Original Article

Treatment failure in children diagnosed with constipation in a paediatric emergency department in relation to Rome III criteria

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Abstract

Objective: To determine if treatment failure varies based on ROME III classification and adherence to guideline congruent therapy among children diagnosed in an emergency department with functional constipation.

Methods: Children aged 1 month to 18 years who were diagnosed with constipation in a paediatric emergency department underwent chart review and 7-day phone follow-up to complete the ROME III questionnaire, confirm treatments administered, and assess treatment failure. Participants were classified according to the ROME III criteria as having functional constipation (FC) or irritable bowel syndrome – constipation (IBS-C) subtype. The primary outcome was treatment failure defined as ≥ 2 of the following: 1) presenting symptom persistence; 2) < 1 bowel movement every other day; 3) pain/difficulty passing stools; and 4) abdominal pain between bowel movements.

Results: Five hundred and thirteen children completed follow-up; 40% (204/513) had FC, 23% (118/513) IBS-C, and 37% (191/513) did not meet either criteria. Treatment failure rates in children who received guideline congruent treatment were 28% (38/135) among those classified as FC and 43% (37/86) among those with IBS-C; $P=0.02$, a difference of 15% (95% confidence interval [CI]: 0.02, 0.27). On regression analysis, ROME III classification was not an independent predictor of treatment failure (odds ratio [OR]: 1.56 [95% CI: 0.97, 2.51]). At 7-day follow up, pain in between bowel movements was present in 22% (44/204) in FC patients versus 45% (53/118) of IBS-C patients; $P=0.001$.

Conclusions: Treatment failure rates in children who receive guideline congruent therapy are higher among those with IBS-C, however, after adjustment for known confounders the relationship was not statistically significant.

Keywords: Abdominal pain; Constipation; Irritable bowel syndrome; Laxatives; Polyethylene glycols.

A diagnosis of functional constipation (FC) is assigned in up to 20% of all paediatric acute abdominal pain emergency department (ED) visits (1). While the Rome Diagnostic Criteria for

Functional Gastrointestinal Disorders (2) represent the gold standard approach employed by gastroenterologists (3), they are not routinely employed by ED physicians and are not even

referred to in leading paediatric emergency medicine textbooks (4).

The Rome III diagnostic criteria were created by the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN/ESPGHAN; see figure supplemental digital content 1) (5). The criteria highlight the distinction between FC (6) and irritable bowel syndrome with constipation (IBS-C). While abdominal pain in between bowel movements is a cardinal feature of IBS-C, it is not a FC criterion. The ROME IV diagnostic criteria, published after study initiation, include guidance that enhances the accuracy of diagnosing IBS (7).

Not surprisingly, outcomes relate to diagnostic accuracy (8). Given the overlap between FC and IBS-C, we employed the Rome III Diagnostic Criteria to reclassify children diagnosed clinically by a paediatric ED physician with constipation as FC or IBS-C. We sought to determine if treatment failure frequency differs according to 1) Rome III classification and 2) administration of guideline congruent therapy. We hypothesized that children who fulfill Rome III FC criteria have a 20% lower treatment failure rate when administered guideline congruent therapy compared to children with IBS-C.

METHODS

Study design and setting

We conducted a retrospective review, with 7-day post-visit follow-up, of a consecutive cohort of children who presented for care to the ED of the Alberta Children's Hospital (Calgary, Alberta). The hospital is a tertiary care paediatric centre with 80,000 annual visits. Ethical approval was provided by the University of Calgary's Conjoint Health Research Ethics Board. Informed consent was obtained from caregivers; assent was obtained when appropriate.

Participants

Eligible children were 1.0 months to 18.0 years of age, had a primary discharge diagnosis of constipation, irritable bowel syndrome without diarrhea, acute anal fissure, lower abdominal pain unspecified, or generalized abdominal pain and the child received discharge therapy consistent with constipation. The latter was defined by administration of an oral laxative (i.e., PEG-3350, lactulose, mineral oil, senna, milk of magnesia, bisacodyl), enema, or suppository (i.e., glycerin).

Children with an underlying organic etiology identified were excluded (e.g., Hirschsprung's disease, hypothyroidism, developmental delay, neurological or neuromuscular disorders, recent exposure to medications known to cause constipation or other significant gastrointestinal diseases, e.g., prior abdominal surgery, inflammatory bowel disease). Additional exclusion criteria included an insurmountable language barrier,

hospitalization at the index visit, prior enrolment in the study, or inability to complete follow-up (e.g., lack telephone access).

Screening was performed through a daily review of the ED's primary discharge diagnosis list. Potentially eligible children underwent chart review to assess eligibility. Confirmed eligible children subsequently underwent a full chart review. Presenting symptoms and duration, physical examination findings, ED treatments, investigations, and disposition medications were collected using a standardized form and entered in a secure database. A follow-up phone call was performed by trained research assistants 7 days after the ED visit to obtain consent and administer the Rome III questionnaire focused on FC and IBS-C diagnoses (9). Additional data collected included pre-ED visit treatment, ED treatments, discharge medications, other treatments administered at home postdischarge, symptom resolution, daycare and work absenteeism, health care visits, and alternative diagnoses. Caregivers who completed follow-up received a \$5 gift card.

