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Review Article: Childhood Gastroparesis is a Unique Entity in Need of Further Investigation

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Abstract

Background: Despite increasing knowledge regarding gastroparesis (**GP**) in adults, little is known regarding the incidence, prevalence, and natural history of childhood GP. Exacerbating the knowledge gap in pediatric GP are both the lack of normative data for gastric emptying scintigraphy in children and lack of GP specific pediatric reported outcome measures.

Purpose: The aim of this article is to review the available literature on pediatric GP and identify similarities and differences with studies in adults. We performed a comprehensive search in MEDLINE and Google Scholar from inception to April 2019 for articles published in English using the following combination of keywords: gastroparesis, pediatric gastroparesis, outcomes, metoclopramide, erythromycin, domperidone, cisapride, and gastric neurostimulator. The limited available pediatric data, often retrospective, suggest marked differences between adult and pediatric GP in several aspects including: etiology, concomitant co-morbidities (e.g., psychiatric disorders), clinical symptom presentation, diagnostic evaluation, response to therapies, and clinical outcome. Further research in pediatric GP is needed and holds the promise to further elucidate the mechanisms of this disorder in children and lead to pediatric focused therapies.

Keywords

pediatric gastroenterology; gastric emptying; gastroparesis; motility

INTRODUCTION

Gastroparesis (**GP**) is defined as delayed gastric emptying of fluids and/or solids in the absence of a mechanical obstruction.[1, 2] GP has been extensively studied in the adult population with resultant treatment guidelines developed to address adult GP.[3] Unfortunately, the same cannot be said about childhood GP. Knowledge regarding pediatric GP with respect to its incidence, prevalence, and natural history is sparse. Nevertheless,

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limited data, often from retrospective studies, suggest marked differences between adult and pediatric GP in several areas. These marked differences may serve as a caution when extrapolating adult data for use in children and underscore the need for GP-specific research in children. The purpose of this review is to summarize key data related to pediatric GP and highlight the uniqueness of pediatric GP relative to adult GP. As such, this review may serve as a platform to identify what is known about pediatric GP and may potentially direct research into areas which require further study.

Epidemiology

The reported prevalence of GP in adults ranges from 1.5% to 3%, with women and the elderly (>65 years of age) accounting for around 70% and 20% of cases, respectively.[4] An adult population based study led by Jung et al. in Olmsted County, Minnesota observed a GP incidence of 2.4 versus 9.8 patients per 100,000 person-years for men and women, respectively.[5] In contrast, Rey et al. estimated a higher GP incidence of 1.8% in the community; however, only 0.02% were actually formally diagnosed as having GP.[6] These different estimates of prevalence are likely related to the use of different methodological approaches (e.g., medical records review vs. community questionnaires).

Due to a lack of epidemiological studies, both the incidence and prevalence of pediatric GP remain unknown. However, based on a nationwide pediatric hospital database, the rate of pediatric GP hospitalizations increased significantly from 2004 to 2013 at a rate of 130 additional hospitalizations per year.[7] The number of unique patients hospitalized with a diagnosis of GP increased from 174 to 723 during those same years.[7] Within children, females and adolescents appear to have more repeat hospitalizations.[7] Though hospitalizations provide insight into the potential increase in incidence of more severe pediatric GP, further studies are needed to determine the overall incidence and prevalence of pediatric GP.

Etiologies

In adults, most cases of GP are idiopathic with diabetes mellitus, drugs, and postsurgical causes following in frequency (Table 1).[5, 8] Other etiologies include Parkinson’s disease and connective tissue diseases.[8] It is estimated that as many as 25% to 55% of adult patients with type 1 diabetes have GP.[8] Most idiopathic cases are believed to occur as a post-viral syndrome, since at least 23% of patients with idiopathic GP had a viral illness prior to GP presentation.[4] Females are more likely to have idiopathic GP, while nonwhites are more likely to have diabetic GP.[9]

One of the proposed mechanisms for GP in adults is macrophage driven loss of, or functional abnormalities in, the interstitial cells of Cajal (**ICCs**), which can lead to gastric dysmotility.[10] Histologic specimens from patients with diabetic and idiopathic GP showed: a decrease in the number of ICCs, with remaining ICCs showing injury; an abnormal immune infiltrate containing macrophages; and a variable decrease in nerve fibers on immunohistochemistry and electron microscopy.[8, 11, 12] Whether these same pathophysiologic findings are present in children with GP is unknown.

In contrast to adults, a pediatric retrospective study by Waseem et al. noted that diabetic GP was the least common cause of GP, with idiopathic GP being the most common (Table 1).[13] Around 39% of pediatric patients had other associated comorbidities including seizure disorders, cerebral palsy, developmental delay, and prematurity; these may or may not have contributed to the presence of GP.[13] Another observational study by Rodriguez et al. found only 18% of pediatric GP cases were of post-viral origin, followed by medications (18%), post-surgical causes (12.5%), mitochondrial diseases (8%), and diabetes mellitus (2%−4%).[14]

Given the small relative contribution of diabetes mellitus as an etiology of GP in children, current research paradigms directed at diabetes mellitus related GP in adults may not translate well to the pediatric GP population. Furthermore, given the extremely large predominance of an idiopathic etiology in pediatric GP, efforts to elucidate the etiology and mechanisms of pediatric GP are needed.

