SPECTRUM OF GASTROPARESIS IN CHILDREN

By

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LIST OF ABBREVIATIONS

BMI	Body mass index
CF	Cystic fibrosis
CNS	Central nervous system
EES	Erythromycin
GES	Gastric emptying scintigraphy
GESt	Gastric electrical stimulator
GI	Gastroenterology
GP	Gastroparesis
ICC	Interstitial cells of Cajal
IV	Intravenous
MCP	Metoclopramide
min	Minutes
MMC	Migrating motor complex
PNS	Peripheral nervous system
t½	Gastric emptying half-time
TPN	Total parenteral nutrition
UF	University of Florida

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Gastroparesis is a condition of abnormal gastric motility characterized by delayed gastric emptying in the absence of mechanical outlet obstruction. Symptoms include nausea, vomiting, post-prandial fullness, early satiety, abdominal bloating and weight loss. In adults, one third of gastroparesis is due to diabetes, one third idiopathic and one third is assumed post surgical. Delayed gastric emptying of a solid-phase meal assessed by radionuclear scintigraphy is considered the gold standard for the diagnosis of gastroparesis. The prevalence of gastroparesis is difficult to estimate due to the lack of a validated, widely available diagnostic test that can be applied in primary care. The extent of the problem with gastroparesis in children is unknown and there are no effective therapies for it.

We studied a cohort of children with delayed gastric emptying, to identify symptoms, co-morbidities, possible risk factors, treatment and outcomes. Patients ranging from 0-21 years who underwent gastric scintigraphy from January 2002 to December 2008 at the University of Florida were identified. Retrospective analysis of 239 patients (52% female, mean age 7.9 yrs) was performed. Variables measured were: indications for gastric scintigraphy (symptoms); gastric empyting half-time (t½) for gastric scintigraphy for solid vs. liquid test meals; response to IV erythromycin or metoclopramide observed during scintigraphy; demographics (age, gender,

height/weight; other medical/surgical diagnosis and psychological diagnosis); identified etiologies ; complications; all therapeutic interventions (dietary modification, prokinetic/anti-emetic agents, nutritional support (enteral/parenteral), gastric electrical stimulation and others); and most recent follow-up encounter assessing gastroparesis symptomatology. Data were aggregated for frequency and percentage.

The frequency of initial presenting symptoms included: vomiting (68%), abdominal pain (51%) nausea (28%), weight loss (27%), early satiety (25%), and bloating (7 %). The most common etiologies were: idiopathic (70%), cerebral palsy (16%), seizure disorder (15.5%), prematurity (13%), and developmental delay (10.5%), Thirty-five percent of patients responded to IV erythromycin injected during scintigraphy compared to only 8.4 % treated with IV metaclopramide during the same procedure. The majority (73.6 %) were treated with EES, while 41% received dietary modifications, 29.7% metoclopramide, 23% enteral feeds, 6.7% tegaserod, and 5.4% azithromycin. After an average of 24 months follow up, the most common complications from gastroparesis were esophageal reflux (67.4%), esophagitis (16.7%), gastritis (15%), and dehydration (3.7%). Nevertheless, by the end of the follow-up period a significant improvement in all symptoms was reported despite different therapeutic modalities over time. Appreciation of different etiologies, symptom presentation, complications, and outcomes of the patients is the basis for better understanding of the course and outcomes for children with gastroparesis.

CHAPTER 1
INTRODUCTION

Gastroparesis (GP) is a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. Many controlled studies have been performed in adults, evaluating etiology and management strategies. The pediatric literature is very limited, with only a few case series and a few randomized controlled trials. Gastroparesis is often not recognized and thus remains untreated in children. This review integrates available adult and pediatric data to summarize the clinical presentation, etiologies, complications, treatments and outcomes, provide management recommendations, and identify areas for additional study.

Epidemiology of Gastroparesis

The true prevalence of gastroparesis in the United States is unknown. In a study conducted by the Center of Health Outcomes Research (MEDTAP International Inc., Bethesda, Maryland), 7 to 15% of the adult population were found to have symptoms suggestive of gastroparesis. [1] A large study on long-term outcomes of gastroparetic adults reported that 82% of patients were female [2]. The actual prevalence of gastroparesis is difficult to estimate due to inconsistent correlation of symptoms with scintigraphy-proven delayed gastric emptying, low use of diagnostic testing and a higher prevalence reported from tertiary medical centers.

Currently, no data are available to estimate the prevalence of gastroparesis in children. One study estimated 5%-10% of otherwise healthy adolescents have had symptoms of nausea and heartburn within a year [3]. Also, 65% of symptomatic adolescents who undergo upper endoscopy have no abnormalities and are classified as having functional dyspepsia [4]. Delayed gastric emptying and early post-prandial upper gastrointestinal symptoms have been demonstrated to be present in children diagnosed with functional dyspepsia [5,6]. In our

experience, most patients with gastroparesis have had multiple other diagnoses and/or multiple other surgical procedures performed.

Etiology

The etiology of gastroparesis in adults is multifactorial. The main categories are diabetes, idiopathic, and post-surgical [2] especially if the vagus nerve is damaged. In children, most cases occur either after viral infection or are idiopathic cases [7]. Patients with post-viral gastroparesis usually present with chronic continuation of upper gastrointestinal symptoms after recovering from a viral syndrome [8]. Other causes of gastroparesis in children include prematurity, medications, thyroid dysfunction, cystic fibrosis, cow milk protein allergy, eosinophilic gastroenteropathy, neurologic disorders, diabetes, muscular dystrophy, inflammatory causes, autoimmune disorders and medications [8]. Gastroparesis may also occur in patients with chronic liver failure, chronic renal insufficiency and intestinal pseudo-obstruction [2,9]. Post-surgical gastroparesis is observed after surgical procedures such as vagotomy, nissen fundoplication, and organ transplantation. In addition, gastroparesis is a common gastrointestinal complication seen in individuals with eating disorders, which are not uncommon in adolescents.

Pathophysiology

Gastric motility results from a complex interaction between gastric smooth muscle, the enteric nervous system and specialized cells, the interstitial cells of Cajal (ICC*)*. Gastric motility results from tonic contractions of the fundus and phasic contractions of the antrum [10,11]. Distinct patterns characterize the fasting (interdigestive) and fed (digestive) phases. During the interdigestive pattern, three cyclical phases known as migrating motor complex (MMC) recur every two hours: Phase 1, Phase II and Phase III. Gastroparesis is characterized by loss of normal fasting MMCs and reduced postprandial antral contractions and, in some cases, pylorospasm

[12]. Small intestinal dysmotilities are detected in 17%-85% of patients with gastroparesis [13]. In pediatric studies, the absence of MMC's predicted a poor response to prokinetic agents [14].

The ICCs or gastric pacemaker cells are located along the greater curvature in the proximal to middle body of the stomach. Originating in the region of ICCs, gastric slow waves sweep across the stomach toward the pylorus. However, these slow waves do not result in contraction of the gastric smooth muscle, but, instead, in the simultaneous release of neurotransmitters from the enteric nerve endings, which leads to contraction of the gastric smooth muscle [15, 16].

Several factors affect gastric motility. These factors include 1) motor dysfunction, e.g., hypomotility and pyloric spasm, 2) sensory dysfunction, e.g., impaired fundic relaxation, accommodation and abnormal sensation, 3) electrical dysfunction, e.g., gastric arrhythmias and abnormal propagation, 4) CNS effects resulting in nausea and vomiting, 5) autonomic nervous system dysfunction, 6) central nervous system dysfunction and, 7) other factors such as bacterial overgrowth, visceral hyperalgesia and gastrointestinal hormones [17]. Moreover, the content of the meal, such as volume, acidity, osmolarity, nutrient density and fat content, also affects gastric emptying. The main pathogenic factors in diabetic gastroparesis are vagal autonomic neuropathy and possible defects in the interstitial cells of Cajal.

Symptoms

Symptoms in gastroparesis consist of a combination of nausea, vomiting, early satiety, bloating, post-prandial fullness, abdominal pain and weight loss. Gastroparesis is diagnosed in a symptomatic patient by a delay in gastric emptying after mechanical obstruction is excluded. A simple severity grading scale has been proposed for stratification of symptoms by Abell, et al. [18]. They described three grades. Grade 1 or mild GP is characterized by symptoms that are easily controlled and patients are able to maintain weight and nutrition on a regular diet or minor

dietary changes. Grade 2 or compensated GP is characterized by moderate symptoms with partial control with medications, patient ability to maintain nutrition with dietary and lifestyle adjustments, and rare hospitalizations. Grade 3 or gastroparesis with gastric failure is characterized with refractory symptoms despite medical therapy, inability to maintain nutrition via oral route and frequent emergency room (ER) visits or hospitalizations. Also, a patient-based symptom instrument, the gastroparesis cardinal symptom index (GCSI) has been developed to assess severity of gastroparesis [19]. The GCSI total scores are based on three subscales of nausea/vomiting, post-prandial fullness/early satiety, and bloating. The GCSI scale is used to rate symptom change by either physicians or by the patient's own self-evaluations. To date, no studies are available in children to confirm the validity of this instrument in the pediatric population.

In a study of 146 adults with gastroparesis, nausea was present in 92%, vomiting in 84%, abdominal bloating in 75%, and early satiety in 60%. Abdominal pain or discomfort was present in 46%-89% of patients but was not the predominant symptom [2]. Constipation may also be associated with gastroparesis. Treatment of constipation with an osmotic laxative improved dyspeptic symptoms, as well as gastric emptying delay [20]. Complications of gastroparesis in the adult literature have been reported to include gastroesophageal reflux, esophagitis, gastritis, anemia, esophageal stricture, small bowel bacterial over-growth, malnutrition, dehydration with acute renal failure secondarily, electrolyte disturbances and bezoar formation [21, 22]. There are no reports available to determine if the pediatric complications of gastroparesis differ from those in adults.

Diagnostic Tests

The following diagnostic tests have mainly been used and validated in adults. There are no pediatric norms or reference values available. Therefore, in children, we use the available adult data/values.

Gastric Scintigraphy

Delayed gastric emptying scintigraphy (GES) of a radio-labeled solid meal is the gold standard for the diagnosis of gastroparesis. This test provides a physiologic, non-invasive and quantitative measure of gastric emptying and provides a sensitive measurement of emptying of solids. Liquid emptying may remain normal despite advanced disease. A variety of foods including chicken, liver, eggs, egg whites, oatmeal, and pancakes are being used as test meals. The content of the meal is one of the most important variables in gastric emptying. Consumption of solids, fats, increased calories, increased fiber and high volumes of a test meal can delay gastric emptying time. Consensus recommendations for a standardized gastric emptying procedure have recommended a universally acceptable 99-m technetium sulfur-colloid labeled low fat, egg-white meal [23]. Medications that alter gastric emptying may be discontinued 48-72 hours in advance, and blood glucose in diabetics should be <275mg/dl on the day of the test. GES is measured at minimum of 1, 2 and 4 hours after test meal ingestion and is performed in the upright position. This periodic measurement of radio-labeled solid meal has a specificity of 62% and a sensitivity of 93% when compared to continuous GES [24]. Emptying of solids exhibits a lag phase followed by a prolonged linear emptying phase.

The results of GES can be reported in two ways. The simplest approach is to report percent retention at defined times (minimum 1, 2, and 4 hours). Retention of over 10% of the solid meal after 4 hours is abnormal. The grading of severity based on 4-hour values has been suggested, i.e., grade 1 (mild), 11-20% retention at 4 hr; grade 2 (moderate), 21-35% retention at

4 hr; grade 3 (severe), 36-50% retention at 4 hr; and grade 4 (very severe), >50% retention at 4 hr [23]. Prokinetics may also be administered intravenously after the last measurement (i.e., 4 hours) to evaluate if patient is a "responder" or "non-responder" to the agent. Again, percent retained or extrapolated t ½ can be calculated to assess response.

Radiopaque markers

After ingestion of indigestible markers, i.e., ten small pieces of nasogastric tubing, none of the markers should remain in the stomach on an X-ray taken 6 hours after ingestion with a meal [25]. This simple test correlates with clinical symptoms of gastroparesis and is readily available and inexpensive.

Ultrasonography

Transabdominal ultrasound has been used to measure emptying of a liquid meal by serially evaluating cross-sectional changes in the volume remaining in the gastric antrum over time [26,27,28]. Emptying is considered complete when the antral area/volume returns to the fasting baseline. Some studies have revealed gastric emptying measurements similar to those seen with scintigraphy [29].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) using gadolinium has been found to accurately measure semi-solid gastric emptying and accommodation using sequential transaxial abdominal scans [30]. MRI provides excellent spatial resolution with a high sensitivity. MRI is also non-invasive and radiation free. Antral propagation waves can be observed and their velocity calculated.

Single-photon emission CT

This technique uses intravenously administered 99-Tc pertechnetate that accumulates within the gastric wall rather than the lumen and provides a three-dimensional outline of the stomach [31]. Measurement of regional gastric volumes can be made in real-time to assess fundic accommodation and intragastric distribution.

Stable isotope breath tests

The noninvasive 13-C-labeled octanoate breath test is an indirect means of measuring gastric emptying. 13-C-labeled octanoate is a medium chain triglyceride which can be bound to a solid meal such as a muffin. After ingestion and stomach emptying, 13-C octanoate is rapidly absorbed in the small intestine and metabolized to 13-CO2 which is expelled from the lungs during expiration. The rate limiting step for the signal appearing in the breath is the rate of gastric emptying. Compared to scintigraphy done over a period of 4 hours, the breath test has a specificity of 80% and sensitivity of 86% [32, 33].

Swallowed capsule telemetry

The ingestible "SmartPill®" (VA Boston Healthcare System, Boston, Massachusettes) or telemetry capsule offers a promising new non-radioactive method for assessing gastric emptying. This capsule measures pH, pressure and temperature using miniaturized wireless sensor technology. This system has been developed for ambulatory assessment of gastrointestinal (GI) transit [32]. It has been shown that gastric transit time calculated using the SmartPill® correlates well with gastric scintigraphy with good sensitivity (82%) and specificity (83%) [34].

Antroduodenal manometry

In antroduodenal manometry, a water perfused or solid-state manometric catheter is passed from the nares or mouth and placed fluoroscopically into the stomach and small bowel to

measure actual gastroduodenal contractile activity. The frequency and amplitude of fasting MMCs, interdigestive and post-prandial contractions can be recorded, and the response to prokinetic agents can be assessed. Gastroparesis is characterized by loss of normal fasting MMCs and reduced postprandial antral contractions and, in some cases, pylorospasm [35].

Electrogastrography

Electrogastrography (EGG) measures gastric slow-wave myoelectrical activity via serosal, mucosal or cutaneous electrodes. EGG is most conveniently recorded with cutaneous electrodes positioned along the long axis of the stomach. Initially a pre-prandial recording for 45 to 60 minutes is captured. Patients are given a 500 Kcal cheese or turkey sandwich and an equivalent postprandial recording is captured. The recorded signals are amplified and filtered to exclude contamination by noise from cardiorespiratory activity and patient movement. Computer analysis converts raw EGG signals to a three-dimensional plot. EGG abnormalities are present in 75% of patients with gastroparesis [36]. EGG is considered by some authors as more of an adjunct to gastric emptying measurement for a comprehensive evaluation of patients with refractory symptoms [36].

Treatment

The general principles of treatment of symptomatic gastroparesis are to: 1) correct fluid, electrolyte, and nutritional deficiencies; 2) identify and rectify the underlying cause of gastroparesis if possible; and 3) reduce symptoms [18, 37]. In addition, patient education and explanation of the condition is an integral part of management.

The disabling chronic symptoms of gastroparesis impact profoundly on the patient's sense of wellbeing, mental state, behavior and social life. Sensitive caring from the clinical team and professional counseling might be necessary to help the patient cope with the disability. Patients should be informed that a number of drugs might be tried in an attempt to discover the

optimal therapeutic regimen and that the aim of treatment is to control rather than cure the disorder [38].

The patient's drug list should be reviewed to eliminate drugs that can cause gastric dysmotility. Common agents that may reduce gastric emptying are opiates, anti-cholinergics, B-adrenergic drugs, calcium channel blockers, glucagon, marijuana, alcohol and tobacco. Management can be tailored to the severity of the gastroparesis. For Grade 1(mild) gastroparesis, dietary modifications should be tried first. Low doses of antiemetic or prokinetic medications can be taken on an as-needed basis. Grade 2 (compensated) gastroparesis is treated by combination of antiemetic and prokinetic medications given at regularly scheduled intervals. These agents relieve more chronic symptoms of nausea, vomiting, early satiety and bloating. They frequently have no effect on abdominal pain. In Grade 3 (severe) gastroparesis or gastric failure, more aggressive treatments including hospitalizations for IV hydration and medications, enteral or parenteral nutritional support and endoscopic or surgical therapy may be needed [18].

Dietary Manipulation

Dietary recommendations rely on measures that promote gastric emptying or, at least theoretically, do not retard gastric emptying. At the outset, it is advisable to engage an experienced dietitian who can discuss and explore the patient's tolerance of solids, semi-solids and liquids as well as dietary balance, meal size and timing of meals. Fats and fiber tend to retard emptying, thus their intake should be minimized. This recommendation should be stressed as many of these patients who often concomitantly also have constipation have been told to take fiber supplementation for treatment of their constipation. Multiple small low-fat meals about 4 or 5 times each day should be recommended. Carbonated liquids should be avoided to limit gastric distention. Patients are also instructed to take fluids throughout the course of the meal and to sit or walk for 1-2 hours after meals. If above measures are ineffective, the patient may be advised

to consume the bulk of their calories as liquid since liquid emptying is often preserved in patients with gastroparesis. Poor tolerance of a liquid diet is predictive of a future poor outcome [18].

Improving Glycemic Control

Patients with diabetes should be counseled to achieve optimal glycemic control. Hyperglycemia itself delays gastric emptying, which is likely mediated by reduced phasic antral contractility and induction of pyloric pressure waves. Hyperglycemia can inhibit the accelerating effects of prokinetic agents [39]. Improvement of glucose control increases antral contractility, corrects gastric dysrhythmias and accelerates emptying [40].

Pharmacologic Therapy

The pharmacotherapy of gastroparesis is stepwise, incremental and long term. The most commonly used drug classes include pro-motility and anti-emetic agents. Few randomized controlled clinical trials have directly compared the different agents [41]. Consequently, the selection of drug treatment is commonly made by trial and error.

Prokinetic agents

Prokinetic medications enhance the contractility of the GI tract, correct gastric dysrythmias, and promote the movement of luminal contents in the antegrade direction. Prokinetics may predominantly improve symptoms of nausea, vomiting and bloating. They do not seem to relieve abdominal pain and early satiety associated with gastroparesis. They should be administered 30 minutes before meals to elicit maximal clinical effects. Bedtime doses are often added to facilitate nocturnal gastric emptying of indigestible solids. The response to treatment is usually judged clinically rather than following with serial gastric emptying tests because symptom improvements correlate poorly with the acceleration of gastric emptying [40]. A meta-analysis assessing benefits of four different drugs in 514 patients in 36 clinical trials reported that the macrolide antibiotic erythromycin is the most potent stimulant of gastric

emptying while the erythromycin and dopamine receptor antagonist, domperidone, is best at reducing symptoms of gastroparesis [41]. Several factors must be considered when choosing a prokinetic drug for patients with gastroparesis including efficacy, toxicity, regional availability and cost.