For presenting symptoms and diagnostic testing that were documented on the chart, the absence of a specific description was interpreted as 'not present' or 'not performed' (10). When multiple documentation sources were present, that of the most senior physician was used. If physician documentation was unavailable, nursing documentation was reviewed. Historical variables were documented prior to reviewing the outcome, investigations, and laboratory results.

Definitions

The Rome III phone questionnaire was employed to assign a diagnosis of FC or IBS-C to each ED encounter in accordance with the Rome III diagnostic criteria. There was no formal education performed regarding the Rome III diagnostic criteria. Based on data collected on the follow-up survey (Rome III questionnaire), some children did not meet IBS-C or FC diagnostic criteria; these children were classified as 'other'. Guideline congruent therapy was assessed according to the NASPGHN/ESPGHAN position statement (5) – children with acute FC require high dose PEG (i.e., 1.0–1.5 gm/kg/day). An acceptable alternative is enema administration followed by PEG at dose 0.4 gm/kg/day. These doses are consistent with the Canadian Paediatric Society guidelines for treatment for FC (11). Due to the difficulty of classifying FC as acute versus chronic based on chart review and parental report in the absence of documented fecal impaction (10) children were deemed to have received guideline congruent therapy if a PEG dose of 0.4 gm/kg/day or higher was provided, regardless of enema administration. We employed the same therapeutic criteria for children with IBS-C because at the time of study design, there were no guidelines on the treatment of children with IBS-C. Moreover, the Rome IV criteria recommend that children with IBS-C initially receive treatment as per FC guidelines (12), i.e., targeting their constipation symptoms (13).

Outcome measures

Since there are no validated outcome scales for FC or IBS-C (14), the primary outcome was treatment failure defined based on the available ED literature, as the presence of ≥ 2 of the following features 7-day postindex ED visit: 1) overall parent or child report of persistence of presenting symptoms; 2) bowel movement frequency less than one every other day; 3) presence of pain or difficulty passing stools; and/or 4) presence of abdominal pain in between bowel movements (15,16). The primary outcome was stratified based on guideline congruent therapy status.

Secondary outcomes included treatment failure based on 1) age; < 4 years versus ≥ 4 years 2) provision of guideline congruent therapy (yes/no). The age-based analysis was performed given the distinct FC diagnostic age-based criteria. Other outcomes included 3) individual treatment failure features; 4) days to symptom improvement; and 5) future health care utilization and daycare/school absenteeism.

Sample size and statistical analysis

We estimated that 25% of children administered guideline congruent treatment would meet study defined treatment failures (15,16). We a priori determined that an absolute 20% higher failure rate among those classified as having IBS-C would be clinically significant. Thus, 98 participants were required in each group to yield 80% power employing an α of 0.05. Sample size calculations were performed employing PASS 14 Power Analysis and Sample Size Software (NCSS, LLC. Kaysville, UT, USA).

Dichotomous variables were expressed as percentages with 95% confidence intervals; continuous variables as means with standard deviations, or medians with inter-quartiles ranges as appropriate. For the primary outcome, chi-square tests were used to compare the proportions between those classified according to the ROME III criteria as having FC and IBS-C. For the secondary outcomes of treatment failure based on age, provision of guideline congruent therapy, individual features of treatment failure, and future health care utilization and daycare absenteeism, chi-square tests were used; when analyses included cell counts < 10 , Fisher's exact test was used. A time to event analysis, employing symptom resolution as the event of interest, was conducted by means of the Kaplan–Meier method. A Bonferroni correction was employed to account for multiple (5) secondary analyses thereby setting the P value of significance at 0.01. Data were analyzed using SPSS 23.0 (SPSS Inc., Chicago, IL). Further multiple logistic regression analysis was conducted with the outcome of treatment failure as the dependent variable and Rome III classification as the independent variable. Variables considered for inclusion in the model were identified based on clinical plausibility and prior work and included education in the ED, PEG dose administered at home,

ED enema administration, gender, age, and physical examination findings (tenderness, distension, palpable stool).

RESULTS

Study participants

During the study period of June 2014 to August 2015, 929 ED visits were screened for eligibility; 85% (795/929) met study inclusion criteria; Figure 1; an additional 9% (83/929) were ineligible. Thus, 712 charts had data abstracted and 513 caregivers participated in the 7-day follow-up calls (72%). The most common ED discharge diagnosis was constipation (67%; 217/322) followed by abdominal pain with possible constipation (30%; 97/322); no participants had a diagnosis of IBS-C assigned.

Forty per cent (204/513) of participants were classified as FC, 23% (118/513) as IBS-C, and 37% (191/513) as 'other'; Table 1. Groups differed as it relates to mean age in years (5.6 ± 3.6 versus 6.5 ± 3.5 ; $P=0.04$); abdominal pain (66% versus 78%; $P=0.03$); frequency of symptoms ≥ 1 /week (55% versus 67%; $P=0.04$) when comparing FC versus IBS-C, respectively. On physical examination, abdominal tenderness was present in 23% of children with FC compared to 12% among those with IBS-C; $P=0.03$.

Symptoms supportive of IBS-C diagnosis but not included in IBS-C ROME III diagnostic criteria were all more frequent in the IBS-C compared to the FC group of children (Table 1). In patients with IBS-C, 37% had bowel movement urgency; tenesmus occurred in 57% and 11% passed phlegm/mucous. Testing was similar between groups (Table 2). