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Acute Constipation In Children Receiving Chemotherapy For Cancer

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ACUTE CONSTIPATION IN CHILDREN RECEIVING CHEMOTHERAPY FOR CANCER.

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We hypothesized that the prevalence of constipation amongst children on chemotherapy would be high, and that certain pharmacologic interventions commonly used in this population (especially vinca alkaloids, narcotic analgesics, and ondansetron) would be associated with constipation. We also hypothesized that constipation would be perceived as an important problem with a significant impact on lifestyle. We prospectively studied 61 children receiving chemotherapy for cancer by administering questionnaires to patients and their parents. We obtained demographics, bowel movement history, interventions for constipation, chemotherapy agents, other medications, perception of constipation as a problem, and impact on lifestyle. 35 of 61 (57% ± 12%) children were found to meet NASPGHAN criteria for constipation during chemotherapy, while 46 of 61 (77% ± 11%) were found to have signs and symptoms suggestive of constipation and 42 of 61 (69% ± 12%) required the use of laxatives while on chemotherapy. Among children with NASPGHAN criteria constipation, 15 of 35 (43% ± 16%) perceived it as a major/significant problem and 8 of 35 (23% ± 14%) noted a major/significant impact on lifestyle. We concluded that criteria for acute constipation were found in 57% of children receiving chemotherapy for cancer, though less stringent criteria suggest a prevalence of up to 77%. Even though this study lacked sufficient power for most associations, combined use of vincristine and opiates was associated with constipation ($p<0.03$). Constipation was found to have a high prevalence in children on chemotherapy, and it is perceived as a significant problem by patients and their parents with an adverse effect on lifestyle.

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Introduction and Background

Constipation is a common problem in the pediatric population in general, however it is particularly common in children receiving chemotherapy for cancer (**1**). This common chemotherapy-associated adverse effect is well known to pediatric oncologists; a 2005 survey of 12 pediatric oncology units (54% response rate) in the United Kingdom demonstrated that 100% perceived constipation as a problem within their patient group, an observation which has been echoed by pediatric oncologists at Yale-New Haven Hospital and at Children's Hospital in Leeds, United Kingdom (**1-3**). Despite this high awareness, there is no published research focused on constipation in the pediatric oncology population (other than that which was published based on this thesis) (**2**). A 2008 systematic review of treatments for constipation in children and young adults undergoing chemotherapy reviewed 1336 abstracts and failed to find even a single article which was suitable for inclusion, as none included pediatric patients (**3**). As far as we are aware, no prior study had yet tried to assess either the extent or the impact of constipation in this population, both of which might currently be underappreciated by clinicians.

We therefore planned a prospective study to evaluate the prevalence of constipation in children undergoing chemotherapy in New Haven county using an in-person interview and questionnaire. We also

tried to assess perceptions of patients and family members about the degree to which constipation was a problem and its impact on quality of life, while also investigating likely risk factors for constipation and treatment strategies used to treat bouts of constipation. For the purposes of this study, we defined constipation according to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) criteria because, which defines constipation as delay or difficulty in defecation for 2 or more weeks (**45**).

Constipation, in the general pediatric population, has a significant healthcare impact. It accounts for 3-10% of visits to general pediatric practitioners and up to 25% of referrals to pediatric gastroenterologists worldwide (**4-6**). Studies on the worldwide prevalence of functional constipation have found that the rate varies from 0.7% to 29.6% and is common in all pediatric age ranges, from infants to young adults (**7,8**). Given this high prevalence, constipation is associated with high healthcare expenditures. Costs per individual are also significant, especially as constipated children have been shown to have more visits to outpatient clinics and emergency departments and more inpatient admissions than matched controls (**9**). A 2006 prospective study calculated the mean annual expenditure for treatment of chronic constipation to be $7,522 per patient, with an average diagnostic study cost of nearly $3,000 per patient (**10**). While a 1993 British study found that

GBP£43 million is spent annually on prescription laxatives, and an analysis of three United States surveys estimated the total health-related cost of adult constipation to be US$235 million in 2001, pediatric constipation in the United States has been estimated using the Medical Expenditure Panel Survey database to cost US$3.9 billion per year (**11-13**).

Stooling frequency and bowel habits reflect a pronounced interindividual variation which makes defining "normal" a frustrating task, however the bounds of normal habits can be loosely defined with regards to age. A 1989 study used diary recordings to characterize the bowel habits of 662 children in Italy. Starting at age three, most children will have between three stools per week to three stools per day, and by age 5 to age 8 most children will have settled into a more consistent medium-sized bowel movement, either daily or every other day, without straining or exhibiting withholding behavior (**14,15**).

Dealing with constipation, however, presents a challenge as the term has many different meanings to different people, from children, to parents, to physicians and researchers (**16**). To patients it can mean the need for excessive straining, hard stools, infrequent stools, infrequent defecation, the inability to defecate when desired, abdominal pain or discomfort, or the sensation of an incompletely evacuated bowel (**17**). Given the nonspecific nature of these symptoms, many of them will be experienced in the absence of any pathology; indeed, a 2011 study

showed that 20% of 10 to 16-year-olds have at least 1 clinical feature of constipation (**18**). As a result, physicians have attempted several times to define more specific criteria for the constipation. Constipation has been traditionally defined as less than 3 bowel movements per week, however patient self-reports of bowel frequency have been shown to be inaccurate and poorly correlated with other signs and symptoms of constipation (**19**). In 1999, gastroenterology clinicians put forward the Rome II criteria for functional constipation based largely on expert opinion, criteria which were soon found to be too restrictive and thus insensitive for constipation (**16**). These standards were then revised and broadened between 2004 and 2006, and they define constipation as having at least two of the following at least weekly for at least 2 months (without evidence of an organic disease which could be causing them): 2 or fewer bowel movements in the toilet per week, episodes of fecal incontinence in children > 4 years of age, history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, history of large diameter stools which may obstruct the toilet, or the presence of a large fecal mass in the abdomen or rectum (**20**). Infants can also be diagnosed with a similar functional disorder, infant dyschezia, if an otherwise healthy infant less than 6 months of age endures 10 minutes of straining and crying before passing soft stools. The changes in the Rome III criteria resulted in a 42% jump in children being

diagnosed with functional constipation (**21**). Alternatively, as the Rome III criteria still sacrifice sensitivity for specificity by having more stringent criteria and longer duration requirements, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) offer an alternate and less restrictive definition of constipation as delay or difficulty in defecation for 2 or more weeks (**45**).

For many children, constipation is triggered by the occurrence of painful bowel movements, often the result of toilet training, delaying defecation, changes in routine, changes in diet, stressful events, or illness (**22**). Peak incidence occurs at about the time of toilet training (**8**). As feces are retained within the colon, more water is reabsorbed over time, and stools become harder and more difficult to pass, and defecation becomes more painful. This can cause the accumulation of hard stool in the rectal vault and the onset of fecal impaction (**22**). It can also lead to overflow fecal incontinence or loss of the normal urge to defecate (**16**). Some children with chronic constipation have also been found to have reduced rectal sensation, increased rectal wall compliance, or both. This can manifest itself as megarectum, though it is unknown whether these sensorimotor dysfunctions are primary or secondary to constipation (**16**,**23**).

Suggested risk factors for constipation include genetics (a family history of constipation), low consumption of fiber (which functions as an

osmotic laxative and a mechanical stimulator of colonic motility), low levels of physical activity, obesity, living in a high-population-density community and low parent education levels (**7,24**). Constipation has also been associated with behavioral problems, though cause and effect can be difficult to discern as constipation can be both a source and a manifestation of behavioral problems (**25**). Inan et al has shown that physical trauma, psychological trauma, abnormal oral habits (considered a proxy for emotional stress), and personal health problems are also all significantly associated with constipation (**26**). Stress-mediated effects likely act through decreased parasympathetic stimulation of the enteric nervous system, resulting in decreased motility, decreased secretions, and constipation. Many of these factors are very relevant to the pediatric patients on chemotherapy, who are at particular risk for decreased oral intake, low activity levels, severe health-related stress, and trauma from the side effects of chemotherapy.

The pathophysiology of pediatric constipation is still not completely understood, though it is certainly multifactorial. In some patients, the constipation is secondary to a known organic disorder or is medication induced. Possible organic causes include intestinal causes (Hirschprung disease, anorectal malformations, neuronal intestinal dysplasia), neuropathic conditions (spinal cord abnormalities, spinal cord trauma, neurofibromatosis, static encephalopathy, tethered cord),

metabolic/endocrine disorders (hypothyroidism, diabetes mellitus, hypercalcemia, hypokalemia, vitamin D intoxication), drug induced (opiates, drugs with anticholinergic effects, antidepressants, vinca alkaloid neuropathy), anorexia nervosa, sexual abuse, scleroderma, cystic fibrosis or a dietary protein allergy. Children on chemotherapy tend to have acute secondary or iatrogenic constipation, often with multiple possible organic causes, however >90% of children presenting with constipation have no obvious organic cause, and a diagnosis of functional constipation is made (**16**). As a result, the available and widely used Rome III and NASPGHAN definitions used to diagnose constipation were developed with functional constipation in mind, and no universally accepted criteria exist for acute secondary or iatrogenic constipation. For the purposes of this thesis, I will evaluate constipation focusing on the less restrictive NASPGHAN definition with its shorter time requirements (2 weeks), which is more applicable to acute constipation than the 2 month requirement stemming from the chronic and functional orientation of the Rome III criteria. I will also show results using the Rome III criteria, removing the 2 month requirement, side-by-side with the NASPGHAN criteria as well as other signs and symptoms suggestive of constipation.

While there are no original studies on the prevalence or treatment of constipation in the pediatric oncology population, many studies have been done regarding adults with cancer. There is much to be learned

from the adult literature which is likely applicable to the pediatric population. It is widely documented that over 50% of adult patients on chemotherapy experience constipation as a result of their treatment (**27-30**). These adverse gastrointestinal effects have been shown to be one of the most distressing symptoms that result from cancer and its treatment with regards to self-esteem, daily living, and social acceptance, emphasizing the importance of addressing this often underestimated complication (**31**). Effects of this condition are, however, more than just psychological. Constipation can cause pain, anorexia, nausea, vomiting, hemorrhoids, anal fissures and perianal abscesses (**32**). Constipation can be particularly dangerous or even fatal in this patient group if fissures or abscesses develop in a neutropenic patient, risking systemic infection. In the adult population, constipation is seen as a failure of prevention, and its continued occurrence and role in hospital admissions is seen as unacceptable. It has been suggested that cancer-related constipation does not get the attention it deserves (**27**).

In the adult population, various chemotherapy agents have already been strongly associated with constipation. Patients receiving vinca alkaloids (vincristine/vinblastine) have been shown to experience constipation at a rate of up to 35%, while for carboplatin one study demonstrated a constipation rate of 70% (**27,33**). Constipation has also been strongly linked to opiates and the antiemetic ondansetron (**34-36**).

The constipating effects of ondansetron are, in particular, most often overlooked as they are less well known to be a side effect. Furthermore, nurses may be more focused on monitoring antiemetic effects than side effects, and constipation may be seen as a worthy trade-off to relieve nausea (**27,37**).

