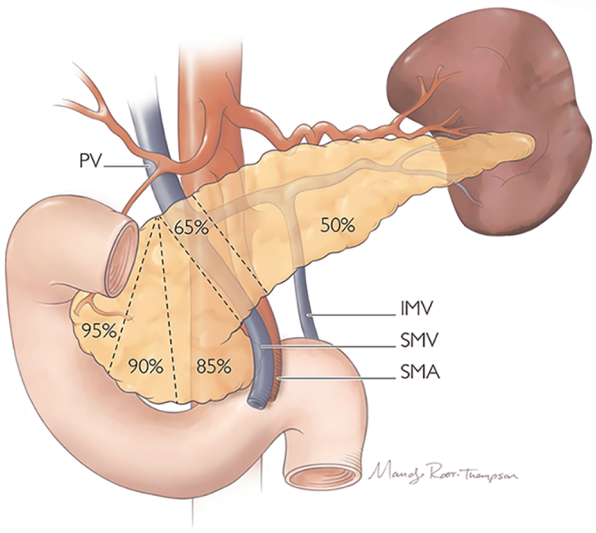

FIGURE 12
Proportions of the pancreas which may be resected during radical or parenchyma-preserving operation.

In a recent meta-analysis of predominantly adults, patients undergoing PD for benign tumors developed new-onset DM in 14% of cases, while 54% developed new-onset exocrine insufficiency (228). In pylorus-preserving PD, 20% of patients developed new-onset DM, and 45% developed new-onset exocrine insufficiency. In the largest series of pediatric patients undergoing open PD, 65 children with a median age of 13 years old from 18 hospitals were evaluated (225). The most common histological diagnoses requiring PD were SPN, followed by PBL, PDAC, and pancreatic NET. Pancreatic leak occurred in 14% of patients, while 32% of patients developed pancreatic insufficiency, and 9% developed delayed gastric emptying. Overall, 22% experienced recurrence and 17% experienced mortality. In this cohort, survival and recurrence were not impacted by the type of PD, neoadjuvant chemotherapy, or the presence of an adult hepatobiliary surgeon. In a smaller study of 22 patients less than 30 years old undergoing PD, intra-abdominal abscess was the most common complication (14%), pancreatic leak occurred in 4.5%, and there were no mortalities reported (219).

DP typically involves resection of some or all of the pancreatic body/tail to the left of the superior mesenteric vein/portal vein, which results in removal of approximately 50% of the gland (226) (**Figure 12**). The operation may include a splenectomy, especially in cases where an oncologic resection is required, or may be spleen-preserving. Spleen-preserving DP and DP with splenectomy have similar clinical outcomes with respect to postoperative pancreatic fistula occurrence (7.6%), wound infection, and re-operation rates in patients with benign or borderline malignant tumors of the pancreas (229–232). However, the incidence of infectious complications is significantly reduced in patients who undergo spleen-preserving DP (9%) compared to those who undergo splenectomy (28%), suggesting that splenic preservation should be maximized when feasible (230). This is especially true in pediatric patients due to their increased risk for overwhelming post-splenectomy infection (OPSI) (233). Further, laparoscopic spleen-preserving DP has also been demonstrated as safe and feasible in children, specifically for treatment of SPN (233, 234).

In the meta-analysis by Beger et al., DP was associated with new-onset DM in 23% of patients and exocrine insufficiency in 17% (228). In a study of patients under 40 years old, 112 underwent DP, most commonly for pancreatic NET, mucinous cystic neoplasm, and SPN (235). However, when a subset of patients ≤18 years old were evaluated, most had pathology for SPN, followed by pancreatic NET. In patients under 40 years old, new-onset diabetes occurred in 15% and exocrine insufficiency in 16%, while 8% of patients ≤18 years old developed new-onset diabetes and none had postoperative exocrine insufficiency. Overall, there were no mortalities related to operation.

Parenchyma-sparing resection may be justified

A variety of surgical methods have been described with the goal to maximize the preservation of pancreatic parenchymal tissue, preserve the gastrointestinal tract anatomy and function, and avoid postoperative endocrine and exocrine dysfunction (217). Among those most commonly performed in children with pancreatic tumors are DPPHR, central pancreatectomy, and enucleation.

A DPPHR procedure was first introduced in 1972 to surgically treat inflammatory masses in the pancreatic head (236). Depending on the extent of the pancreatic head resection, DPPHR is classified as total or partial, with total DPPHR often being implemented to avoid incomplete resection in the setting of malignancy. Concurrent segmental resection of the duodenum may also be performed to obtain an appropriate oncologic resection (217). In 1994, Nako et al. described DPPHR with segmental resection of the periampullary duodenum, and in 1999, Beger reported DPHHR without segmental resection of the duodenum (237, 238). The Berne procedure was subsequently introduced as a technical simplification of the Beger procedure, as it avoids division of the pancreatic neck over the portal vein (239). Frey also reported an operation which combines DPPHR and longitudinal pancreaticojejunostomy (240). DPPHR is best suited for benign and low-grade malignant tumors in the pancreatic head including SPN, pancreatic NET, serous cystic adenoma, and intraductal papillary mucinous neoplasm (IPMN), producing favorable outcomes in these patients (217, 241). Laparoscopic DPPHR (LDPPHR) has also been proven a safe and effective surgical procedure (217, 236, 241). Compared to laparoscopic PD, LDPPHR has similar outcomes related to postoperative complications, pancreatic fistula, 30-day readmission, and 90-day mortality, while also being a shorter operation (217).

Quantitative comparisons with PD have also demonstrated both short-term and long-term benefits (242). DPPHR demonstrated less new-onset DM (5%) compared to PD (15.7%) and less exocrine insufficiency (6.7% vs. 44.3%) (228). Following PD, significant impairment was measured in the gastrointestinal hormones gastrin, motilin, insulin, secretin, PP, and gastric inhibitory polypeptide (GIP), while no change in the response of these hormones was seen after DPPHR (227). In 21 children with an average age of 11.7 years who underwent DPPHR, most had pathology for SPN ($n = 10$) (242). Thirty-three percent required exocrine enzymatic replacement therapy, though there were no mortalities. In appropriately selected patients with pancreatic head masses, DPPHR may be preferable to preserve native gastrointestinal anatomy and avoid long-term pancreatic insufficiency with its related consequences.

Since central pancreatectomy was first reported in 1984 by Dagradi and Serio, at least 1,305 cases have been reported in the literature (243, 244). Often, tumors located in the pancreatic neck or proximal body create a challenge for surgeons, requiring either an extended PD or extended distal pancreatectomy. However, in benign and borderline disease, this substantial loss of normal pancreatic tissue results in increased and unnecessary endocrine and exocrine dysfunction for the patient (245). Also known as a middle or medial pancreatectomy, central pancreatectomy is a parenchyma-sparing procedure used to resect benign and low-grade malignant tumors located in the pancreatic neck and proximal body. Typically, these include SPNs, pancreatic NETs, and small tumors which are deeply embedded within the parenchyma and not amenable to enucleation (246). Typically, a Roux-en-Y jejunal limb is created, with a pancreaticojejunostomy anastomosis performed at the distal remnant pancreatic stump (**Figure 13**). In a meta-analysis by Iacono et al., most distal pancreatic stumps in central pancreatectomies were managed by pancreaticojejunostomy (58%) or pancreaticogastrostomy (38%), while the proximal stump was closed by suturing (64%) or stapling (30%) or anastomosed via pancreaticojejunostomy (6%).

Mortality rates following central pancreatectomy in adults are low (0.5%–0.8%), and pancreatic fistula is the most common complication, reported in 35%–41% of cases (243, 246). However, the use of a pancreaticogastrostomy anastomosis has been associated with significantly higher pancreatic fistula incidence and severity compared to pancreaticojejunostomy (247). Pancreatic fistula rates following central pancreatectomy are also higher compared to rates after PD or DP (246). Compared to PD, central pancreatectomy is associated with lower intraoperative blood loss, shorter operative time, and shorter hospital stay. However, compared to DP, central pancreatectomy is associated with longer operative time and hospital stay. New-onset DM and exocrine insufficiency is significantly lower following central pancreatectomy, compared to both PD and DP (246).

Evidence related to central pancreatectomy performed in children is limited to case series and reports but has been reported for the management of PBL and SPN, where complete surgical resection was possible (218, 248–251). Two cases are reported with the use of a pancreaticogastrostomy anastomosis, and two other cases are reported using a Roux-en-Y jejunal limb, with one being performed robotically (248, 249). One 16-year-old with PBL underwent resection and adjuvant chemotherapy, which led to prolonged disease-free survival without the development of pancreatic endocrine and exocrine insufficiency (250). Central pancreatectomy has also been reported for resection of a Ewing sarcoma in a young child who had undergone neoadjuvant chemotherapy (Figure **13**) (8). Overall, although pancreatic fistula occurrence is higher than that in PD and DP, central pancreatectomy provides important clinical benefits due its ability to preserve normal pancreatic parenchyma in pediatric patients with expected long-term survival.

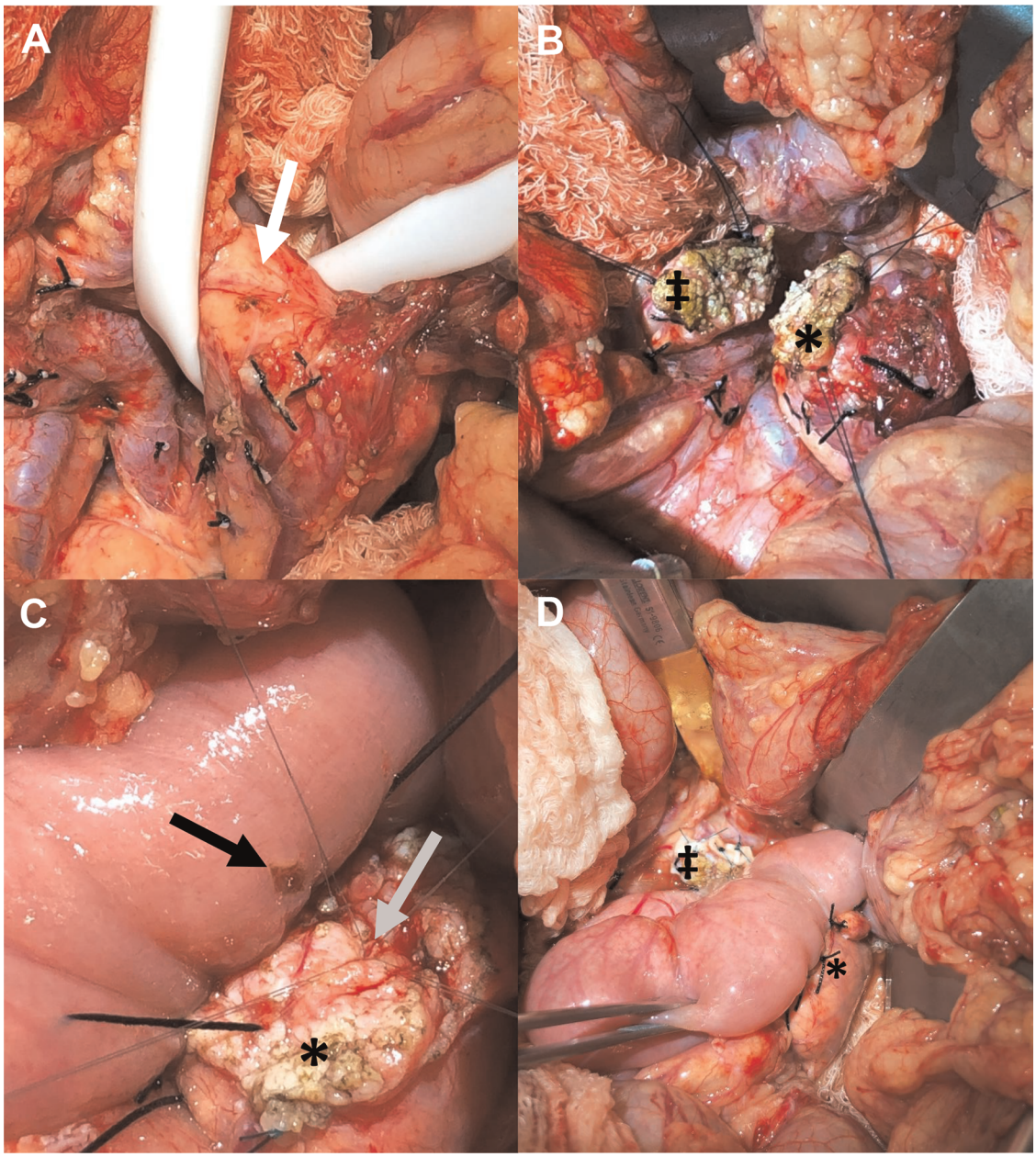

FIGURE 13
Central pancreatectomy. (A) Ewing sarcoma is demonstrated within the neck of the pancreatic parenchyma (white arrow). (B) Following resection of the neck of pancreas with mass, edges of the transected pancreatic head (‡) and body (*) are demonstrated. (C) For reconstruction, a Roux-en-Y jejunal enterotomy is made (black arrow), and the main pancreatic duct (gray arrow) within the distal pancreatic remnant (*) is prepared for anastomosis. (D) Reconstruction involving anastomosis of the Roux-en-Y jejunal limb to the distal pancreatic remnant (*) creating a complete pancreaticojejunal anastomosis. The remnant pancreatic head is also demonstrated (‡). IMV: inferior mesenteric vein; PV: portal vein; SMA: superior mesenteric artery; SMV, superior mesenteric vein.

Enucleation has also been considered reasonable surgical management for benign and low-grade malignancies. However, it should be avoided in certain tumors greater than 2 cm in size (i.e., non-functioning pancreatic NET), embedded deep within the gland, located less than 2–3 mm from the main pancreatic duct, and without clearly benign pathology (i.e., margins cannot be compromised) (252–254). Enucleation is most commonly performed for insulinomas and non-functioning pancreatic NETs. It is particularly useful for benign symptomatic pancreatic NETs, like insulinoma, because it provides excellent outcomes even when margins are positive, while also maintaining quality of life for the patient.

Varying rates of pancreatic fistula have been reported (21%–61%). Although these rates are sometimes higher than that seen in standard resection, they do not necessarily result in higher morbidity and mortality (254, 255). In a large series, new-onset DM was demonstrated in 0%–5% of patients undergoing enucleation, while exocrine insufficiency has been reported in just 4% (228, 254).

Conclusion

In conclusion, pancreatic tumors are uncommon in children but have better survival and overall outcomes compared to adults with pancreatic tumors. PBL and SPN are the most common pancreatic tumors diagnosed in children and are best managed by complete surgical resection. Insulinomas remain the most common pancreatic NET and may undergo enucleation in certain cases where tumors are small (<2 cm) and benign. Although some tumors overlap in their clinical presentation and imaging characteristics, AIP may be especially challenging to distinguish from PDAC, resulting in unnecessary radical pancreatic resections. However, EUS has become an important adjunct in diagnostic imaging and may provide helpful guidance toward an accurate diagnosis. Lastly, while malignant tumors require radical oncologic resection, often with PD or DP, parenchyma-sparing surgical management should be a considered alternative for benign and low-grade malignancy, as it has been shown to be safe and effective while preserving pancreatic endocrine and exocrine function in children.

Author contributions

KNP, ATT, AS, MA, and JDN conceptualized and designed the review, coordinated data collection, drafted the initial manuscript, and reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J Pediatr Surg*. (2009) 44(1):197–203. doi: 10.1016/j.jpedsurg.2008.10.039

2. Digestive system tumours. *WHO Classification of tumours editorial board*. 5th ed. Lyon, France: IARC Publications; 2019.

3. Chung EM, Travis MD, Conran RM. Pancreatic tumors in children: radiologic-pathologic correlation. *Radiogr*. (2006) 26(4):1211–38. doi: 10.1148/rg.264065012

4. Wood LD, Klimstra DS. Pathology and genetics of pancreatic neoplasms with acinar differentiation. *Semin Diagn Pathol*. (2014) 31(6):491–7. doi: 10.1053/j.semdp.2014.08.003

5. Mylonas KS, Doulamis IP, Tsilimigras DI, Nasioudis D, Schizas D, Masiakos PT, et al. Solid pseudopapillary and malignant pancreatic tumors in childhood: a systematic review and evidence quality assessment. *Pediatr Blood Cancer*. (2018) 65(10):e27114. doi: 10.1002/pbc.27114

6. Reggiani G, Affinita MC, Dall'Igna P, Virgone C, Sorbara S, Bisogno G. Treatment strategies for children with relapsed pancreatoblastoma: a literature review. *J Pediatr Hematol Oncol*. (2021) 43(8):288–93. doi: 10.1097/MPH.0000000000002033

7. Klimstra DS, Wenig BM, Adair CF, Heffess CS. Pancreatoblastoma. A clinicopathologic study and review of the literature. *Am J Surg Pathol*. (1995) 19 (12):1371–89. doi: 10.1097/00000478-199512000-00005

8. Qiu L, Trout AT, Ayyala RS, Szabo S, Nathan JD, Geller JI, et al. Pancreatic masses in children and young adults: multimodality review with pathologic correlation. *Radiogr*. (2021) 41(6):1766–84. doi: 10.1148/rg.2021210008

9. Hoorens A, Gebhard F, Kraft K, Lemoine NR, Klöppel G. Pancreatoblastoma in an adult: its separation from acinar cell carcinoma. *Virchows Arch*. (1994) 424 (5):485–90. doi: 10.1007/BF00191433

10. Dunn JL, Longnecker DS. Pancreatoblastoma in an older adult. *Arch Pathol Lab Med*. (1995) 119(6):547–51.

11. Cavallini A, Falconi M, Bortesi L, Crippa S, Barugola G, Butturini G. Pancreatoblastoma in adults: a review of the literature. *Pancreatol*. (2009) 9(1-2):73–80. doi: 10.1159/000178877

12. Balasundaram C, Luthra M, Chavalitdhamrong D, Chow J, Khan H, Endres PJ. Pancreatoblastoma: a rare tumor still evolving in clinical presentation and histology. *Jop*. (2012) 13(3):301–3. doi: 10.6092/1590-8577/661

13. Roebuck DJ, Yuen MK, Wong YC, Shing MK, Lee CW, Li CK. Imaging features of pancreatoblastoma. *Pediatr Radiol*. (2001) 31(7):501–6. doi: 10.1007/s002470100448

14. Solcia E, Capella C, Kloppel G. *Atlas of tumor pathology: Tumors of the pancreas*. Washington, DC: Armed Forces Institute of Pathology (1997).