Symptoms and Symptom Assessment

There are significant differences between GP symptoms in pediatric and adult patients. A study led by Soykan et al. at a large tertiary medical center reported that the main symptoms in adult patients with GP (n=146) were nausea and vomiting (Table 1).[15] Jung et al. also noted that nausea (73.5%) and vomiting (53%) were the most common symptoms among patients with GP (n=83), followed by abdominal pain (44.6%), bloating (31.3%), weight loss (30.1%), postprandial fullness (22.9%), and early satiety (28.9%).

In children, age significantly influences GP symptom expression (Table 1); [13, 14] a finding that is seen in other pediatric disorders.[16, 17] Vomiting is most common in infants and young children whereas abdominal pain predominates in older children and adolescents (Table 1). [13, 14] These data highlight that symptom assessment in children should be tailored to the age of the child.

Objective Symptom Assessment—In adults, the Gastroparesis Cardinal Symptoms Index (**GCSI**) is a validated patient-reported instrument often used to assess GP severity, derived from the lengthier Patient Assessment of Upper Gastrointestinal Symptoms (**PAGI-SYM**) questionnaire.[18] The GCSI consists of three subscales: nausea/vomiting, postprandial fullness/early satiety, and bloating. Pain, which is reported by a large number of adults and older children is not included in the GSCI.[4] GSCI scores unfortunately do not appear to correlate with gastric emptying rate.[19]

A study by Jehangir et al. sought to assess adult patients with GP by comparing the PAGI-SYM to the Rome IV Diagnostic Questionnaire, which is used to diagnosed functional GI disorders.[20] Interestingly, they found that the majority of patients with GP (n=187/218) met the criteria for more than one functional GI disorder, with postprandial distress syndrome and chronic nausea and vomiting syndrome being the most common.[20] Outcomes were not evaluated in this study. These findings suggest that GP and functional GI disorders might overlap frequently, and thus treatment decisions should be carefully tailored to the patients and their predominant symptoms.

In children, a GP specific patient reported symptom measure has not been developed. In an attempt to address this deficiency, one pediatric study trialed a modified version of the adult GCSI, with a reduction from the 6-point Likert-type scale to a 5-point Likert-type scale and the addition of abdominal pain (although not included in the total GCSI calculation).[21] Similar to adult studies, no association was found between the total modified GCSI score and degree of emptying delay.[21] When evaluating how well the children understood the symptoms, no symptom consistently achieved "complete" understanding.[21] Given this and that the 5-point scale used has not actually been validated in children with GP, development of such a scale is needed. Such a scale would provide objective and reliable means to assess GP outcomes.

Gender

As noted above, in adults GP is more predominant in females; [5, 9, 13–15] the reason(s) is unknown. One theory is that stomach motility is dependent on neuronal nitric oxide synthesis, which may be regulated by estrogen.[22] In female rats, it appears gastric neuronal nitric oxide synthase expression and nitrergic relaxation are substantially elevated, which is accompanied by significantly reduced intragastric pressure.[23] This might imply that females have a higher dependency on the nitrergic mechanisms when compared to males, and thus greater vulnerability to gastric dysfunction.[23]

Parkman et al. demonstrated in adults with GP, gender may influence etiology and severity. [9] Females were more likely to have an idiopathic etiology (69% females vs 46% males), whereas males were more likely to have GP related to diabetes (54% males vs 31% females).[9] In contrast, another study by his group showed a female predominance for both idiopathic and diabetic GP (females: 89% idiopathic, 70.5% type 1, 76.3% type 2).[24]

Adult females (vs. males) with GP had worse symptom severity (greater GCSI score).[9] However, more adult males required hospitalization (53% vs 39% females).[9] These differences did not appear to be related to gastric emptying delay.[9]

In contrast, the female:male ratio in pediatric GP varies by age (Table 1). It is unknown why these age-related gender differences exist in the pediatric population, but they may suggest different pathophysiologic factors playing a role in the development of GP, particularly prior to adolescence. It seems that as age increases, female predominance increases suggesting a potential hormonal involvement as is postulated in adults (Table 1). Whether gender influences etiology and/or symptom severity in children with GP, to our knowledge, remains to be clarified.

Psychiatric Co-Morbidities

Differences between adult and pediatric GP extend to mental health issues. Adults with GP may have psychiatric and/or abuse comorbidities in up to 62% of cases (Table 1).[15, 24] GP patients with psychiatric co-morbidities tend to experience longer hospital stays and reduced work hours.[25]

Psychiatric comorbidities are less common in children with GP compared with adults. In one study (n=239) they were found in 28% of pediatric patients with GP (Table 1).[13] No

differences were observed with regard to frequency and prevalence between sexes. Whether the decreased frequency of psychiatric comorbidities in children with GP leads to better outcomes is unknown. Similarly, how psychiatric comorbidities in children may or may not evolve over time with continued GP symptoms is unclear.

Narcotic Usage

Opioids may worsen gastric emptying, increase the risk of narcotic bowel syndrome, and potentially cause addiction, tolerance, and/or overdose.[26] They also are associated with poor quality of life, increased hospitalization, and increased use of antiemetic and pain modulator medications compared with nonuse.[27] Unfortunately, at least 31% to 50% of adults with GP are prescribed opioids for their abdominal pain.[27]

Although the data are limited, one study in children found that only 2% of patients with GP were taking narcotics (n=239).[13] Thus, pediatric (vs. adults) with GP appear to generally have significantly less exposure to opioids.