Erythromycin: Erythromycin is a macrolide antibiotic which is also a motilin receptor agonist [42]. The intravenous form is the most potent stimulant of solid and liquid gastric emptying [43, 44]. Motilin is a polypeptide hormone present in the distal stomach and duodenum which increases lower esophageal sphincter pressure and is responsible for initiating the MMC in the antrum of the stomach [45,46]. Interestingly, erythromycin has also shown to accelerate emptying in post-vagotomy and antrectomy patients [47]. This may be due to its stimulatory effects on the fundus.

Metoclopramide: Metoclopramide is a substituted benzamide with several prokinetic actions and anti-emetic effects. The prokinetic properties of metoclopramide are limited to the proximal gut. Metoclopromide increases esophageal, fundic and antral contractile amplitudes, elevates lower esophageal sphincter pressure, and improves antropyloroduodenal coordination. Metoclopramide is administered orally in pill or liquid suspension form. Intravenous forms commonly are reserved for inpatients that cannot retain oral medications.

Domperidone: Domperidone, is a benzimidazole derivative with benefits similar to those of metoclopramide. Domperidone does not cross the blood-brain barrier and consequently has fewer central side effects compared to metoclopramide. Because brainstem structures regulating vomiting are outside the blood-brain barrier, domperidone has potent central anti-emetic action.

Tegaserod: Tegaserod is a 5-HT4 receptor partial agonist used in the treatment of constipation predominant with irritable bowel syndrome. In healthy volunteers the drug

stimulates small intestinal motility and post-prandial antral and intestinal motility. Tegaserod has been shown to accelerate gastric emptying in some [48] but not all studies of healthy volunteers [49]. Tegaserod was completely withdrawn from the US market in April, 2008, due to a reported increase in the risk of cardiovascular adverse effects.

Cispride: Cisapride is a 5-HT4 receptor agonist with weak 5-HT3 antagonist properties that once was widely used for gastroparesis. This drug was withdrawn from the market in the United States in 2000 because of numerous reports of sudden death from cardiac arrhythmias [50].

Bethanechol: Bethanechol is an approved smooth muscle muscarinic agonist that increases lower esophageal sphincter pressure and evokes fundoantral contractions but does not induce propulsive contractions or accelerate gastric emptying [51]. Rarely, the drug may be used as an adjunct with other prokinetic medications in patients refractory to standard treatment with prokinetics and anti-emetic drugs.

Anti-emetic medications

At least one component of the clinical benefits observed with some of the available prokinetic drugs, such as metoclopromide and domperidone, stem from their anti-emetic actions on brain-stem nuclei. Nausea and vomiting are the most disabling symptoms of gastroparesis found in adults and anti-emetic agents without stimulatory activity are often used alone or in concert with prokinetic drugs to treat gastroparesis. Antiemetic medications act on a broad range of distinct receptors subtypes in the peripheral and central nervous systems. Like prokinetics, the choice of antiemetic is empirical and a reasonable approach would initiate treatment with less expensive therapies.

Phenothiazines: These are the most commonly prescribed traditional antiemetics which include prochlorperazine and tiethyperazine. These drugs are both dopamine and cholinergic

receptor antagonists. Prochlorperazine can be administered in the tablet form, liquid suspension, suppository and by injection. These drugs are suitable for long-term use, especially in children, due to their extrapyramidal side effects.

Serotonin 5-HT3 receptor antagonists: These medications include ondansetron, granisetron, and dolasetron and are useful for treating nausea and vomiting. These drugs may act on the chemoreceptor trigger zone as well as on peripheral afferent nerve fibers within the vagus nerve [44]. Ondansetron has no effect on gastric emptying in healthy volunteers and patients with gastroparesis and moreover can cause constipation [52, 53].

Antihistamines: Antihistamines acting on H1 receptors exhibit central antiemetic effects [37]. Commonly prescribed antiemetics include diphenhydramine, dimenhydrinate and meclizine. These agents are most useful to treat symptoms related to motion sickness. The mechanism of action is poorly understood but is likely to involve both labyrinthine and chemoreceptor trigger zones.

Low dose tricyclic antidepressants: Tricyclic antidepressants (TCAs) impair gastrointestinal motility through their anticholinergic activity but have been shown to relieve nausea, vomiting and pain in functional dyspepsia [54, 55]. Formal prospective trials of these antidepressants for the treatment of gastroparesis have not been performed, thus their use is still considered off-label.

Medications for control of symptoms other than nausea and vomiting

Early satiety: Early satiety has been related to defects in fundic accommodation in patients with functional dyspepsia [56]. Nitrates, buspirone, sumitriptan, and selective serotonin reuptake inhibitors promote fundic relaxation in this condition [57, 58]. The use of fundic relaxants in managing early satiety in gastroparesis has not been investigated.

Abdominal pain: Epigastric pain is disabling in some individuals with gastroparesis and can result in excessive utilization of healthcare resources. The pathogenesis of this pain is poorly understood and treatments for this symptom are largely unsatisfactory. The pain in gastroparesis has been postulated to be due to sensory rather than motor dysfunction, and therapies to reduce afferent dysfunction may be more effective for this symptom [59]; however, this hypothesis has not been tested. Although non-steriodal anti-inflammatory drugs (NSAIDs) have been shown to ameliorate gastric slow wave dysrhythmias in several healthy subjects [60], their adverse effects including renal dysfunction and ulcerogenic properties limit their usage on a chronic basis [60]. Anti-depressent medications may help with gastroparesis-associated neuropathic pain [61]. These include low dose tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (SNRI) and combined serotonin/noradrenaline reuptake inhibitors. Opiates, including milder agents such as tramadol, should be avoided because of their inhibitory effects on motility as well as risk of addiction.

Nutritional Support

Some patients with refractory gastroparesis benefit from enteral or parenteral nutrition intermittently for symptom flares or rarely, for permanent support. Patients with chronic symptoms of gastroparesis may develop dehydration, electrolyte abnormalities and/or extreme malnutrition. The choice of nutritional support and its administration route depends on the severity of disease. The indications for supplementation of enteral nutrition include unintentional loss of 10% or more of the usual body weight during a period of 3 to 6 months, inability to achieve the recommended weight by the oral route, repeated hospitalizations for refractory symptoms, interference with delivery of nutrients and medications, need for nasogastric intubation to relieve symptoms, and nausea and vomiting resulting in poor quality of life [18]. Except in cases of profound malnutrition or electrolyte disturbance, enteral feeding is preferable

to chronic parenteral nutrition because of the significant risks of infection and liver disease in the latter treatment. On the other hand, short-term total parenteral nutrition (TPN) can reverse rapid weight decline and ensure adequate fluid delivery. Home TPN may be needed for individuals who cannot tolerate enteral feeding.

Several options for enteral access and feeding are available and no data exists favoring one approach over the other. However, nasogastric tubes and gastrostomy tubes (G-tubes) are not encouraged due to the possibility of worsening gastroparesis and risk of pulmonary aspiration. Jejunostomy tubes are preferred in order to bypass the gastroparetic stomach except if the patient has small bowel dysmotility. Short-term nasojejunal feeding is often used to help determine if the patient will tolerate chronic small bowel feeding through a permanent enteral access. Formulas that are low in osmolarity (e.g., Peptamen, Isocal) and have a caloric density of 1.0-1.5 cal per ml are recommended. Initially, infusion rates should be low and then advanced every 4-12 hours as tolerated to meet caloric needs. Eventually, infusions can be converted to nocturnal feedings to free up daytime hours for optional oral intake and to participate in normal daily activities.

Endoscopic Treatment

Therapeutic endoscopy with pyloric injection of botulinum toxin A may provide benefit in some patients with gastroparesis. Botulinum toxin A is a bacterial toxin that inhibits acetylcholine release causing muscle paralysis. Manometric studies in patients with diabetic gastroparesis have shown evidence of prolonged pylorospasm producing a functional outlet obstruction [35]. Use of botulinum toxin for gastroparesis is considered off-label and should be considered when other accepted therapies have failed or produced unacceptable side effects. To date, few adverse effects have been reported with botulinum toxin therapy. At our pediatric gastroenterology practice, we do not use this modality of treatment.

Surgical Treatment

Surgical intervention is increasingly used to treat medically refractory/severe gastroparesis. Limited data is available concerning surgical treatment of gastroparesis [62]. The most common procedure is the implantation of the gastric electrical stimulator (GESt) (Enterra Therapy, by Medtronic Inc.). This device delivers electrical stimulation by two electrodes placed in the seromuscular part of the stomach in proximity to the pacemaker area of the stomach. Although the exact mechanism of action of the GESt is unknown, the clinical effect is believed to be mediated by local neurostimulation [63]. The stimulation impulses used are able to excite nerves but are too weak to excite gastric smooth muscles. Other procedures offered include venting/feeding gastrostomy and jejunostomy tubes, surgical pyloroplasy, gastrectomy and surgical drainage procedures and pancreatic transplantation in diabetic patients. Apart from GESt and feeding tubes, other surgical procedures are performed as a last resort in carefully evaluated patients with profound gastric stasis [62].

All of the above mentioned diagnostic tests and therapies are derived from adult literature. There is no published data available describing the spectrum of pediatric gastroparesis. The goal of our study is to provide a comprehensive analysis of a large population with gastroparesis, advance the understanding of pediatric gastric dysmotility and better plan therapeutic interventions for children.

Goals of the Study

All of the afore-mentioned diagnostic tests and therapies are derived from adult literature. There are no published data available describing the spectrum of pediatric gastroparesis. The goals of our study were to provide a comprehensive analysis of a large pediatric population with gastroparesis, advance the understanding of pediatric gastric dysmotility and better plan therapeutic interventions for children. While most cases in children are post-viral and self-

limited, chronic symptoms often occur in idiopathic cases. We therefore performed a retrospective study of pediatric patients with GP.

The indications for gastric scintigraphy and the outcomes of patients with gastroparesis were defined. We accomplished this by: (a) recording characteristics such as demographics, symptoms, co-morbidities, psychological aspects and etiologies of patients with gastroparesis, and (b) analyzing long term follow-up to understand the effectiveness of therapy, the course of the disease and outcomes.

CHAPTER 2
MATERIALS AND METHODS

Patient Ascertainment and Case Definition

This study was approved by the Institutional Review Board of the University of Florida (UF). All UF pediatric gastroenterology practice patients, ages ranging from 0 to 21 years, diagnosed with delayed gastric emptying between January, 2002, and December, 2008, were identified. This was done by using the UF radiology-nuclear medicine database which identified all patients who had undergone gastric scintigraphy during that time period. Subsequently, electronic chart review was conducted to identify cases that fulfilled the following criteria: 1.) clinical symptoms of nausea, vomiting, abdominal pain, early satiety, bloating and weight loss were present without anatomical or mechanical obstruction, and 2.) radiologic evidence of delayed gastric emptying of a radionuclide solid meal (t ½ of ≥ 90 min) or radionuclide liquid meal (t ½ of ≥ 60 min)

Gastric scintigraphy is routinely performed to evaluate patients with gastric emptying delay at our institution. All patients who are ≥3 years are asked to fast overnight and younger patients are not fed for 4 hours prior to the test. Smokers are asked not to smoke the morning of the exam and patients must stop all medications known to affect gastric emptying, e.g., prokinetics and narcotics, for 48 hrs. After an overnight fast patients are fed with either a solid or liquid meal. Solid meal constitutes one grade AA egg (~50ml) cooked scrambled with Tc-99 sulfur colloid (0.5mCi) served with two pieces of white bread with one teaspoon of butter spread on the bread, and 50 ml of water to help ingestion (total calories: 280 kcal, 30 grams of carbohydrates, 13 grams of protein and 10 grams of fat). The liquid meal consists of 60 ml of radio-labeled formula or Pediasure (60 kcals) administered with 0.5mCi of Tc-99m sulfur colloid. After administration of the meal, the patients are imaged continuously for 120 min at 1

min per frame using a single-headed gamma camera, equipped with low energy, high resolution collimator, positioned in the left anterior oblique position to minimize the effects of varying gastric attenuation on quantification of the gastric emptying rate. Alternatively, a dual-headed camera may be used with similar positioning with calculation of geometric mean activity. In addition, for liquid emptying, fast imaging acquisition at 10/frame is performed to allow for gastroesophageal reflux. A simple linear fit is applied to the rate of gastric emptying with calculation of the gastric emptying half-time by extrapolation. Normal half-time for solids is defined as 45-90 min and normal for liquids is <60min. At 80 min into the oral examination patients are administered IV EES at 2.8mg/kg/dose up to a maximum of 250 mg (adult dose), infused over 20 min. Calculation of gastric emptying half-times pre- and post-erythromycin is performed. With liquid meals IV EES is infused after 60 min instead of 80 min. Prior to the year 2005, IV metoclopramide was also infused at 0.05mg/kg/dose up to a maximum of 3 mg/dose.

We excluded patients: 1) who were not UF pediatric gastroenterology practice patients, 2) whose gastric emptying times were not extrapolated in half-times, 3) who had gastric scintigraphy performed which was not ordered by pediatric GI faculty, 4) who were not followed by pediatric GI for gastroparesis, and 5) who had no follow up visits after gastric scintigraphy.

Data Collection

To ensure reliability and high quality data collection, we designed a data collection form using Microsoft Access (Appendix). All data were collected from electronic medical records, including all inpatient and outpatient records. Variables were obtained from a thorough review of the physician notes, past medical and surgical history, medication history, review of symptoms, radiological studies, endoscopy and histology. Each clinical record was reviewed and data extracted by an experienced pediatric gastroenterologist and a second year pediatric resident in the same office location. Any uncertainties in data abstraction were discussed thoroughly with

the pediatric gastroenterologist. Patients were followed from the time of diagnosis of gastroparesis to the last GI encounter or until December, 2008. The following information was collected from the complete review of medical records:

- Demographics: age at the time of diagnosis and gender
- Height (in cm) and weight (in kg) at the time of diagnosis to calculate BMI
- Gastric emptying half-time determined by GES and type of meal used
- Response to IV EES and/or IV metoclopramide during gastric scintigraphy and response recorded as t½ returning within normal emptying range as recorded in the GES electronic report
- Presenting symptoms: nausea, vomiting, post-prandial early satiety, bloating, abdominal pain and weight loss.
- Medication history: all medications prior to gastric scintigraphy were recorded, including use of PPI and H2 blockers which were recorded as a separate variable.
- Other medical diagnosis and surgical history.
- Complications of gastroparesis: anemia, esophageal stricture, esophagitis, gastritis, reflux, small bowel bacterial overgrowth, pneumonia, bronchitis, malnutrition, dehydration and bezoars.
- Psychological diagnosis: depression, anxiety, attention deficit hyper activity disorder (ADHD), bipolar disorders and any other psychiatric/behavioral disorder.
- Treatment of gastroparesis: with medications, e.g., erythromycin, azithromycin, tegesarod, metoclopramide, and any other prokinetic/anti-emetic medication, dietary recommendations, enteral feeds, TPN, gastric electrical stimulator, and any other treatments.
- Last gastric scintigraphy if any, type of meal used, time interval in months between first and last gastric scintigraphy
- Age at last encounter, height (in cm) and weight (in kg) at last encounter to calculate last encounter BMI
- Symptoms at last encounter: nausea, vomiting, early satiety, bloating, abdominal pain and weight loss
- Etiology of gastroparesis was recorded based on medical record evidence of any of the following:
    - Idiopathic causes
    - Post-viral causes
    - Medication causes, e.g., opiates, anti-cholinergics, B-adrenergics, calcium channel blockers, glucagon, marijuana, alcohol, tobacco and others
    - Surgical causes, e.g., vagotomy, fundoplication, Whipple's resection, heart/lung transplant and others
    - CNS causes, e.g., cerebrovascular accidents/trauma, central tumors, labyrinthine disorders, cerebral palsy, seizures and others
    - PNS causes, e.g., Guillain Barre syndrome, multiple sclerosis, peripheral autonomic dysfunction and others
    - Neuropsychiatric disorders, e.g., anorexia nervosa, bulimia, rumination syndrome, and others

- Rheumatologic disorders, e.g., scleroderma, SLE, polymyositis/dermatomyositis, and others
- Endocrine and metabolic causes, e.g., diabetes, hypothyroidism, parathyroidism, cystic fibrosis, electrolyte imbalance, renal insufficiency, neoplastic/paraneoplastic disorders and others
- Miscellaneous conditions, e.g., chronic intestinal pseudoobstruction, myotonic disorders, cow-milk protein, prematurity, eosinophilic gastroenteropathy including esophagitis

Statistical Analysis

We used Minitab statistical software (Cary, NC) and SPSS 16.0 (Chicago, IL) for data analysis. Data were imported into both software packages and descriptive statistics were calculated for both continuous and binary variables. These results were expressed as either a proportion or mean with standard deviation. The data set was then divided into separate cohorts based on age, gender, severity of the gastroparesis, type of meal used, and response to medications. Continuous variables were analyzed using either paired T-test or 2-sample T-test as appropriate. Binary variables (yes / no) were studied with the Fisher's exact test of proportions or Chi-squared test where appropriate. P-values less than 0.05 were considered significant and 95% confidence intervals for each are also shown.

CHAPTER 3
RESULTS

Patient Characteristics

A total of 912 pediatric patients had undergone gastric scintigraphy from January, 2002, to December, 2008, at the University of Florida. From this group 408 patients (45%) were identified to have delayed gastric emptying. However, 169 patients (41%) from the delayed gastric emptying group were excluded from the study due to our exclusion criteria, i.e., those who were not UF pediatric gastroenterology practice patients, gastric emptying times not extrapolated in t½, gastric scintigraphy not ordered by pediatric GI faculty, patients not followed by pediatric GI for gastroparesis, and patients who had no follow up visits after gastric scintigraphy.

Among the 239 eligible cases of delayed gastric emptying, 123 patients (51.5%) were female and 116 (48.5%) were male. The mean age (±SD) at presentation among all the patients was 7.9 (±5.9) years, mean BMI (n=212) at presentation was 18.6 (±5.3). The mean t½ of amongst all patients irrespective of type of meal was 146 min (±72.32). However, mean t½ for solid meal was 163 min (90-500 min) and 121 min (62-300 min) for liquid meals. (Figure 3-1). Twenty-eight patients underwent a repeat gastric scintigraphy with a mean t½ of 108 min (±66.6) during an interval of 2 to 68 months (mean 28.5 months ±18.8). Of these, 10 patients (36%) had solid emptying delay while 18 patients (64%) were found to have liquid emptying delay. First and last t½ differences in these patients were not significant (p-value=0.098).

Using the Pearson correlation test we found a correlation between t½ and presenting symptoms of nausea and abdominal pain only. But, when we performed this test on individual cohorts of solid and liquid emptying, we found a correlation between solid emptying and weight loss, but no correlation between liquid emptying and any of the symptoms.

Among the cohort of 239 patients, 84 patients (35%) responded to IV EES, 20 patients (8.4%) were non-responders to IV EES, 20 patients (8.4%) responded to IV MCP, 28 patients (11.7%) were non-responders to IV MCP and 135 patients (56.5%) were not tested with either of these drugs at the time of scintigraphy. Of the 94 patients who underwent liquid testing of emptying, 19 patients (20%) responded to IV EES, 15 patients (16%) were non-responders to IV EES, 1 patient (1%) responded to IV MCP and 11 patients (11.7%) were non-responders of IV MCP. However, of the 145 patients who underwent solid meal testing of gastric emptying, 65 patients (45%) responded to IV EES, 5 patients (3.5%) were non-responders to IV EES, 19 patients (13%) responded to IV MCP and 11 patients (11.7%) were non-responders to IV MCP. Chi-squared test revealed patients with solid emptying delay responded better to IV EES than those with liquid emptying delay, i.e., 45% vs. 20% (p-value=<0.001).

