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Update in Pediatric Gastroparesis

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Gastroparesis is characterized by delay in gastric emptying in the absence of mechanical obstruction. The etiology and management of gastroparesis have been well studied in adults, but limited in the pediatric population. Most common identifiable etiologies of pediatric gastroparesis include: post-viral illness, drug side effects, post-surgical complications, diabetes mellitus, and mitochondrial disease. The most common symptoms are usually age-dependent. Nausea and abdominal pain are more common in older children and adolescents, while vomiting is more common in younger children. The gold standard for diagnosing gastroparesis remains gastric emptying scintigraphy, although normal values in children are limited. Treatment includes dietary modifications, pharmacotherapy, and gastric electrical stimulation, maintenance of nutrition, attention to glucose control, and psychological aspects.

INTRODUCTION

Gastroparesis is characterized by delay in gastric emptying associated with upper gastrointestinal symptoms without mechanical obstruction.[1] The care for these patients is often complex, difficult, and frustrating.[2] In adults, the most common etiologies are secondary to complications from diabetes or surgical interventions[3] as well as "idiopathic". The gold standard for the diagnosis of gastroparesis is a scintigraphic gastric emptying study.[4]

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There is a robust body of evidence for the etiology and management of adult gastroparesis, but limited in the pediatric population. Pediatric gastroparesis is usually overlooked and can remain untreated for a long period of time.[5,6] In children, the most common identifiable causes for gastroparesis are secondary to viral illness or complications of a surgical intervention.[7] The aim of this review is to provide the most up to date evidence on the spectrum of pediatric gastroparesis, emphasize the differences from the adult setting as well as extensively address management approaches and treatment recommendations.

Etiology and Pathophysiology

The normal gastrointestinal function is complex and depends on coordination between the smooth muscles, enteric, and central nervous systems. The most common gastrointestinal dysfunctions associated with adult gastroparesis include: impaired gastric accommodation, postprandial antral hypomotility, pyloric dysfunction,

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duodenal dysmotility, dysfunction of the autonomic nervous system, and visceral hypersensitivity.[8] However, in infants and children there are developmental aspects which are superimposed on these recognized abnormalities.

Delayed gastric emptying occurs very frequently in premature infants[9-11] (< 28 weeks gestation) as the normal gastric emptying gradually matures with age. At 32 weeks gestation, the gastric emptying patterns are similar to older infants, children, and even adults.[1,10] In normal term infants, expressed breast milk leads to faster gastric emptying compared to formula. Also, larger volume feedings are associated with a slower gastric emptying rate.[10]

In two large pediatric studies examining the etiology of gastroparesis, no recognized cause was found in up to 70% of cases (idiopathic). The identifiable causes included: viral gastroenteritis (18%), drug side effects (18%), post-surgical complications (12.5%), mitochondrial disease (8%), and diabetes mellitus (2%-4%).[1] Recognized pathogens associated with post-infectious gastroparesis include: parvovirus-like agents, Lyme disease, and rotavirus.[12] In the vast majority of post-viral gastroparesis, the emptying delay tends to improve or resolve spontaneously over days to several months.[12,13] At the time of presentation, identifying a virus may be problematic but a preceding gastroenteritis-like illness can be elicited from the family. Therefore, this raises the question whether so called "idiopathic" gastroparesis represents a latent post-gastroenteritis neuronal injury; this type of gastroparesis also spontaneously resolves. In adults, there have been many reports of histological abnormalities associated with gastroparesis which include: depleted or reduced numbers of interstitial cells of Cajal,[14,15] degeneration of the myenteric plexus combined with loss of ICC[16] myopathic gastroparesis,[17] stomach muscular layer eosinophilia,[18] and lymphocytic myenteric ganglionitis.[19] There have been no similar reports in pediatric gastroparesis based on our research of the literature.

Post-surgical gastroparesis has been described as a complication for antireflux surgery.[20] The main cause is an accidental injury to the vagus nerve which is an infrequent complication. Infrequently, patients with autoimmune diseases (i.e. systemic scleroderma) can present with delayed gastric emptying.[7,21] Mitochondrial disorders are often associated with intestinal dysmotility disorders. Screening for mitochondrial disorders involved serum levels of lactate or pyruvate, while confirmation can be accomplished by sequencing of the mitochondrial DNA or/and muscle or liver biopsy. In a small study looking at patients with mitochondrial disorders, delayed gastric emptying had poor response to prokinetic therapy.[22] Patients with hypertrophic pyloric stenosis have been extensively followed up. To date, there is no evidence of increased gastroparesis following the surgical correction (pyloromyotomy).[23,24]

Pseudo-obstruction is a rare but well described entity (familial or acquired) characterized by deficiency in the smooth muscles or nerves of the gastrointestinal tract. Gastroparesis is present in some of these patients as part of the diffuse involvement of the gastrointestinal tract, and particular attention needs to be paid to assessing the gastric emptying in children being considered for a subtotal colectomy for refractory constipation, in addition to histologically assess the resected colon smooth muscle histology.

Pediatricians often encounter infants with regurgitation or "reflux". Gastroesophageal reflux (GER) of infancy is a normal physiologic event that requires no therapy and generally improves over time. Empiric treatment of GER for these infants is generally not recommended if this GER is without complications, but a subset of infants with GER may also have significantly delayed gastric emptying for which prokinetic therapy may be helpful.[25]

Other important distinction from gastroparesis is cyclic vomiting syndrome (CVS), which is characterized by intense and stereotypical episodes of emesis. Patients with CVS usually are asymptomatic between episodes, without complains of abdominal pain or postpandrial distress, and have normal gastric emptying.

Clinical Symptoms of Gastroparesis

In children, presenting symptoms of gastroparesis appear to be different from those noted in adults.[5,26] In infants with gastroparesis, vomiting appears to be the most prevalent presenting symptom while both vomiting and abdominal pain are more commonly noted in young children between 1 and 10 years of age. Like adults, adolescents report more abdominal pain and nausea than younger children, but the incidence of nausea in adolescents still remains less than that which is noted in adults with gastroparesis. Nausea is quite common in adults with gastroparesis — noted in more than 80% — and is more common in diabetic

gastroparesis than idiopathic gastroparesis. Vomiting is also more commonly noted in adults versus adolescents and is noted in 60% and 90% of idiopathic and diabetic gastroparesis in adults.[27] Other symptoms present in children with gastroparesis include early satiety and weight loss which are present in approximately 25% of children of either gender. Bloating is less common and reported in fewer than 10% of children. One apparent reason for this age-related symptom difference in children may be the inability of infants and young children to express and describe symptoms of abdominal pain and nausea.

Gender differences also appear to be more pronounced in adults with gastroparesis. In adults, gastroparesis is predominantly noted in females which comprise approximately 80% of patients.[28] When analyzed as a single group, children with gastroparesis appear to be nearly equally divided between male and female gender. However, male-female incidence appears to change with age at diagnosis. Gastroparesis appears to be slightly more common in male children (<12 years of age) who comprise over 61- 72% of patients in this age group.[5, 26] Adolescents with gastroparesis tend to be overwhelmingly female and comprise approximately ¾ of patients in this age group. This is consistent with current theories related to explaining female susceptibility to gastrointestinal motility disorders in adults through the hormonal changes experienced after puberty.

The presence of comorbid conditions has been noted in children with gastroparesis. Unlike adults, non-psychiatric comorbidities are commonly noted in children diagnosed with gastroparesis with 38% of children suffering from some other major neurologic disorder—seizure disorder, cerebral palsy, developmental delay, or prematurity. Psychiatric symptoms have been noted in adults with gastroparesis with higher depression and anxiety scores on psychological testing and rates of depression exceeding 60%.[3,29] In one study in children, only 28% of children with gastroparesis were noted to suffer from psychiatric disorders which included attention-deficit hyperactivity disorder, depression, anxiety, bipolar disorder, or other behavioral problems.[5]

Based in our literature review, an association between gastroparesis and pervasive developmental disorders, attention deficit and hyperactivity disorder (ADHD), or Down's syndrome in children is not evident. Rumination syndrome is an entity that needs to be clearly differentiated from nausea and vomiting of gastroparesis, and gastric emptying in rumination is generally normal. Finally, there is an overlap between adolescents with eating disorders (anorexia, bulimia) and gastroparesis, and in this setting, identifying the diagnosis and instituting appropriate treatment is a challenging problem.

Diagnosis

Gastroparesis is a condition of delayed gastric emptying without evidence of mechanical obstruction and is typically associated with symptoms of nausea, vomiting, abdominal pain, early satiety, or bloating. It is imperative that mechanical obstruction (i.e. hypertrophic pyloric stenosis, intestinal webs, malrotation, duodenal atresia, anular pancreas, etc.) be considered and ruled out when necessary, particularly in young children or children with severe or significant symptoms.

Gastric emptying may be recognized as early as the 12th week of gestation possibly coinciding with increased amniotic fluid volume and the development of the suck reflex in utero. The percentage of fetuses that demonstrate normal gastric emptying also appears to increase in frequency in late gestation.[30] Gastric emptying appears to play a critical role in the developmental process and gastroparesis can be suspected if there is an abnormality in the normal process of growth or developmental milestones.

The gold standard for diagnosing gastroparesis remains gastric emptying scintigraphy. In this test, the solid or liquid contents of a test meal are radiolabelled so the amount of radiolabelled food remaining in the stomach at specified time intervals can be used to compute the rate of gastric emptying. A recent consensus statement in adults favors a 4 hour gastric emptying scintigraphy scan over a shorter 2 hour scan since the sensitivity of the test appears to improve with a 4 hour duration.[31] While consensus exists regarding adult normative values, normal values in children are limited. A small study in infants and children revealed a gastric emptying of 32-64% one hour after ingestion of radiolabelled milk and 44-58% in children receiving radiolabelled milk feedings.[32] In children 5-10 years of age, the time to empty half of a child-friendly Rice Krispie™ cake technetium 99m-radiolabelled meal was 107.2 minutes. Most pediatric centers use consensus-defined adult normal values published using a standardized meal consisting of egg-whites, toast, jelly, and water or as appropriate for age. Using this adult protocol, gastric emptying is defined as normal if less

than 90%, 60%, 30%, and 10% of the test meal remains in the stomach 1, 2, 3, and 4 hours following ingestion. In children as in adults, vomiting or an inability to ingest the test meal and its radiolabelled tracer must be noted since either of these may affect baseline and residual tracer counts noted during scintigraphy.

Wireless capsule motility testing (SmartPill™) is another modality that has been used to detect gastroparesis. This device is an orally ingested 26mm X 13mm non-digestible pill taken following ingestion of a standard test meal. b5 measure luminal pressure, pH and temperature throughout the entire GI tract and is thereby able to quantitate rates of gastric emptying, small bowel transit and colonic transit. While this device is currently FDA approved for use in adults, it is not approved for use in children. There are inherent challenges in this age group as the smart pill is difficult to swallow in younger children and normal values are not well-established. Nevertheless, there is limited data supporting its use in children. In a small study of 22 symptomatic children age 8-17 years old, wireless motility capsule testing was well tolerated with no adverse events and had 100% sensitivity and 50% specificity in detecting gastroparesis when compared to a 2 hour scintigraphic gastric emptying study.[33] Its major asset is being able to measure small bowel and colon transit thus providing a total profile of gut transit to assist in therapeutic decisions without use of radiation. In this limited pediatric study, the capsule was also found to have greater sensitivity in detecting abnormalities of small bowel motility when compared with antroduodenal manometry, perhaps because the capsule asseses the entire small bowel actively.

Breath testing is another means of assessing gastric emptying in children. In breath testing, orally ingested food is enriched with naturally occurring 13-carbon. A number of 13-carbon enriched substrates are utilized such as radiolabelled 13C-octanoic acid for solids and 13C-sodium acetate for liquids. After ingestion, these 13-carbon substrates are rapidly metabolized in the liver upon leaving the stomach and following their absorption in the duodenum. After oxidation in the liver, these isotopes are excreted from the blood into the exhaled breath. The rate of gastric emptying is the rate limiting step in excretion of this compound in exhaled breath.[34] As a result, quantitative measurement of this 13-carbon dioxide can help in determining the rate of gastric emptying. Multiple studies have validated its use in adults. Small studies in children of various ages seem to support a role for breath testing in analysis of gastric emptying in children. For example, use of radiolabelled 13C-octanoic acid breath testing did reveal good correlation with scintigraphy in assessment of gastric emptying of solids in 25 children 5 to 10 years of age.[35] Use of breath testing in small studies of both premature infants and term infants also demonstrates a potential role for 13-carbon breath testing with reproducibility and correlation with other methods including scintigraphic testing.[36,37] The major benefit is that the patient does not have radiation exposure and also it can be repeated multiple times to assess the response to treatment. This method is now FDA approved for use in adults only. In gastroparesis, where there is accompanying small bowel bacterial overgrowth (SIBO) in more than 50% of patients, there is a concern that this SIBO can interfere with metabolism and absorption of 13C-octanoic acid thus changes the calculations required for assessment of gastric emptying by breath testing. Hence its future role in adults with gastroparesis remains unclear; for now is it not approved in children.

Treatment

The management of gastroparesis can be complex (Figure 1). Initial efforts should correct fluid and electrolyte abnormalities since correction of these derangements can assist with management of gastroparesis.[38,39] Hyperglycemia is often noted in exacerbations of diabetic gastroparesis. Hyperglycemia can delay gastric emptying and contribute to symptoms of gastroparesis in both idiopathic and diabetic gastroparesis.[40] It is accepted that acute hyperglycemic states (serum glucose >250mg/dl) will delay gastric emptying and is a major contributor of nausea and vomiting in the newly diagnosed diabetic where an infection (often urinary) may be the trigger. Correcting this hyperglycemia may therefore also enhance gastric emptying. Chronic gastroparesis related to diabetes takes up to 5-10 years to evolve.

Dietary Management

Dietary modification is a key first step in the management of gastroparesis. In children as in adults, small frequent meals may be helpful in managing gastroparesis. Low fat, low fiber foods can also be helpful in managing gastroparesis since fat and fiber can retard gastric emptying and since fiber may be associated with an increased risk of bezoar formation in individuals with gastroparesis. Blenderized foods and ingestion of liquids

during meals may also be helpful since gastric emptying of solids may be slower than liquids. A study in adults with diabetic gastroparesis revealed that a low particle size diet consisting of "foods" that were mashable with a fork" resulted in improvement in symptoms as well as more significant improvement in rates of gastric emptying when compared to a control group taking a low fat, low fiber diet.[41]

Dietary management of infants can be difficult due to their dietary restrictions, but there may be some strategies that may be helpful. In infants who are predominantly fed commercial formula, a small study of 6 infants revealed a significant difference and more rapid gastric emptying when those infants were fed infant formula containing high medium-chain triglyceride versus high long-chain triglyceride formula and when those infants were fed glucose-polymer containing formulas versus lactose-containing formulas.[42] In separate studies, gastric emptying in infants fed breast milk appeared to be more rapid when compared to infants fed commercial formula.[37] There are also some studies that revealed an increased rate of gastric emptying in infants and non-infants when fed a formula containing whey protein or whey hydrosylate, although data regarding protein content in infant formula and rates of gastric emptying are conflicting.[43-45]

Pharmacological Management

Since nausea and vomiting are common symptoms in children with gastroparesis, antiemetics may be helpful. Studies supporting their use appear to be limited, and recommendations for antiemetic therapy appear to be largely based on anecdotal experience and the adult literature. Furthermore, while use of antiemetic agents may result in improvement in symptoms in patients with gastroparesis, they do not appear to have beneficial effects on gastric emptying.[39] since their main source of action is centrally with the chemorector trigger zone at the floor of the 4th ventricle. Ondansetron, a 5HT-3 antagonist and antiemetic, can be helpful in management of vomiting associated with gastroparesis or other pediatric gastrointestinal disorders, such as cyclic vomiting syndrome, and doses of 4-8 mg every 8 hours are generally recommended in children and adolescents and can be administered orally, intravenously, or rectally if necessary.[46] Promethazine can be used in children but only with caution. The FDA issued a 2004 black box warning that recommended use of promethazine only in children greater than 2 years of age and only with

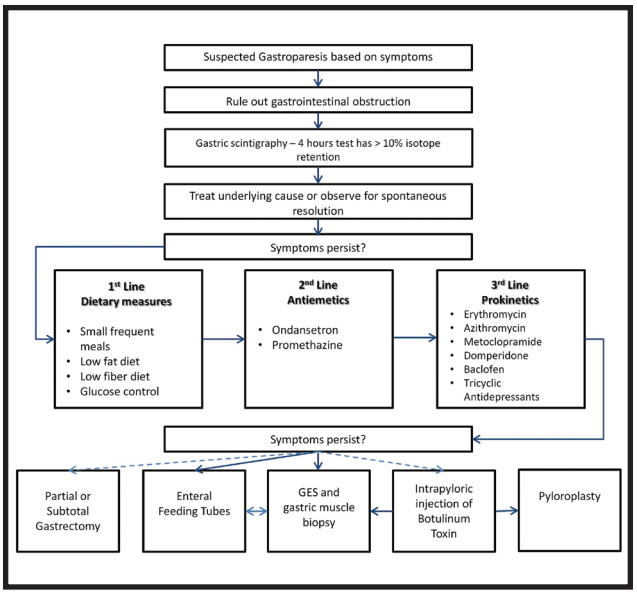

Figure 1. Algorithm for Pediatric Gastroparesis

Suggested algorithm for the diagnosis and management of pediatric gastroparesis. GES (Gastric Electrical Stimulator)

the lowest effective dose since there have been several reports of respiratory depression and death with use. Furthermore, a more recent FDA warning recommended that injectable promethazine be administered only via the deep and intramuscular route and not into the skin or artery since there may be a risk of gangrene with these routes of administration. Oral and rectal routes of promethazine administration are also treatment options. Other over-the-counter antiemetic with some antiemetic effect include: meclizine, ginger, peppermint drops, and some homeopathic remedies.

With continued symptoms of gastroparesis unresponsive to conservative measures, use of prokinetics may be helpful. Only a few agents exist that can accelerate gastric emptying in children, and there are problems that can arise with use of most of these agents. Since erythromycin is a potent stimulator of gastric contractions, it can be utilized as an "off label" use of the agent. The main mechanism of action is to occupy the motilin receptor in the stomach and mimic the action of motilin. Lower doses of erythromycin are recommended in a range of 1-3mg/kg every 6 to 8 hours, since this can delay tachyphylaxis which occurs with chronic erythromycin use and usually occurs within 4 weeks of starting the medication.[47] Symptoms of nausea and vomiting can actually be provoked with higher doses of erythromycin most commonly used for infections (10 mg/kg/dose). Prolongation of the QTc

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and interaction with other inhibitors of cytochrome P-450 3A have been reported to result in cardiac arrhythmias and even death in individual case reports in adults. Azithromycin may theoretically be used as an alternative since it has fewer drug interactions, less incidence of QTc interval prolongation, a longer half-life, and fewer gastrointestinal adverse effects.[48,49] The dose of azithromycin is twice that for erythromycin. Data supporting its use is lacking at this time. Ingestion of oral azithromycin and erythromycin should be used with caution in infants if the exposure occurs in the first 2 weeks of life as the possibility of increasing the risk of developing infantile hypertrophic pyloric stenosis has been reported.[50]

Metoclopramide is an FDA approved drug for gastroparesis in adults but not in children, although it is commonly used in management of children with gastroparesis. While there is a large amount of experience using metoclopramide in adults, the published evidence supporting its use in children is limited. In a small study of 6 post-surgical infants with gastroparesis, metoclopramide more than doubled the rate of gastric emptying but no beneficial effect of metoclopramide was noted in premature infants. There remains some concern over adverse events accompanying long-term use of metoclopramide including a potential risk of tardive dyskinesia and Parkinson-like syndrome. Akathisia, anxiety, hyperactivity, tremor, and sleepiness can develop in the first few days to months after treatment is initiated. These symptoms are completely reversible after decreasing the dose or stopping the medication. A recent 2009 FDA black box warning recommended metoclopramide only for short term use less than 12 weeks. A recent 2015 Canadian federal health warning recommended that metoclopramide should not be used in children less than 1 year of age since they appear to be at higher risk of extrapyramidal symptoms The Canadian recommendation further states that metoclopramide not be used in children greater than 1 year of age unless treatment is clearly necessary. The Canadian report states that the Canadian health department (HealthCanada) has identified only 8 reports of extrapyramidal symptoms suspected of being associated with metoclopramide in children receiving the recommended daily dose. However, the Health Canada warning cites a recent review of the European data that found cases of EPS in children less than 18 years of age treated with metoclopramide with most cases occurring when recommended doses were used. As a result, caution should be emphasized when considering this agent for children, and follow up is essential for monitoring for side effects. The tardive dyskinesia adverse events may be irreversible in some cases.

Less commonly used medications may be necessary when symptoms persist. Domperidone can enhance gastric emptying and may be considered for use in children. An FDA administered IND must be obtained prior to administering this agent. Domperidone is useful where chronic prokinetic therapy is being contemplated or when metoclopramide and erythromycin have resulted in side effects or are not effective. It is a dopamine 2 receptor inhibitor, as is metoclopramide, but it does not cross the blood-brain barrier decreasing the risk for extrapyramidal side effects. Its effects are antiemetic acting centrally and as a prokinetic acting peripherally. Dosing is similar to metoclopramide in adults, starting at 10 mg four times a day but its benefit is lack of significant side effects and dosing can be increase up to 80 mg a day in adolescents. An electrocardiogram needs to be followed to address the rare reports of prolong Q-T intervals.

Baclofen is a γ-Aminobutyric acid (GABA)–B receptor agonist which increases lower esophageal sphincter pressure and decreases the transient lower esophageal sphincter relaxations. In children, Baclofen significantly improved the gastric emptying compared to placebo in a trial involving 30 children.[51] In adults, Baclofen is commonly used for refractory GERD but there are no randomized trials for its use in gastroparesis. The baclofen dose in adults is 10 mg four times a day, while in children is 0.5 mg/kg/dose to a max of 40 mg a day.

Other agents can also be helpful for management of associated abdominal pain accompanying gastroparesis. Low-dose tricyclic antidepressants or cyproheptadine are also potentially helpful since they have been utilized in other functional abdominal pain disorders such as irritable bowel syndrome and cyclic vomiting syndrome.

Interventional: Surgical and Endoscopic Options

Placement of a gastrostomy tube for venting or jejunostomy for feeding may be helpful in severe cases. Parenteral nutrition may be necessary in severe and refractory cases to help in maintaining nutrition. However, a jejunostomy tube is the recommendation

due to severe TPN complications and costs.

Gastric electrical stimulation (GES) has emerged as a reasonable alternative in those with refractory symptoms of gastroparesis or where oral medications are not tolerated or are ineffective; this occurs in approximately 25% of adult patients with gastroparesis. With few good pharmacologic options and with the concerns over adverse drug effects, this approach has recently garnered more support. The history of gastric electrical stimulation and pacing date back to the 1960's.[52] In 2000, the FDA approved the Enterra system for humanitarian use in which a surgically implanted pacer delivers high frequency electrical pulses to electrodes placed at the junction of the antrum and body. A recent meta-analysis in adults revealed that gastric electrical stimulation appeared to result in significant improvement in symptoms of gastroparesis in individuals with diabetic and non-diabetic gastroparesis. Improvement in gastric emptying is not a goal.[53] Guidelines published by the American College of Gastroenterology in 2013 recommend this approach only for compassionate use in adults or children with refractory symptoms, particularly nausea and vomiting. Some uncontrolled data does exist supporting the use of gastric electrical stimulation in children. In a study of 9 children aged 8-17 years, all 9 children reported symptom improvement and quality of life improvement following gastric electrical stimulation during a follow up of 8 to 42 months.[54] In another study in 16 children age 4-19 years, there was significant improvement noted in all children with improvements in severity of both nausea and vomiting.[55] As noted in adults with idiopathic gastroparesis, there was not clear improvement in gastric emptying noted in those children who received gastric electrical stimulation which is consistent with the mechanism of action of GES which is to affect central control of nausea and vomiting via vagal afferents. It is important to remember that abdominal pain is not a target for GES since the main goal is to improve nausea and vomiting.

Surgical intervention may be necessary in cases of severe, symptomatic gastroparesis that appears to persist despite aggressive nutritional and pharmacologic intervention. Use of enteral feeding tubes may be necessary to maintain or improve nutrition, hydration, or metabolic derangements. Placement of these tubes may also allow venting for patients with excessive gastric distention or enteral secretions with simultaneous feedings as in instances where gastrojejunal feeding tubes with gastric and jejunal access are placed. They also permit the administration of medications via the enteral tube which improves the absorption of prokinetics and antiemetics, as well as "other agents" (i.e. antiseizure, pain medication, etc). Current recommendations by the American College of Gastroenterology favor a trial of nasoenteric postpyloric feedings prior to jejunostomy feeding tube placement in individuals with weight loss of more than 10% or refractory symptoms of gastroparesis.[39] In 2 large pediatric series, surgical placement of either a gastrostomy or jejunostomy tube was required to aid with management in a small percentage (4%, 19/469) children.[5,26] In one of these series, all five children requiring surgical feeding tube placement were noted to have CNS comorbidities and developmental delays complicating their management.[5] A large study in adults with gastroparesis reported improvement following jejunostomy tube placement with 39% reporting improved nausea and vomiting, 52% fewer hospitalizations, 56% with improved nutrition, and 81% with improvement in overall health status.[56]) Enteral feeding devices offer good reversible and, in some cases, temporary measures for treating children with severe, complicated gastroparesis who are unresponsive to more dietary or pharmacologic conservative intervention. It should be emphasized that when the patient has reached the stage of requiring a feeding tube, it will be advisable to consider a GES placement for symptomatic control of the nausea and emesis. Also, a jejunal feeding tube approach is preferable from a percutaneous endoscopic Gastro-Jejunal tube placement as it facilitates maintenance and most importantly, smooth muscle biopsy can be obtained at the time of the surgical jejunostomy to assess the ICC and neuronal status.