15. Basturk O, Kloppel G, Klimstra DS. Tumors of the exocrine pancreas. In: C Fletcher, editor. *Diagnostic histopathology of tumors*. 5th ed: Philadelphia, PA: Elsevier Inc; 2021. p. 568–99.

16. Bien E, Roganovic J, Krawczyk MA, Godzinski J, Orbach D, Cecchetto G, et al. Pancreatoblastoma in children: eXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer*. (2021) 68(S4):e29112. doi: 10.1002/pbc.29112

17. Abraham SC, Wu TT, Klimstra DS, Finn LS, Lee JH, Yeo CJ, et al. Distinctive molecular genetic alterations in sporadic and familial adenomatous polyposis-associated pancreatoblastomas: frequent alterations in the APC/beta-catenin pathway and chromosome 11p. *Am J Pathol*. (2001) 159(5):1619–27. doi: 10.1016/S0002-9440(10)63008-8

18. Bien E, Godzinski J, Dall'igna P, Defachelles AS, Stachowicz-Stencel T, Orbach D, et al. Pancreatoblastoma: a report from the European cooperative

study group for paediatric rare tumours (EXPeRT). *Eur J Cancer*. (2011) 47 (15):2347–52. doi: 10.1016/j.ejca.2011.05.022

19. Kissane JM. Pancreatoblastoma and solid and cystic papillary tumor: two tumors related to pancreatic ontogeny. *Semin Diagn Pathol*. (1994) 2:152–64.

20. Saif MW. Pancreatoblastoma. *JOP: Journal of the Pancreas*. (2007) 8(1):55–63.

21. Ohike N, Jürgensen A, Pipeleers-Marichal M, Klöppel G. Mixed ductal-endocrine carcinomas of the pancreas and ductal adenocarcinomas with scattered endocrine cells: characterization of the endocrine cells. *Virchows Arch*. (2003) 442(3):258–65. doi: 10.1007/s00428-002-0751-5

22. Singhi AD, Lilo M, Hruban RH, Cressman KL, Fuhrer K, Seethala RR. Overexpression of lymphoid enhancer-binding factor 1 (LEF1) in solid-pseudopapillary neoplasms of the pancreas. *Mod Pathol*. (2014) 27(10):1355–63. doi: 10.1038/modpathol.2014.40

23. Nishimata S, Kato K, Tanaka M, Ijiri R, Toyoda Y, Kigasawa H, et al. Expression pattern of keratin subclasses in pancreatoblastoma with special emphasis on squamoid corpuscles. *Pathol Int*. (2005) 55(6):297–302. doi: 10.1111/j.1440-1827.2005.01829.x

24. Montemarano H, Lonergan GJ, Bulas DI, Selby DM. Pancreatoblastoma: imaging findings in 10 patients and review of the literature. *Radiol*. (2000) 214 (2):476–82. doi: 10.1148/radiology.214.2.r00fe36476

25. Gupta AK, Mitra DK, Berry M, Dinda AK, Bhatnagar V. Sonography and CT of pancreatoblastoma in children. *AJR Am J Roentgenol*. (2000) 174 (6):1639–41. doi: 10.2214/ajr.174.6.1741639

26. Stephenson CA, Kletzel M, Seibert JJ, Glasier CM. Pancreatoblastoma: mR appearance. *J Comput Assist Tomogr*. (1990) 14(3):492–3.

27. Huang Y, Yang W, Hu J, Zhu Z, Qin H, Han W, et al. Diagnosis and treatment of pancreatoblastoma in children: a retrospective study in a single pediatric center. *Pediatr Surg Int*. (2019) 35(11):1231–8. doi: 10.1007/s00383-019-04524-y

28. Défachelles AS, Martin De Lassalle E, Boutard P, Nelken B, Schneider P, Patte C. Pancreatoblastoma in childhood: clinical course and therapeutic management of seven patients. *Med Pediatr Oncol*. (2001) 37(1):47–52. doi: 10.1002/mpo.1162

29. Dhebri AR, Connor S, Campbell F, Ghaneh P, Sutton R, Neoptolemos JP. Diagnosis, treatment and outcome of pancreatoblastoma. *Pancreatology*. (2004) 4(5):441–51.; discussion 52–3. doi: 10.1159/000079823

30. Dall'igna P, Cecchetto G, Bisogno G, Conte M, Chiesa PL, D'Angelo P, et al. Pancreatic tumors in children and adolescents: the Italian TREP project experience. *Pediatr Blood Cancer*. (2010) 54(5):675–80. doi: 10.1002/pbc.22385

31. Frantz V. Papillay tumors of the pancreas - benign or malignant? Atlas of tumor pathology, tumors of the pancreas. *Armed Forces Inst of Pathol*. (1959) 36:32–3.

32. Shorter NA, Glick RD, Klimstra DS, Brennan MF, LaQuaglia MP. Malignant pancreatic tumors in childhood and adolescence: the memorial sloan-kettering experience, 1967 to present. *J Pediatr Surg*. (2002) 37(6):887–92. doi: 10.1053/jpsu.2002.32897

33. Speer AL, Barthel ER, Patel MM, Grikscheit TC. Solid pseudopapillary tumor of the pancreas: a single-institution 20-year series of pediatric patients. *J Pediatr Surg*. (2012) 47(6):1217–22. doi: 10.1016/j.jpedsurg.2012.03.026

34. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. *J Am Coll Surg*. (2005) 200(6):965–72. doi: 10.1016/j.jamcollsurg.2005.02.011

35. Yu P-F, Hu Z-H, Wang X-B, Guo J-M, Cheng X-D, Zhang Y-L, et al. Solid pseudopapillary tumor of the pancreas: a review of 553 cases in Chinese literature. *World J Gastroenterol*. (2010) 16(10):1209. doi: 10.3748/wjg.v16.i10.1209

36. van den Akker M, Angelini P, Taylor G, Chami R, Gerstle JT, Gupta A. Malignant pancreatic tumors in children: a single-institution series. *J Pediatr Surg*. (2012) 47(4):681–7. doi: 10.1016/j.jpedsurg.2011.11.046

37. Laje P, Bhatti TR, Adzick NS. Solid pseudopapillary neoplasm of the pancreas in children: a 15-year experience and the identification of a unique immunohistochemical marker. *J Pediatr Surg*. (2013) 48(10):2054–60. doi: 10.1016/j.jpedsurg.2013.02.068

38. Mao C, Guvendi M, Domenico DR, Kim K, Thomford NR, Howard JM. Papillary cystic and solid tumors of the pancreas: a pancreatic embryonic tumor? Studies of three cases and cumulative review of the world's Literature. *Surg*. (1995) 118(5):821–8. doi: 10.1016/S0039-6060(05)80271-5

39. Burford H, Baloch Z, Liu X, Jhala D, Siegal GP, Jhala N. E-cadherin/beta-catenin and CD10: a limited immunohistochemical panel to distinguish pancreatic endocrine neoplasm from solid pseudopapillary neoplasm of the pancreas on endoscopic ultrasound-guided fine-needle aspirates of the pancreas. *Am J Clin Pathol*. (2009) 132(6):831–9. doi: 10.1309/AJCPVT8FCLFDTZWI

40. Zhu H, Xia D, Wang B, Meng H. Extrapancreatic solid pseudopapillary neoplasm: report of a case of primary retroperitoneal origin and review of the literature. *Oncol Lett*. (2013) 5(5):1501–4. doi: 10.3892/ol.2013.1242

41. Elorza Orúe JL, Ruiz Díaz I, Tubía Landaberea J, San Vicente Leza M. [Solid and papillary tumor on ectopic pancreas in transversal mesocolon]. *Rev Esp Enferm Dig*. (1991) 79(6):429–31.

42. Tornóczky T, Kálmán E, Jakso P, Méhes G, Pajor L, Kajtár G, et al. Solid and papillary epithelial neoplasm arising in heterotopic pancreatic tissue of the mesocolon. *J Clin Pathol*. (2001) 54(3):241–5. doi: 10.1136/jcp.54.3.241

43. Kövári E, Járay B, Pulay I. Papillary cystic neoplasms in the ectopic pancreas. *Orv Hetil*. (1996) 137(17):923–5.

44. Ahmed TS, Chavhan GB, Navarro OM, Traubici J. Imaging features of pancreatic tumors in children: 13-year experience at a pediatric tertiary hospital. *Pediatr Radiol*. (2013) 43(11):1435–43. doi: 10.1007/s00247-013-2721-2

45. Ishikawa O, Ishiguro S, Ohhigashi H, Sasaki Y, Yasuda T, Imaoka S, et al. Solid and papillary neoplasm arising from an ectopic pancreas in the mesocolon. *Am J Gastroenterol (Springer Nature)*. (1990) 85(5):597–601.

46. Mahida JB, Thakkar RK, Walker J, Shen R, Kenney BD, Prasad V, et al. Solid pseudopapillary neoplasm of the pancreas in pediatric patients: a case report and institutional case series. *J Pediatr Surg Case Rep*. (2015) 3(4):149–53. doi: 10.1016/j.epsc.2015.02.006

47. Liu BA, Li ZM, Su ZS, She XL. Pathological differential diagnosis of solid-pseudopapillary neoplasm and endocrine tumors of the pancreas. *World J Gastroenterol*. (2010) 16(8):1025–30. doi: 10.3748/wjg.v16.i8.1025

48. Hwang J, Kim DY, Kim SC, Namgoong JM, Hong SM. Solid-pseudopapillary neoplasm of the pancreas in children: can we predict malignancy? *J Pediatr Surg*. (2014) 49(12):1730–3. doi: 10.1016/j.jpedsurg.2014.09.011

49. Nguyen NQ, Johns AL, Gill AJ, Ring N, Chang DK, Clarkson A, et al. Clinical and immunohistochemical features of 34 solid pseudopapillary tumors of the pancreas. *J Gastroenterol Hepatol*. (2011) 26(2):267–74. doi: 10.1111/j.1440-1746.2010.06466.x

50. Song JS, Yoo CW, Kwon Y, Hong EK. Endoscopic ultrasound-guided fine needle aspiration cytology diagnosis of solid pseudopapillary neoplasm: three case reports with review of literature. *Korean J Pathol*. (2012) 46(4):399–406. doi: 10.4132/KoreanJPathol.2012.46.4.399

51. Gou S, Yu J, Wang C, Liu T, Cui P, Li X. Three female familial cases of solid pseudopapillary tumors with a protease serine 1 gene mutation. *Pancreas*. (2013) 42(1): 168–73. doi: 10.1097/MPA.0b013e3182554276

52. Klimstra DS, Wenig BM, Heffess CS. Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential. *Semin Diagn Pathol*. (2000) 17(1):66–80.

53. Kim SA, Kim MS, Kim MS, Kim SC, Choi J, Yu E, et al. Pleomorphic solid pseudopapillary neoplasm of the pancreas: degenerative change rather than high-grade malignant potential. *Hum Pathol*. (2014) 45(1):166–74. doi: 10.1016/j.humpath.2013.08.016

54. Kim MJ, Jang SJ, Yu E. Loss of E-cadherin and cytoplasmic-nuclear expression of beta-catenin are the most useful immunoprofiles in the diagnosis of solid-pseudopapillary neoplasm of the pancreas. *Hum Pathol*. (2008) 39 (2):251–8. doi: 10.1016/j.humpath.2007.06.014

55. Sclafani LM, Coit DG, Brennan MF, Reuter VE. The malignant nature of papillary and cystic neoplasm of the pancreas. *Cancer*. (1991) 68(1):153–8. doi: 10.1002/1097-0142(19910701)68:1<153::AID-CNCR2820680128>3.0.CO;2-N

56. Lee DH, Yi BH, Lim JW, Ko YT. Sonographic findings of solid and papillary epithelial neoplasm of the pancreas. *J Ultrasound Med*. (2001) 20(11):1229–32. doi: 10.7863/jum.2001.20.11.1229

57. Friedman AC, Lichtenstein JE, Fishman EK, Oertel JE, Dachman AH, Siegelman SS. Solid and papillary epithelial neoplasm of the pancreas. *Radiology*. (1985) 154(2):333–7. doi: 10.1148/radiology.154.2.3880903

58. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. *Radiol*. (1996) 199(3):707–11. doi: 10.1148/radiology.199.3.8637992

59. Choi BI, Kim KW, Han MC, Kim YI, Kim CW. Solid and papillary epithelial neoplasms of the pancreas: cT findings. *Radiol*. (1988) 166(2):413–6. doi: 10.1148/radiology.166.2.3336716

60. Dong DJ, Zhang SZ. Solid-pseudopapillary tumor of the pancreas: cT and MRI features of 3 cases. *Hepatobiliary Pancreat Dis Int*. (2006) 5(2):300–4.

61. Nakatani K, Watanabe Y, Okumura A, Nakanishi T, Nagayama M, Amoh Y, et al. MR Imaging features of solid-pseudopapillary tumor of the pancreas. *Magn Reson Med Sci*. (2007) 6(2):121–6. doi: 10.2463/mrms.6.121

62. Kurihara K, Hanada K, Serikawa M, Ishii Y, Tsuboi T, Kawamura R, et al. Investigation of fluorodeoxyglucose positron emission tomography for the diagnosis of solid pseudopapillary neoplasm of the pancreas: a study associated with a national survey of solid pseudopapillary neoplasms. *Pancreas*. (2019) 48 (10):1312–20. doi: 10.1097/MPA.0000000000001424

63. Lam KY, Lo CY, Fan ST. Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. *World J Surg*. (1999) 23(10):1045–50. doi: 10.1007/s002689900621

64. Kaufman SL, Reddick RL, Stiegel M, Wild RE, Thomas CG. Papillary cystic neoplasm of the pancreas: a curable pancreatic tumor. *World J Surg*. (1986) 10 (5):851–9. doi: 10.1007/BF01655258

65. de Castro SM, Singhal D, Aronson DC, Busch OR, van Gulik TM, Obertop H, et al. Management of solid-pseudopapillary neoplasms of the pancreas: a comparison with standard pancreatic neoplasms. *World J Surg*. (2007) 31 (5):1130–5. doi: 10.1007/s00268-006-0214-2

66. Nagri S, Abdu A, Anand S, Krishnaiah M, Arya V. Liver metastasis four years after Whipple's Resection for solid-pseudopapillary tumor of the pancreas. *Jop*. (2007) 8(2):223–7.

67. Peng CH, Chen DF, Zhou GW, Yang WP, Tao ZY, Lei RQ, et al. The solid-pseudopapillary tumor of pancreas: the clinical characteristics and surgical treatment. *J Surg Res*. (2006) 131(2):276–82. doi: 10.1016/j.jss.2005.11.585

68. Frago R, Fabregat J, Jorba R, García-Borobia F, Altet J, Serrano MT, et al. Solid pseudopapillary tumors of the pancreas: diagnosis and curative treatment. *Rev Esp Enferm Dig*. (2006) 98(11):809–16. doi: 10.4321/S1130-01082006001100002

69. Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K, Hayashi I. Papillary cystic tumors of the pancreas. Assessment of their malignant potential. *Cancer*. (1993) 71(1):82–92. doi: 10.1002/1097-0142(19930101)71:1<82::AID-CNCR2820710114>3.0.CO;2-Y

70. Todani T, Shimada K, Watanabe Y, Toki A, Fujii T, Urushihara N. Frantz's tumor: a papillary and cystic tumor of the pancreas in girls. *J Pediatr Surg*. (1988) 23(2):116–21. doi: 10.1016/S0022-3468(88)80137-4

71. Rebhandl W, Felberbauer FX, Puig S, Paya K, Hochschorner S, Barlan M, et al. Solid-pseudopapillary tumor of the pancreas (frantz tumor) in children: report of four cases and review of the literature. *J Surg Oncol*. (2001) 76 (4):289–96. doi: 10.1002/jso.1048

72. Choi SH, Kim SM, Oh JT, Park JY, Seo JM, Lee SK. Solid pseudopapillary tumor of the pancreas: a multicenter study of 23 pediatric cases. *J Pediatr Surg*. (2006) 41(12):1992–5. doi: 10.1016/j.jpedsurg.2006.08.024

73. Zauls JA, Dragun AE, Sharma AK. Intensity-modulated radiation therapy for unresectable solid pseudopapillary tumor of the pancreas. *Am J Clin Oncol*. (2006) 29(6):639–40. doi: 10.1097/01.coc.0000190457.43060.fd

74. Antoniou EA, Damaskos C, Garmpis N, Salakos C, Margonis GA, Kontzoglou K, et al. Solid pseudopapillary tumor of the pancreas: a single-center experience and review of the literature. *In Vivo*. (2017) 31(4):501–10. doi: 10.21873/invivo.11089

75. Matsunou H, Konishi F. Papillary-cystic neoplasm of the pancreas. A clinicopathologic study concerning the tumor aging and malignancy of nine cases. *Cancer*. (1990) 65(2):283–91. doi: 10.1002/1097-0142(19900115)65:2<283::AID-CNCR2820650217>3.0.CO;2-X

76. Shimizu M, Matsumoto T, Hirokawa M, Monobe Y, Iwamoto S, Tsunoda T, et al. Solid-pseudopapillary carcinoma of the pancreas. *Pathol Int*. (1999) 49 (3):231–4. doi: 10.1046/j.1440-1827.1999.00852.x

77. Sibio S, Di Carlo S. Current highlights on solid pseudopapillary neoplasm of the pancreas. *World J Hepatol*. (2022) 14(1):300–3. doi: 10.4254/wjh.v14.i1.300

78. Lanke G, Ali FS, Lee JH. Clinical update on the management of pseudopapillary tumor of pancreas. *World J Gastrointest Endosc*. (2018) 10 (9):145–55. doi: 10.4253/wjge.v10.i9.145

79. Borse NNGJ, Dellinger AM, Rudd RA, Ballesteros MF, Sleet DA. CDC Childhood Injury Report: Patterns of Unintentional Injuries among 0 −19 Year Olds in the United States, 2000-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2008.

80. Lüttges J, Stigge C, Pacena M, Klöppel G. Rare ductal adenocarcinoma of the pancreas in patients younger than age 40 years. *Cancer*. (2004) 100(1):173–82. doi: 10.1002/cncr.11860

81. Ivy EJ, Sarr MG, Reiman HM. Nonendocrine cancer of the pancreas in patients under age forty years. *Surg*. (1990) 108(3):481–7.

82. Cofer B. Pancreatic Tumors. 2022. In: The Pediatric Surgery NaT [Internet]. American Pediatric Surgical Association and Unbound Medicine).

83. Brune K, Abe T, Canto M, O'Malley L, Klein AP, Maitra A, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *Am J Surg Pathol*. (2006) 30(9):1067–76.

84. Esposito I, Segler A, Steiger K, Klöppel G. Pathology, genetics and precursors of human and experimental pancreatic neoplasms: an update. *Pancreatology*. (2015) 15(6):598–610. doi: 10.1016/j.pan.2015.08.007

85. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med*. (2009) 133(3):365–74. doi: 10.5858/133.3.365

86. Potjer TP, Schot I, Langer P, Heverhagen JT, Wasser MN, Slater EP, et al. Variation in precursor lesions of pancreatic cancer among high-risk groups. *Clin Cancer Res*. (2013) 19(2):442–9. doi: 10.1158/1078-0432.CCR-12-2730

87. Matthaei H, Semaan A, Hruban RH. The genetic classification of pancreatic neoplasia. *J Gastroenterol*. (2015) 50(5):520–32. doi: 10.1007/s00535-015-1037-4

88. Schlitter AM, Segler A, Steiger K, Michalski CW, Jäger C, Konukiewitz B, et al. Molecular, morphological and survival analysis of 177 resected pancreatic ductal adenocarcinomas (PDACs): identification of prognostic subtypes. *Sci Rep*. (2017) 7:41064. doi: 10.1038/srep41064

89. Eibl G, Rozengurt E. Obesity and pancreatic cancer: insight into mechanisms. *Cancers (Basel)*. (2021) 13(20):5067. doi: 10.3390/cancers13205067

90. Klimstra D, Adsay NV. Tumors of the pancreas. In: Odze RaG, editor. *Surgical pathology of the GI tract, biliary tract, and pancreas*. Philadelphia, PA: Elsevier; 2015. p. 1081–119.

91. Thompson L, Basturk O, Adsay NV. *Pancreas. Sternberg's Diagnostic pathology*. Philadelphia, PA: Wolters Kluwer; 2015. p. 1557–662.

92. Nagata K, Horinouchi M, Saitou M, Higashi M, Nomoto M, Goto M, et al. Mucin expression profile in pancreatic cancer and the precursor lesions. *J Hepatobiliary Pancreat Surg*. (2007) 14(3):243–54. doi: 10.1007/s00534-006-1169-2

93. Mergo PJ, Helmberger TK, Buetow PC, Helmberger RC, Ros PR. Pancreatic neoplasms: mR imaging and pathologic correlation. *Radiographics*. (1997) 17 (2):281–301. doi: 10.1148/radiographics.17.2.9084072

94. Kloppel GHR, Longnecker D, Adler G, Kern S, Partanen T. Ductal adenocarcinoma of the pancreas. In: SAL Hamilton, editors. *WHO Classification of tumours: pathology and genetics of tumours of the digestive system. Lyon*. France: IARC Press (1996). p. 222–30.

95. Brahmi SA, Khattab M, Mesbahi OE. Obstructive jaundice secondary to pancreatic head adenocarcinoma in a young teenage boy: a case report. *J Med Case Rep*. (2011) 5:439. doi: 10.1186/1752-1947-5-439

96. Thompson ED, Wood LD. Pancreatic neoplasms with acinar differentiation: a review of pathologic and molecular features. *Arch Pathol Lab Med*. (2020) 144 (7):808–15. doi: 10.5858/arpa.2019-0472-RA

97. Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. *Am J Surg Pathol*. (1992) 16 (9):815–37. doi: 10.1097/00000478-199209000-00001

98. Hruban RHPM, Klimstra DS. *Tumors of the pancreas*. 4th ed Washington, DC: American Registry of Pathology (2007).

99. Gill AJKD, Lam AK, Washington AK. *Tumors of the pancreas*. 5th ed. Lyon, France: International Agency for Research on Cancer; 2019.

100. Morikawa M, Nakazawa T, Kato S, Fujimoto D, Koneri K, Murakami M, et al. Acinar cell carcinoma of the pancreas in childhood. *Int Cancer Conf J*. (2016) 5(3):140–5. doi: 10.1007/s13691-016-0245-y

101. Chmielecki J, Hutchinson KE, Frampton GM, Chalmers ZR, Johnson A, Shi C, et al. Comprehensive genomic profiling of pancreatic acinar cell carcinomas identifies recurrent RAF fusions and frequent inactivation of DNA repair genes. *Cancer Discov*. (2014) 4(12):1398–405. doi: 10.1158/2159-8290.CD-14-0617

102. La Rosa S, Sessa F, Capella C. Acinar cell carcinoma of the pancreas: overview of clinicopathologic features and insights into the molecular pathology. *Front Med (Lausanne)*. (2015) 2:41. doi: 10.3389/fmed.2015.00041

103. Burns WA, Matthews MJ, Hamosh M, Weide GV, Blum R, Johnson FB. Lipase-secreting acinar cell carcinoma of the pancreas with polyarthropathy. A light and electron microscopic, histochemical, and biochemical study. *Cancer*. (1974) 33(4):1002–9. doi: 10.1002/1097-0142(197404)33:4<1002::AID-CNCR2820330415>3.0.CO;2-R

104. Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. *J Clin Oncol*. (2002) 20 (24):4673–8. doi: 10.1200/JCO.2002.02.005

105. Cingolani N, Shaco-Levy R, Farruggio A, Klimstra DS, Rosai J. Alpha-fetoprotein production by pancreatic tumors exhibiting acinar cell differentiation: study of five cases, one arising in a mediastinal teratoma. *Hum Pathol*. (2000) 31(8):938–44. doi: 10.1053/hupa.2000.9075

106. Nojima T, Kojima T, Kato H, Sato T, Koito K, Nagashima K. Alpha-fetoprotein-producing acinar cell carcinoma of the pancreas. *Hum Pathol*. (1992) 23(7):828–30. doi: 10.1016/0046-8177(92)90354-6

107. Tatli S, Mortele KJ, Levy AD, Glickman JN, Ros PR, Banks PA, et al. CT And MRI features of pure acinar cell carcinoma of the pancreas in adults. *AJR Am J Roentgenol*. (2005) 184(2):511–9. doi: 10.2214/ajr.184.2.01840511

108. Schmidt CM, Matos JM, Bentrem DJ, Talamonti MS, Lillemoe KD, Bilimoria KY. Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma. *J Gastrointest Surg*. (2008) 12(12):2078–86. doi: 10.1007/s11605-008-0705-6

109. Kitagami H, Kondo S, Hirano S, Kawakami H, Egawa S, Tanaka M. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from pancreatic cancer registry of Japan pancreas society. *Pancreas*. (2007) 35(1):42–6. doi: 10.1097/mpa.0b013e31804bfbd3

110. Matos JM, Schmidt CM, Turrini O, Agaram NP, Niedergethmann M, Saeger HD, et al. Pancreatic acinar cell carcinoma: a multi-institutional study. *J Gastrointest Surg*. (2009) 13(8):1495–502. doi: 10.1007/s11605-009-0938-z

111. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg*. (2010) 14(3):541–8. doi: 10.1007/s11605-009-1115-0

112. Garnier HLC, Czauderna P, Vasudevan S. Pediatric gastrointestinal stromal tumors and neuroendocrine tumors. In: RPT Dasgupta, editor. *Surgical oncology clinics of North America*. 30: Philadelphia, PA: Elsevier Inc; 2020. p. 219–33.

113. Kloppel GPA, Sipos B, Klimstra DS. Tumors of the endocrine pancreas. In: C Fletcher, editors. *Diagnostic histopathology of tumors*. Philadelphia, PA: Elsevier, Inc (2021). p. 1395–411.

114. Latif F, Tory K, Gnarra J, Yao M, Duh F-M, Orcutt ML, et al. Identification of the von hippel-lindau disease tumor suppressor gene. *Science*. (1993) 260 (5112):1317–20. doi: 10.1126/science.8493574

115. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi S-E, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. (1997) 276(5311):404–7. doi: 10.1126/science.276.5311.404

116. Lo C-Y, Lam K-Y, Kung AWC, Lam KSL, Tung PHM, Fan S-T. Pancreatic insulinomas: a 15-year experience. *Arch Surg*. (1997) 132(8):926–30. doi: 10.1001/archsurg.1997.01430320128023

117. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma–incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*. (1991) 66(7):711–9. doi: 10.1016/S0025-6196(12)62083-7

118. Shames JM, Dhurandhar NR, Blackard WG. Insulin-secreting bronchial carcinoid tumor with widespread metastases. *Am J Med*. (1968) 44(4):632–7. doi: 10.1016/0002-9343(68)90065-X

119. Miyazaki K, Funakoshi A, Nishihara S, Wasada T, Koga A, Ibayashi H. Aberrant insulinoma in the duodenum. *Gastroenterol*. (1986) 90(5):1280–5. doi: 10.1016/0016-5085(86)90397-5

120. Adamson AR, Grahame-Smith DG, Bogomoletz V, Maw DS, Rothnie NG. Malignant argentaffinoma with carcinoid syndrome and hypoglycaemia. *Br Med J*. (1971) 3(5766):93–4. doi: 10.1136/bmj.3.5766.93

121. Kiang DT, Bauer GE, Kennedy BJ. Immunoassayable insulin in carcinoma of the cervix associated with hypoglycemia. *Cancer*. (1973) 31(4):801–5. doi: 10.1002/1097-0142(197304)31:4<801::AID-CNCR2820310407>3.0.CO;2-J

122. MA A. Strumal carcinoid of the ovary associated with hyperinsulinaemic hypoglycaemia and cutaneous melanosis. *Histopathol*. (1995) 27(5):463–7. doi: 10.1111/j.1365-2559.1995.tb00311.x

123. Stefanini P, Carboni M, Patrassi N, Basoli A. Beta-islet cell tumors of the pancreas: results of a study on 1,067 cases. *Surg*. (1974) 75(4):597–609.

124. Donow C, Pipeleers-Marichal M, Stamm B, Heitz PU, Klöppel G. Pathologie des insulinoms und des gastrinoms: lokalisation, größe, multizentrizität, assoziation mit der multiplen endokrinen neoplasie typ I und malignität. *Dtsch Med Wochenschr*. (1990) 115(37):1386–91. doi: 10.1055/s-2008-1065168

125. Grosfeld JL, Vane DW, Rescorla FJ, McGuire W, West KW. Pancreatic tumors in childhood: analysis of 13 cases. *J Pediatr Surg*. (1990) 25 (10):1057–62. doi: 10.1016/0022-3468(90)90218-X

126. Buetow PC, Miller DL, Parrino TV, Buck JL. Islet cell tumors of the pancreas: clinical, radiologic, and pathologic correlation in diagnosis and localization. *Radiographics*. (1997) 17(2):453–72.; quiz 72A–72B. doi: 10.1148/radiographics.17.2.9084084

127. Buetow PC, Parrino TV, Buck JL, Pantongrag-Brown L, Ros PR, Dachman AH, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. *AJR Am J Roentgenol*. (1995) 165(5):1175–9. doi: 10.2214/ajr.165.5.7572498

128. Ruttman E, Klöppel G, Bommer G, Kiehn M, Heitz PU. Pancreatic glucagonoma with and without syndrome. Immunocytochemical study of 5 tumour cases and review of the literature. *Virchows Arch A Pathol Anat Histol*. (1980) 388(1):51–67. doi: 10.1007/BF00430676

129. Solcia E, Capella C, Fiocca R, Rindi G, Rosai J. Gastric argyrophil carcinoidosis in patients with zollinger-ellison syndrome due to type 1 multiple endocrine neoplasia: a newly recognized association. *Am J Surg Pathol*. (1990) 14(6):503–13. doi: 10.1097/00000478-199006000-00001

130. Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. *N Engl J Med*. (1979) 301(6):285–92. doi: 10.1056/NEJM197908093010601

131. Williams TBP. The pancreas. In: DBP Stringer, editor. *Pediatric gastrointestinal imaging and intervention*. 2nd ed. Hamilton, Ontario, Canada: Decker; 2000.

132. Capelli P, Martignoni G, Pedica F, Falconi M, Antonello D, Malpeli G, et al. Endocrine neoplasms of the pancreas: pathologic and genetic features. *Arch Pathol Lab Med*. (2009) 133(3):350–64. doi: 10.5858/133.3.350

133. Kim H, An S, Lee K, Ahn S, Park DY, Kim JH, et al. Pancreatic high-grade neuroendocrine neoplasms in the Korean population: a multicenter study. *Cancer Res Treat*. (2020) 52(1):263–76. doi: 10.4143/crt.2019.192

134. Fang JM, Shi J. A clinicopathologic and molecular update of pancreatic neuroendocrine neoplasms with a focus on the new world health organization classification. *Arch Pathol Lab Med*. (2019) 143(11):1317–26. doi: 10.5858/arpa.2019-0338-RA

135. King AD, Ko GT, Yeung VT, Chow CC, Griffith J, Cockram CS. Dual phase spiral CT in the detection of small insulinomas of the pancreas. *Br J Radiol*. (1998) 71(841):20–3. doi: 10.1259/bjr.71.841.9534694

136. Thoeni RF, Mueller-Lisse UG, Chan R, Do NK, Shyn PB. Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. *Radiol*. (2000) 214(2):483–90. doi: 10.1148/radiology.214.2.r00fe32483

137. Gouya H, Vignaux O, Augui J, Dousset B, Palazzo L, Louvel A, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *AJR Am J Roentgenol*. (2003) 181(4):987–92. doi: 10.2214/ajr.181.4.1810987

138. de Herder WW, Kwekkeboom DJ, Valkema R, Feelders RA, van Aken MO, Lamberts SW, et al. Neuroendocrine tumors and somatostatin: imaging techniques. *J Endocrinol Invest*. (2005) 28(11 Suppl International):132–6.

139. Kurita Y, Hara K, Kobayashi N, Kuwahara T, Mizuno N, Okuno N, et al. Detection rate of endoscopic ultrasound and computed tomography in diagnosing pancreatic neuroendocrine neoplasms including small lesions: a multicenter study. *J Hepatobiliary Pancreat Sci*. (2022) 8:950–9. doi: 10.1002/jhbp.1144

140. Pitre J, Soubrane O, Palazzo L, Chapuis Y. Endoscopic ultrasonography for the preoperative localization of insulinomas. *Pancreas*. (1996) 13(1):55–60. doi: 10.1097/00006676-199607000-00007

141. Klotter H, Rückert K, Kümmerle F, Rothmund M. The use of intraoperative sonography in endocrine tumors of the pancreas. *World J Surg*. (1987) 11 (5):635–41. doi: 10.1007/BF01655840

142. Rösch T, Lightdale CJ, Botet JF, Boyce GA, Sivak Jr MV, Yasuda K, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med*. (1992) 326(26):1721–6. doi: 10.1056/NEJM199206253262601

143. Schumacher B, Lübke H, Frieling T, Strohmeyer G, Starke A. Prospective study on the detection of insulinomas by endoscopic ultrasonography. *Endoscopy*. (1996) 28(03):273–6. doi: 10.1055/s-2007-1005452

144. Machado MC, da Cunha JE, Jukemura J, Bacchella T, Penteado S, Abdo EE, et al. Insulinoma: diagnostic strategies and surgical treatment. A 22-year experience. *Hepatogastroenterol*. (2001) 48(39):854–8.