Among all the patients the most common presenting symptoms were vomiting and abdominal pain (67.8% and 50.6%, respectively) (Table 3-1). Other symptoms included nausea (28.4%), weight loss (26.8%), early satiety (24.7%) and bloating (7.1%). Subsequently, a decrease in the frequency of all symptoms, especially vomiting, was observed at the last encounter.

Most patients were treated with combination therapy which predominantly consisted of EES (73.64%) and dietary modifications (41.4%), but other forms of treatment with drugs such as metaclopramide (29.7%), azithromycin (5.4%), tegaserod (6.7%), enteral feeds (23%), and TPN (3%) were also tried.. Medications such as cisapride, propulsid, anti-histamines, anti-emetics and tricyclic antidepressants were used by 4% of the patients. None of the patients received pyloric botox injections or gastric electrical stimulation.

The most common complication of gastroparesis was esophageal reflux (67.4%), followed by histologically diagnosed esophagitis and gastritis (16.7% and 15%, respectively). Other complications included dehydration (3.7%), anemia (2.5%), bezoars (1.67%), small bowel bacterial over growth (1.26%), malnutrition (1.26%), and esophageal strictures (0.42%).

Patients were found to have multiple presumed etiologies for gastropareis. Among all the patients, the most common cause was identified to be idiopathic gastroparesis in 167 patients (70%) (Table 3-2). A significant number of patients had CNS disease, which was presumed as the etiology of their GP. CNS disorders included cerebral palsy, seizure disorder, developmental delay, cerebrovascular accident and related prematurity. The other main categories in descending order included fundoplication, post-viral causes and others i.e. diabetes, hypothyroid, eosinophilic esophagitis, eating disorders, cystic fibrosis etc. Co-morbid psychiatric conditions such as ADHD were reported in 20 patients (8.4%), behavioral problems in 19 patients (8%), anxiety in 15 patients (6.3%), depression in 10 patients (4%), and bipolar disorder in 4 patients (1.7%).

Outcomes for the Entire Cohort

This hospital-based cohort study was followed for a mean of 24 months. Our outcome variables were change in symptoms, e.g. nausea, vomiting, early satiety, abdominal pain, bloating, and weight loss. We found significant improvement in outcomes at the end of the follow-up period regardless of type of treatment used (Figure 3-2). The mean BMI changed from 18.6 (±5.3) to 19.8 (±8.1) but this change was not significant (p-value=0.415). Using the Fisher exact T-test, we found a significant difference in all symptom outcomes (Table 3-1). The same test was applied to compare the symptom outcomes of total responders with total non-responders of IV EES but showed no significant difference. Of those who underwent repeat GES (n=28),

improvements were noted in vomiting (p-value=<0.001) and weight loss (p-value=0.009). Other symptom outcomes were unchanged at the end of follow-up for this group.

Outcomes According to Gender

For females, the mean age (±SD) at presentation was 9 (±5.9) years and for males it was 6.7 (±5.7) years (p-value=0.002). There was not a significant difference in the frequency of presenting symptoms between the genders except that females reported more nausea than weight loss (Table 3-6). In addition, their individual outcomes revealed significant improvement in last encounter symptoms.

We did not find a significant difference in symptom outcomes when comparing males with females except for abdominal pain, which was more commonly reported by females (Table 3-3). Also, we found no significant difference between the genders in regard to co-morbid psychiatric disorders, i.e., ADHD, depression, anxiety, behavior disorders and bipolar disorder.

Outcomes According to Age Groups

We categorized patients according to the following age groups, <1yr, 1-5 yrs, 6-10 yrs, 11-16 yrs and > 17 yrs, and then we performed descriptive analysis as well as Fisher exact test of proportion to measure outcomes (Table 3-4).

<1 yr: A total of 29 patients who were <1yr of age were diagnosed with delayed gastric emptying with mean t ½ of 120 min (±61.8). Twenty-one patients (72.4%) were males and 8 patients (27.5%) were females. Vomiting was the presenting symptom in the majority of the patients; second most common was weight loss. Improvement in both vomiting and weight loss were observed at follow-up. Other symptom outcomes were unchanged at the end of follow-up.

1-5 yrs: Sixty-eight patients were diagnosed with gastroparesis in this age group with mean t ½ of 128 min (±66). Thirty-four patients (50%) were males and 34 patients (50%) were females. Vomiting and abdominal pain were the most common presenting symptom followed by

weight loss, early satiety, nausea, and bloating. At follow-up we noted decreased vomiting, early satiety, and weight loss.

6-10 yrs: A total of 48 patients had gastroparesis with mean t ½ of 144 min (±70). Twenty-five patients (52%) were males and 23 patients (48%) were females. Again, vomiting and abdominal pain were the most common presenting symptoms followed by early satiety, nausea, weight loss, and bloating. Only the rates of vomiting, early satiety and abdominal pain improved at follow-up.

11-16 yrs: Seventy-six younger teenage patients were identified with a mean t ½ of 168 min (±75). Forty-six patients (60.5%) were females and 30 patients (39.5%) were males. Symptoms by decreasing frequency included abdominal pain, vomiting, nausea, early satiety, weight loss, and bloating. All symptoms outcomes except for bloating were improved at follow-up.

>17 yrs: Eighteen patients in this age group were diagnosed with gastroparesis with a mean t ½ of 175 min (±75). Twelve patients (66.7%) were females and 6 patients (33.3%) were males. Symptoms by decreasing frequency included abdominal pain, nausea, vomiting, early satiety, weight loss and bloating. Only early satiety improved at follow-up.

Severity Scale-Related Outcomes

We further divided our cohort into 4 categories of delayed solid emptying and 3 categories of delayed liquid emptying. Both were stratified by t½. Therefore, solid emptying delay (n=145) was divided into the following categories: very severe (>241 min), severe (191-240 min), moderate (141-190 min) and mild (90-140 min) (Table 3-5). Liquid emptying delay (n=94) was divided into categories of: severe (>141 min), moderate (101-140 min) and mild (61-100 min) (Table 3-6).

Solid Emptying Delay Outcomes

Very severe (>241 min): We had 24 patients with very severe solid emptying delay who had a mean age at presentation of 12.5 yrs (±4.7). Sixteen patients were females (66.6%) and 8 patients were males (33.3%). Patients presented with abdominal pain, nausea, vomiting, weight loss, early satiety and bloating in decreasing frequency. Improvements in weight loss, abdominal pain, vomiting and nausea were noted at follow-up.

Severe (191-240 min): Thirteen patients were identified with severe delay with mean age at presentation of 13.8 (±3.6). Ten patients (77%) were females and 3 patients (23%) were males. Most patients presented with abdominal pain, followed by vomiting, nausea, weight loss, early satiety and bloating. With this small group only vomiting improved at follow-up.

Moderate (141-190 min): Twenty-four patients were identified with moderate delay in gastric emptying with mean age at presentation of 11.4 yrs (±3.7). Females were 15 in number (62.5%) and males 9 (37.5%). This group presented primarily with abdominal pain and vomiting, then in decreasing frequency with nausea, early satiety, weight loss and bloating. Improvements in vomiting and early satiety were seen at follow-up.

Mild (90-140 min): We had eighty-four patients in this group with mean age of 10.5 yrs (±4.5). Forty-five patients (53.7%) were females and 39 patients (46.4%) were males. Abdominal pain and vomiting were predominant, followed by nausea, early satiety, weight loss and bloating. Improvements in abdominal pain, early satiety, vomiting and nausea were seen at follow-up.

Liquid Emptying Delay Outcomes

Severe (>141 min): Seventeen patients were identified with mean age of 3.5 yrs (±4.6). Of these, 9 patients (53%) were females and 8 patients (47%) were males. Vomiting was present

in the majority of the patients, then weight loss, nausea, abdominal pain, early satiety and bloating. Improvement was seen only in vomiting.

Moderate (101-140 min): We had 30 patients in this group with mean age at presentation of 2.8 yrs (±3.5). Twelve females (40%) and 18 males (60%) were identified. Again, most presented with vomiting, then weight loss, abdominal pain, early satiety and bloating. Improvements in vomiting and weight loss only were observed at follow-up.

Mild (61-100 min): Forty-seven patients were in this group, with mean age of 2.3 yrs (±3.3). Sixteen patients (34%) were females and 31 patients (66%) were males. In decreasing frequency, presenting symptoms were vomiting, weight loss, abdominal pain, early satiety, nausea and bloating. Improvements in weight loss, abdominal pain, and vomiting were observed at follow-up.

Outcomes Based on Presumed Etiology of Gastroparesis

Most of the patients had multiple presumed etiologies of GP. It was impossible to differentiate a single etiology as the definitive cause of GP in these patients. Nevertheless, we divided our cohort into 6 most common categories of etiology: 1) idiopathic GP, 2) GP due to cerebral palsy, 3) GP due to seizure disorder, 4) GP due to prematurity, 5) post-fundoplication GP, and 6) post-viral GP. Outcomes based on these categories follow.

Idiopathic causes: The majority of GP patients (167 patients, 70%) belonged to this group. There were 82 females (49%) and 85 (51%) males. Mean age at presentation was 8 yrs (±5.8) and mean t ½ was 143 min (±69.6). Sixty-four percent had vomiting, 55.7% had abdominal pain, 31% had nausea, 29% had satiety, 23% had weight loss and 6% had bloating. Improvement in all symptoms except weight loss was observed at follow up.

Cerebral palsy: Thirty-nine patients were identified to have cerebral palsy and GP, with mean age of 4.8yrs (±4.7) and mean t ½ of 147 min (±72). There were more males (22 patients,

56%) than females (17 patients, 43.6%) in this group. Patients presented mostly with vomiting (82%) and weight loss (31%). The rest of the symptoms in decreasing frequency were abdominal pain (18%), nausea (18%), early satiety (13%) and bloating (10%). Symptom improvement in this group was observed for abdominal pain and vomiting only.

Seizure disorder: There were 37 patients in this group, with mean age of presentation at 5.2 yrs (±5.4), mean t ½ of 131 min (±60.6) and male/female percentages of 51 (19 patients) and 49 (18 patients) respectively. Again, patients mainly presented with vomiting (84%) and weight loss (24%). Other frequencies were abdominal pain 16%, nausea 13.5% and bloating 2.7%. None of the symptoms improved at follow-up.

Prematurity: Thirty-two patients were born prematurely and presented at mean age of 6 yrs (±5) and mean t ½ of 123 min (±45). Their male/female ratio was 56% (18 patients) and 44% (14 patients) respectively. Eighty one percent had vomiting, 28% had abdominal pain, 15.6% had nausea, 15.6% had early satiety, 12.5% had weight loss and 6% had bloating. Improvement only in abdominal pain and early satiety was observed at follow-up.

Post-fundoplication: Sixteen patients who developed GP underwent Nissen-fundoplication. Mean age was 5 yrs (±5.8) at presentation with mean t ½ of 142 min (±67) . Ten patients (62.5%) were females and 6 patients were males (37.5%). Again, vomiting and weight loss were predominant presenting symptoms (87.5% and 25% respectively) followed by abdominal pain (12.5%) and nausea (6.2%). At follow-up there was improvement only in weight loss.

Post-viral GP: Twelve patients were diagnosed with post-viral GP, with mean age of 12 yrs (±5) at onset and mean t ½ of 179 min (±91). Males and females were 41.6% (5 patients) and 58.3% (7 patients) respectively. Both vomiting and abdominal pain presented with equal

frequency of 66.6% each, followed by both nausea and early satiety at 41.7% each, weight loss in 33.3% and bloating in 8.3%. These patients had symptom improvements in vomiting, early satiety, abdominal pain and weight loss. Other symptoms did not improve at follow-up.

Table 3-1. Frequency of symptoms at first and last encounter

Symptoms	N (%) first encounter	N (%) last encounter	p-value
Vomiting	162 (67.8)	47 (19.7)	<0.001
Abdominal pain	121 (50.6)	70 (29.3%)	<0.001
Nausea	68 (28.5)	36 (15)	<0.001
Weight loss	64 (26.8)	22 (9.2)	<0.001
Early satiety	59 (24.7)	15 (6.3)	<0.001
Bloating	17 (7.1)	7 (2.9)	0.035

Table 3-2. Etiology of gastroparesis

Cause of gastroparesis	n (%)
Idiopathic	167 (70)
Cerebral palsy	39 (16.3)
Seizure disorder	37 (15.5)
Prematurity	32 (13.4)
Fundoplication	16 (6.7)
Post-viral	12 (5)
Others	77 (32)

Table 3-3. Frequency and outcomes of symptoms in males and females

	Males n=116 (%)			Females n=123 (%)			Comparison of outcomes between males and females
Symptoms	First encounter	Last encounter	P-value	First encounter	Last encounter	P-value	P value
Vomiting	87 (75)	25 (21.5)	<0.001	75 (61)	22 (18)	<0.001	0.5
Abdominal pain	52 (45)	24 (20.7)	<0.001	69 (56)	46 (37.4)	<0.001	0.004
Weight loss	30 (26)	8 (7)	<0.001	34 (27.6)	14 (11.4)	0.004	0.23
Nausea	29 (25)	13 (11.2)	0.002	38 (31)	23 (18.7)	0.014	0.104
Early satiety	30 (26)	6 (5)	<0.001	29 (23.5)	9 (7.3)	<0.001	0.5
Bloating	5 (4)	3 (2.6)	0.687	12 (9.7)	4 (3.2)	0.057	0.76

Table 3-4. Symptom outcomes by age group

	< 1 yr (n=29)			1-5 yr (n=68)			6-10 yr (n=48)			11-16 yrs (n=76)			>17 yrs (n=18)		
Symptoms	First symp** %	Last symp %	p-value	First symp %	Last symp %	p-value	First symp %	Last symp %	p-value	First symp %	Last symp %	p-value	First symp %	Last symp %	p-value
Nausea	0	3.5		10	4.4		25	18.7		48.7	18.4	*	61	50	
Vomiting	96.5	20.7	*	72	19	*	73	21	*	52.6	17	*	55.5	28	
Early satiety	7	0		16	3	*	27	6.2	*	33	10.5	*	44.4	11	*
Abdominal pain	3.5	3.5		28	17.6		67	31	*	75	43.4	*	66.7	50	
Bloating	0	7		6	1.5		10.4	2		5.3	1.3		22	11	
Weight loss	31	7	*	25	5.9	*	20	8		27.6	11.8	*	39	16.6	

* p-value<0.05

**Symp = symptom

Table 3-5. Outcomes of solid emptying delay based on severity

Symptoms	Very severe (>241min) n=24 1st symp** %	Last symp %	p-value	Severe (191-241 min) n=13 1st symp %	Last symp %	p-value	Moderate (141-190min) n=24 1st symp %	Last symp %	p-value	Mild (90-140min) n=84 1st symp %	Last symp %	p-value
Nausea	62.5	12.5	*	38	23		37.5	25		42	25	*
Vomiting	85.3	20.8	*	61.5	23	*	58	16.6	*	56	23	*
Early satiety	37.5	16.7	*	23	7.7		33.3	8.3	*	37	7	*
Abdominal pain	71	41.7		84.6	53.8		66.6	41.7		74	43	*
Bloating	8.3	4		7.6	0		12.5	0		9.5	3.5	
Weight loss	41.6	12.5	*	31	23		21	12.5		16.7	8.3	

*p-value<0.05
**Symp = symptom

Table 3-6. Outcomes of liquid emptying delay based on severity

Symptoms	Severe (141 min) N=17 1st symp** %	Last symp %	p-value	Moderate (101-140 min) N=30 1st symp %	Last symp %	p-value	Mild (61-100 min) N=47 1st symp %	Last symp %	p-value
Nausea	11.7	0		2	3.3		2	4.3	
Vomiting	88	5.9	*	83	16.7	*	83	21.3	*
Early satiety	6	5.9		8.5	0		8.5	2	*
Abdominal pain	11.7	11.7		17	10		17	4.3	
Bloating	6	11.7		2	3.3		2	0	
Weight loss	35	17.6		32	0	*	32	6.4	*

* $p < 0.05$
**symp = symptom

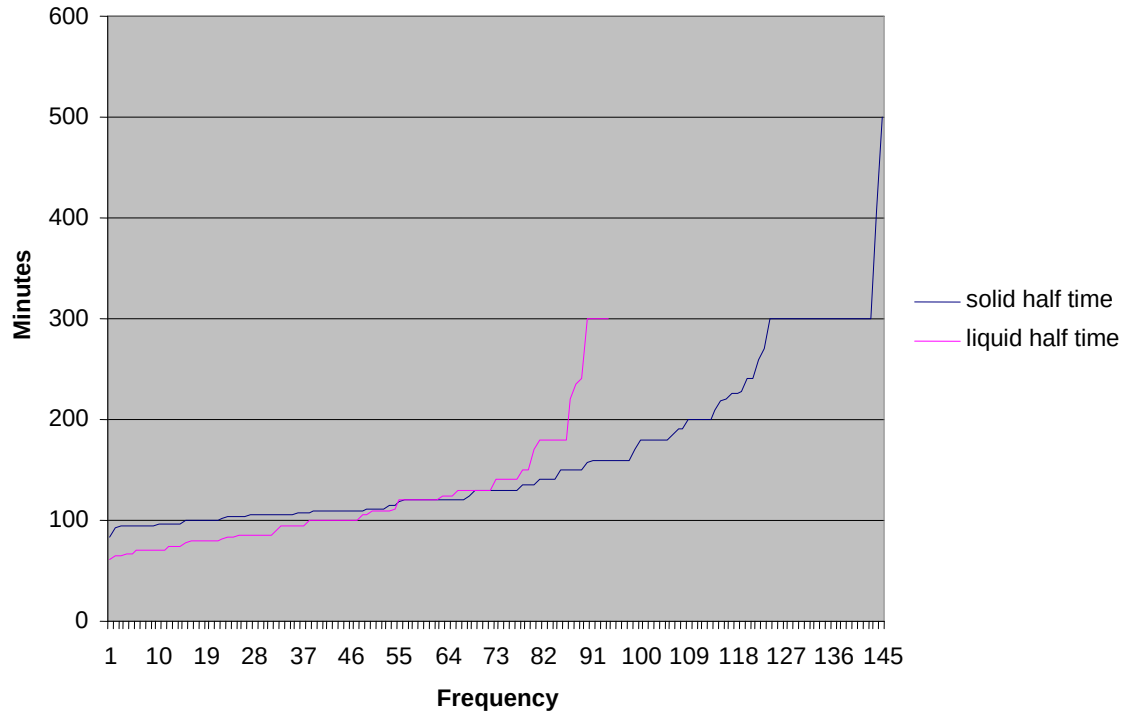


Figure 3-1. Frequency of t½ in solids and liquids

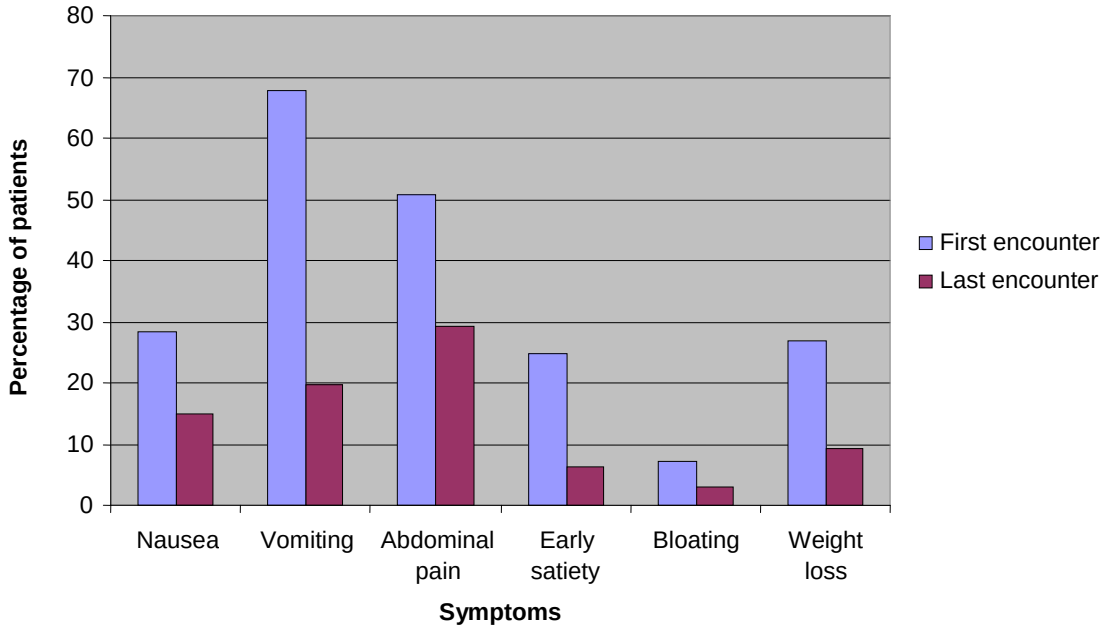


Figure 3-2. Symptom outcomes of all patients

CHAPTER 4
DISCUSSION

In a large cohort of pediatric patients (n=239) referred to a large academic medical center, we have attempted to define the full spectrum of gastroparesis in the pediatric population. Most of the previous data on this condition has been reported from adult studies, which may not reflect the spectrum of gastroparesis in children. Adult cohorts have consistently revealed an overwhelming female predominance (~80%) in this condition [2, 64]. In addition, the etiologic categories in adults have been 1/3 idiopathic, 1/3 diabetic and 1/3 post-surgical/miscellaneous causes [2, 17, 64]. Adult literature establishes high morbidity and mortality of this condition [18,64].

Our study revealed important differences from the reported adult literature, with an almost equal distribution of between male and female pediatric patients (51.5% and 48.5% respectively) and similar etiologies for each gender. The gender differences started to increase as the age increased, such that with patients over 17 yrs of age, about 2/3 were female. Males presented at an earlier age of 6 yrs versus females who presented at 9 yrs, but both genders were found to have similar outcomes. This finding has differs from adult studies, where females have shown a poorer prognosis [2, 64].

Existing literature does not reveal any correlation between t½ and symptoms. With our data we were able to correlate between severity of gastroparesis by t½ and frequency of presenting symptoms of nausea and abdominal pain. Unfortunately, in this retrospective analysis, we could not assess the severity of the symptoms by other measures such as number of episodes of emesis per day.

Etiologies in pediatric GP were found to differ from adults, as there was a predominance of idiopathic gastroparesis (70%) whereas the single most common cause of gastroparesis in the

adult population is diabetes. The lack of a predominant diabetic cause in our cohort may reflect the time that is required for diabetes to cause gastric dysmotility. The next most common causes or associated factors were CNS causes, e.g., cerebral palsy, seizure disorder, and developmental delay. Again, in this retrospective study, it is difficult to separate associated diagnoses from actual causative factors. Also, prematurity seemed to be a risk factor for developing gastroparesis. This information suggests the need for further investigation into the pathophysiology of GP and possibly a significant role of the CNS and its relationship with the enteric nervous system in the pathogenesis of gastroparesis. Two hundred and six patients out of 239 had associated co-morbidities which may be contributing to GP or reflect complications of the condition itself.

Another important factor to consider is that only 3 patients were taking opiates and 4 patients were smokers, therefore a majority of our patients were not exposed to medications or behaviors that have been implicated in adult gastroparesis. Most series describing gastroparesis in adults document the extensive use of such medications or behaviors.

Mandatory prokinetic testing during scintigraphy is a valuable addition to the GES protocol in our institution and to our knowledge is not widely performed. This practice enabled us to further divide the cohort to responders and non-responders to IV EES or IV MCP. We found that IV EES was more effective in improving solid emptying when compared to liquid emptying at the time of gastric emptying study. A possible explanation maybe that liquid emptying delay is considered an indicator of progressively worsening gastroparesis; therefore, these patients may have more severe disease with poorer response rates to prokinetics. It is unclear whether patients who respond to these medications have an improved outcome or not, as

tachyphylaxis still develops during clinical use. We plan to further study this sub population of patients to assess the effect of medications.

The frequency of presenting symptoms is different from adults, who usually present with nausea and vomiting [2, 64]. In our cohort, we noted that abdominal pain was a very common presenting feature. This was observed even in the older children and in adolescents. Interestingly, in our older age group (>17 yrs), abdominal pain and nausea were prominent presenting symptoms. The prominence of abdominal pain in our pediatric patients with gastroparesis may be due to the pronounced association of pain with idiopathic gastropareis, which in turn is a major cause of GP in children [2]. Another important finding is related to mental health. When compared to adults, patients in this study had far fewer (28.4% vs 62%) co-morbid psychiatric conditions [2]. Again, this may be due to the duration of symptoms – patients with severe gastroparesis have a tendency to become depressed and anxious.

The finding of gastroesophageal reflux as the most common complication of GP is a reminder that patients with reflux and non-ulcer dyspepsia can have delayed gastric emptying [63, 64]. Although 67% of GP patients were diagnosed with gastroesophageal reflux, only 17% and 15% were found to have histological evidence of esophagitis or gastritis respectively. Hence, whether vomiting symptoms are due to GP or reflux cannot be distinguished in the pediatric population.

Most patients were treated with EES and dietary modifications (73.6% and 41% respectively). Although IV EES significantly improves gastric emptying of a solid meal, oral EES is not as effective. Nevertheless, significant improvement was observed in the outcomes of patients regardless of type of therapy. Patients who do not respond well to oral EES could be tried on IV EES. Subcutaneous MCP has also been tried in this setting if tolerated [18].

Whatever the form of treatment used, we found a statistically significant improvement in all symptoms at the end of the mean 2-year follow-up with similar results in both genders. One possible reason is that the natural history of idiopathic pediatric gastroparesis may result in improvement over time. In future studies, we will plan to study the outcomes of patients with and without pharmacologic treatment and attempt to identify those cases which do not respond to conventional treatments. The frequency and prevalence of co-morbid psychiatric conditions was the same in both the genders, and since the overall incidence of these disorders compared to adults was also lower, this indicated that psychiatric conditions are not a major risk factor in pediatric GP co-morbidity as reported in adults [2].

The most common age groups with GP were the 11-16 yrs (76) or 1-5 yrs (68) categories. We will analyze these groups in detail for future studies, as the likely etiologies and treatments will differ. The most prominent outcome improvement within all age groups was seen in vomiting. As for severity of emptying delay, patients with either mild or very severe emptying delay had more improvement in all their symptoms; however patients with moderate or severe delay had improvement in vomiting only.

Literature on liquid emptying delay is very limited. Based on adult data it is considered as an “end-stage” indicator of gastroparesis. But most of our liquid emptying meals were performed due to the age (infants/toddlers) of patients instead of intolerance to solid meals. We had six patients who had t ½ >240 min (>4 hrs emptying delay) with liquid emptying. These patients had very severe emptying delay. Five of those six required enteral feeds, and underwent fundoplication, g-tube placement and pyloroplasty. In addition, these five patients had CNS disorders and developmental delays. The remaining patient was thought to have post-viral

gastroparesis. This again reinforces the fact that CNS conditions may possibly play a major role in the pathophysiology of GP.