Outcomes

In adults with GP several factors (e.g., male sex, age ≥ 50 years, post-viral etiology) have been found to be independently associated with reduced symptoms at 48 weeks (Table 1).[28] Additional factors include none to mild abdominal pain, mild gastroesophageal reflux disease severity, and no to mild depression.[28] Unfortunately, these characteristics encompass less than a third of patients with GP, implying the majority of adults with GP may be at risk for significant disease burden.[28] Indeed, a study in adults with GP identified only 28% of 262 patients reporting GCSI score reductions of 1 or more at 48 weeks.[9] Improvement in scores was found to be similar among different ethnic/racial groups, however vomiting improved more in non-Hispanic blacks compared with non-Hispanic whites.[9] GP is associated with a mortality rate of 4% to 12% in adults, and is typically higher in patients with diabetic GP.[4, 29]

In contrast, clinical outcomes have been evaluated retrospectively in children with GP and suggest a higher likelihood for improvement. Rodriguez et al. reported 52% of 204 children with GP (outcome data available on 204/230 subjects, mean age 9.1 years of age) had resolution of their symptoms.[14] Of those who had resolution, 42% reported resolution within 6 months, 84% within 12 months, and 100% by 36 months.[14] Factors associated with symptom resolution included: younger age (infants>children>adolescents); male gender; shorter duration of symptoms at time of presentation; absence of mitochondrial dysfunction; post-viral etiology; and a favorable response to prokinetic drugs (Table 1).[14] Out of 41 patients diagnosed with post-viral GP, 73% responded well to prokinetic drugs and 63% had resolution of their symptoms within 2 years. Fifty-five percent of patients (n=90) reported a positive response to prokinetic drugs regardless of age, with 58% of those reporting symptom resolution.[14]

In another retrospective study of children with GP (mean age 7.9 ± 5.9 years) by Waseem et al., 60% of 239 patients reported significant improvement in nausea, vomiting, abdominal pain, early satiety, bloating, and weight loss at 2-year followup regardless of sex, age, or degree of emptying delay.[13] With the exception of abdominal pain (reported more often by

girls), no other significant difference in symptom outcomes was found comparing girls to boys.[13] Patients in the 11–16 year age range had the most improvement in all symptoms, whereas the >17-year-old group reported the least improvement.[13] It should be noted, however, that a large proportion (~40–50%) of children with GP did not have symptom resolution within 2–3 years.[13] Whether differences in etiology, gender, or other factors contribute to the more favorable outcomes in children compared with adults with GP remains to be determined. Prospective studies are needed to elucidate why and how these and other factors relate to favorable outcomes in pediatric GP, as well as understand the different therapeutic options available to treat pediatric GP.

Economic Impact

The average cost of hospital care for adults with GP has increased from $13,350 per patient in 1997 to $34,585 in 2013.[30] The number of hospitalizations also has increased, with one study finding an 18-fold rise from 1993–2009 and another finding a 4-fold increase from 1997–2013 (from 3,978 to 16,460).[29, 30] Despite this, no increase in GP incidence has been identified. Admissions for GP in adults tend to be longer and are associated with higher charges when compared to other GI conditions.[29] Additionally, these patients seem to have a lower annual income and higher disability rates.[31, 32]

A recent study found that the national cost of hospital care for children with GP is rising dramatically as well, with an increase at a rate of about $3.4 million per year from 2004 to 2013, representing a 5.8-fold increase in cost.[7] The increase was related to the higher number of pediatric GP admissions and not increases in cost per hospitalization.[7] This rise in hospitalizations could be due to either an increase in the diagnosis and awareness of GP, increase in overall severity of GP, or both. Whether the increase in hospitalizations in children with GP is related to an increase in incidence/prevalence remains unknown.

DIAGNOSTIC EVALUATION

Gastric Emptying Scintigraphy

The gold standard for diagnosing GP is gastric emptying scintigraphy (**GES**) using a radiolabeled standardized solid meal mixed with Tc-99m sulfur colloid. This should be consumed within a short period of time, usually no more than ten minutes.[33] The percentage of radioactivity, which correlates with the amount of food remaining in the stomach, is calculated. Methodology varies among different centers, but the recommended technique is the 4-hour imaging protocol with scans taken at 0, 1, 2, and 4 hours after ingestion of the meal.[34] Several adult and pediatric studies have shown patients with normal GES studies at two hours ultimately resulted in a diagnosis of GP when extended to four hours.[35–37] GES is considered delayed if retention is greater than 60% at 2 hours postprandially and/or greater than 10% at 4 hours.[34] In adults, a proposed severity grading of emptying delay according to the percent retention at the fourth hour has been determined: mild delay is defined as 11–20% retention; moderate delay is defined as 21–35%; severe delay is defined as 36–50% retention; and very severe delay is defined as greater than 50% retention.[34] Unfortunately adult studies have not identified a correlation between the degree of gastric emptying delay and symptoms.[34] In addition, the degree of gastric emptying

severity has not been found to relate to outcomes.[28] Prospective studies assessing symptom severity and outcomes related to the degree of gastric retention have yet to be completed in children.

Because a GES exposes children to radiation, normal values for healthy children have not been established, and thus adult values have been extrapolated for use in children. Therefore, it should be emphasized that labeling pediatric patients as having normal vs. delayed gastric emptying should be interpreted with caution given this lack of normative data for each pediatric age group.

This extrapolation of values is also a limitation of previous and current studies of pediatric GP. Previous studies from our group suggest this may be most problematic in infants and children aged 7–10 years of age, as these groups had more difficulty completing the GES meal.[38, 39] Compared with older children, they less frequently tolerated the standard meal (i.e., vomited) or could consume the entire meal.[39] In addition, we found that children with delayed gastric emptying were significantly younger and smaller than those without. This may be due to younger and smaller children truly having slower emptying compared to older children and/or that the meal size relative to stomach size is greater than in older children and adults resulting in greater time needed to empty the meal relative to older children.[39]

Stable isotope breath test

Breath tests using the stable, nonradioactive isotope ^{13}C given in a substrate such as octanoic acid or the plant *Spirulina platensis* have been used successfully in adults and children to assess gastric emptying.[40] Their cost is similar to scintigraphy.[22] Advantages of using breath tests include the capability of doing these tests at the bedside and avoidance of radiation which allows studies in children and pregnant or breastfeeding women.[41] The ^{13}C-*Spirulina platensis* breath test is approved by the FDA for measuring gastric emptying in adults. When digested, *S. platensis* is rapidly absorbed in the duodenum and afterwards metabolized in the liver, giving rise to CO_2 enriched in ^{13}C.[22, 40] The $^{13}CO_2$ abundance over time can be measured in breath and reflects the gastric emptying rate of the meal.

Previous studies in adults carrying out GES and the ^{13}C-*Spirulina platensis* breath test simultaneously in the same individual suggest that the breath test provides an acceptable assessment of gastric emptying of solids, with comparable acceptable coefficients of variation.[42] The concordance of half emptying times (t1/2) between the breath test and scintigraphy in patients (not healthy controls) with rapid, normal, or delayed gastric emptying was 0.86.[42] Combining three breath sampling time points (45, 150, and 180 minutes) yielded a receiver operator area under the curve of 89% sensitivity and 80% specificity for diagnosing delayed gastric emptying compared with GES in the same individual.[42] A more recent study by Bharucha et al. found that five breath samples (45, 90, 120, 180, and 240 min) were extremely accurate for detecting delayed gastric emptying, demonstrating strong concordance between the breath test and GES in adults.[43]

The ^{13}C-acetate breath test and GES carried out simultaneously have been used to measure gastric emptying in children (n=29). The ^{13}C-acetate breath test had a sensitivity of 100% and specificity of 85% when using a cut-off of $t_{1/2}^{breath} > 90$ min ($P<0.00001$).[44] The ^{13}C-

octanoic breath test also has been carried out simultaneously with GES in children (n=25), showing a good correlation between T1/2 ^{13}C and T1/2 GES (r=0.92).[40] Given its safety, the ^{13}C breath test provides an opportunity to define normal values of gastric emptying in healthy children and can be carried out simultaneously with GES in children suspected of GP. Validation of the ^{13}C breath test versus GES would then allow extrapolation of normal (and abnormal values) to children undergoing GES.

Wireless Motility Capsule

The wireless motility capsule (**WMC**) is a non-digestible, orally ingested capsule that measures intraluminal pressure, temperature, pH, and allows calculation of transit times in the GI tract.[45] It has been approved by the FDA for the evaluation of gastric emptying and colonic transit in adults.[22] One advantage of the WMC in GP is that it can measure gastric emptying time without exposing patients to radiation. An adult study led by Kuo et al. showed a correlation of 0.73 and a sensitivity (0.65)/specificity (0.87) comparable to 4-hour GES, making it a reasonable diagnostic study for GES.[46] Conversely, a recent study led by Hasler et al. demonstrated a correlation of only 53% between WMC and GES, and a lower prevalence of emptying delays with WMC when compared to GES.[47]

Data on the WMC in pediatrics is very limited. One single-center pediatric study (n=21) found the WMC had a sensitivity of 100% and specificity of 50% for detecting GP when compared to the GES at two hours (the protocol at the institution was a 2-hour rather than a 4-hour GES).[45] The authors argue that allowing an additional 2 hours might have identified more cases of GP.

Endoscopy

Esophagogastroduodenoscopy (**EGD**) is commonly used as part of the GP evaluation as it can help rule out other causes of delayed emptying (e.g., gastric outlet obstruction due to pyloric stenosis, neoplasia, or active ulcer disease) and allows visualization of fasting gastric contents, including bezoars, excess bilious fluid, and/or retained food.[48, 49] It is recommended that adults who present with postprandial upper abdominal symptoms undergo an EGD prior to a GES.[22] Depending on EGD findings (retained food contents, no significant pathology in the presence of upper GI symptoms), motility or other testing can be pursued afterward.

In pediatrics, there is no consensus yet as to whether patients should undergo an EGD prior to GES. A recent pediatric retrospective case-control study by Altepeter el al. found similar clinically significant endoscopic findings amongst controls (35%, n=44) and children with GP (43%, n=30), with gastritis and esophagitis being the most common histological findings in both groups.[50] Similar findings were noted by Thakkar et al. at our center in children undergoing EGD evaluation for abdominal pain; endoscopy provided a diagnostic yield of 38%, with reflux esophagitis (23%) being the most common diagnosis, followed by H. pylori (5%), peptic ulcers (3%), and erosive esophagitis (2%).[51] These two studies argue for endoscopy in these patients given the relatively high prevalence of positive histological findings. In contrast, Wong et al. found that children with GP had fewer abnormal histological findings (27%, 19/70) when compared to children with normal gastric emptying

(42%, 23/55), with gastritis and esophagitis also being the most common findings in the latter group.[52] Whether the abnormal findings in children with GP contribute to the delay in gastric emptying is unclear. However, given the relatively high likelihood of positive histologic findings in children presenting with GP, endoscopic evaluation may be warranted. That said, preliminary studies from our group show that only 54% (n=103) of children with diagnosed GP underwent EGD and/or upper GI evaluation; this may be related to the fact that GES may be ordered by non-gastroenterologists.

TREATMENT OPTIONS

Dietary and Lifestyle Modifications

The first line of treatment for GP in both adults and children is dietary and lifestyle modifications, regardless of disease severity. Since these patients can experience early satiety, they are encouraged to eat small, frequent meals and avoid fatty foods as well as high-fiber content meals, as these delay gastric emptying.[2, 22] If patients cannot tolerate solid meals, they can consume their required calories in liquid form, given liquid emptying is often preserved despite the presence of solid-phase delayed emptying.[2, 4]

For both populations, the oral route is preferred; however, sometimes enteral nutrition via nasojejunal tube or jejunostomy may be required for patients with severe symptoms and impaired nutritional status.[53] Patients who fail enteral feeds must resort to total parenteral nutrition.

Pediatric studies have shown that few children respond to diet modification as a sole therapy for GP.[14] However, used as an adjunctive treatment it seems to result in more responders.[14]

Prokinetics

a) Macrolide antibiotics—Prokinetics promote motility in the GI tract and can improve gastric emptying.[2] Macrolide antibiotics at reduced antimicrobial dosages, such as erythromycin, increase motility by acting on the motilin receptor. This is believed to regulate phase III of the migrating motor complex, reflecting its peristaltic activity in the antrum and duodenum.[54] Unfortunately, patients usually develop rapid tolerance and tachyphylaxis to erythromycin, requiring that the drug be stopped for a period of time and then restarted which can make it difficult to use long term.[2] Clinical response usually decreases after four weeks; however, some patients may experience some benefit for a longer period.[3]

Adult studies have demonstrated the effectiveness of erythromycin over other motility agents.[55–57] A systematic analysis of 36 studies with 514 patients comparing prokinetic agents showed erythromycin was associated with greater symptom improvement when compared to other prokinetic agents.[58] However, a more recent systematic review noted that the available data is very limited given that the existing studies consist of small sample sizes, uncontrolled designs, short duration, and inadequate symptom assessment, calling for more well-designed trials to assess symptom relief in these patients.[59–63] Regardless, the limited data suggests erythromycin can be a potent prokinetic agent. Table 2 lists available adult studies.

Erythromycin might not have the same beneficial effect in children. Rodriguez et al. showed that 51% of patients (19/37) had a significant response to erythromycin, but only 5% of patients reported complete resolution of symptoms, the lowest when compared to other prokinetics (metoclopramide, domperidone, and tegaserod).[14] However, a randomized, double blind trial comparing erythromycin and metoclopramide showed that erythromycin might be as effective as metoclopramide, thus making it preferable due to the absence of extrapyramidal side effects.[64] Of note, this study aimed to compare the effects of using metoclopramide vs erythromycin as premedication in children undergoing tonsillectomy and not in children with GP.[64] Erythromycin has been trialed in low birth weight and premature infants to assess improvements in feeding tolerance, but the results are conflicting (Table 2).[65–72] Consequently, a recent systematic review recommended using erythromycin only for high risk preterm neonates with persistent feeding intolerance.[73] Of note, it is thought that the migrating motor complex is not observed until 32 weeks of gestation, thus erythromycin might not be of benefit for preterm infants < 32 weeks of age.[54, 73]

b) Metoclopramide—Another commonly used prokinetic agent with antiemetic properties is metoclopramide, which acts as an antagonist of the dopamine 2 receptor (promoting gastric emptying) and also binds to the serotonin 5-HT_4 receptor, which stimulates cholinergic neural pathways in the stomach.[54, 74] Currently, metoclopramide is the only medication approved by the Federal Drug Administration in the United States for the treatment of GP and is usually the first-line treatment for GP in adults.[25, 74] Unfortunately, metoclopramide has a black box warning for tardive dyskinesia associated with duration and total cumulative dose, which has resulted in a 50% reduction in its use (although the risk is believed to be less than 1%).[2, 4, 54] Thus, many recommend not using metoclopramide for more than 12 weeks. It also is associated with other central nervous system side effects, including irritability and a lowered seizure threshold, as it can cross the blood-brain barrier.[75]

Several adult studies comparing metoclopramide to placebo have found that metoclopramide improves symptoms and gastric emptying time.[54, 76–79] A recent systematic review and meta-analysis demonstrated that metoclopramide significantly improved gastric emptying and upper GI symptoms.[80] However, studies have shown that central nervous system side effects are more notable with metoclopramide when compared with other medications used for GP.[81] Interestingly, metoclopramide may be more effective in females than males.[82] Table 2 shows available adult studies.

The limited available pediatric studies suggest metoclopramide might not be as effective in children. Rodriguez et al. showed that metoclopramide resulted in a low response (20%) and low GP resolution rate (11%).[14] It also was associated with the highest rate of adverse events (24%) among all prokinetic drugs; side effects included headaches, vomiting, behavioral changes, dystonia, movement disorders, drowsiness, dizziness, and galactorrhea.[14] A randomized controlled study by Hyman et al. showed that metoclopramide did not improve gastric emptying in infants whose GP was related to prematurity, however it did improve the rate of emptying in patients with regurgitation and after abdominal surgery.[83]

c) Domperidone—Domperidone acts as a dopamine 2 receptor antagonist, leading to antroduodenal contractions and improved peristalsis.[54] It usually is used in adults who fail a trial of metoclopramide. Adult studies have shown domperidone to be similar in efficacy to metoclopramide, with the added benefit of having less central nervous system side effects, as it does not cross the blood brain barrier as easily as metoclopramide.[54, 81] The most serious side effect is cardiac arrhythmias.[84] Unfortunately, domperidone is currently not readily available in the United States and can only be prescribed through a FDA Investigational New Drug application.

A recent systematic review and meta-analysis in adults by Vijayvargiya et al. evaluated improvement of gastric emptying time and upper GI symptoms after the use of prokinetics and found that dopamine 2 receptor antagonists (metoclopramide, domperidone) significantly improved gastric emptying time (>20%) and GI symptoms.[80] Previous studies have shown no correlation between improvement in gastric emptying and GI symptoms with the use of prokinetics but this recent review cited study limitations that included the use of a variety of drugs, doses, lengths of treatments, and a limited number of studies available.[80] Multiple open label and randomized controlled studies in adults have shown an improvement in symptom intensity when comparing domperidone to placebo.[81, 85–93] See Table 2 for available studies.

Rodriguez et al. showed that domperidone administration resulted in 74% of pediatric patients with GP reporting a positive response and 26% reporting complete symptom resolution, the highest rate among prokinetic drugs.[14] In this study, domperidone resulted in less adverse events (6%) when compared to metoclopramide.[14] A placebo-controlled, randomized trial by Franzese et al. showed domperidone to be superior to cisapride in decreasing symptoms in children with GP related to insulin-dependent diabetes mellitus.[94] Domperidone also has been trialed in preterm neonates, showing a significant reduction in gastric emptying time (47 minutes) when compared to control (68 minutes).[95] The limited available pediatric data suggests domperidone might be of clinical benefit in this population.

d) Cisapride—Cisapride is a serotonin 5-HT_4 agonist. Its actions lead to the release of acetylcholine, resulting in increased antral and duodenal motility and more rapid gastric emptying of solids and liquids.[54] Unlike metoclopramide, cisapride lacks central depressant or antidopaminergic effects.[96] Cisapride was removed from the market in July 2000 after multiple studies showed it could result in serious adverse cardiac events, even among low risk groups.[97] It is available through a compassionate use protocol from Janssen Pharmaceutica.

Several adult studies in patients with diabetic GP showed an improvement in symptoms with the use of cisapride, however these results were not always reproducible.[97–102] Two randomized, double-blind, placebo-controlled trials demonstrated that cisapride resulted in improved gastric emptying time but did not result in significant improvement in GI symptoms.[103, 104] Table 2 lists the available adult studies.

In a randomized placebo-controlled pediatric study by Franzese et al., cisapride was found to be less effective than domperidone in terms of symptom score, reduction in gastric emptying

time, normalization of gastric electrical activity, and decreasing the prevalence of episodes of gastric dysrhythmia in children with insulin-dependent diabetes mellitus.[94] Multiple trials have been conducted in preterm infants to evaluate the efficacy of cisapride, however there was no improvement in gastric emptying time or reduction in the incidence of feeding intolerance.[105–110]

Dosing: Treatment doses for the abovementioned medications mostly have been extrapolated from adult data, as there are limited to no available dosing or pharmacokinetic studies in children.[54] In addition, potential genetic polymorphisms in drug metabolizing enzymes rarely have been taken into account. [54] Of the studies available, most have either a small population and/or are focused on the neonatal population, which likely is of limited applicability to older patients (i.e., adolescents).[54] Unfortunately, there are no standardized guidelines for the treatment of pediatric GP.[54] Many providers consider prokinetic medications as first line therapy, however they might not be as effective in children as they are in adults.[54] For example, erythromycin administration has been shown to improve symptoms and gastric emptying in adults, but did not result in resolution of symptoms in older children.[14, 55, 56] Further prospective and randomized controlled trials should be conducted in this population to determine the appropriate dose and frequency, as well as utility of the treatment.