Importantly, some of the adult literature emphasizes the importance of prophylactic treatment with laxatives before the onset of constipation. As Smith put it in the opening of his review on constipation in the oncology patient, "A need to treat constipation is often due to a failure to prevent it" (**27**). In one study which tracked ten newly-diagnosed osteosarcoma patients entering treatment, six were admitted for reasons related to constipation, and four developed systemic infections from an anal fissure or abscess (**27**). Authors have noted that intervention is often delayed until a significant problem sets in, and that this is likely due to a lack of consensus on treatment protocols (**27,38**). Significantly, protocols for prophylaxis do exist for morphine, codeine, vinca alkaloids, and ondansetron (**27**). The need for similar prophylactic protocols has been proposed for children on chemotherapy as well (**1**).

While no data exists in the pediatric oncology literature regarding constipation, many studies have been done regarding prophylaxis and treatment of nausea and vomiting for children (**2**). One such study was a double-blind, crossover, randomized study evaluating the safety and

efficacy of two doses of granisetron for the prophylactic prevention of nausea when receiving emetogenic doses of carboplatin (**39**). As Berrak notes in that study, "Without effective prophylaxis, severe and protracted nausea and vomiting may result in dehydration, electrolyte imbalance, malnutrition, aspiration pneumonia, and increased hospitalization rates (**40**). Furthermore, these symptoms may be so distressing that the patients' quality of life can be affected, leading to the discontinuation of life-saving medications (**41**). Therefore, effective and well-tolerated antiemetic therapy is vital for patients receiving intensive chemotherapy." A very similar argument could be made for constipation.

As we could find no data on constipation in children receiving chemotherapy for cancer, we designed a prospective survey study to establish the prevalence of constipation in this population. We also studied the prevalence of suspected risk factors for constipation in this group, the association of certain chemotherapy agents and drugs to constipation, and the degree to which constipation was perceived as a problem with an impact on the lives of patients and their families. We also looked at laxative use patterns and their effectiveness. The validity and clinical utility of a brief bowel habit questionnaire to detect the presence of medically significant constipation (MSC) has been established by Wald et al in 2011, with the questionnaire having a sensitivity of 59.6% (95% confidence interval [CI] of 46.7%-71.4%) and a specificity of 82.9% (95% CI

77.0%-87.1%). The questionnaire was classified as positive if a child scored 2 or higher, with 1 point each for <3 bowel movements per week, at least one stool accident in the previous two weeks, straining at stool >25% of the time, passing "very large stools" >25% of the time, avoidance >25% of the time, or discomfort with defecation >25% of the time. MSC was established prospectively with a detailed diary (**42**). It should be noted that this study was focusing on functional constipation, not acute iatrogenic constipation and thus involved frequency of symptoms. Parent-reported answers to questions in surveys to measure for the opinions of patients when they are either too young or too sick to give a self-report (**43**)

Purpose, Hypothesis, and Specific Aims

Consideration of palliative care in the treatment of cancer in children is widely recognized as an essential cornerstone of appropriate management in caring for these patients. In the pediatric literature, it is widely accepted that addressing side effects of cancer treatment is essential to maximizing acceptance of, and compliance with, life-saving treatment regimens (**39**). Severe constipation may also cause life-threatening complications which require a reduction in the intensity of anticancer treatment (**44**). Of equal importance, constipation has a large and likely underestimated effect on quality of life in children on

chemotherapy (**1,3**). Limited studies of treatment policies of oncology practices have shown that protocols for prophylaxis or standard treatment of constipation while administering chemotherapy are uncommon, while standardization is absent (**1,27**). A recent systematic review of treatments for constipation in children and young adults undergoing cancer treatment failed to find even a single study eligible for inclusion. No study to our knowledge has even attempted to quantify the problem, demonstrating a need to address this widely-known but possibly under-addressed side effect of cancer treatment. We thus designed a prospective study to establish the prevalence of constipation in the pediatric oncology population receiving chemotherapy, which may suggest a need for more aggressive and possibly prophylactic management. We also aimed to demonstrate the association of certain chemotherapy agents and drugs to constipation, and the degree to which constipation was perceived as a problem with an impact on the lives of patients and their families. While not a principle aim of this study, we also looked at laxative use patterns with a goal of characterizing their use and commenting on their effectiveness and the consistency of regimens. This would have the potential to provide the basis to suggest the need for future work to evaluate strategies for the management of constipation.

We hypothesized that the prevalence of constipation amongst children on chemotherapy would be high, and that certain pharmacologic interventions commonly used in this population (especially vinca alkaloids, narcotic analgesics, and ondansetron) would be associated with constipation. We also hypothesized that constipation would be perceived as an important problem with a significant impact on lifestyle.

The specific aims of this study were to 1) determine the prevalence of constipation in children on chemotherapy, 2) assess the association of factors such as chemotherapy type and the use of narcotic analgesics with the prevalence of constipation, and 3) assess the perceived impact of constipation on the well being and lifestyle of pediatric patients receiving chemotherapy.

Methods

Participants were recruited from sites of the Yale Pediatric Oncology Program at Yale-New Haven Hospital and Pediatric Hematology/Oncology Associates in Guilford, CT. We attempted to recruit all pediatric patients with cancer and on chemotherapy under age 21 when they presented at Yale-New Haven Hospital or the clinic in Guilford for chemotherapy infusions or office visits, and eligibility was determined by attending pediatric oncologists. Recruitment continued until an average of zero new patients were being identified per clinic day. Patients and their families were not approached on a given day if any caregiver expressed any misgivings about whether the child was well enough for the discussion to be appropriate. 62 children were approached between June 2008 and February 2009, and only one patient/family member refused participation. Approximately 75 new cases of cancer requiring chemotherapy were diagnosed each year at the time of recruitment, and we had an original goal of recruiting 75 patients, however the rate of new patient recruitment became too slow after 61 were recruited. All work regarding the gathering of data, including identifying potential participants, approaching patients and their families to explain the research and obtain consent/assent, interviewing patients/family members while administering the

questionnaire, and obtaining information from hospital/clinic charts, was performed by me.

