Pancreatic Insufficiency in Children

Pancreatic exocrine insufficiency is a relatively rare condition in pediatric patients but should be considered in any child with failure to thrive, steatorrhea, and symptoms of malabsorption. The most common cause of pancreatic insufficiency in children is cystic fibrosis, but other syndromic causes as well as isolated pancreatic enzyme deficiencies exist. Pancreatic function testing can be difficult and time consuming, and the sweat test to rule out cystic fibrosis and 72-hour fecal fat test to quantify fat losses are important to consider in the face of possible exocrine dysfunction. More invasive testing such as pancreatic stimulation with secretin and cholecystokinin can be performed and should be considered in certain clinical scenarios. Treatment consists of pancreatic enzyme replacement, use of acid suppression to prevent enzyme degradation, replacement of fat-soluble vitamins, and nutritional support.

**INTRODUCTION**

Insufficiency of the exocrine pancreas should be considered in the work-up of any pediatric patient who presents with features of malabsorption such as failure to thrive, chronic diarrhea, hypoalbuminemia, anemia, or symptoms of trace vitamin and mineral deficiencies. Testing for pancreatic insufficiency can be cumbersome due to the time commitment involved in many of the non-invasive testing techniques and the invasive nature of some of the more accurate tests. Additionally, the health care provider must have a significant understanding of testing to allow for interpretation of results. The purpose of this review article is to discuss causes and treatment of pancreatic insufficiency in children as well as to discuss in detail current testing techniques for pancreatic exocrine disease.

The exocrine function of the pancreas involves excretion of digestive enzymes and bicarbonate into the duodenal lumen after meal stimulation. The ability of
the pancreas to maintain exocrine function despite injury is impressive and as much as 98% of pancreatic enzyme production may be lost before steatorrhea occurs. Steatorrhea is defined as fat excretion exceeding 7% of fat intake. Symptoms of steatorrhea in children can be difficult to determine but should be considered in any child with failure to thrive, chronic diarrhea, symptoms consistent with bacterial overgrowth, hypoalbuminemia, edema (due to impaired protein hydrolysis), and trace element or mineral deficiency (1).

**DIFFERENTIAL DIAGNOSIS**

There are a large number of diseases to consider when evaluating a child for possible exocrine pancreatic insufficiency (Table 1). Although the differential diagnosis is quite large and includes many rather uncommon diseases, a physician should realize that the majority of children with pancreatic insufficiency have one of two possible diseases, namely cystic fibrosis or Shwachman-Diamond syndrome (2). Cystic fibrosis (CF) is an autosomal recessive disease that affects 1 in 2000 white births, and it is the most common cause of pancreatic insufficiency in children (3). The underlying gene defect is on chromosome 7, which leads to dysfunction of the CF transmembrane conductance regulatory protein (CFTR) causing decreased chloride and water secretion (4). The most common mutation involves the loss of phenylalanine at position 508 (ΔF508) of the CFTR protein (1). As a result, inspissated pancreatic secretions lead to acinar destruction and pancreatic fibrosis (Figure 1). A positive sweat test is diagnostic of this disease. The second most common cause of pancreatic insufficiency is Shwachman-Diamond syndrome which is a phenotypic description of pancreatic exocrine disease, bone marrow abnormalities, metaphyseal dystosis, growth retardation, and immunodeficiency with recurrent infections as well as other physical abnormalities (Figure 2A and B) (5).

Obviously, chronic pancreatitis can cause exocrine insufficiency due to the gradual loss of pancreatic function, but this entity occurs less commonly in the pediatric population than in adults. Underlying causes of chronic pancreatitis in children include anatomical abnormalities such as pancreas divisum, hereditary pancreatitis, α1-antitrypsin deficiency, toxin exposure, and viral or bacterial processes. Other extremely rare causes of pediatric pancreatic insufficiency should be considered in certain clinical scenarios. Johanson-Blizzard syndrome presents in an autosomal recessive pattern with steatorrhea from pancreatic exocrine dysfunction as well as other phenotypic features including failure to thrive, deafness, hypothyroidism, microcephaly, abnormal hair pattern, nasal cartilage hypoplasia, and small or absent permanent teeth. Pearson’s bone marrow syndrome presents with pancreatic insufficiency, sideroblastic anemia, and bone marrow precursor