Botulinum Toxin

It is believed that a subset of patients with GP have pyloric dysfunction. Botulinum toxin injections directed at the pylorus muscle have been used for refractory GP, as it decreases contractility and acetylcholine release.[111] Adult studies are contradictory regarding the clinical benefits.[112] Most open label studies have reported a clinical improvement in symptoms and gastric emptying in adults with idiopathic, diabetic, or postsurgical GP. [111–114] However, two randomized placebo-controlled trials did not show improvement of symptoms nor gastric emptying with the use of botulinum injections when compared to placebo.[115, 116] Reasons for these results might be poor depth and inaccurate location of the injection, inappropriate dose (the suggested dose for GP is 100 units), and inadvertent diffusion of botulinum toxin into the gastric antrum.[111, 115] A retrospective analysis of 179 patients with GP showed that higher doses of botulinum toxin (200 units), female gender, age <50 years, and an idiopathic GP diagnosis were associated with a better response.[117] See Table 2 for available studies.

Data in pediatrics is limited. A retrospective open label study showed children ages >12 years and those with vomiting as the main indication for the injection had a better response (response was defined as: symptoms improved but still requiring medications, able to stop medications, or having complete resolution of symptoms).[112] Prospective controlled pediatric studies are needed.

Gastric Neurostimulator

The gastric neurostimulator is an implantable device that delivers high frequency, low amplitude current to the smooth muscle of the stomach.[118, 119] The mechanism of action is not completely understood but may involve improved gastric relaxation and accommodation.

[2] Multiple open label studies in adults suggest the neurostimulator to be effective in terms of improving clinical symptoms; however, findings in blinded controlled trials have not been as favorable, suggesting a significant placebo effect.[120]

A recent study in children undergoing placement of a permanent neurostimulator (n=67) showed a significant reduction in all individual symptoms, including: nausea, emesis, bloating, pain, and early satiety; total symptom score; GP medication use; and total number of hospitalizations.[119] The cumulative long term failure rate was 10.4%.[119] Large, randomized, blinded, placebo controlled multicenter studies are needed to help understand the potential benefits of this device in children, but the data seems promising.[119]

CONCLUSIONS

GP is a complex syndrome characterized by delayed gastric emptying combined with upper GI symptoms that may significantly impair a patient's quality of life. Available data suggest a marked difference between adults and children with GP in several areas including etiology, gender predominance, and symptom presentation amongst others. In addition, data related to diagnostic modalities and therapeutic approaches for children with GP are limited, particularly relative to that available for adult GP. This limitation has led to extrapolation of adult data to the pediatric population, which limits interpretability of pediatric studies, specifically studies pertaining to imaging as well as therapeutic alternatives and dosing.

Unfortunately, many of the existing pediatric GP studies are retrospective and are subject to selection bias. Given that there are no established pediatric guidelines on how to approach GP, different institutions may have their own established protocols for when to pursue gastric scintigraphy; which standard to use (2 hrs. vs 4 hrs.); and when and how to pursue therapy. This, and the limited available data in several areas underscore the need for more rigorous studies to evaluate the epidemiology of pediatric GP, addressing areas of need such as the best diagnostic approach and therapies.

Both the development of a pediatric GP specific patient reported outcome instrument and establishment of normal values for assessment of pediatric gastric emptying have the potential to provide important foundational pieces that will significantly advance science in the field of pediatric GP.

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Abbreviations:

GP	gastroparesis

ICCs	interstitial cells of Cajal
GCSI	Gastroparesis Cardinal Symptoms Index
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
GES	gastric emptying scintigraphy
WMC	wireless motility capsule
EGD	esophagogastroduodenoscopy
EGG	electrogastrography

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Table 1:

Summary of differences between adult and pediatric GP

	Adults	**Children**
Incidence (estimated)	0.4% to 3%	Unknown
Etiology	From most common to least common[5, 8]: 1) Idiopathic (30–50%) 2) Diabetes mellitus (25%) 3) Medications (22%) 4) Post-surgical (7%)	From most common to least common[13]: 1) Idiopathic (70%) 2) Medications (18%) 3) Post-surgical (12.5%) 4) Post-viral (5%) 5) Diabetes Mellitus (4%)
Predominant Symptoms	Nausea (>90%) Vomiting (84%) Bloating (75%) Early Satiety (60%) Abdominal pain (46%) [15]	Age dependent [13, 14]: - Infants: vomiting (96.5%), weight loss (31%) - Ages 1–10 years of age: vomiting (72–73%), abdominal pain (28–67%) - Ages ≥ 11 years of age: abdominal pain (66.7–75%), nausea (48.7–61), vomiting (52.6–55%)
Gender	4:1 female: male ratio [15, 28]	Age dependent [13]: - Ages < 1 year: boys (72.4%) - Ages 1–10 years of age: equal ratios - Ages > 10 years: girls>boys
Psychiatric Comorbidities	Found in 62% of adults (n=262) [15]: 1) Moderate/severe depression (41.6%) 2) Severe anxiety (32.8%) 3) Severe trait anxiety (30.5%)	Found in 28% of children (n=239) [13]: 1) Attention hyperactivity disorder (8.4%) 2) Behavioral problems (8%) 3) Anxiety (6.3%) 4) Depression (4%) 5) Bipolar disorder (1.7%)
Outcomes	Factors independently associated with improved outcomes [28]: - Male sex - Age ≥ 50 years - Post viral GP - Antidepressant use - 4-hour gastric retention > 20% - Nonsmokers - BMI <25mg/m^2 - No pain medication use	Factors independently associated with improved outcomes [14]: - Male sex - Younger age - Post viral GP - Shorter duration of symptoms - Response to promotility drugs - Absence of mitochondrial dysfunction

Table 2:

Summary of available evidence of commonly used medications for GP (Only results from randomized controlled trials are summarized)

Medication	Mechanism of Action	Available Evidence in Adults	Available Evidence in Children
Erythromycin	Motilin receptor agonist	- SR *(2003)[59] - SA *(1999)[58] - DB *, PC *, XO * – improved antroduodenal motor activity (1997)[55] - RC *, DB, PC – accelerated gastric emptying (1995)[56] - OL *(1994)[60] - OL (1994)[61] - OL (1993)[63] - RC, DB, XO with metoclopramide – improved symptoms, more pronounced with erythromycin (1993)[62] - RC, DB, PC, XO – accelerated gastric emptying (1990)[57]	- Re (2012)[14] - SR (in neonates) (2005)[73] - RC, DB, PC – no difference (2003)[70] - RC, DB, PC – no difference (2003)[71] - RC, DB, vs metoclopramide study (2001)[64] - RC, DB, PC – accelerated gastric emptying (2001)[68] - P, RC, DB, PC – improved enteral feeding (2001)[69] - RC, DB, PC – improved gastric emptying (2001)[72] - RC, DB, PC – no difference (2000)[66] - RC, DB – no difference (1998)[67]
Metoclopramide	Dopamine D2 receptor antagonist, serotonin 5-HT4 agonist	- MA *, SR (2019)[80] - RC, DB, PC – reduction in GP symptoms in women but not men (2015)[82] - RC, DB, vs domperidone – equally effective but more pronounced CNS side effects with metoclopramide (1999)[81] - RC, DB, XO with erythromycin – improved symptoms, more pronounced with erythromycin (1993)[62] - RC, DB, PC XO – improved symptoms (1985)[79] - OL (1984)[121] - RC, PC – improved symptoms, accelerated gastric emptying (1983)[78] - RC, DB, PC, XO – improved symptoms and vomiting, acceleration of gastric emptying (1982)[76] - RC, DB, PC – improved symptoms (1979)[77] - OL (1977)[122]	- Re (2015)[75] - Re (2012) [14] - RC, DB, PC – accelerated gastric emptying in infants with regurgitation and infants with GP following abdominal surgery, no change in infants with GP related to prematurity (1988)[83]
Domperidone	Dopamine D2 receptor antagonist but with lower central side effects when compared to metoclopramide	- MA, SR (2019)[80] - RC, PC, vs metoclopramide – equally effective but more pronounced CNS side effects with metoclopramide (1999)[81] - RC, PC, withdrawal study – improved symptoms (1998)[90] - OL (1997)[86] - Re(1990)[87] - OL (1989)[88] - RC, PC, XO – improved symptoms (1989)[91] - OL (1985)[89] - OL (1985)[85] - RC, PC, XO – accelerated gastric emptying (1983)[92] - RC, PC, XO- no difference (1981)[93]	- Re (2012)[14] - RC, PC, XO (2010)[95] - RC, PC vs cisapride – domperidone superior to cisapride in improving symptoms and accelerating gastric emptying (2002) [94]
Cisapride	Serotonin $5HT_4$ agonist, serotonin $5\text{-}HT_3$ antagonist	- MA, SR (2019)[80] - RC, PC – accelerated gastric emptying (2002)[100] - RC, DB, PC, XO – no difference (1999)[101] - RC, DB, PC, XO – no difference (1999)[102] - RC, DB, PC – accelerated gastric emptying but no improvement in symptoms (1993)[104] - DB, PC – accelerated gastric emptying but no improvement in symptoms (1989)[123] - RC, DB, XO – accelerated gastric emptying but no improvement in symptoms (1987)[103]	- RC, PC, vs cisapride – domperidone superior to cisapride in improving symptoms and accelerating gastric emptying (2002) [94] - RC, PC – improved feeds only in extremely low birth weight infants, but significant QTc prolongation (2005)[106] - RC, PC, XO – no difference (2001)[107]

Medication	Mechanism of Action	Available Evidence in Adults	Available Evidence in Children
		- RC, vs metoclopramide, PC – accelerated gastric emptying with both, significant with cisapride (1987) [98] - DB, PC, XO – no difference (1987)[99]	- RC, DB, PC – no difference (2000) [105] - RC, DB, PC – no difference (2000) [108] - RC, DB, PC – delayed gastric emptying (1999)[110] - RC, DB, PC – no difference (1998) [109]
Botulinum Toxin	Decreases pylorus muscle contractility and acetylcholine release	- Re, OL (2014)[124] - Re, OL (2009)[117] - RC, DB – no difference (2008)[115] - RC, DB, XO – no difference (2007)[116] - Re, OL (2005)[125] - P, OL (2002)[114] - P, OL (2002)[113]	- Re, OL (2012)[112]

* Re= Retrospective, R= Randomized controlled, OL= open label, P= prospective, DB= double-blind, XO= crossover, PC= placebo-controlled, SR= systematic review, SA= systematic analysis, MA= meta-analysis