The questionnaire was used first to collect demographic information, including name, date of birth, and medical record number to allow information to be gathered from the patient's chart. This information was later removed for data analysis. Other demographic information included age, sex, weight, height, BMI, and clinic location. Patients or their parents were asked about cancer diagnosis, date of first cancer diagnosis, relapse information, current and past chemotherapy agents, history of pain medications, history of antiemetic medications, other medications, history of abdominal radiation, surgical history, and other medical history. Patients were asked to qualify their activity level and oral intake as severely reduced, reduced, normal or high. Any history of dehydration was noted. Laxative use was explored in detail, including current laxatives with doses, previous laxative use during chemotherapy, whether laxative agents were changed and why, whether laxative use was prophylactic or as needed, and whether patients/parents thought that each laxative was effective. The patient's chart was reviewed for any additional information regarding the above parameters. Specific information regarding bowel habits was obtained, and children and parents were asked about these parameters throughout the chemotherapy period to assess for constipation. Constipation was

defined according to the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) criteria, defined as a delay or difficulty in defecation for 2 or more week and sufficient to cause significant distress to the patient (**2,45**). History-based elements of the Rome III criteria for diagnosis of functional constipation were also obtained, specifically 2 or fewer bowel movements in the toilet per week, episodes of fecal incontinence in children > 4 years of age, history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, history of large diameter stools which may obstruct the toilet, and duration of constipation (**20**). Any perceived relationship of constipation to chemotherapy or other medications were also noted. Patients/parents were also asked about formal diagnosis of constipation by a medical doctor, radiographic evidence of constipation, number of bowel movements per week, history of seeking physician care for constipation, longest period without a bowel movement after chemotherapy, and whether any constipation was worst at the beginning of chemotherapy. Patients were asked about any history of diarrhea while on chemotherapy, and whether there was any relation of diarrhea to laxative use. Any history of constipation prior to chemotherapy was noted, including any formal diagnosis by a physician, any baseline bowel movement frequency <3 per week, history of abdominal pain with bowel movements, episodes of fecal incontinence after age 4, history of

retentive posturing or excessive volitional stool retention, history of hard bowel movements, or previous laxative use. Finally, the perceived impact of constipation was noted. Children and parents were asked to qualify constipation on a scale of 0-3, with 0 indicating "not a problem," 1 a "minor problem," 2 a "significant problem," or 3 a "major problem." They were also asked to rate the impact of constipation on their lifestyle also on a scale of 0-3, with 0 being "no impact," 1 being "mild," 2 being "significant," or 3 being "severe impact."

Statistical analysis of the association of various parameters with constipation was assessed using the Fisher exact test using a 2x2 contingency table, with significance accepted at a *P* value of less than 0.05. These parameters included age group (<10 year, >10years), sex, obesity, abdominal radiation, previous history of constipation, or isolated or combined use of medications such as vincristine, methotrexate, 6-mercaptopurine, cytosine arabinoside, and opiates. Results of demographic data are presented as a mean and percent, while prevalence data is expressed as a percent ± the margin of error corresponding to a confidence interval of 95%.

This study was approved by the Human Investigation Committee of Yale University School of Medicine, HIC#0711003295. I obtained informed consent from all parents of children less than 18 years of age and all

patients 18 years of age or older, and I obtained assent from all children ages 7 to 17.

Results

We were able to recruit sixty-one children to participate in this study. Information regarding their demographic information, cancer diagnosis, chemotherapy agents received, and opiate use are included in Table 1. No children were diagnosed with a gastrointestinal tract malignancy, and two children were subjected to abdominal radiation alongside their chemotherapy. In addition to the chemotherapy agents listed, other chemotherapy agents included cyclophosphamide (n=13), doxorubicin (n=11), daunorubicin (n=6), bleomycin (n=6), etoposide (n=6), vinblastine (n=4), carboplatin (n=3), dacarbazine (n=3), temozolomide (n=2), actinomysin (n=2), gleomycin (n=2), and alpha-interferon (n=1). Besides chemotherapy, other commonly used medications included ondansetron (n=33), diphenhydramine (n=11), and acid suppression therapy (n=23) which included famotidine, ranitidine, and lansoprazole. 8 children

TABLE 1. *Demographic Data*	
Patients	61
Mean age (y)	10.6
Age range (y)	1.1 to 20.4
Age < 10y	29 (48%)
Male	34 (55%)
Obese (BMI>95th percentile)	12 (20%)
Diagnosis:	
Acute lymphoid leukemia	33 (54%)
Lymphomas	10 (16%)
Brain neoplasms	3 (5%)
Myeloid leukemia	3 (5%)
Other solid tumors	12 (20%)
Chemotherapy:	
Vincristine	47 (77%)
Methotrexate	33 (54%)
6-mercaptopurine	28 (46%)
Cytosine arabinoside	12 (20%)
Mean chemotherapy duration (mo)	13
Chemotherapy duration range (mo)	1 to 48
Intermittent opiate use:	
Any opiate	17 (28%)
Codeine	14 (23%)
Morphine	5 (8%)
Oxycodone	5 (8%)
Hydromorphone	2 (3%)

underwent surgery for tumor resection, while 2 children had a history of inguinal hernia repair.

Table 2 shows the bowel movement parameters recorded for children on chemotherapy for cancer. 35 of 61 children, or 57% ± 12% (margin of error corresponding to a 95% confidence interval [95% CI]) met NASPGHAN criteria for constipation by having delayed or difficult defecation for 2 weeks. The mean duration of constipation was 2.4 wks, with a range of 2 to 6 weeks. 35 of 61 (57% ± 12% [95% CI]) children met two or more Rome III criteria for constipation, while 29 of 61 (48% ± 13%

[95% CI]) children (or their parents) reported that they had been diagnosed by a physician with constipation. 47 of 61 children (77% ± 11% [95% CI]) demonstrated some evidence of constipation, defined by any of the Rome III or NASPGHAN criteria. 46 of 61 (75% ± 11% [95% CI]) children (or their parents) reported that they had noticed a change in bowel habits they identified as constipation in the days immediately following receiving chemotherapy. Of those who met NASPGHAN criteria for constipation, 33 patients or parents were asked if they noted the severity of constipation to be different early in the chemotherapy protocol. 27/33 (75% ± 11% [95% CI]) of these patients demonstrating constipation described the constipation as worst early in the protocol, such as during the induction phase. 15 of 61 (25% ± 11% [95% CI]) patients had at least one episode of diarrhea during chemotherapy.

Association with Risk Factors, Medications, and Chemotherapy agents:

The thirty-five children who satisfied the NASPGHAN criteria for constipation were assessed for risk factors for constipation and associations with medications and chemotherapy agents. Seven of eight children (87.5% ± 23% [95% CI]) with a history of constipation before chemotherapy developed constipation while on chemotherapy. No risk factors for constipation, including

TABLE 2. *Bowel Movement (BM) Parameters of Children on Cancer Chemotherapy*

Bowel Movement Parameters	Numbers	Percentage (±95%CI)
NASPGHAN definition of constipation:		
Delayed or difficult defecation for 2 wks	35/61	57% ± 12%
Rome III Criteria:		
Painful or hard stools	46/61	75% ± 11%
Two or fewer defecations in the toilet per week	26/61	43% ± 12%
Large diameter stools which may obstruct the toilet	19/61	31% ± 12%
Retentive posturing or excessive volitional stool retention	10/61	16% ± 9%
>1 episode of fecal incontinence (in children > 4 years of age)	4/54	7.4% ± 7.0%
Rome III definition of constipation (without 2 month duration requirement):		
2+ Rome III Criteria Met	35/61	57% ± 12%
X-Ray evidence of constipation	6/61	10% ± 7%
Physician diagnosis of constipation	29/61	48% ± 13%
Any above evidence suggestive of constipation	47/61	77% ± 11%
Association with receiving chemotherapy:		
Constipation within days after receiving chemotherapy	46/61	75% ± 11%
Constipation noted to be worst early in chemotherapy protocol*	27/33	82% ± 13%
Longest duration after chemotherapy without a BM is at least 3d	23/61	38% ± 12%
Longest duration after chemotherapy without a BM is at least 7d	7/61	8% ± 8%
Diarrhea:		
Episode of diarrhea while on chemotherapy	15/61	25% ± 11%

NASPGHAN indicates North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
**Question asked of smaller subset of 25 patients with NASPGHAN constipation*

prior history of constipation as well as age group [either less than or greater than 10 years of age], sex, obesity, and abdominal radiation, reached statistical significance for association with constipation. Amongst medications and chemotherapy agents, only combined use of vincristine and opiates was significantly associated with the development of constipation in children ($p<0.03$). Isolated and combined use of other medications, including vincristine, methotrexate, 6-mercaptopurine, cytosine arabinoside, and opiates were also assessed for relation to constipation, however no other statistically significant associations were found.

Laxative Use

Table 3 shows the characterization of laxative use by children on chemotherapy. 42 of 61 children (69% ± 12% [95%CI]) on chemotherapy used a laxative at some point during their treatment regimen, and rates of individual laxatives are shown in table 3. 17 of 61 children (28% ± 11% [95% CI]) were placed on prophylactic laxative therapy. Amongst these 42 children, there were 60 different treatment regimens, with some children changing regimens over the course of their chemotherapy. Of these 60 regimens, 53 (88% ± 8% [95% CI]) were thought by patients or their parents to be effective, while 7 of 60 (12% ± 8% [95% CI]) had to be changed as they were thought to be ineffective. While several of these ineffective regimens involved more than one agent, the involvement of the most common laxatives (polyethylene glycol [PEG] 3350, oral docusate, and senna glycosides) in these failed regimens is shown in table 3.

TABLE 3. *Laxative Use of Children on Cancer Chemotherapy*

Laxative Use	Numbers	Percentage (±95%CI)
Types of laxatives used:		
Any laxative	42/61	69% ± 12%
Docusate (oral)	18/61	30% ± 11%
Senna glycosides	11/61	18% ± 10%
Polyethylene glycol (PEG) 3350	33/61	54% ± 13%
Effectiveness and failures of laxative therapy:		
Laxative regimens thought to be ineffective*	7/60	12% ± 8%
Ineffective regimens which included docusate (oral)	4/7	57% ± 37%
Ineffective regimens which included senna glycosides	3/7	42% ± 37%
Ineffective regimens which included both docusate and senna	2/7	29% ± 33%
Ineffective regimens which included PEG 3350	1/7	14% ± 26%
Laxative users who eventually found an effective regimen	41/41	100% ± 0%
Laxative regimen tolerance:		
Docusate (oral) regimens not tolerated (all discontinued)	1/18	6% ± 11%
Senna glycosides regimens not tolerated (all discontinued)	1/11	10% ± 17%
PEG 3350 regimens not tolerated (all discontinued)	2/33	6% ± 8%

**Some patients received multiple regimens*

The one ineffective regimen which included PEG 3350 was a regimen of a standing dose of oral docusate with PEG 3350 used on an as needed basis. This was changed to a regimen of a standing dose of PEG 3350, which was effective. Other regimens were discontinued due to failure of the patient to tolerate the laxative medication, due to either taste or the size of the medication pill. These are also summarized in table 3. Notably, 8 children who used PEG 3350 as a laxative had diarrhea at some point during their chemotherapy, though in only 3 of 33 (9% ± 9% [95% CI]) PEG 3350-containing regimens was the diarrhea temporally related to taking the PEG 3350.

Impact of constipation

Fourteen of thirty-five constipated children (40% ± 16% [95% CI]) sought the care of a medical doctor explicitly for constipation as their chief complaint during their course of chemotherapy, either in the office (9) or emergency room (3), and 2 were admitted for constipation after a visit for another reason. When asked about the degree to which constipation was a problem on a 0 to 3 scale, 4 of 35 constipated children or their parents (11% ± 11% [95% CI]) stated that constipation was not a problem, 16 of 35 (46% ± 17% [95% CI]) stated that constipation was a minor problem, and 15 of 35 (43% ± 16% [95% CI]) stated that constipation was either a significant or a major problem. This is summarized in figure 1. When asked about their perception of the degree to which constipation had impacted their lives on a 0 to 3 scale, 14 of 35 constipated children or their parents (40% ± 16% [95% CI]) stated that constipation had no

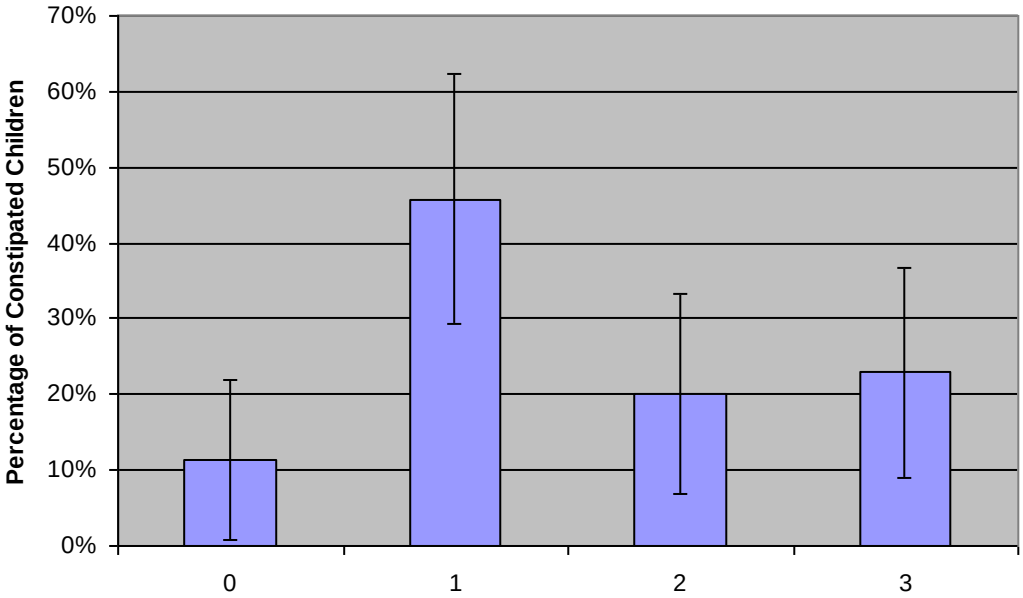

FIGURE 1. Perception of the degree to which constipation is a problem among 35 children meeting NASPGHAN criteria for constipation, on a scale of 0 to 3. (0=no problem, 1=minor, 2=significant, 3=major)

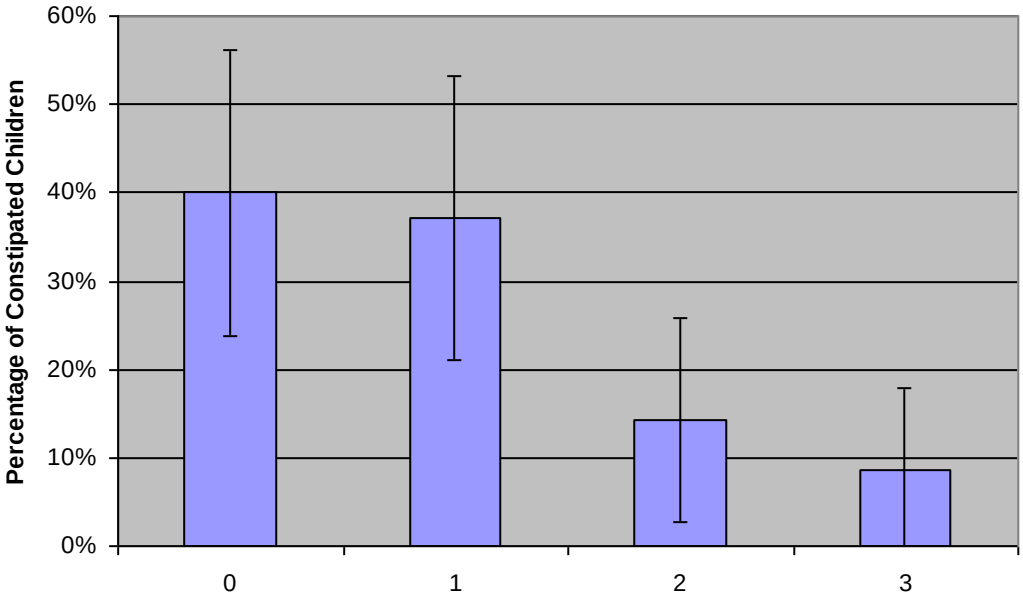

FIGURE 2. Perception of the impact of constipation on lifestyle among 35 children meeting NASPGHAN criteria for constipation, on a scale of 0 to 3. (0=no impact, 1=minor, 2=significant, 3=major impact)

Note: Error bars in all figures indicate the margin of error corresponding to a 95% confidence interval.

impact, 13 of 35 (37% ± 16% [95% CI]) stated that constipation had a minor impact, and 8 of 35 (23% ± 14% [95% CI]) stated that constipation had a significant or major impact on lifestyle. These results are summarized in figure 2.

Discussion

Of 61 children receiving chemotherapy for cancer enrolled in this study, 57% ± 12% (95% CI) were found to have experienced acute constipation, defined as delayed or difficult defecation for 2 weeks. If the 2 month time requirement of the Rome III criteria for functional constipation is set aside, the same prevalence is seen when this criteria is applied. Both of these values are significantly higher than estimations for constipation in the general pediatric population of 0.7% to 29.6%, $p<0.05$ (**16**). However, the sensitivity of both of these instruments is demonstrably low, given that 77% ± 11% (95% CI) had some signs and symptoms which are evidence of constipation including the onset of hard or painful stools, 75% ± 11% (95% CI) noted self-described constipation within days of receiving chemotherapy, and 69% ± 12% (95% CI) required the use of a laxative regimen. Defining constipation in children has been a devilishly difficult task, one which has required experts to frequently revise their widely used consensus expert opinions several times to address concerns about low sensitivity (**16,46**). The issue with regards to the pediatric

oncology population is further complicated by the fact that >90% of cases of pediatric constipation in the literature are functional in nature, with no identifiable organic cause (**16**). As functional constipation is a chronic condition, and as constipation's signs and symptoms are so nonspecific (a 2011 study showed that 20% of 10 to 16-year-olds have at least 1 clinical feature of constipation [**18**]), expert consensus opinions such as the NASPGHAN or Rome III criteria have always attached a duration requirement to a combination of signs or symptoms in order both to increase specificity at the expense of sensitivity and to ensure that any changes in defecation are prolonged enough to warrant intervention. These concerns are ill-suited to a situation of acute iatrogenic constipation, as experienced by pediatric cancer patients. As our results have shown, constipation in this population is experienced more as an acute reaction in the days immediately following receiving chemotherapy, especially during induction chemotherapy. 75% ± 11% (95% CI) of patients described a bout of constipation within days of chemotherapy, with 38% ± 12% (95% CI) going at least three days after chemotherapy infusion without a bowel movement (BM), and with 8% ± 8% going a full 7 days or longer without a BM. This level of constipation is not just very distressing to the patient but is also potentially dangerous, especially if fissures or abscesses develop in a neutropenic patient, risking systemic infection.

No adequate or universally accepted criteria exist for the diagnosis of acute constipation in the pediatric oncologic population, and we are not aware of any definitions which have even been proposed. It is clear, however, that current diagnostic algorithms are inadequate for this situation, and that this problem may be partially responsible for the lack of research into the effective management of constipation, which in turn may be contributing to undertreatment and the high prevalence of constipation in this community. Based on the consistent stories of the 75% of children and parents who noted constipation within days after receiving chemotherapy, and based on the widely accepted existing Rome III and NASPGHAN criteria, I would thus propose that constipation in children on chemotherapy be defined as a deviation from baseline bowel habits in the days immediately following chemotherapy of any of the following: a delayed bowel movement defined as failing to have a BM within 24h of expected based on baseline BM frequency; difficulty with defecation such as straining, retentive posturing or excessive volitional stool retention; a painful or hard stool; or a large diameter stool which may obstruct the toilet. As these changes come at a time when the pretest probability of constipation is very high (based on the results of this study), false positives would not be the problem that would likely be seen were these rules applied to the general population. The temporal association of these bowel changes to chemotherapy, in addition to the

associated opiate use, antiemetic use, decreased oral intake, decreased activity level, poor hydration, and new psychological effects of chemotherapy infusions; strongly suggest that any changes to bowel habits are real and related to the jarring biological and psychological insult of chemotherapy.

The lack of a good definition for constipation certainly is a key piece of why so little information is known about the pervasiveness of the problem and how it should be addressed. There are, however, other barriers as well. Some authors have suggested that uncertainty regarding diagnosis conspires with a general lack of awareness or appreciation for the importance and scope of the issue (**1,3**). Another problem is likely funding, as is evidenced by the large amount of quality information for more profitable medications for other common side effects of chemotherapy such as ondansetron and granisetron for nausea (**36,39**). As Phillips and Gibson point out in their review of constipation treatments for children receiving chemotherapy (which found no studies for inclusion), "it is difficult and expensive to set up, find sponsorship and data collection systems [sic] for a multicentre study" on therapeutic approaches to constipation for which treatments are relatively inexpensive (**3**). They recommend including palliative care questions as two study arms tied into larger therapeutic trials, and this seems like a reasonable recommendation.

The diagnoses of our patients reflected the more common pediatric cancer diagnoses, and 90% of the patients recruited for our study had diagnoses of either acute lymphoid leukemia, non-CNS solid tumors, or lymphoma. We assessed for several risk factors for constipation in our population. For example, 12% ± 20% (95% CI) of our recruited patients were obese, which was recently shown to be a risk factor for constipation in children (**47**). Obesity was not related to constipation in our study, though this study may not have been sufficiently powered to make this association should one exist. The range of patient ages recruited for our study was broad (1.1y to 20.4y), although this means that fewer patients were gathered from each age group. As 1-year-olds are certainly very different from 10-year-olds, who are in turn very different from 20-year-olds, the lower power afforded by our sample size may not have been able to resolve any differences that might be seen amongst different age groups.