145. Aspestrand F, Kolmannskog F, Jacobsen M. CT, MR imaging and angiography in pancreatic apudomas. *Acta Radiol*. (1993) 34(5):468–73. doi: 10.1177/028418519303400508

146. Chung MJ, Choi BI, Han JK, Chung JW, Han MC, Bae SH. Functioning islet cell tumor of the pancreas. Localization with dynamic spiral CT. *Acta Radiol*. (1997) 38(1):135–8. doi: 10.1080/02841859709171257

147. Hennrich U, Benešová M. [(68)Ga]ga-DOTA-TOC: the first FDA-approved (68)Ga-radiopharmaceutical for PET imaging. *Pharmaceuticals (Basel)*. (2020) 13(3):38. doi: 10.3390/ph13030038

148. Wong KP, Tsang JS, Lang BH-H. Role of surgery in pancreatic neuroendocrine tumor. *Gland Surg*. (2018) 7(1):36–41. doi: 10.21037/gs.2017.12.05

149. Mehta S, Rusyn L, Ginsburg H, Hajdu C, Kohn B. Pancreatic neuroendocrine tumor in a young child with tuberous sclerosis Complex 1. *J Endocr Soc*. (2019) 3(6):1201–6. doi: 10.1210/js.2019-00051

150. Panzuto F, Rinzivillo M, Fazio N, de Braud F, Luppi G, Zatelli MC, et al. Real-world study of everolimus in advanced progressive neuroendocrine tumors. *Oncologist*. (2015) 20(5):570. doi: 10.1634/theoncologist.2014-0037erratum

151. Peltola E, Hannula P, Huhtala H, Metso S, Kiviniemi U, Vornanen M, et al. Characteristics and outcomes of 79 patients with an insulinoma: a nationwide retrospective study in Finland. *Int J Endocrinol*. (2018) 2018:2059481. doi: 10.1155/2018/2059481

152. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinol*. (2016) 103(2):153–71. doi: 10.1159/000443171

153. Hopper AD, Jalal M, Munir A. Recent advances in the diagnosis and management of pancreatic neuroendocrine tumours. *Frontline Gastroenterol*. (2019) 10(3):269–74. doi: 10.1136/flgastro-2018-101006

154. Lüttges J, Pierré E, Zamboni G, Weh G, Lietz H, Kussmann J, et al. [Malignant non-epithelial tumors of the pancreas]. *Pathol*. (1997) 18(3):233–7. doi: 10.1007/s002920050211

155. Golhar A, Ray S, Haugk B, Singhvi SK. Cytogenetically confirmed primary Ewing's Sarcoma of the pancreas. *BMJ Case Rep*. (2017) 2017. doi: 10.1136/bcr-2017-219219

156. Nishizawa N, Kumamoto Y, Igarashi K, Nishiyama R, Tajima H, Kawamata H, et al. A peripheral primitive neuroectodermal tumor originating from the pancreas: a case report and review of the literature. *Surg Case Rep*. (2015) 1:80. doi: 10.1186/s40792-015-0084-7

157. Kilpatrick SE, Reith JD, Rubin B. Ewing sarcoma and the history of similar and possibly related small round cell tumors: from whence have we Come and where are we going? *Adv Anat Pathol*. (2018) 25(5):314–26. doi: 10.1097/PAP.0000000000000203

158. Yoshida A, Sekine S, Tsuta K, Fukayama M, Furuta K, Tsuda H. NKX2.2 Is a useful immunohistochemical marker for ewing sarcoma. *Am J Surg Pathol*. (2012) 36(7):993–9. doi: 10.1097/PAS.0b013e31824ee43c

159. Meyers PA. Systemic therapy for osteosarcoma and ewing sarcoma. *Am Soc Clin Oncol Educ Book*. (2015) 35:e644–7. doi: 10.14694/EdBook_AM.2015.35.e644

160. Bosma SE, Ayu O, Fiocco M, Gelderblom H, Dijkstra PDS. Prognostic factors for survival in ewing sarcoma: a systematic review. *Surg Oncol*. (2018) 27(4):603–10. doi: 10.1016/j.suronc.2018.07.016

161. Facchinelli D, Boninsegna E, Visco C, Tecchio C. Primary pancreatic lymphoma: recommendations for diagnosis and management. *J Blood Med*. (2021) 12:257–67. doi: 10.2147/JBM.S273095

162. Asare EAED, Tsai S. Unusual pancreatic tumors. In: JLCA Cameron, editor. *Current surgical therapy*. 13th ed. Philadelphia, PA: Elsevier 2020. p. 568–74.

163. Ng YY, Healy JC, Vincent JM, Kingston JE, Armstrong P, Reznek RH. The radiology of non-Hodgkin's Lymphoma in childhood: a review of 80 cases. *Clin Radiol*. (1994) 49(9):594–600. doi: 10.1016/S0009-9260(05)81874-4

164. Gureş N, Gurluler E, Alim A, Berber I, Gurkan A. Cystic pancreatic lymphangioma. *Rare Tumors*. (2012) 4(2):e27. doi: 10.4081/rt.2012.e27

165. Barnes EL, Lee LS. Got milk? An unusual cause of abdominal pain. *Gastroenterol*. (2015) 148(3):e1–2. doi: 10.1053/j.gastro.2014.09.035

166. Karajgikar J, Deshmukh S. Pancreatic lymphangioma: a case report and literature review. *J Comput Assist Tomogr*. (2019) 43(2):242–4. doi: 10.1097/RCT.0000000000000818

167. Santes O, Chan C. Cystic lymphangioma of the pancreas: a rare entity. *J Gastrointest Surg*. (2016) 20(12):2100–1. doi: 10.1007/s11605-016-3191-2

168. Fonseca R, Pitman MB. Lymphangioma of the pancreas: a multimodal approach to pre-operative diagnosis. *Cytopathol*. (2013) 24(3):172–6. doi: 10.1111/j.1365-2303.2011.00897.x

169. Patino MPA, Sainani N, Catalano O, Sahani D. *Pancreas. CT and MRI of the whole body*. 46: Philadelphia, PA: Elsevier, Inc; 2017. p. 1406–78.

170. Henzel JH, Pories WJ, Burget DE, Smith JL. Intra-abdominal lymphangiomata. *Arch Surg*. (1966) 93(2):304–8. doi: 10.1001/archsurg.1966.01330020096015

171. Ferrozzi F, Zuccoli G, Bova D, Calculli L. Mesenchymal tumors of the pancreas: cT findings. *J Comput Assist Tomogr*. (2000) 24(4):622–7. doi: 10.1097/00004728-200007000-00021

172. Sohn BK, Cho CH, Chae HD. Cystic lymphangioma of the pancreas. *J Korean Surg Soc*. (2011) 81(2):141–5. doi: 10.4174/jkss.2011.81.2.141

173. Merrow AC, Gupta A, Patel MN, Adams DM. 2014 Revised classification of vascular lesions from the international society for the study of vascular anomalies: radiologic-pathologic update. *Radiogr*. (2016) 36(5):1494–516. doi: 10.1148/rg.2016150197

174. Mathew D, Mahomed N. Pancreatic kaposiform hemangioendothelioma complicated by kasabach-merritt phenomenon: a rare entity. *SA J Radiol*. (2019) 23(1):1760. doi: 10.4102/sajr.v23i1.1760

175. Ryu YJ, Choi YH, Cheon J-E, Kim WS, Kim I-O, Park JE, et al. Imaging findings of kaposiform hemangioendothelioma in children. *Eur J Radiol*. (2017) 86:198–205. doi: 10.1016/j.ejrad.2016.11.015

176. Triana PJ, Dore M, Nuñez VC, Jimenez JG, Miguel MF, Díaz MG, et al. Pancreatic kaposiform hemangioendothelioma not responding to sirolimus. *Eur J Pediatr Surg Rep*. (2017) 5(1):e32–e5. doi: 10.1055/s-0037-1604358

177. Leung M, Chao NS, Tang PM, Liu K, Chung KL. Pancreatic kaposiform hemangioendothelioma presenting with duodenal obstruction and kasabach-merritt phenomenon: a neonate cured by whipple operation. *Eur J Pediatr Surg Rep*. (2014) 2(1):7–9. doi: 10.1055/s-0033-1361835

178. Croteau SE, Liang MG, Kozakewich HP, Alomari AI, Fishman SJ, Mulliken JB, et al. Kaposiform hemangioendothelioma: atypical features and risks of kasabach-merritt phenomenon in 107 referrals. *J Pediatr*. (2013) 162(1):142–7. doi: 10.1016/j.jpeds.2012.06.044

179. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. (2012) 25(9):1181–92. doi: 10.1038/modpathol.2012.72

180. Putra J, Gupta A. Kaposiform haemangioendothelioma: a review with emphasis on histological differential diagnosis. *Pathol*. (2017) 49(4):356–62. doi: 10.1016/j.pathol.2017.03.001

181. Wang H, Guo X, Duan Y, Zheng B, Gao Y. Sirolimus as initial therapy for kaposiform hemangioendothelioma and tufted angioma. *Pediatr Dermatol*. (2018) 35(5):635–8. doi: 10.1111/pde.13600

182. Mester M, Trajber HJ, Compton CC, de Camargo Júnior HS, de Almeida PC, Hoover Jr HC. Cystic teratomas of the pancreas. *Arch Surg*. (1990) 125(9):1215–8. doi: 10.1001/archsurg.1990.01410210141024

183. Lane J, Vance A, Finelli D, Williams G, Ravichandran P. Dermoid cyst of the pancreas: a case report with literature review. *J Radiol Case Rep*. (2012) 6(12):17–25. doi: 10.3941/jrcr.v6i12.1152

184. Jacobs JE, Dinsmore BJ. Mature cystic teratoma of the pancreas: sonographic and CT findings. *AJR Am J Roentgenol*. (1993) 160(3):523–4. doi: 10.2214/ajr.160.3.8430545

185. Lyons DA, Coberly EA, Hammoud GM, Nicholl MB. Case report of pancreatic dermoid cyst: can fine needle aspiration make the diagnosis? *Jop*. (2013) 14(6):653–6. doi: 10.6092/1590-8577/1787

186. Chen ZT, Lin YX, Li MX, Zhang T, Wan DL, Lin SZ. Inflammatory myofibroblastic tumor of the pancreatic neck: a case report and review of literature. *World J Clin Cases*. (2021) 9(22):6418–27. doi: 10.12998/wjcc.v9.i22.6418

187. An N, Luo Y, Wang J, Wang XL, Man GD, Song YD. [Inflammatory myofibroblastic tumor of thyroid: a case report]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. (2018) 53(2):148–9.

188. Gao F, Zhong R, Li GH, Zhang WD. Computed tomography and magnetic resonance imaging findings of inflammatory myofibroblastic tumors of the head and neck. *Acta Radiol*. (2014) 55(4):434–40. doi: 10.1177/0284185113500165

189. Thavamani A, Mandelia C, Anderson PM, Radhakrishnan K. Pediatric inflammatory myofibroblastic tumor of the liver: a rare cause of portal hypertension. *ACG Case Rep J*. (2019) 6(3):1–4. doi: 10.14309/crj.0000000000000028

190. Palanisamy S, Chittawadagi B, Dey S, Sabnis SC, Nalankilli V, Subbiah R, et al. Inflammatory myofibroblastic tumor of colon mimicking advanced malignancy: report of two cases with review of literature. *Indian Journal of Surgery*. (2020) 82(6):1280–3. doi: 10.1007/s12262-020-02215-w

191. İflazoğlu N, Kozan SK, Biri T, Ünlü S, Gökçe H, Doğan S, et al. Pancreatic inflammatory myofibroblastic tumor presenting with extracolonic obstruction. *Turkish Journal of Surg*. (2020) 36(2):233. doi: 10.5578/turkjsurg.4325

192. Liu HK, Lin YC, Yeh ML, Chen YS, Su YT, Tsai CC. Inflammatory myofibroblastic tumors of the pancreas in children: a case report and literature review. *Med (Baltimore)*. (2017) 96(2):e5870. doi: 10.1097/MD.0000000000005870

193. McClain MB, Burton E, Day D. Pancreatic pseudotumor in an 11-year-old child: imaging findings. *Pediatr Radiol*. (2000) 30(9):610–3. doi: 10.1007/s002470000227

194. Mahajan P, Casanova M, Ferrari A, Fordham A, Trahair T, Venkatramani R. Inflammatory myofibroblastic tumor: molecular landscape, targeted

therapeutics, and remaining challenges. *Curr Probl Cancer*. (2021) 45(4):100768. doi: 10.1016/j.currproblcancer.2021.100768

195. Hassan KS, Cohen HI, Hassan FK, Hassan SK. Unusual case of pancreatic inflammatory myofibroblastic tumor associated with spontaneous splenic rupture. *World J Emerg Surg*. (2010) 5:28. doi: 10.1186/1749-7922-5-28

196. Dagash H, Koh C, Cohen M, Sprigg A, Walker J. Inflammatory myofibroblastic tumor of the pancreas: a case report of 2 pediatric cases—steroids or surgery? *J Pediatr Surg*. (2009) 44(9):1839–41. doi: 10.1016/j.jpedsurg.2009.06.025

197. Matsubayashi H, Uesaka K, Sasaki K, Shimada S, Takada K, Ishiwatari H, et al. A pancreatic inflammatory myofibroblastic tumor with spontaneous remission: a case report with a literature review. *Diagnostics*. (2019) 9(4):150. doi: 10.3390/diagnostics9040150

198. Som P, Brandwein M, Maldjian C, Reino A, Lawson W. Inflammatory pseudotumor of the maxillary sinus: cT and MR findings in six cases. *AJR Am J Roentgenol*. (1994) 163(3):689–92. doi: 10.2214/ajr.163.3.8079869

199. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol*. (1991) 22(4):387–95. doi: 10.1016/0046-8177(91)90087-6

200. Sarles H, Sarles J-C, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis*. (1961) 6 (7):688–98. doi: 10.1007/BF02232341

201. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. (2001) 344(10):732–8. doi: 10.1056/NEJM200103083441005

202. Khandelwal A, Inoue D, Takahashi N. Autoimmune pancreatitis: an update. *Abdom Radiol (NY)*. (2020) 45(5):1359–70. doi: 10.1007/s00261-019-02275-x

203. Scheers I, Palermo JJ, Freedman S, Wilschanski M, Shah U, Abu-El-Haija M, et al. Autoimmune pancreatitis in children: characteristic features, diagnosis, and management. *Am J Gastroenterol*. (2017) 112(10):1604–11. doi: 10.1038/ajg.2017.85

204. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. (2012) 366(6):539–51. doi: 10.1056/NEJMra1104650

205. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol*. (2011) 23(1):108–13. doi: 10.1097/BOR.0b013e3283413469

206. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol*. (2010) 17(5):303–32. doi: 10.1097/PAP.0b013e3181ee63ce

207. Shinagare S, Shinagare AB, Deshpande V. Autoimmune pancreatitis: a guide for the histopathologist. *Semin Diagn Pathol*. (2012) 29(4):197–204. doi: 10.1053/j.semdp.2012.07.007

208. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the mayo Clinic's HISORt criteria. *J Gastroenterol*. (2007) 42(Suppl 18):39–41. doi: 10.1007/s00535-007-2046-8

209. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the mayo clinic experience. *Clin Gastroenterol Hepatol*. (2006) 4(8):1010–6.; quiz 934. doi: 10.1016/j.cgh.2006.05.017

210. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the international association of pancreatology. *Pancreas*. (2011) 40(3):352–8. doi: 10.1097/MPA.0b013e3182142fd2

211. Khandelwal A, Shanbhogue AK, Takahashi N, Sandrasegaran K, Prasad SR. Recent advances in the diagnosis and management of autoimmune pancreatitis. *Am J Roentgenol*. (2014) 202(5):1007–21. doi: 10.2214/AJR.13.11247

212. Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol*. (2009) 44 (7):742–50. doi: 10.1007/s00535-009-0062-6

213. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest Endosc*. (2005) 61(3):467–72. doi: 10.1016/S0016-5107(04)02802-0

214. Crosara S, D'Onofrio M, De Robertis R, Demozzi E, Canestrini S, Zamboni G, et al. Autoimmune pancreatitis: multimodality non-invasive imaging diagnosis. *World J Gastroenterol*. (2014) 20(45):16881–90. doi: 10.3748/wjg.v20.i45.16881

215. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterol*. (2008) 134(3):706–15. doi: 10.1053/j.gastro.2007.12.009

216. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut*. (2013) 62(12):1771–6. doi: 10.1136/gutjnl-2012-303617

217. Chen X, Chen W, Zhang Y, An Y, Zhang X. Short-Term outcomes of laparoscopic duodenum-preserving total pancreatic head resection compared with laparoscopic pancreaticoduodenectomy for the management of pancreatic-head benign or low-grade malignant lesions. *Med Sci Monit*. (2020) 26:e927248. doi: 10.12659/MSM.927248

218. Jones RE, Zagory JA, Tatum M, Tsui WS, Murphy J. A retrospective analysis of pancreas operations in children. *Transl Gastroenterol Hepatol*. (2021) 6:39. doi: 10.21037/tgh-20-260

219. Mansfield SA, Mahida JB, Dillhoff M, Porter K, Conwell D, Ranalli M, et al. Pancreaticoduodenectomy outcomes in the pediatric, adolescent, and young adult population. *J Surg Res*. (2016) 204(1):232–6. doi: 10.1016/j.jss.2016.04.049

220. Sacco Casamassima MG, Gause CD, Goldstein SD, Abdullah F, Meoded A, Lukish JR, et al. Pancreatic surgery for tumors in children and adolescents. *Pediatr Surg Int*. (2016) 32(8):779–88. doi: 10.1007/s00383-016-3925-y

221. Muller CO, Guérin F, Goldzmidt D, Fouquet V, Franchi-Abella S, Fabre M, et al. Pancreatic resections for solid or cystic pancreatic masses in children. *J Pediatr Gastroenterol Nutr*. (2012) 54(3):369–73. doi: 10.1097/MPG.0b013e31823cef45

222. Beger HG. Benign tumors of the pancreas-radical surgery versus parenchyma-sparing local resection-the challenge facing surgeons. *J Gastrointest Surg*. (2018) 22(3):562–6. doi: 10.1007/s11605-017-3644-2

223. Esposito C, De Lagausie P, Escolino M, Saxena A, Holcomb 3rd GW, Settimi A, et al. Laparoscopic resection of pancreatic tumors in children: results of a multicentric survey. *J Laparoendosc Adv Surg Tech A*. (2017) 27(5):533–8. doi: 10.1089/lap.2016.0630

224. Adzick NS, De Leon DD, States LJ, Lord K, Bhatti TR, Becker SA, et al. Surgical treatment of congenital hyperinsulinism: results from 500 pancreatectomies in neonates and children. *J Pediatr Surg*. (2019) 54(1):27–32. doi: 10.1016/j.jpedsurg.2018.10.030

225. Vasudevan SA, Ha TN, Zhu H, Heaton TE, LaQuaglia MP, Murphy JT, et al. Pancreaticoduodenectomy for the treatment of pancreatic neoplasms in children: a pediatric surgical oncology research collaborative study. *Pediatr Blood Cancer*. (2020) 67(9):e28425. doi: 10.1002/pbc.28425

226. Lancaster WPAD. Management of chronic pancreatitis. In: JLCA Cameron, editor. *Current surgical therapy*. 13 ed. Philadelphia, PA: Elsevier, Inc; 2020. p. 541–5.

227. Beger HG, Mayer B, Poch B. Resection of the duodenum causes long-term endocrine and exocrine dysfunction after whipple procedure for benign tumors - results of a systematic review and meta-analysis. *HPB (Oxford)*. (2020) 22 (6):809–20. doi: 10.1016/j.hpb.2019.12.016

228. Beger HG, Mayer B, Vasilescu C, Poch B. Long-term metabolic morbidity and steatohepatosis following standard pancreatic resections and parenchyma-sparing, local extirpations for benign tumor: a systematic review and meta-analysis. *Ann Surg*. (2022) 275(1):54–66. doi: 10.1097/SLA.0000000000004757

229. He Z, Qian D, Hua J, Gong J, Lin S, Song Z. Clinical comparison of distal pancreatectomy with or without splenectomy: a meta-analysis. *PLoS One*. (2014) 9 (3):e91593. doi: 10.1371/journal.pone.0091593

230. Shoup M, Brennan MF, McWhite K, Leung DH, Klimstra D, Conlon KC. The value of splenic preservation with distal pancreatectomy. *Arch Surg*. (2002) 137(2):164–8. doi: 10.1001/archsurg.137.2.164

231. Richardson D, Scott-Conner C. Distal pancreatectomy with and without splenectomy. A comparative study. *Am Surg*. (1989) 55(1):21–5.

232. Aldridge M, Williamson R. Distal pancreatectomy with and without splenectomy. *Br J Surg*. (1991) 78(8):976–9. doi: 10.1002/bjs.1800780827

233. Mukherjee K, Morrow SE, Yang EY. Laparoscopic distal pancreatectomy in children: four cases and review of the literature. *J Laparoendosc Adv Surg Tech A*. (2010) 20(4):373–7. doi: 10.1089/lap.2009.0247

234. Namgoong J-M, Kim D-Y, Kim S-C, Kim S-C, Hwang J-H, Song K-B. Laparoscopic distal pancreatectomy to treat solid pseudopapillary tumors in children: transition from open to laparoscopic approaches in suitable cases. *Pediatr Surg Int*. (2014) 30(3):259–66. doi: 10.1007/s00383-014-3471-4

235. Pranger BK, van Dam JL, Groen JV, van Eijck CH, Koerkamp BG, Bonsing BA, et al. Pancreatic resection in the pediatric, adolescent and young adult population: nationwide analysis on complications. *HPB (Oxford)*. (2021) 23 (8):1175–84. doi: 10.1016/j.hpb.2020.10.029

236. Cao J, Li GL, Wei JX, Yang WB, Shang CZ, Chen YJ, et al. Laparoscopic duodenum-preserving total pancreatic head resection: a novel surgical approach for benign or low-grade malignant tumors. *Surg Endosc*. (2019) 33(2):633–8. doi: 10.1007/s00464-018-6488-2

237. Nakao A, Harada A, Nonami T, Kishimoto W, Takeda S, Ito K, et al. Prognosis of cancer of the duodenal papilla of vater in relation to clinicopathological tumor extension. *Hepatogastroenterol.* (1994) 41(1):73–8.

238. Beger HG, Schlosser W, Siech M, Poch B. The surgical management of chronic pancreatitis: duodenum-preserving pancreatectomy. *Adv Surg.* (1999) 32:87–104.

239. Gloor B, Friess H, Uhl W, Büchler MW. A modified technique of the beger and frey procedure in patients with chronic pancreatitis. *Dig Surg.* (2001) 18 (1):21–5. doi: 10.1159/000050092

240. Frey CF, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. *Ann Surg.* (1994) 220(4):492. doi: 10.1097/00000658-199410000-00008

241. Beger HG, Gansauge F, Siech M, Schwarz M, Poch B. Duodenum-preserving total pancreatic head resection for cystic neoplastic lesions in the head of the pancreas. *J Hepatobiliary Pancreat Surg.* (2008) 15(2):149–56. doi: 10.1007/s00534-007-1227-4

242. Snajdauf J, Rygl M, Petru O, Nahlovsky J, Frybova B, Durilova M, et al. Indications and outcomes of duodenum-preserving resection of the pancreatic head in children. *Pediatr Surg Int.* (2019) 35(4):449–55. doi: 10.1007/s00383-018-4410-6

243. Xiao W, Zhu J, Peng L, Hong L, Sun G, Li Y. The role of central pancreatectomy in pancreatic surgery: a systematic review and meta-analysis. *HPB (Oxford).* (2018) 20(10):896–904. doi: 10.1016/j.hpb.2018.05.001

244. Dagradi ASG. Pancreatectomia intermedia. Enciclopedia Medica italiana: pancreas. 11. *Florence: Scientifiche.* (1984) 11:850–1.

245. Kahl S, Malfertheiner P. Exocrine and endocrine pancreatic insufficiency after pancreatic surgery. *Best Pract Res Clin Gastroenterol.* (2004) 18(5):947–55. doi: 10.1016/S1521-6918(04)00089-7

246. Iacono C, Verlato G, Ruzzenente A, Campagnaro T, Bacchelli C, Valdegamberi A, et al. Systematic review of central pancreatectomy and meta-analysis of central versus distal pancreatectomy. *Br J Surg.* (2013) 100 (7):873–85. doi: 10.1002/bjs.9136

247. Borel F, Ouaissi M, Merdrignac A, Venara A, De Franco V, Sulpice L, et al. Pancreatico-jejunostomy decreases post-operative pancreatic fistula incidence and severity after central pancreatectomy. *ANZ J Surg.* (2018) 88(1-2):77–81. doi: 10.1111/ans.14049

248. van Ramshorst TME, Zwart MJW, Voermans RP, Festen S, Daams F, Busch OR, et al. Robotic central pancreatectomy with roux-en-Y pancreaticojejunostomy. *J Vis Exp.* (2021) 177. doi: 10.3791/62862

249. Fisher JC, Kuenzler KA, Bodenstein L, Chabot JA. Central pancreatectomy with pancreaticogastrostomy in children. *J Pediatr Surg.* (2007) 42(4):740–6. doi: 10.1016/j.jpedsurg.2006.12.023

250. Dumitrascu T, Stanciulea O, Herlea V, Tomulescu V, Ionescu M. Central pancreatectomy for pancreatoblastoma in a 16-year-old girl. *J Pediatr Surg.* (2011) 46(8):e17–21. doi: 10.1016/j.jpedsurg.2011.04.010

251. Nachulewicz P, Rogowski B, Obel M, Woźniak J. Central pancreatectomy as a good solution in frantz tumor resection: a case report. *Med (Baltimore).* (2015) 94(29):e1165. doi: 10.1097/MD.0000000000001165

252. Sperti C, Pasquali C, Ferronato A, Pedrazzoli S. Median pancreatectomy for tumors of the neck and body of the pancreas. *J Am Coll Surg.* (2000) 190(6):711–6. doi: 10.1016/S1072-7515(00)00286-6

253. Iacono C, Bortolasi L, Serio G. Is there a place for central pancreatectomy in pancreatic surgery? *J Gastrointest Surg.* (1998) 2(6):509–16.; discussion 16–7. doi: 10.1016/S1091-255X(98)80050-4

254. Faitot F, Gaujoux S, Barbier L, Novaes M, Dokmak S, Aussilhou B, et al. Reappraisal of pancreatic enucleations: a single-center experience of 126 procedures. *Surg.* (2015) 158(1):201–10. doi: 10.1016/j.surg.2015.03.023

255. Hüttner FJ, Koessler-Ebs J, Hackert T, Ulrich A, Büchler MW, Diener MK. Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms. *Br J Surg.* (2015) 102(9):1026–36. doi: 10.1002/bjs.9819

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Nutrition in children with exocrine pancreatic insufficiency

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Exocrine pancreatic insufficiency (EPI) is a condition defined as pancreatic loss of exocrine function, including decreased digestive enzymes and bicarbonate secretion, which leads to maldigestion and malabsorption of nutrients. It is a common complication in many pancreatic disorders. If left undiagnosed, EPI can cause poor digestion of food, chronic diarrhea, severe malnutrition and related complications. Nutritional status and fat-soluble vitamins should be carefully assessed and monitored in patients with EPI. Early diagnosis of EPI is clinically important for appropriate nutritional support and initiating pancreatic enzyme replacement therapy (PERT) which could significantly improve patient outcomes. The evaluation of nutritional status and related unique management in children with EPI will be discussed in this review.

KEYWORDS

exocrine pancreatic insufficiency, pancreatitis, nutrition, fat-soluble vitamins, calories, malnutrition, PERT, cystic fibrosis

1. Introduction

The pancreas has two essential functions: exocrine function to help break down food by producing digestive enzymes and endocrine function to regulate blood sugar by secreting hormones including insulin. Exocrine pancreatic insufficiency (EPI) is a condition defined as pancreatic loss of exocrine function, including decreased digestive enzymes and bicarbonate secretion, which leads to maldigestion and malabsorption of nutrients. In pediatrics, more common causes of EPI include cystic fibrosis, chronic pancreatitis, Shwachman-Diamond syndrome, Pearson syndrome, and Johanson-Blizzard syndrome. Pancreatic hypoplasia, pancreatic aplasia, Jeune syndrome, pancreatectomy and isolated pancreatic enzyme deficiencies are less common causes (1–3). EPI can also occur in systemic diseases such as diabetes, inflammatory bowel disease, celiac disease, Sjogren's syndrome, etc. Microvascular damage may cause fibrosis and atrophy of the pancreas in patients with diabetes. Transient decrease of fecal elastase-1 has been reported in patients with inflammatory bowel disease or celiac disease (2) (**Table 1**). Clinically significant EPI presenting with steatorrhea results after greater than 90% of pancreatic acini are permanently compromised (3). If left undiagnosed, EPI can cause maldigestion of food and result in steatorrhea, weight loss, and fat-soluble micronutrient malabsorption. It can also impact the quality of life due to persistent gastrointestinal symptoms (4). To recognize EPI early is clinically critical for providing appropriate nutritional support including initiating pancreatic enzyme replacement therapy (PERT). In this review, we will discuss the evaluation of nutritional status and the management of EPI in children.

Abbreviations
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; EF-1, fecal elastase-1; ePFT, endoscopic pancreatic function tests; EPI, exocrine pancreatic insufficiency; LU, lipase unit; NASPGHAN, North American society for pediatric gastroenterology, hepatology and nutrition; PERT, pancreatic enzyme replacement therapy; sMRCP, secretin-enhanced magnetic resonance cholangiopancreatography.

TABLE 1 Etiologies for EPI.

Pancreatic – focused diseases	Systemic diseases
Cystic fibrosis	Diabetes
Chronic pancreatitis	Inflammatory bowel disease
Shwachman-Diamond syndrome	Celiac disease
Pearson syndrome	Sjogren's syndrome
Johanson-Blizzard syndrome	
Pancreatic hypoplasia	
Pancreatic aplasia	
Isolated pancreatic enzyme deficiencies	
Jeune syndrome	
Pancreatectomy-partial or total including Total Pancreatectomy with Islet Auto Transplantation (TPIAT)	

2. Pathophysiology

The adult pancreas delivers approximately 2.5 L of fluid secretion to the duodenum daily. During meals, the flow can rise from 0.2 ml/min to 4.0 ml/min. In children, the secretion volume and rate in response to secretin has a strong correlation with body surface area (BSA) (5, 6). Pancreatic fluid is isotonic, slightly alkaline (pH~8.2) and protein rich, containing HCO3 – (up to 140 mEq/L), other electrolytes, and water. Acinar cells synthesize, store, and release digestive proenzymes which are proteolytic, lipolytic, or amylolytic, and contain nuclease. These proenzymes are synthesized in the endoplasmic reticulum. Apices of acinar cells contain zymogen granules which are vesicles containing proenzymes. The release of zymogen into the intercalated ducts is controlled through receptors and mediated by calcium. These proenzymes are activated in the intestine following trypsin activation by enterokinase found on the mucosal surface of small intestine. Trypsin in turn activates the remaining proenzymes, including trypsinogen, by enzymatic cleavage. Ductal cells secrete 1–2 L of neutral pH juice, mainly water and HCO3–, devoid of Cl–, through the regulated action of the cystic fibrosis transmembrane conductance regulator (CFTR), intracellular carbonic anhydrase, and other membrane channels. Pancreatic secretion is regulated by hormones and neural mediators including secretin, acetylcholine (Ach), cholecystokinin (CCK), substance P, vasoactive intestinal polypeptide (VIP), Peptide YY (PYY) and gastrin-releasing peptide (GRP) (6–8).

Malabsorption usually occurs when pancreatic secretion is decreased by 90% or more (9, 10). In patients with chronic pancreatitis, steatorrhea represents the most significant digestive malfunction in EPI. It usually develops years before overt malabsorption of protein and starch and is often more severe than azotorrhea (11). This can be due to several mechanisms: (1) lipase secretion diminishes earlier compared to amylase and proteases (12); (2) lipase destruction in the small intestinal lumen occurs more rapidly than other enzymes (13); (3) lipid digestion in humans is almost entirely through pancreatic lipase. Lipolytic enzymes of gastric origin contribute little to lipid digestion. By contrast, if pancreatic proteolytic activity was inhibited, protein digestion was maintained in animal studies. Similarly, brush border oligosaccharidases and salivary amylase accomplish around 80% of starch digestion in the absence of pancreatic amylase (14); (4) ileal nutrient exposure variation caused by pancreatic exocrine insufficiency may impair ileal inhibitory effect and subsequently decrease biliary secretion (15). A decrease in bile acids may further worsen lipid digestion and absorption (11, 16, 13). Steatorrhea is often accompanied by diarrhea and enhanced gastric emptying and small intestinal transit in patients with EPI can contribute to this. Accelerated gastric emptying after a high-fat liquid meal was observed in patients with CP and EPI (17). These disorders can cause inadequate mixing of food, bile acid, and digestive enzymes, as well as reduce contact time between chyme and the intestinal mucosa leading to diarrhea (18). On the other hand, another study in patients with CF demonstrated a prolonged small intestinal transit time. This may increase the contact time of chyme with the mucosa, however, is also prone to the risk of developing intestinal bacterial overgrowth and contributing to secondary malabsorption (19).

HCO3- secretion is mediated through CFTR which drives osmotic fluid secretion in the pancreatic duct. HCO3- is required to control the pH at the epithelial surface of the pancreatic duct as well as the expansion of secreted mucins. In patients with CFTR mutation, a lower luminal pH could cause the accumulation of hyperviscous mucus in the pancreatic duct which subsequently obstructs the lumen and results in microbial colonization and inflammation of the pancreas (20, 21). Additionally, a high level of HCO3- is considered essential to maintain the inactive state of the secreted digestive enzymes while still located in the ductal tree (21, 22).

3. EPI and malnutrition

EPI causes malnutrition through maldigestion and malabsorption. Malnutrition is an imbalance between nutritional intake, basal energy requirements, and expenditure. Malnutrition can be further characterized as undernutrition or overnutrition. In this manuscript, we focus on undernutrition, thus, malnutrition in this review specifically refers to undernutrition. Pediatric undernutrition is defined as the state in which there is a deficit in nutritional intake in relation to requirements (23, 24). This results in cumulative macro or micronutrient insufficiencies or deficiencies which adversely affect growth and development (24).

3.1. Undernutrition

Patients with EPI often complain of abdominal discomfort, poor weight gain or weight loss, steatorrhea, undernutrition and vitamin deficiency symptoms (25). Steatorrhea is defined as bulky oily or greasy material in stools. Despite their often-late appearance in EPI, it remains important to evaluate the stool features even if these characteristics are neither specific nor sensitive for detection of steatorrhea (26).

Chronic malabsorption without intervention leads to malnutrition, more specifically undernutrition. One single center pediatric study identified malnutrition in 25% of children with chronic pancreatitis (CP). 17.3% of patients were detected with moderate malnutrition, and 0.96% with severe malnutrition. 152 patients were evaluated with CFA. The mean output among 38 malnourished patients was 6.69 g/100 g/day which was significantly higher than 2.27 g/100 g/day of 114 well-nourished children (27), indicating EPI is a major factor causing undernutrition. In patients with CF, protein malabsorption has been reported prior to newborn screen implementation, but is not common in the current era (28).

Other than maldigestion and malabsorption resulting from EPI, various factors may contribute to undernutrition owing to the nature of the underlying diseases. Patients with steatorrhea may self-limit fat intake due to diarrhea. Patients with chronic pancreatitis suffering from chronic pain may have decreased oral feeding. Those with additional complications such as diabetes, requiring frequent interventional procedures, having frequent pancreatitis attacks, or having a hypermetabolic state due to chronic inflammation such as cystic fibrosis leading to increased energy expenditure (29), may all potentially worsen or compound the undernutrition of patients with EPI.

Patients with steatorrhea are prone to develop fat-soluble vitamin deficiency. Because of the decrease of pancreatic enzymes, malabsorption and diarrhea, the deficiencies of water-soluble vitamins such as vitamin B12, folic acid, electrolytes such as calcium, magnesium, zinc, may also be detected (30). Vitamin B12 is bound to haptocorrin (HC) in the stomach; pancreatic proteases and pH changes degrades HC and transfer B12 to intrinsic factors in the duodenum for its absorption in the distal ileum. Despite the risks, the Vitamin B12 deficiency is still rare case in patients with EPI (31, 32). On top of changes in composition of fat and muscle tissue, undernutrition may result in homeostasis disruption on bone mass and mineral density (27).

In one adult study, 32 patients with chronic pancreatitis with exocrine pancreatic sufficiency (EPS) and 26 patients with EPI were measured for bone mineral density (BMD) and bone mineral content (BMC) using a dual-energy x-ray absorptiometry (DXA) method. The mean z-score of BMD was -1.16 ± 1.29 in EPS group and 1.32 ± 0.90 in EPI. For BMC, it was -1.02 ± 1.17 vs. -1.39 ± 0.987 respectively. In both groups mean 25 (OH)D and mean 1.25(OH)2D were below reference range. The author concluded that the patients with chronic pancreatitis and severe EPI, were at risk to develop significant bone loss (33, 34). Bone mineral content (BMC) and lean body mass (LBM) are more delicate indicators of undernutrition than BMI (36, 37). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) based methods to assess bone density and skeletal muscle mass are promising research fields to assess changes in body composition due to pancreas-related cachexia and osteopenia (37).

3.2. Fat-soluble vitamin deficiency

Vitamins are mainly acquired through diet as the human body cannot synthesize them on its own. There are nine water-soluble vitamins and four fat-soluble vitamins found in the diet. Fat-soluble vitamins are absorbed and stored in adipose tissues, liver, and muscle (38). Patients with EPI are prone to developing fat malabsorption, subsequently leading to insufficient absorption of fat-soluble vitamins (41).

Fat-soluble vitamins are divided further into subgroups according to their molecular structure. Vitamin A is classified into two forms: retinoids and carotenoid. Retinoids include retinol, retinal, and retinyl esters. Carotenoids, such as beta carotene, are plant sources (39, 41). Xerophthalmia and night blindness are associated with vitamin A deficiency (42, 43) along with decreased opacity of the cornea and dry conjunctiva. Vitamin A deficiency can damage the epithelial lining of the gastrointestinal, respiratory, and genitourinary tracts resulting from the dryness of epithelial cells, subsequently increasing risk of infection (38, 44).

The main forms of vitamin D are ergosterol (vitamin D2) and cholecalciferol (vitamin D3) (45). Vitamin D deficiency can lead to a disruption of bone mineralization, compromising the growth and strength of bones in children and affecting density of bones in adults, leading to rickets, osteomalacia, osteoporosis, and osteopenia (38). Vitamin D has also been discovered to have other vital functions besides bone health, such as, inhibiting cancer cell growth, assisting in infection control, and decreasing inflammation (46).

Tocopherols and the tocotrienols are vitamin E, each comprising of four subgroups (47). Vitamin E deficiency can lead to neurological problems, i.e., ataxia, dysarthria, lower limb areflexia, and peripheral neuropathy. In infants it is associated with hemolytic anemia.

Vitamin K is classed into the phylloquinones and menaquinones. The metabolism of each fat-soluble vitamin is complex, with lipid being essential for their absorption in the intestinal lumen and carrier proteins, or lipoproteins, required for transportation. The fat-soluble vitamins are conveyed to the adipose tissue, liver and muscle for usage and storage (48, 49, 38). Vitamin K deficiency can lead to coagulopathy, observed as subcutaneous bleeding with prolonged prothrombin time. Lack of vitamin K may also play a factor in poor bone density (38, 50).

4. Diagnosis of EPI

Early diagnosis of EPI in children remains challenging. Exocrine pancreatic function is often assessed by direct and indirect pancreatic function tests (PFTs). Indirect PFTs include fecal elastase-1 (FE-1), 72-hour fecal fat test, and triglyceride breath test mixed with 13^C; the latter is not available in the United States (1, 3, 53, 55). Steatorrhea is traditionally diagnosed with 72-hour fecal fat test which measures the coefficient of fat absorption (CFA). Feces are collected for 3 days, and daily dietary fat intake is recorded. Fecal fat is measured. For patients over 6 months old, when stool fat excretion surpasses 7 g for every100 g fat taken from diet per day, i.e., unabsorbed stool fat is >7% of dietary fat, the patient has steatorrhea. If patient is less

than 6 months old, >15% is diagnostic (10). The 72-hour fecal fat test is laborious and unpleasant for personnel to handle and is not commonly performed by most centers. FE-1 is currently the most widely used method to screen for EPI. In general, A FE-1 > 200 ug/g is considered normal, 100–200 ug/g is indeterminate and may associate with possible decreased exocrine pancreatic function, and a FE-1 < 100 ug/g is abnormal and most likely indicating EPI. FE-1 usually detects EPI in the severe range and may miss mild to moderate cases (1). The FE-1 level may also be affected if measured during diarrhea caused by other etiologies (non-steatorrhea) due to dilutional effect or during an acute pancreatitis episode when fewer digestive enzymes might be produced. The sensitivity for FE-1 in meta-analysis in mild EPI was reported around 49% (56). The lack of sensitivity and specificity of FE-1 in mild to moderate EPI limits its use as a reliable tool for early EPI detection. Dreiling tube test is a traditional direct PFT which involves the fluoroscopic placement of an oroduodenal tube, administration of secretin or CCK then intermittent suction through the tube to collect duodenal pancreatic secretion (53). This modality is cumbersome, uncomfortable, and time-consuming and is not generally performed in pediatric centers. Endoscopic pancreatic function test (ePFT), which directly measures the pancreatic exocrine function, is considered the most accurate and feasible modality in diagnosing EPI. An esophagogastroduodenoscopy (EGD) will be performed under general anesthesia. A secretin (0.2 mcg/kg) or CCK (0.04 mcg/kg) is administrated intravenously to stimulate the pancreas secretion, followed by suction of pancreatic juice from duodenum at the different time interval. Pancreatic digestive enzymes including amylase, lipase, trypsin and chymotrypsin as well as bicarbonate concentration would be measured at the various time interval (55). Currently the protocol used by each center varies. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Pancreas Committee published a position paper that reviewed the advantages of ePFT, including it being technically safe and easy to perform, although it should be recognized that it is still an invasive procedure and carries risks of standard anesthesia and EGD. EPFT modality has been proved to be sensitive and specific in EPI diagnosis. The NASPGHAN pancreas committee proposed a standard ePFT protocol in children (56). Compared to the Dreiling tube pancreatic function test, ePFT is the preferred direct pancreatic function test given its technical superiority with improved efficacy. Despite its advantages as the most promising method for early EPI diagnosis, the main limitation for ePFT in children is the lack of age-specific normal reference ranges, often making it difficult to reliably interpret the results (56). Secretin-enhanced magnetic resonance cholangiopancreatography (sMRCP) is often utilized to investigate the pancreatic and biliary ductal system. Secretin-enhanced secretion of pancreatic fluid may contribute to non-invasive diagnosis for EPI. Calculation of pancreatic secretory function to secretin stimulation by MRI has been evaluated for adult patients and still being investigated in children (5).

5. Monitoring nutritional status and management in EPI

5.1. Overall malnutrition assessment

Appropriate assessment of nutritional status is essential for early identification of those at risk for malnutrition with EPI. There is a current lack of a standard, validated, universal approach to the screening and evaluation of pediatric malnutrition. Routine assessment remains inconsistent both nationally and internationally. The American Society for Parenteral and Enteral Nutrition (ASPEN) and Academy of Nutrition and Dietetics Consensus guidelines recommend using several indicators in evaluating malnourishment: caloric and nutrient intake, calculation of energy and protein needs, and physical exam findings (i.e., muscle wasting, subcutaneous fat thickness, fluid accumulation, Tanner staging). Diagnostic parameters include anthropometric measures and their proxies such as weight gain velocity, mid-upper arm circumference, growth parameters, and handgrip strength (23). In the United States, it has become standard practice to use the World Health Organization Multicenter Growth Reference Study for children less than 2 years of age (https://www.who.int/childgrowth/standards/weight_for_height/en/), and the Centers for Disease Control and Prevention growth charts as references for children greater than 2 years of age (https://www.cdc.gov/growthcharts/clinical_charts.htm) (57).

Current recommendations support the use of "*z*-scores" in the evaluation of pediatric nutrition. Utilizing *z*-score criterion is especially useful when a single data point is available such as weight for height or length (0–2 years), BMI for age (2–18 years), length or height for age, or middle upper arm circumference (MUAC) (23). The *z*-score is a statistical representation of the number of standard deviations (SD) which is a value either above or below the mean in a normal Gaussian (bell) curve distribution (57). One standard deviation from the mean encompasses 68% of the data set under the bell curve, 2 standard deviations from the mean encompasses 95% of the data, and 3 standard deviations from the mean encompasses 99.7% of the data. Thus, the *z*-score implies variance from a normal mean value, and more specifically – the degree of variation. With z-scores, pediatric undernutrition can be classified by severity. Mild malnutrition is specified as a *z*-score −1 to −1.99, moderate malnutrition is specified as a *z*-score −2 to −2.99 and severe malnutrition is a *z*-score equal to or less than −3 (23) (**Table 2**).

When multiple data points are available for use, *z*-scores for deceleration in weight for length or height may be used, in which case, a decline of 1 *z*-score correlates with mild malnutrition, a decline of 2 *z*-scores correlates with moderate malnutrition and a decline of 3 *z*-scores correlates with severe malnutrition (23) (**Table. 2**).

The nutrition status of patients with EPI requires close monitoring and documentation at each visit.

TABLE 2 Assessment of malnutrition.

Grade	Percentage of TBW lost	Growth velocity	Inadequate nutrient intake	*Z*-scores (single value)	*Z*-scores (multiple values)
Mild	5%	<75% of normal	51%–75% estimated caloric/protein need	−1 to −1.99	Decline of 1 *z*-score
Moderate	7.5%	<50% of normal	26%–51% estimated caloric/protein need	−2 to −2.99	Decline of 2 *z*-scores
Severe	10%	<25% of normal	<25% estimated caloric/protein need	≤−3	Decline of 3 *z*-scores

TBW, total body weight.
Z-score criterion is for anthropometric measures i.e., weight for height or length (<2 yo), BMI for age (2–18 yo), length or height for age, or middle upper arm circumference (MUAC). *Z*-score criterion is especially useful when only a single data point is available.

5.2. PERT

Pancreatic enzyme replacement therapy (PERT) can often reverse the clinical course of malabsorption. PERT is required for EPI patients to support weight gain, to prevent fat-soluble vitamin and essential fatty acid deficiencies, to avoid malnutrition, as well as to improve symptoms of maldigestion and steatorrhea (58). 80%–90% of patients with cystic fibrosis need PERT to avert malnutrition (59). Current understanding of PERT in EPI is mainly based on expert consensus experience from cystic fibrosis.

For PERT, porcine pancreas is the usual source of pancreatic enzymes. It features high enzyme activity of all three classes including amylases, lipases, and proteases. Lipase is the main supplemental pancreatic enzyme yet is the least stable. It is highly sensitive to acid environment and proteolysis (60). Since 2010, several pancreatic enzyme replacement products were approved for the treatment of EPI by the Food and Drug Administration (FDA). All brands but VIOKACE are available in delayed-release forms comprising enteric-coated spheres, microspheres, microtablets or beads. Enteric-coated enzymes safeguard lipase from denaturation caused by gastric acid. These products include Creon, PANCREAZE, ZENPEP, PERTZYE (61). VIOKACE is the only one with an uncoated enzyme formulation. It has an immediate release thus it should be used together with an acid suppressant medication i.e., proton pump inhibitor (PPI) to maximize its activity (2, 62). In general, delayed-release (enteric-coated) capsules are recommended for pediatric patients. The safety and effectiveness of VIOKACE has not been established in pediatric patients. Due to greater degradation in the acidic environment, VIOKACE may be less efficacious than enteric-coated formulations (63, 64). VIOKACE used alone in pediatric patients may increase the risk of inadequate treatment of EPI. The efficacy of VIOKACE was established with concomitant PPI therapy in adult patients (63, 64). The long-term safety of PPI use in pediatric patients has not been established. RELiZORB is a digestive enzyme cartridge that connects directly to the feeding tube. The enzyme lipase is attached to small bead carriers and interacts with lipid as the formula passes through. It is useful for patients who are tube fed, however, it only contains lipase to breakdown fat in the formula (65).

Once ingested and passed through the duodenum, the acid-resistant enteric coating degrades in the intestine's higher pH, permitting the release of enzymes for digestion. PERT should be taken with meals and snacks (2, 66).

The goal of PERT is to optimize the nutritional status and alleviate the symptoms. The optimal dosage for an individual may differ based on body weight, severity of steatorrhea, and dietary fat intake. In pediatrics, PERT dosing recommendations for EPI is age dependent. For infants, 2,000–4,000 lipase units (LU) per 120 ml of infant formula or each breast feeding is recommended. For under 4 years of age, 1,000 LU/kg/meal and 500 LU/kg/snacks are recommended. For greater than 4 years of age, 500 LU/kg/meal and 250 LU/kg/snack are recommended (3) (**Table 3**). The ideal PERT therapy is established on its clinical effectiveness, the initial dose might be adjusted based on the clinical requirement and efficacy (2, 34, 67–69).

For children with difficulty swallowing capsules, delayed release forms may be opened, and enteric coated microspheres may be sprinkled on low pH food (applesauce, etc). Foods like milk has a pH greater than 7.3, should be avoided as the enteric coating may dissolve in higher pH, and the enzymes can be denatured by gastric acid and lose activity. It is recommended to avoid crushing or chewing or holding the pancreatic lipase in the mouth as this may cause local irritation (3, 70). As the dissolution rate and extent of each brand are unique, they are not deemed interchangeable (2). If a different brand of PERT is initiated, optimization of the new PERT dose should be considered.

PERT products are generally well tolerated. Over time, it has shown an acceptable safety and tolerability profile. Headache, dizziness, abdominal pain, gassiness, and diarrhea are commonly observed adverse effects (71). In cystic fibrosis patients, fibrosing colonopathy has also been described with higher doses (72). According to 1995 consensus conference of the U.S. Cystic Fibrosis Foundation on the use of PERT, it is recommended that the daily dose of pancreatic enzymes should not exceed 2,500 LU per kilogram per meal and 10,000 LU per kilogram per day. Higher doses should be used with vigilance and only if able to clinically demonstrate significant improvement of malabsorption (2, 72, 73).

Regardless of the causes of EPI, a suboptimal response to standard PERT dosage should lead clinicians to investigate

TABLE 3 PERT dosage by Age.

Age	PERT dosage in Lipase Units (LU)
Infant	2,000–4,000 LU per 120 ml of infant formula or each breast feeding
<4-year-old	1,000 LU/kg/meal and 500 LU/kg/snacks
>4-year-old	500 LU/kg/meal and 250 LU/kg/snack

PERT, pancreatic enzyme replacement therapy.

TABLE 4 Fat soluble vitamins supplement.

Vitamins	Dosage
Vitamin A	
Birth to 6 months	400 mcg of (RAE)
Infants between 7 and 12 months	500 mcg RAE
1–3 years	300 mcg RAE
4–8 years	400 mcg
9–13 years	600 mcg RAE
Boys at 14–18 years	900 mcg
Girls at14–18 years	700 mcg RAE
Vitamin D	
Infants	400–500 IU daily
1–10 years	800–1,000 IU daily
>10 years	800–2,000 IU daily
Vitamin D deficiency without hypoglycemia	Vitamin D ranging from 25 to 125 mcg (1,000–10,000 IU) per day should be provided for 8–12 weeks to quickly correct the deficiency, then continue 10–25 mcg (400–1,000 IU) per day as maintenance.
Vitamin D Deficiency with hypocalcemia	Additional 30–75 mg/kg/day of elemental calcium
Vitamin E	
Infants	40–50 IU
toddlers	80–150 IU
4–8 years	100–200 IU
>8 years	200–400 IU
Vitamin E Deficiency	start at 10–25 IU/kg/day and may be increased by small increments (25–50 IU/kg/day every 3–4 weeks) to a maximum of 100–200 IU/kg/day, best offered as a single morning dose
Vitamin K (with prolonged INR)	
	2.5–5 mg oral or 1–2 mg I.M., I.V., subcutaneous

RAE, retinol activity equivalents.

adherence to therapy first. If adherence is satisfactory, a small increments of PERT dosage change is recommended. Acid suppressive therapy (i.e., PPI) to reduce acid denaturation of enzymes can be initiated (74, 75). It has been suggested that combining a proton pump inhibitor (PPI) in cystic fibrosis patients who have refractory steatorrhea not responding well to PERT will aid efficacy (34, 67–69). However, in a retrospective cohort of pediatric patients with cystic fibrosis treated with PERT jointly with PPIs, there was no statistically significant improvement (76). In an adult study, up to 40% of patients with EPI secondary to chronic pancreatitis have concomitant intestinal bacterial overgrowth (77). Alternative etiologies of malabsorption should be evaluated in cases of less ideal response to the treatment (2, 74, 75).

5.3. Fat-soluble vitamins

Children with EPI are prone to develop fat-soluble vitamin deficiency. The Cystic Fibrosis Foundation (CFF) recommends regular screening for deficiencies in fat-soluble vitamins at the time of diagnosis and then annually and after any dose change (78) And children with CP should have fat-soluble–vitamin levels measured every 6–12 months (79, 80). If patients are supplemented with vitamins, levels should be monitored 3 months after dose adjustment (80). Fat-soluble vitamins deficiency is secondary to fat malabsorption, improvement is expected with optimized PERT supplement. Fat-soluble vitamins should be supplemented for deficiencies accordingly.

5.3.1. Vitamin A

The predominant circulating vitamin A is in the form of retinol. Serum retinol levels are not useful in assessing vitamin A body stores. They reflect vitamin A storage in the liver when they are either depleted (less than 0.07 μmol/g liver) or exceedingly high (greater than 1.05 μmol/g liver) (51). In the middle of these levels, serum retinol is physiologically well controlled and kept at a homeostatic range. Thus, its level is not correlated with vitamin A deficiency and may not correlate in response to vitamin A supplementation. The serum retinol is useful when measured in a population and provides valuable information on the vitamin A status of a population. The serum retinol defines whether vitamin A deficiency is a public health problem in that population (56, 85). Vitamin A is bound to retinol-binding protein (RBP) for transportation. RBP is produced in liver. The molar ratio of retinol to RBP can be assessed to guide if vitamin A supplementation is necessary in patients with malnutrition or liver disease. A ratio of <0.8 suggests true vitamin A deficiency and requirement of vitamin A supplementation (81, 78).

Vitamin A is found in fruits, vegetables, eggs, milk, meat, and seafood. The daily Recommended Dietary Allowance (RDA) for vitamin A in children is age dependent (**Table 4**). According to National Institutes of Health (NIH): During birth to 6 months, 400 mcg of retinol activity equivalents (RAE) is recommended, Infants between 7 and 12 months require 500 mcg RAE; Children at 1–3 years require 300 mcg RAE; Children at 4–8 years require 400 mcg RAE; Children at 9–13 years 600 mcg RAE; teenage boys at 14–18 years require 900 mcg RAE; and teenage girls at14–18 years require 700 mcg RAE. This intake level is easy to reach if plenty of whole foods are consumed. However, to prevent toxicity, it is important not to exceed the 3,000 mcg per day (83). There are two supplements form of vitamin A are available: provitamin A as carotenoids and pre-formed vitamin A as retinol or retinyl ester. If a product contains both, the amount of pre-formed vitamin A is used to determine if it is safe. It is important to note that vitamin A may also be an ingredient in some topical products, such as serums, creams, and lotions (83). Toxicity of hypervitaminosis A secondary to the supplement is rare, it may involve multiple organ system including the bone, nervous system, kidney and liver (84). Hypercalcemia due to vitamin A toxicity was reported in patients with CF (85).

5.3.2. Vitamin D

Vitamin D level can be classified as severe deficiency (<5 ng/ml), deficiency (5–15 ng/ml), insufficiency (15–20 ng/ml), and sufficiency (20–100 ng/ml) (86). In children, 20 ng/ml for 25(OH)-D levels is still considered sufficiency (87, 88), however, a higher cutoff of

32–100 ng/ml is suggested in adults (88). The US Cystic Fibrosis Foundation recommends levels >30 ng (89).

Vitamin D is naturally present in some foods, fatty fish and fish liver oils are some the best sources (90). It is also produced endogenously when skin is exposed to ultraviolet (UV). In foods and dietary supplements, D2 (ergocalciferol) and D3 (cholecalciferol) are the two main forms, which differ only in their sidechain (90, 91). UV light converts cutaneous 7-dehydrocholesterol to previtamin D3, which subsequently transform into vitamin D3 (90, 92). Pharmacologic doses of vitamin D ranging from 25 to 125 mcg (1,000–10,000 IU) per day should be provided for 8–12 weeks to quickly correct the deficiency, and once corrected, then 10–25 mcg (400–1,000 IU) per day should be continued as maintenance. Patients with hypocalcemia may need calcium supplementation, in which case, 30–75 mg/kg/day of elemental calcium should be offered. It is recommended to start at a higher dose then wean down to the lower range (**Table 4**). Vitamin D level should be monitored during the therapy (86). Toxicity of hypervitaminosis D is also rare which may be related to excessive long-term vitamin D intake. Clinically characterized by symptoms associated with severe hypercalcemia (93).

5.3.3. Vitamin E

Alpha and gamma tocopherol levels are monitored in laboratory. Alpha Vitamin E reflects vitamin E mainly from supplement and gamma Vitamin E from food intake primarily from plant.

For vitamin E deficiency, oral vitamin E is available in standard forms of tocopherol, tocopherol acetate, tocopherol succinate or tocopherol nicotinate. The dose is recommended to start at 10–25 IU/kg/day and may be increased by small increments (25–50 IU/kg/day every 3–4 weeks) to a maximum of 100–200 IU/kg/day (**Table 4**). Since bile flow is maximal with breakfast in the morning, vitamin E is best offered as a single morning dose (81, 97).

5.3.4. Vitamin K

Serum vitamin K level is not very useful in reflecting the deficiency status, as it only indicates the vitamin K intake over past 24 h (98). Protein induced by vitamin K absence or antagonism (PIVKA) and des-gamma-carboxy-prothrombin (PIVKA-II) are functionally defective coagulation factors in vitamin K deficiency status, PIVKA-II and undercarboxylated osteocalcin (uc-OC) are sensitive markers to reflect vitamin K deficiency but are not available at clinical settings (99–101). In clinical practice, prothrombin time/International Normalized Ratio (PT/INR) is usually used to reflect vitamin K deficiency (99). However, INR prolongs when prothrombin level is below 50% of normal, thus it does not identify early vitamin K deficiency (95). PT/INR measurement is indirect, less sensitive but more readily available in clinical settings.

Phylloquinone is the main dietary form of vitamin K coming primarily from green leafy vegetables (100, 101). Menaquinones are mainly of bacterial origin from various animal-based and fermented foods (100, 102, 103).

If prolonged INR is considered secondary to vitamin K deficiency, 2.5–5 mg oral or 1–2 mg I.M., I.V., subcutaneous (SC) vitamin K1 could be given as a single dose (104) (**Table 4**). The PT/INR could be normalized as soon as within 30 min after intake (105). Cystic fibrosis foundation recommended for patients with EPI, oral 0.3–0.5 mg/day high doses vitamin K1 may be administered until PERT supplement is optimized (106). If oral dosing is ineffective, alternative route of vitamin K1, i.e., IM/IV/SC should be considered (107).

5.4. Other nutrients

5.4.1. Water-soluble vitamins, trace elements and minerals

Research data in studying water-soluble vitamin deficiencies in pediatric patients with EPI is limited. Vitamin C and vitamin B12 level could be low in adults patients with CP (80, 108, 109).

Patient with severe phenotype of CF often has EPI, who may experience iron deficiency due to GI tract or sputum loss (110). Patients with CF have abnormal transport of sodium and chloride in the sweat glands. Sodium chloride deficits can be problematic in infant with CF (99). Selenium levels are low in patients with CP or CF (113, 114). In patients with inadequately treated EPI, zinc deficiency can occur due to steatorrhea (113). Calcium requirements should be optimized in patients with EPI which is important for bone health along with Vitamin D and Vitamin K (114). Specific dosage recommendations for water-soluble vitamin supplementation do not exist in CF (99). Unless suspecting deficiencies, routine screening of water-soluble vitamins, trace elements or minerals are not recommended in pediatric patients with chronic pancreatitis (80).

5.4.2. Essential fatty acid

Essential fatty acid deficiency (EFAD) can be observed in patients with CF (99). Essential fatty acids include polyunsaturated fatty acids which can be metabolized to alpha-linolenic acid (n-3) and linoleic (n-6). N-3 fatty acid is metabolized to docosohexaenoic acid (DHA) and N-6 fatty acid is metabolized to arachidonic acid (AA). The benefits of supplementation of antioxidants or DHA were observed in some studies; however, they were not consistent to recommend routine supplements yet (99, 116).

5.5. Other support

A balanced diet with carbohydrates, protein, fat, vegetables and fruits should be encouraged. The American Heart Association recommends that 30%–35% of calories are derived from fat for children 2–3 years of age and 25%–35% for 4–18 years of age. The majority of fats should come from polyunsaturated and monounsaturated fatty acid sources like fish, nuts and vegetable oils (117). In patients with a hypermetabolic state due to chronic inflammation (i.e., cystic fibrosis), it is important to achieve the recommended high-energy level intake at 110%–200% of the

estimated average requirement (EAR) given increased energy expenditure (79, 118). It is also important to encourage children to remain well hydrated and refrain from consuming alcohol or tobacco products which are associated with CP and subsequent EPI (118). The mechanisms underlying malnutrition in patients with EPI can be complex. Like patients with CF, factors such as higher energy demands, greater energy losses, decreased nutrient intake, and declining lung function all contribute to poor nutrition status and necessitate special attention. Ideally, a multidisciplinary team including registered dietitians, pharmacists, registered nurses, clinicians and social workers can be of great help to manage individual nutritional and caloric requirements.

Other than maldigestion and malabsorption secondary to EPI, various factors may contribute to undernutrition owing to the nature of the underlying diseases. Specific measures for the underlying disease should be considered. For patients with steatorrhea who may self-limit fat intake due to diarrhea, it is important to adjust PERT dosage and encourage a balanced diet. Optimizing pain control for patients with chronic pancreatitis and chronic pain is also important.

6. Summary

Exocrine pancreatic insufficiency (EPI) is a common condition in patients with pancreas disorders which leads to maldigestion and malabsorption of nutrients. Early diagnosis of EPI is clinically important for appropriate nutritional support and initiation of PERT. The nutritional status of patients with EPI should be assessed carefully and accurately. The goal of PERT is to optimize the nutritional status and alleviate symptoms. Fat-soluble vitamins deficiency is secondary to fat malabsorption, improvement is expected with optimized PERT supplement. Fat-soluble vitamins should be supplemented for deficiencies accordingly. Additional support may be needed to improve patient outcomes.

Author contributions

All authors made substantial contributions to the work, drafted, or revised the manuscript and gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work. YZ: prepared initial manuscript, SM contributed to the sections of the manuscript. Both reviewed, edited and extended the draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Taylor CJ, Chen K, Horvath K, Hughes D, Lowe ME, Mehta D, et al. Espghan and naspghan report on the assessment of exocrine pancreatic function and pancreatitis in children. *J Pediatr Gastroenterol Nutr*. (2015) 61(1):144–53. doi: 10.1097/MPG.0000000000000830

2. Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG, et al. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol*. (2019) 12:129–39. doi: 10.2147/CEG.S168266

3. Uc A, Fishman DS. Pancreatic disorders. *Pediatr Clin North Am*. (2017) 64 (3):685–706. doi: 10.1016/j.pcl.2017.01.010

4. Nikfarjam M, Wilson JS, Smith RC; Australasian Pancreatic Club Pancreatic Enzyme Replacement Therapy Guidelines Working Group. Diagnosis and management of pancreatic exocrine insufficiency. *Med J Aust*. (2017) 207:161–5. doi: 10.5694/mja16.00851

5. Trout AT, Serai SD, Fei L, Sun Q, Abu-El-Haija M. Prospective assessment of normal pancreatic secretory function measured by MRI in a cohort of healthy children. *Am J Gastroenterol*. (2018) 113(9):1385. doi: 10.1038/s41395-018-0190-9

6. Pandol SJ. Normal pancreatic function. The pancreapedia: exocrine pancreas knowledge base. *Pancreas*. (2015) V1:1–13. doi: 10.3998/panc.2015.17

7. Fisher WE, Andersen DK, Windsor JA, Saluja AK, Brunicardi FC. Schwartz's Principles of Surgery. *Pancreas*. (2012). 1–26. Available at: https://accesssurgery.mhmedical.com/content.aspx?bookId=980&sectionId=59610875#1117750488.

8. Foglio E, Eisses J. Normal anatomy, development,and physiology. [book auth.] christine waasdorp hurtado. *NASPGHAN eBook*. (2016) 1:521–5. Available at: https://naspghan.org/board-review-book/.

9. DiMagno EP, Go VL, Summerskill HJ. Intraluminal and postabsorptive effects of amino acids on pancreatic enzyme secretion. *J Lab Clin Med*. (1973) 82 (2):241–8. PMID: 4721379.

10. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme ouputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med*. (1973) 288(16):813–5. doi: 10.1056/NEJM197304192881603

11. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut*. (2005) 54(Suppl):1–28. doi: 10.1136/gut.2005.065946

12. DiMagno EP, Clain JE, Layer P. *Chronic pancreatitis*. New York: Raven Press (1993).

13. Layer P, Hotz J, Goebell H. Stimulatory effect of hypercalcemia on pancreatic secretion is prevented by pretreatment with cholecystokinin and cholinergic agonists. *Pancreas*. (1986) 1:478–82. doi: 10.1097/00006676-198611000-00002

14. Moreau H, Laugier R, Gargouri Y, Ferrato F, Verger R, et al. Human preduodenal lipase is entirely of gastric fundic origin. *Gastroenterology*. (1988) 95:1221–6. doi: 10.1016/0016-5085(88)90354-X

15. Layer P, Peschel S, Schlesinger T, Goebell H, et al. Human pancreatic secretion and intestinal motility: effects of ileal nutrient perfusion. *Am J Physiol*. (1990) 258: G196–20. doi: 10.1152/ajpgi.1990.258.2.G196 PMID: 1689548.

16. DiMagno EP, Malagelada JR, Go VL. Relationship between alcoholism and pancreatic insufficiency. *Ann N Y Acad Sci*. (1975) 252:200–7. doi: 10.1111/j.1749-6632.1975.tb19157.x

17. Long WB, Weiss JB. Rapid gastric empiying of fatty meals in panerealic insufficiency. *Gaslroenterotogy*. (1974) 67:920–5. doi: 10.1016/S0016-5085(19)32744-1

18. Bruno MJ, Haverkort EB, Tytgat GN, van Leeuwen DJ, et al. Maldigestion associated with exocrine pancreatic insufficiency: implications of gastrointestinal physiology and properties of enzyme preparations for a cause-related and patient-tailored treatment. *Am J Gastroenterol*. (1995) 90(9):1383–93. PMID: 7661155.

19. Bali A, Stableforth DE, Asquith P. Prolonged small-inlestina! transit 93. Time in cystic fibrosis. *Br Med J*. (1983) 287:1011–3. doi: 10.1136/bmj.287.6398.1011

20. Kim D, Liao J, Hanrahan JW. Large pH oscillations promote host defense against human airways infection. *J Exp Med*. (2021) e20201831. doi: 10.1084/jem.20201831

21. Lee MG, Ohana E, Park HW, Yang D, Muallem S, et al. Molecular mechanism of pancreatic and salivary gland fluid and HCO3-secretion. *Physiol. Rev*. (2012) 92:39–74. doi: 10.1152/physrev.00011.2011

22. Angyal D, Bijvelds MJC, Bruno MJ, Peppelenbosch MP, de Jonge HR. Bicarbonate transport in cystic fibrosis and pancreatitis. *Cells*. (2021) 11:54–71. doi: 10.3390/cells11010054

23. Becker P, Carney LN, Corkins MR, Monczka J, Smith E, Smith SE, et al. Consensus statement of the academy of nutrition and dietetics/American society for parenteral and enteral nutrition: indicators recommended for the identification and documentation of pediatric malnutrition. *Nutr Clin Pract*. (2015) 30(1):147–61. doi: 10.1177/0884533614557642

24. Mehta NM, Corkins MR, Lyman B, Malone A, Goday PS, Carney LN, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *J Parenter Enteral Nutr*. (2013) 37(4):460–81. doi: 10.1177/0148607113479972

25. Andersen DK. Mechanisms and emerging treatments of the metabolic complications of chronic pancreatitis. *Pancreas*. (2007) 35(1):1–15. doi: 10.1097/mpa.0b013e31805d01b0

26. Dumasy V, Delhaye M, Cotton F, Deviere J. Fat malabsorption screening in chronic pancreatitis. *Am J Gastroenterol*. (2004) 99(7):1350–4. doi: 10.1111/j.1572-0241.2004.30661.x

27. Kolodziejczyk E, Wejnarska K, Dadalski M, Kierkus J, Ryzko J, Oracz G. The nutritional status and factors contributing to malnutrition in children with chronic pancreatitis. *Pancreatology*. (2014) 14(4):275–9. doi: 10.1016/j.pan.2014.04.030

28. Wolfe AG, Gilley SP, Waldrop SW, Olson C, Harding E, Widmer K, et al. Case report: cystic fibrosis with kwashiorkor: a rare presentation in the era of universal newborn screening. *Front Pediatr*. (2022) 10:1083155. doi: 10.3389/fped.2022.1083155

29. Vaisman N, Pencharz PB, Corey M, Canny GJ, Hahn E. Energy expenditure of patients with cystic fibrosis. *J Pediatr*. (1987) 111:496–500. doi: 10.1016/S0022-3476(87)80107-5

30. Meier RF, Beglinger C. Nutrition in pancreatic diseases. *Best Pract Res Clin Gastroenterol*. (2006) 20:507–29. doi: 10.1016/j.bpg.2006.01.004

31. Gueant JL, Champigneulle B, Gaucher P, Nicolas JP. Malabsorption of vitamin B 12 in pancreatic insufficiency of the adule and of the chid. *Pancreas*. (1990) 5:559–67. doi: 10.1097/00006676-199009000-00011

32. Gueant JL, Alpers DH. Vitmin B12 absorption and malabsoprtion. *Vitam Horm*. (2022) 119:241–74. doi: 10.1016/bs.vh.2022.01.016

33. Haaber AB, Rosenfalck AM, Hansen B, Hilsted J, Larsen S. Bone mineral metabolism, bone mineral density, and body composition in patients with chronic pancreatitis and pancreatic exocrine insufficiency (article). *Int J Pancreatol*. (2000) 27:21–7. doi: 10.1385/IJGC:27:1:21

34. Keller J, Layer P. Diagnosis of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreapedia*. (2015) 1:1–7. doi: 10.3998/panc.2015.37

35. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clinical*. (2016) 35(3):557–77. doi: 10.1016/j.clnu.2016.03.004

36. Alicandro G, Bisogno A, Battezzati A, Bianchi ML, Corti F, Colombo C. Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis. *J Cyst Fibros*. (2014) 13:328–34. doi: 10.1016/j.jcf.2013.11.001

37. Bieliuniene E, Frøkjær JB, Pockevicius A, Kemesiene J, Lukosevicius S, Basevicius A, et al. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) based methods to assess bone density and skeletal muscle mass are promising research fields to assess changes in body composition due to pancreas-related cachexia, sarcopenia, and os. *Medicina*. (2019) 55(10):649. doi: 10.3390/medicina55100649

38. Stevens SL. Fat-soluble vitamins. *Nurs Clin North Am*. (2021) 56(1):33–45. doi: 10.1016/j.cnur.2020.10.003

39. Aurélie Goncalves, Stéphanie Roi, Marion Nowicki, Amélie Dhaussy, Alain Huertas, Marie-Josèphe Amiot, et al. Fat-soluble vitamin intestinal absorption: absorption sites in the intestine and interactions for absorption. *Food Chem*. (2015) 172:155–60. doi: 10.1016/j.foodchem.2014.09.021

40. Thomas DR. Vitamins in aging, health, and longevity. *Clin Interv Aging*. (2006) 1(1):81–91. doi: 10.2147/ciia.2006.1.1.81

41. Riccioni G, D'Orazio N, Menna V, De Lorenzo A, et al. Fat soluble vitamins and immune system: a overview. *Eur J Inflamm*. (2003) 1(2):59–64. doi: 10.1177/1721727X0300100202

42. Csapo J, Cs A, Prokisch J. The role of vitamins in the diet of the elderly I. Fatsoluble vitamins. Acta Universitatis Sapientiae. *Alimentaria*. (2017) 10:127–45. doi: 10.1515/ausal-2017-0009

43. Tanumihardjo SA, Russell RM, Stephensen CB, Gannon BM, Craft NE, Haskell MJ, et al. Biomarkers of nutrition for development (BOND)—vitamin A review. *J Nutr*. (2016) 146(9):1816S–48S. doi: 10.3945/jn.115.229708

44. Stephenson CB. Vitamin A, infection, and immune function. *Annu Rev Nutr*. (2001) 21:167–02. doi: 10.1146/annurev.nutr.21.1.167

45. Borel P, Desmarchelier C. Bioavailability of fat-soluble vitamins and phytochemicals in humans: effects of genetic variation. *Annu Rev Nutr*. (2018) 38:69–96. doi: 10.1146/annurev-nutr-082117-051628

46. NIH. NIH. NIH vitamin D. [Online] (2022).

47. Lee GY, Han SN. The role of vitamin E in immunity. *Nutrients*. (2018) 10(11):161. doi: 10.3390/nu10111614

48. Albahrani AA, Greaves RF. Fat-soluble vitamins: clinical indications and current challenges for chromatographic measurement. *Clin Biochem Rev*. (2016) 37(1):27–47. PMID: 27057076.

49. Kono N, Arai H. Intracellular transport of fat-soluble vitamins A and E. *Traffic*. (2015) 16(1):19–34. doi: 10.1111/tra.12231

50. Koletzko B, Decsi T, Sawatzki G. Vitamin E status of low birthweight infants fed formula enriched with long-chain polyunsaturated fatty acids. *Int J Vitam Nutr Res*. (1995) 65(2):101–4. PMID: 7591527.

51. Gabriele C, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis and management. *Clin Exp Gastroenterol*. (2019) 12:129–39. doi: 10.2147/CEG.S168266

52. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2018) 16:1220–8. doi: 10.1016/j.cgh.2018.01.027

53. Lindkvist B. Diagnosis and treatment of pancreatic exocrine. *World J Gastroenterol*. (2013) 19(42):7258–66. doi: 10.3748/wjg.v19.i42.7258

54. Dreiling DA, Hollander F. Studies in pancreatic function, preliminary series of clinical studies with the secretin test. *Gastroenterology*. (1948) 11:714–29. PMID: 18100241.

55. Abu-El-Haija M, Conwell DL. Pancreatic insufficiency: what is the gold standard? *Gastrointest Endosc Clin N Am*. (2018) 28:521–8. doi: 10.1016/j.giec.2018.05.004

56. Patel N, Sellers ZM, Grover A, Liu QY, Maqbool A, Morinville VD, et al. Endoscopic Pancreatic Function Testing (ePFT) in children: a position paper from the NASPGHAN pancreas committee. *J Pediatr Gastroenterol Nutr.*. (2021) 72:144–50. doi: 10.1097/MPG.0000000000002931

57. Bouma S. Diagnosing pediatric malnutrition: paradigm shifts of etiology-related definitions and appraisal of the indicators. *Nutr Clin Pract*. (2017) 32(1):52–67. doi: 10.1177/0884533616671861

58. Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. *Best Pract Res Clin Gastroenterol*. (2006) 20(3):531–46. doi: 10.1016/j.bpg.2005.11.006

59. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insuJiciency: present and future. *Clin Exp Gastroenterol*. (2011) 4:55–73. doi: 10.2147/CEG.S17634

60. Carrière F, Renou C, Ransac S, Lopez V, De Caro J, Ferrato F, et al. Inhibition of gastrointestinal lipolysis by orlistat during digestion of test meals in healthy volunteers. *Am J Physiol Gastrointest Liver Physiol*. (2001) 281(1):G16–G28. doi: 10.1152/ajpgi.2001.281.1.G16

61. In brief: pancreatic enzyme replacement. *Med Lett Drugs Ther*. (2017) 59(1531):170. PMID: 28977808.

62. Trang T, Chan J, Graham DY. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21(st) century. *World J Gastroenterol*. (2014) 20(33):11467–85. doi: 10.3748/wjg.v20.i33.11467

63. Gow R, Bradbear R, Francis P, Shepherd R Comparative study of varying regimens to improve steatorrhoea and creatorrhoea in cystic fibrosis: effectiveness of an enteric-coated preparation with and without antacids and cimetidine. *Lancet*. (1981) 2(8255):1071–4. doi: 10.1016/S0140-6736(81)91276-9

64. Ansaldi-Balocco N, Santini B, Sarchi C. Efficacy of pancreatic enzyme supplementation in children with cystic fibrosis: comparison of two preparations by random crossover study and a retrospective study of the same patients at two different ages. *J Pediatr Gastroenterol Nutr*. (1988) 7(Suppl 1):S40–5. doi: 10.1097/00005176-198811001-00009

65. ReliZORB. ReliZORB. [Online] ReliZORB. Available at: https://www.relizorb.com/.

66. Brady MS, Garson JL, Krug SK, Kaul A, Rickard KA, Caffrey HH, et al. An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic

fibrosis: a prospective, randomized study. *J Am Diet Assoc*. (2006) 106:1181–6. doi: 10.1016/j.jada.2006.05.011

67. Sinaasappel HG, Stern M, Littlewood M, Wolfe J, Steinkamp S, Heijerman G. Nutrition in patients with cystic fibrosis: a European consensus. *J Cyst Fibros*. (2002) 1:51–75. doi: 10.1016/S1569-1993(02)00032-2

68. Foundation CF, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic fibrosis foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. (2009) 155:S73–S93. doi: 10.1016/j.jpeds.2009.01.072

69. Sermet-Gaudelus I, Mayell SJ, Southern KW, European Cystic Fibrosis Society NSWG. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. *J Cyst Fibros*. (2010) 9:323–9. doi: 10.1016/j.jcf.2010.04.008

70. Pezzilli R, Andriulli A, Bassi C, Balzano G, Cantore M, Delle Fave G, et al. Exocrine Pancreatic Insufficiency Collaborative (EPIc) group. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian association for the study of the pancreas. *World J. Gastroenterol*. (2013) 19:7930–46. doi: 10.3748/wjg.v19.i44.7930

71. Ramesh H, Reddy N, Bhatia S, Rajkumar JS, Bapaye A, Kini D, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. *Pancreatology*. (2013) 13(2):133–9. doi: 10.1016/j.pan.2013.01.009

72. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy consensus committee. *J Pediatr*. (1995) 127(5):681–4. doi: 10.1016/S0022-3476(95)70153-2

73. Lloyd-Still JD. Cystic fibrosis and colonic strictures: a new "iatrogenic" disease. *J Clin Gastroenterol*. (1995) 21:2–5. doi: 10.1097/00004836-199507000-00001

74. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, VilariñoInsua M. Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. *Gut*. (2006) 55 (7):1056–7. doi: 10.1136/gut.2006.094912

75. Domínguez-Muñoz JE. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency: when is it indicated, what is the goal and how to do it? *Adv Med Sci*. (2011) 56(1):1–5. doi: 10.2478/v10039-011-0005-3

76. Woestenenk JW, van der Ent CK, Houwen RH. Pancreatic enzyme replacement therapy and coefficient of fat absorption in children and adolescents with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. (2015) 61(3):355–60. doi: 10.1097/MPG.0000000000000784

77. Casellas F, Guarner L, Vaquero E, Antolín M, de Gracia X, Malagelada JR. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. *Pancreas*. (1998) 16(4):481–6. doi: 10.1097/00006676-199805000-00004

78. Sankararaman S, Hendrix SJ, Schindler T. Update on the management of vitamins and minerals in cystic fibrosis. *Nutr. Clin. Prac*. (2022) 37:1074–87. doi: 10.1002/ncp.10899

79. Sankararaman S, Schindler T, Sferra TJ. Management of exocrine pancreatic insufficiency in children. *Nutr Clin Pract*. (2019) 34:S27–S42. doi: 10.1002/ncp.10388

80. Abu-El-Haija M, Uc A, Werlin SL, Freeman AJ, Georgieva M, Jojkic-Pavkov D, et al. Nutritional considerations inpediatric pancreatitis: a position paper from the NASPHAN PancreasCommittee. *J Pediatr Gastroenterol Nutr*. (2018) 67(1):131–43. doi: 10.1097/MPG.0000000000002023

81. WHO. Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations (2017). Geneva: World Health Organization (WHO). Available at: https://apps.who.int/iris/handle/10665/85859

82. Feranchak AP, Gralla J, King R, Ramirez RO, Corkill M, Narkewicz MR, et al. Comparison of indices of vitamin A status in children with chronic liver disease. *Hepatology*. (2005) 42(4):782–92. doi: 10.1002/hep.20864

83. Vitamin A and Carotenoids. Professionals, NIH Fact Sheet for Health (2022).

84. Lippe B, Hensen L, Mendoza G, Finerman M, Welch M. Chronic vitamin A intoxication: a multisystem disease that could reach epidemic proportions. *Am J Dis Child*. (1981) 35:634–6. doi: 10.1001/archpedi.1981.02130310040014

85. Safi KH, Filbrun AG, Nasr SZ. Hypervitaminosis a causing hypercalcemia in cystic fibrosis. Case report and focused review. *ATC journals*. (2014) 11:1244–7. doi: 10.1513/AnnalsATS.201404-170BC

86. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. (2008) 122:398–417. doi: 10.1542/peds.2007-1894

87. Saggese G, Vierucci F, Prodam F, Cardinale F, Irene , Chiappini E, et al. Vitamin D in pediatric age: consensus of the Italian pediatric society and the Italian society of preventive and social pediatrics, jointly with the Italian federation of pediatricians. *Ital J Pediatr*. (2018) 44:51. doi: 10.1186/s13052-018-0488-7

88. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr*. (2005) 135(2):317–22. doi: 10.1093/jn/135.2.317

89. Green D, Carson K, Leonard A, Davis JE, Rosenstein B, Zeitlin P, et al. Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate. *J Pediatr*. (2008) 153:554–9. doi: 10.1016/j.jpeds.2008.04.058

90. Ross AC. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): Cambridge University Press (2011).

91. Silva MC, Furlanetto TW. Intestinal absorption of vitamin D: a systematic review. *Nutr Rev*. (2018) 76:60–76. doi: 10.1093/nutrit/nux034

92. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc*. (2013) 88:720–55. doi: 10.1016/j.mayocp.2013.05.011

93. Tebben PJ, Singh RJ, Kumar R. Vitamin D–mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev*. (2016) 37:521–47. doi: 10.1210/er.2016-1070

94. Matthai J. Vitamin E updated. *Indian J Pediatr*. (1996) 63(2):242–53. doi: 10.1007/BF02845251

95. Conway SP, Wolfe SP, Brownlee KG, White H, Oldroyd B, Truscott JG, et al. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. *Pediatrics*. (2005) 115(5):1325–31. doi: 10.1542/peds.2004-1242

96. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. (2002) 35(3):246–59. doi: 10.1097/00005176-200209000-00004

97. Rucker RB. Improved functional endpoints for use in vitamin K assessment: important implications for bone disease. *Am J Clin Nutr*. (1997) 65(3):883–4. doi: 10.1093/ajcn/65.3.883

98. Krzyżanowska P, Pogorzelski A, Skorupa W, Moczko J, Grebowiec P, Walkowiak J. Exogenous and endogenous determinants of vitamin K status in cystic fibrosis. *Sci Rep*. (2015) 5(1):1–8. doi: 10.1038/srep12000

99. Medicine, Institute of. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. s.l.: National Academy Press, 2001.

100. NIH, Fact Sheet for Health Professionals. NIH officail of dietary supplement. NIH Vitamin K. [Online] (2021). Availabele at: https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/.

101. NIH, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press (2001).

102. Booth SL. Vitamin K: food composition and dietary intakes. *Food Nutr Res*. (2012) 56. doi: 10.3402/fnr.v56i0.5505

103. Elder SJ, Haytowitz DB, Howe J, Peterson JW, Booth SL. Vitamin K contents of meat, dairy, and fast food in the U. S. Diet. *J Agric Food Chem*. (2006) 54:463–7. doi: 10.1021/jf052400h

104. Lexicomp. Lexicomp (2022). Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/chilla_f/133825?cesid=4kWqMIECbMY&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvitamin%2BK%26t%3Dname%26va%3Dvitamin%2BK#dop.

105. Bershad EM, Suarez JI. Prothrombin complex concentrates for oral anticoagulant therapy-related intracranial hemorrhage: a review of the literature. *Neurocrit Care*. (2010) 12(3):403–13. doi: 10.1007/s12028-009-9310-0

106. Cystic Fibrosis FoundationBorowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic fibrosis foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. (2009) 155:S73–S93. doi: 10.1016/j.jpeds.2009.09.001

107. Eden RE, Coviello JM. Vitamin K deficiency. NIH (2022). Available at: https://www.ncbi.nlm.nih.gov/books/NBK536983/.

108. Girish BN, Rajesh G, Vaidyanathan K, Balakrishnan V, et al. Assessment of oxidative status in chronic pancreatitis and its relation with zinc status. *Indian J Gastroenterol*. (2011) 30:84–8. doi: 10.1007/s12664-011-0094-8

109. Glasbrenner B, Malfertheiner P, Büchler M, Kuhn K, Ditschuneit H, et al. Vitamin B12 and folic acid deficiency in chronic pancreatitis: a relevant disorder? *Klin Wochenschr*. (1991) 69:168–72. doi: 10.1007/BF01665861

110. Reid DW, Withers NJ, Francis L, Wilson JW, Kotsimbos TC. Iron deficiency in cystic fibrosis: relationship to lung disease severity and chronic pseudomonas aeruginosa infection. *Chest*. (2002) 121(1):48–54. doi: 10.1378/chest.121.1.48

111. Bowrey DJ, Morris-Stiff GJ, Puntis MC. Selenium deficiency and chronic pancreatitis: disease mechanism and potential for therapy. *HPB Surg*. (1999) 11:207–15. doi: 10.1155/1999/97140

112. Mathew P, Wyllie R, Van Lente F, Steffen RM, Kay MH, et al. Antioxidants in hereditary pancreatitis. *Am J Gastroenterol*. (1996) 91:1558–62. PMID: 8759661.

113. Van Biervliet S, Van Biervliet J-P, Robberecht E. Serum zinc in patients with cystic fibrosis at diagnosis and after one year of therapy. *Biol Trace Elem Res*. (2006) 112(3):205–11. doi: 10.1385/BTER:112:3:205

114. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated

meta-analysis from the national osteoporosis foundation. *Osteoporos Int*. (2016) 27 (1):367–76. doi: 10.1007/s00198-015-3386-5

115. Dos Santos Simon MIS, Dalle Molle R, Silva FM, Rodrigues TW, Feldmann M, Forte GC, et al. Antioxidant micronutrients and essential fatty acids supplementation on cystic fibrosis outcomes: a systematic review. *J Acad Nutr Diet*. (2020) 120 (6):1016–33. doi: 10.1016/j.jand.2020.01.007

116. Association, American Heart. American Heart Association (2022). Available at: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/dietary-recommendations-for-healthy-children#:~:text=Keep%20total%20fat%20intake%20between,fish%2C%20nuts%20and%20vegetable%20oils

117. Andersson R, Löhr J-M, Working Group for Chronic Pancreatitis Guidelines (Sweden), et al. Swedish National guidelines for chronic pancreatitis. *Scand J Gastroenterol*. (2021) 56(4):469–83. doi: 10.1080/00365521.2021.1881815

118. Woestenenk JW, Dalmeijer GW, van der Ent CK, Houwen RH. The relationship between energy intake and body-growth in children with cystic fibrosis. *Clin Nutr*. (2019) 38(2):920–5. doi: 10.1016/j.clnu.2018.02.005

119. R5, Gibson. *Principles of nutritional assessment. s.l.* Oxford, UK: Oxford University Press (2005).

120. Rashid M, Durie P, Andrew M, Kalnins D, Shin J, Corey M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. *Am J Clin Nutr*. (1990) 70(3):378–82. doi: 10.1093/ajcn/70.3.378

121. Wilson D C, Rashid M, Durie P R, Tsang A, Kalnins D, Andrew M, et al. Treatment of vitamin K deficiency in cystic fibrosis: effectiveness of a daily fat-soluble vitamin combination. *J Pediatr*. (2001) 138(6):851–5. doi: 10.1067/mpd.2001.113633

122. Prykhodko O, Pierzynowski SG, Nikpey E, Arevalo Sureda E, Fedkiv O, Weström BR. Pancreatic and pancreatic-like microbial proteases accelerate gut maturation in suckling rats. *PLoS One*. (2015) 10(2):e0116947. doi: 10.1371/journal.pone.0116947

123. Stefan G Pierzynowski, Peter C Gregory, Rafal Filip, Jaroslaw Wolinski, Kateryna Goncharova Pierzynowska, et al. Glucose homeostasis dependency on acini–islet–acinar (AIA) axis communication: a new possible pathophysiological hypothesis regarding diabetes mellitus. *Nutr Diabetes*. (2018) 8:55. doi: 10.1038/s41387-018-0062-9

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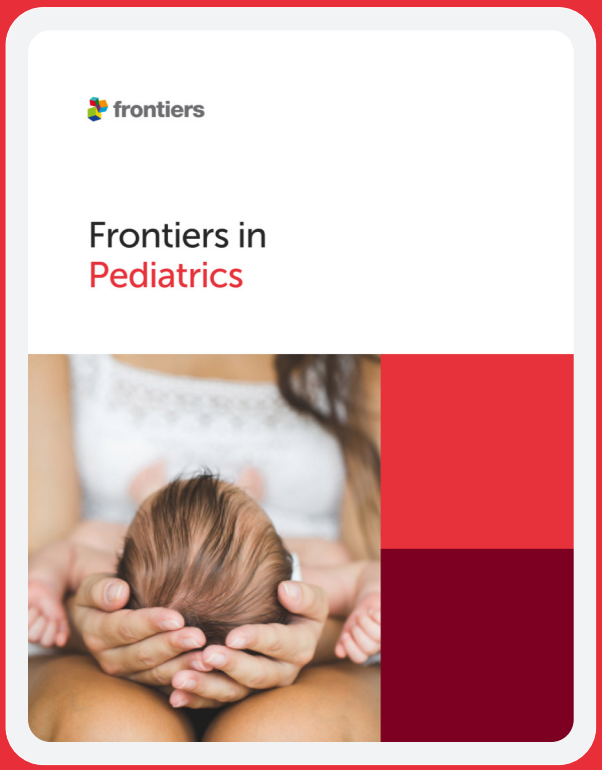

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