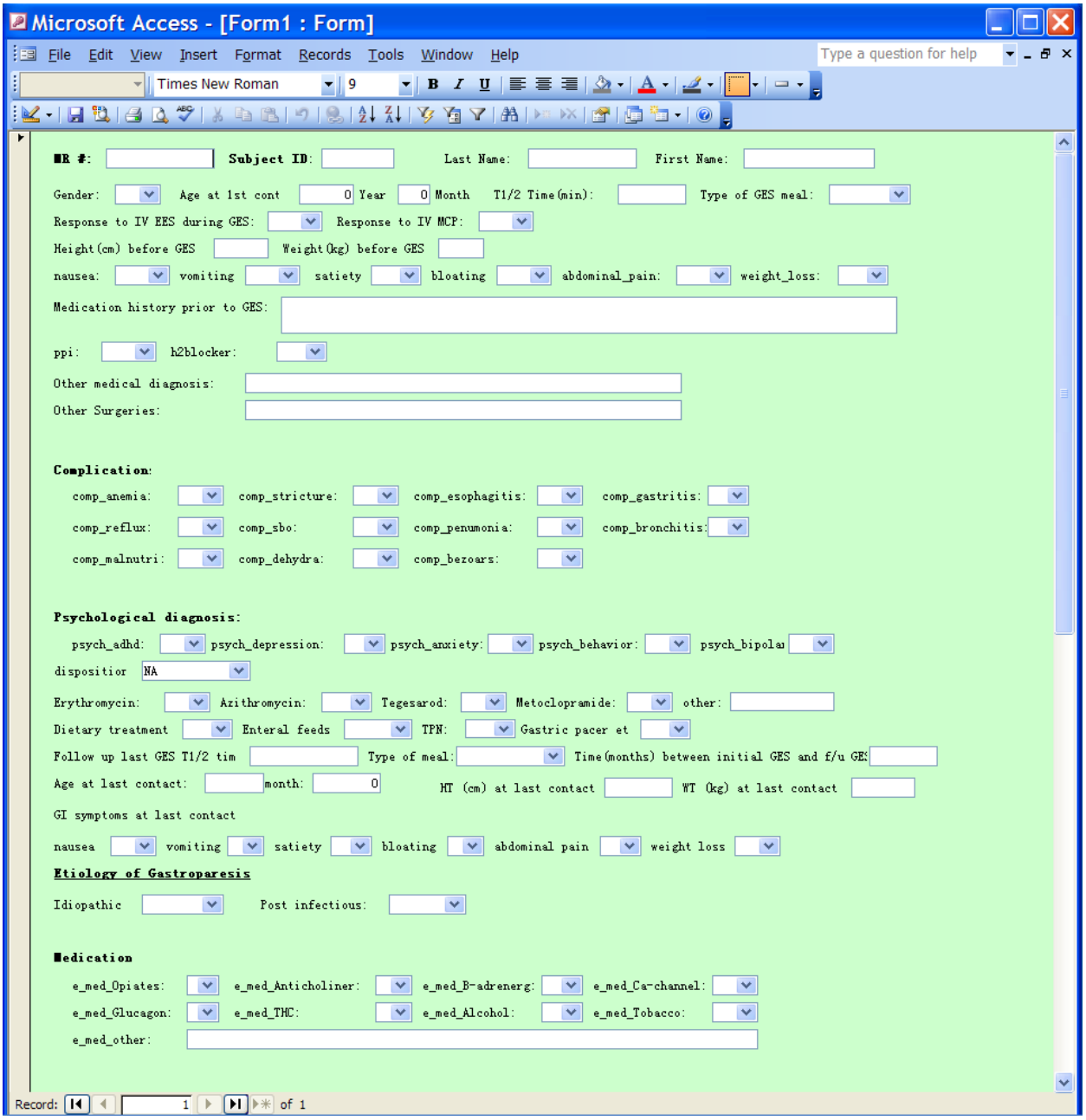
Diabetic gastroparesis was present only in nine patients (4%) of the cohort and these patients were all type 1 diabetics. This information is contrary to adult literature, where 1/3 of GP patients are diabetics. Four (44%) of the 9 patients also had cystic fibrosis. Whether the gastric emptying delay in these 4 patients was due to diabetes-related neuropathy or GI dysmotility found in CF patients is unknown. The correction of hyperglycemia in diabetics is essential in obtaining optimal management results.

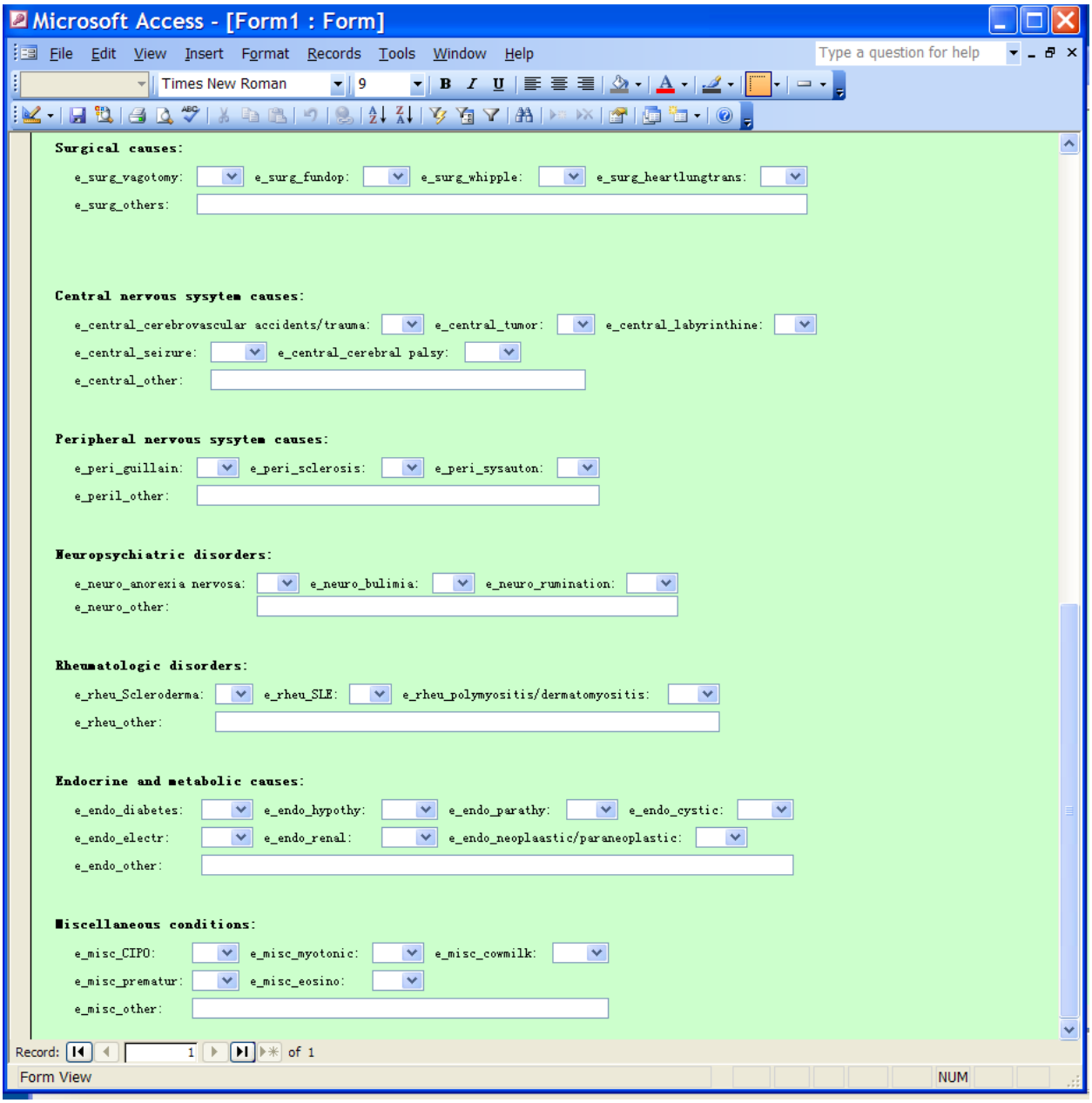
The current study has some limitations. First, this was a retrospective cohort and hence misclassification of gastroparesis variables in records may potentially change our estimates. Second, we did not record duration of treatment, which was difficult to extrapolate solely from electronic records; therefore, outcomes based on duration of treatment could not be performed. This limitation may be the basis of a future prospective study. Third, we did not report ethnicity in this study, and it may not be representative of all ethnic groups with GP because our cohort consisted mainly of a white population. Hence, whether ethnic differences influence the epidemiology of pediatric GP is unknown. Fourth, since this is a hospital-based study instead of a population-based study or case-control study, we were unable to estimate the prevalence of GP. Tertiary care center bias was present and this study may be representative of more severe cases instead of milder presentation in the general population. A key issue is whether primary care providers under-report or under-recognize GP in children. Finally, the gastric emptying scintigraphy protocol used at UF is not in accordance with the recent consensus recommendations of gastric emptying scintigraphy published in 2008 [23]. However, our protocol of continuous scanning for 2 hrs is validated by the Nuclear Medicine Society [67].

In summary, this is, to our knowledge, the first large hospital-based study to describe the demographics, etiologies and outcomes of gastroparesis in the pediatric population. Gastroparesis is an uncommon condition in the community compared with tertiary-based hospital settings, but still represents a major disease burden. Most patients with gastroparesis need continuous medical care, but long-term outcome in the pediatric population seems promising despite limited therapeutic choices. This study will be the springboard for future studies in which we will more accurately describe sub-populations of children with gastroparesis, develop and validate quality of life and severity tools for this condition, and assess newer therapies for this debilitating condition.

APPENDIX

Data collection form




Microsoft Access - [Form1 : Form]
File Edit View Insert Format Records Tools Window Help
Type a question for help
Times New Roman 9
Surgical causes:
e_surg_vagotomy: e_surg_fundop: e_surg_whipple: e_surg_heartlungtrans:
e_surg_others:
Central nervous sysytem causes:
e_central_cerebrovascular accidents/trauma: e_central_tumor: e_central_labyrinthine:
e_central_seizure: e_central_cerebral palsy:
e_central_other:
Peripheral nervous sysytem causes:
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e_peril_other:
Neuropsychiatric disorders:
e_neuro_anorexia nervosa: e_neuro_bulimia: e_neuro_rumination:
e_neuro_other:
Rheumatologic disorders:
e_rheu_Scleroderma: e_rheu_SLE: e_rheu_polymyositis/dermatomyositis:
e_rheu_other:
Endocrine and metabolic causes:
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e_endo_electr: e_endo_renal: e_endo_neoplaastic/paraneoplastic:
e_endo_other:
Miscellaneous conditions:
e_misc_CIPO: e_misc_myotonic: e_misc_cowmilk:
e_misc_prematur: e_misc_eosino:
e_misc_other:
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BIOGRAPHICAL SKETCH

Shamaila Waseem received her medical degree from the most prestigious and oldest medical school in Pakistan, King Edward Medical College, in 1997. She completed her pediatric training at the University of Florida, Jacksonville, in 2006. She will be completing sub-specialty training in pediatric gastroenterology, hepatology and nutrition at the University of Florida, Gainesville, in August 2009. Her Master of Science was completed during her time as a gastroenterology fellow. She will be joining the University of Indiana, Indianapolis, as faculty assistant professor in the Division of Pediatric Gastroenterology, Hepatology and Nutrition.