**Table 1**

<table>
<thead>
<tr>
<th>Causes of Pancreatic Insufficiency in Children</th>
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<tbody>
<tr>
<td>• Cystic fibrosis (most common cause of pancreatic insufficiency)</td>
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<tr>
<td>• Shwachman-Diamond syndrome (second most common cause of pancreatic insufficiency)</td>
</tr>
<tr>
<td>• Chronic pancreatitis (anatomical obstruction, hereditary pancreatitis, α1-antitrypsin deficiency, etc.)</td>
</tr>
<tr>
<td>• Johanson-Blizzard syndrome</td>
</tr>
<tr>
<td>• Pearson’s bone marrow syndrome</td>
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<tr>
<td>• Congenital rubella syndrome</td>
</tr>
<tr>
<td>• Pancreatic isolated enzyme defects</td>
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<td>• Pancreas agenesis/hypoplasia</td>
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**Figure 1.** Abdominal ultrasound of a 12-year-old boy with cystic fibrosis reveals fatty infiltration of the pancreas due to progressive acinar destruction. Pancreatic exocrine insufficiency is present.

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vacoulization. Various selected enzyme deficiencies (lipase, colipase, trypsin, amylase, enterokinase), congenital rubella syndrome, and congenital pancreatic agenesis have been described but are extremely rare and outside the scope of this review (1–3, 5).

EXOCRINE PANCREAS TESTING

Sweat Test and Other Cystic Fibrosis Testing

The sweat test is the first order of priority in any pediatric patient suspected of having pancreatic insufficiency due to the relatively common prevalence of cystic fibrosis. Standard testing requires a quantitative collection of sweat in which sodium and chloride concentrations are measured by pilocarpine iontophoresis. A chloride concentration greater than 60 mmol/L is consistent with cystic fibrosis, and approximately 98% of cystic fibrosis patients will have this abnormal value. False positives can occur in diseases that cause an increased chloride elevation (glycogen storage disease type I, familial cholestasis, hypothyroidism, eczema, etc.). False negative testing can occur if the patient is edematous, if an inadequate amount of sweat is collected, or if a methodological testing error occurs (6). Sweat testing can be difficult to perform in infants, and alternative testing may be necessary. More than 500 CFTR gene mutations have been described, and genetic analysis can be performed at some referral laboratories. Measurement of nasal potential difference quantifies the electrical potential inherent to nasal mucosa. If performed accurately, this technique is an effective measurement technique for testing children as young as the first day of life. Unfortunately, this test requires much expertise and should be only performed in experienced centers (6,7).

Stool Smear for Fat/72-Hour Fecal Fat

The presence of steatorrhea makes microscopic examination of stool fat losses an easy screening test for pancreatic insufficiency. A simple qualitative technique for measuring fat malabsorption utilizes the Sudan stain in which neutral fat globules are visualized under the microscope (“fecal fat smear”). This technique is not,
however, an accurate assessment of total fat losses. For example, petroleum jelly lubricants used during a rectal exam can cause false-positive results. On the other hand, the 72-hour fecal fat collection is an effective technique for fat loss quantification. This test is generally reserved for infants greater than 6 months of age as younger children can have fecal fat output greater than 7% due to immaturity of pancreatic secretion. Adequate fat intake (i.e., greater than 100 grams fat/day in adults or 3 grams fat/kg/day in children) is required for the test to be valid. All stools must be collected over a 72-hour period for determination of the fractional excretion of fecal fat. Important limitations of this test should be considered. Stool collected from a toilet bowl can be lost in toilet water, so samples must be collected in an appropriate container system. At our institution, we have noted that absorbent infant diapers also lead to a similar mechanism of unrecoverable fat loss, and we recommend that diapers be reversed to allow for accurate collection. All stool samples must be refrigerated to prevent bacterial degradation of fat. Constipation can cause a false-negative result, and the collection time may have to be extended to 5 days in such clinical scenarios. Once the specimen is collected, it is important to consider what processing technique is utilized. For example, the van de Kamer method does not detect medium-chain triglycerides, and it is not a useful test for patients already consuming a diet consisting of this fat source (1,4).

**Steatocrit**

Another simple technique for evaluating fat malabsorption is stool centrifugation in hematocrit tubing to measure the amount of separated lipid stool. This technique (“steatocrit”) is only a crude technique to demonstrate the presence of fat malabsorption. It provides a very imprecise measurement and does not correlate well with 72-hour fecal fat testing (4,8).

**Trypsin/Chymotrypsin**

Both trypsin and chymotrypsin are exclusively created in the pancreas, and their quantitative measurement can be used to indicate pancreatic function. Both enzymes, especially trypsin, are susceptible to bacterial degradation. A significant amount of chymotrypsin is trapped in insoluble stool residue and can appear artificially low on measurement. Testing by the photometric method has been shown to be fairly accurate, and pancreatic stimulation with cholecystokinin (CCK) may improve testing sensitivity (1). Serum trypsinogen measurement by radioimmunoassay also has potential to determine pancreatic function over time. Patients with cystic fibrosis have trypsinogen levels well below normal by 7 years of age, and the test has been validated in this disease (3,9).