Intrapyloric injection of botulinum toxin has also been investigated as a potential treatment for gastroparesis due to encouraging results in multiple small series of patients with gastroparesis. A small open-label retrospective study of intrapyloric botulinum injection in children with gastroparesis revealed that approximately two-thirds of children reported improvement in a variety of symptoms and 40% of responders requiring only one injection. The uncontrolled and open-label nature of this study are obvious limitations, and similar encouraging findings have also been noted in uncontrolled open-label adult studies. Two double-blind, placebo-controlled studies examining the effects of botulinum injection in adults

with gastroparesis reveal no improvement in symptoms compared with placebo.[57,58] Based on these placebo-controlled trials, botulinum use is not recommended for children or adults with gastroparesis.[39] While the use of intrapyloric injection of botulinum toxin is not approved or endorsed, there is interest in its future role since it could be a first-step where a good response to botulinum injection could predict if a pyloroplasty can be beneficial in the long term.

Pyloroplasty has also been used in the management of gastroparesis and has the advantage of less radical alteration of the gastric anatomy compared with gastrectomy.[59] In one large adult series of 50 patients with gastroparesis, 83% reported symptom improvement following laparascopic pyloroplasty, and there was also significant improvement in gastric emptying noted on scintigraphy with median preoperative T1/2 of 180+/-73 minutes and postoperative T1/2 of 60+/-23 minutes ($p < 0.001$). 68% of these patients had previous foregut procedures and/or cholecystectomy and 64% underwent concomitant procedures, such as paraesophageal hernia repair and gastrostomy takedown, at the time of their pyloroplasty. More recently in adults, pyloroplasty is being combined with GES placement with excellent results since gastric emptying can be normalized, a goal not achieved by GES alone.[60]

Partial or subtotal gastrectomy is also a potential treatment for severe, refractory gastroparesis, but larger studies supporting its use are largely confined to adult populations. In one series of seven adults patients with vomiting due to gastroparesis, subtotal gastrectomy with removal of 70% of the stomach and creation of a Roux-en-Y loop of jejunum to prevent reflux gastritis resulted in substantial subjective improvement in all but one of seven patients.[61] A larger series of 62 adult patients with postvagotomy gastoparesis who underwent near-total complete gastrectomy with a Roux-en-Y reconstruction revealed symptom relief in 43% of patients. A high percentage of postoperative complications were also noted in this larger study in 40% of patients and included narcotic withdrawal syndrome (18%), ileus (10%), wound infection (5%), intestinal obstruction (2%), and anastomotic leak (5%). There was also significant reduction in nausea (93% to 50%), vomiting (79% to 30%), and postprandial pain (58% to 30%) following surgery, but there were not significant differences in chronic pain, diarrhea, and dumping syndrome in this study. Gastrectomy should therefore be reserved only for those with severe symptoms unresponsive to other interventions. Data from McCallum et al. indicates that about 3-5% adult patients who failed GES for gastroparesis will require a total gastrectomy. If the patient has a previous gastric surgery (Billroth I or II) or GIS tumor resection, a GES is not recommended as the best approach but rather they should undergo a subtotal gastrectomy.

TAKE HOME CLINICAL PEARLS FOR THE PRACTITIONER

1. Pediatric gastroparesis is not similar to the adult gastroparesis. The diagnosis and treatment for gastroparesis is well established in adult but there is limited evidence-base literature in the pediatric gastroparesis.
2. The most common etiologies in pediatric gastroparesis are idiopathic and post-viral. Most gastroparesis in children tends to resolve spontaneously without any treatment implying that many "idiopathic" gastroparesis could be subclinical gastrointestinal infection cases. Also, treating the underlying pathology (infection, hyperglycemia, etc.) will improve the gastric emptying.
3. Symptoms for pediatric gastroparesis include: nausea, vomiting, and abdominal pain. Gastric emptying scintigraphy remains the gold standard to diagnose gastroparesis in children despite the lack of normal values in pediatric patients.
4. The treatment for pediatric gastroparesis should start with dietary modifications. Pharmacological therapy is the second and third line of therapy for persisting pediatric gastroparesis. A GES is the choice of the treatment for those cases refractory to medical therapy.
5. Future research in the etiology and treatment for persistent gastroparesis is very much needed in the pediatric population, particularly focusing on histological changes in neurons, ICC, and smooth muscle of the gastric muscularis propia. ■

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