This low power also restricted finding associations between constipation and certain suspect medications. While the combination of vincristine and opiates was significantly associated with an increased risk of constipation ($p<0.03$) and likely has a particularly strong association, no other medication associations reached statistical significance in this study. This included isolated and combined use of vincristine, methotrexate, 6-mercaptopurine, cytosine arabinoside, and opiates. Vincristine affects

the gut through the induction of gastrointestinal neuropathy, which slows gastrointestinal motility. Opiates have a similar effect by inhibiting mu receptors in the gastrointestinal nervous system, which inhibits peristalsis and also slows motility, and so the two medications may have a synergistic effect. When a child is receiving both opiates and vincristine, providers must be especially vigilant for (or prophylax for) constipation.

The importance of addressing constipation is readily apparent in the data from this study. While only 11% ± 11% (95% CI) of children with constipation by NASPGHAN criteria said that constipation was not a problem, 43% ± 16% (95% CI) identified it as a significant or major problem. This was in families dealing with the huge distracting problem of a life-threatening cancer diagnosis in a child and all of the side effects of chemotherapy that entails. That constipation was such a large problem to this group of people is very telling. Indeed, in children functional constipation has been shown to negatively affect quality-of-life scores more than inflammatory bowel disease (**48**). 23% ± 11% (95% CI) also reported that constipation had either a significant or major effect on their lifestyle. Beyond the patient experience, if a neutropenic child develops acute abdominal pain and abdominal distention from constipation, this can easily be confused with the presentation of neutropenic enterocolitis (**2**). If constipation causes an anal fissure or abscess in a neutropenic patient, this can lead to systemic infection and even death. Constipation

also was shown to contribute to healthcare costs in this group, with 14 children seeking a physician's care specifically for constipation, including 9 in an outpatient setting, 3 in the emergency department, and 2 admitted to the inpatient wards.

The adult literature treats constipation in patients on chemotherapy as a failure of prevention, and this may be a useful paradigm in the pediatric population as well (**27**). Of note, every child we recruited who required the use of a laxative was able to find a regimen which was effective. While our study was not designed or powered to evaluate or compare laxative regimens and is inadequate to reach definitive conclusions regarding therapy recommendations, interesting observations can be made. Firstly, a wide range of management strategies, laxative agents, and dosages was used, demonstrating high variability in approaches to constipation. This highlights the need to standardize treatments, both so that comparative studies can be carried out and because some physicians' "strongly-held, beliefs driven and self-introduced management strategies … [are] sometimes even harmful to children" (**46**). 60 individual laxative regimens were used in 42 of 61 (69% ± 12% [95% CI]) children (some children used different successive regimens), with PEG 3350 being the most common component (54% ± 13% [95% CI]) followed by oral docusate (30% ± 11% [95% CI]) and senna glycosides (18% ± 10% [95% CI]). Of these regimens, 4 were not tolerated due to

taste or the size of the pills involved (two PEG 3350 regimens due to taste, one oral docusate regimen due to pill size and one senna glycosides regimen for an unknown reason). 7 regimens were discontinued as they were ineffective at controlling constipation. Interestingly, while four of these regimens included oral docusate and three involved senna glycosides (all of which were changed to PEG 3350 which was subsequently effective), the only PEG 3350-containing regimen which was ineffective was a regimen consisting of a standing dose of oral docusate with PEG 3350 taken as needed. This regimen was switched to daily PEG 3350, which was effective, and thus there were actually no treatment failures beyond intolerance to taste in 2 of 33 cases (6% ± 8% [95% CI]) observed with PEG 3350. PEG 3350 may therefore be a promising candidate for prophylactic treatments or standardized regimens. Based on current guidelines for the treatment of functional constipation in children, I would recommend either prophylactic PEG 3350 0.26-0.84g/kg/day starting the day of chemotherapy or a stepwise protocol of daily dose increases starting from 0.26-0.84g/kg/day (maintenance dose) increasing to 1-1.5 g/kg/day (disimpaction dose) for a missed bowel movement after chemotherapy (**46**).

There are several important limitations to this study. In addition to the low power afforded by the relatively low sample size we were practically able to recruit, this survey study is susceptible to recall bias,

where knowing the study is about constipation on chemotherapy may lead to either an increase or decrease in the observed prevalence of constipation if false associations of constipation memories with chemotherapy are made or if patients have forgotten episodes of constipation. Response bias, where patients deliberately conceal episodes of constipation for reasons of embarrassment or invent episodes to please the interviewer, is also a possibility which would increase or decrease the observed rates of constipation, respectively. Furthermore, the temporal associations between episodes of chemotherapy and constipation may be the result of physicians' warnings of the side effects of treatment. Regarding self-reported perceptions of the degree to which constipation was a problem or impacted one's lifestyle, it is possible that children and parents associated the stress and side effects of chemotherapy with any episodes of constipation, inflating the impact attributed to constipation (**2**).

In conclusion, the study's principle goal was achieved, supporting the hypothesis that the prevalence in constipation in children receiving chemotherapy was high, observed at 57% ± 12% (95% CI) using the NASPGHAN criteria for constipation, though the actual prevalence may be higher. This prevalence is certainly higher than previous estimates for the general pediatric population. Constipation is significantly associated with the combination of vincristine and opiates ($p<0.03$), even in this study

of limited power. Furthermore, this constipation is seen as either a significant or major problem in 43% ± 16% of cases, with a significant or major impact on lifestyle in 23% ± 14% of cases. It is a side effect which requires greater attention, standardization of treatment, and further research into comparative laxative effectiveness in order to address this important condition.

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