**Breath Testing**

The breath test has been utilized as a measurement of pancreatic exocrine function; however, its usefulness in children is limited due to obvious physical coordination difficulties of younger children. The loss of antibacterial
activities inherent to pancreatic enzymes as well as impaired small bowel peristalsis may lead to bacterial overgrowth in patients with impaired exocrine function. Therefore, the hydrogen breath test with glucose administration has been used to demonstrate bacterial overgrowth and pancreatic exocrine insufficiency in adult patients with chronic pancreatitis (10). Other breath test techniques such as the 13C-mixed triglyceride CO₂ exhalation test have been attempted, but there is no clear differentiation between normal and pathologic values (11).

**Secretin/Cholecystokinin**

The “gold standard” for pancreatic exocrine insufficiency testing is intravenous stimulation and duodenal intubation for collection of pancreatic secretions. Secretin (SecreFlo™, RepliGen Corporation, Waltham, Massachusetts), cholecystokinin (Sinalide™, Bracco Diagnostics, Princeton, New Jersey), or a combination of the agents are administered, and duodenal fluid is collected within 10 minutes using collection tubing passed through the operating channel of an endoscope (Figure 3). Fluid is then analyzed for pancreatic enzyme concentrations (12–14). Decreased fluid collection has been reported if collection is performed after 10 minutes of intravenous administration of either agent. It is necessary to check specimen pH for gastric acid contamination, and fluid with a pH less than 7 will have artificially low enzyme levels (12). Drawbacks for this technique include its inherent invasiveness, extreme care needed to prevent duodenal fluid contamination, and lack of standard testing techniques.

**Fecal Elastase**

A new technique that holds significant promise in the diagnosis of pancreatic exocrine function is measurement of fecal elastase. Fecal pancreatic elastase 1 is excreted in stool, can be directly measured from stool samples, and is not affected by bacterial degradation or pancreatic enzyme supplementation. Steatorrhea is considered present if the fecal elastase concentration is less than 200 µg/g. This test has excellent sensitivity but decreased specificity when evaluating for exocrine pancreatic insufficiency in children. In particular, it is a useful measurement of pancreatic function in cystic fibrosis, but low fecal elastase levels can occur in children with short gut syndrome (perhaps due to stool dilution) as well as patients with Shwachman-Diamond syndrome who otherwise have normal pancreatic function (15,16).

**TREATMENT**

The cornerstone of effective treatment for pancreatic exocrine deficiency in childhood is enzyme replacement. Therapy for all children with pancreatic insufficiency generally follows guidelines that exist for cystic fibrosis patients. Infants should receive 2000–4000 U lipase for every 120mL of formula (17). Patients greater than 1 year of age with CF should receive enzymes at a dosage of 500 U lipase/kg/meal and 250 U lipase/kg/snack. Dosing can be increased as needed to 2500 U lipase/kg/meal or up to 10,000 U lipase/kg/day. Adequate enzyme replacement can be measured by monitoring for steatorrhea, following weight gain, and performing appropriate pancreatic testing (3,18). Infants will require formulas high in medium-chain triglycerides due to impaired lipolysis, and fat-soluble vitamin supplementation is recommended in all cases of pancreatic dysfunction.

Care must be given to patients with cystic fibrosis who undergo enzyme replacement therapy as supratherapeutic dosing can lead to colonic wall thickening and narrowing. The entity, described as fibrosing colonopathy, presents with progressive symptoms of bowel obstruction, abdominal pain, emesis, constipation, and inflammatory colitis. Often, this disorder can mimic distal intestinal obstruction syndrome (DIOS). Diagnosis requires a full-thickness colonic biopsy, which reveals fibrosis in the lamina propria. Pediatric patients have an increased risk of fibrosing colonopathy, and enzyme replacement greater than 6000 U lipase/kg/meal for at least 6 months is a significant risk factor (4,18,19).

Patients with CF have a low post-prandial duodenal pH and acid suppression via H₂-antagonists or proton pump inhibitors can be helpful in maximizing enzyme efficacy (4,18). Enteric-coated enzyme preparations and acid-resistant microspheres are also helpful in preventing untoward effects of gastric acid (2,3).

In summary, the primary care provider should be aware of the causes of pancreatic exocrine insufficiency in children. Cystic fibrosis always must be initi-
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A SPECIAL ARTICLE

References

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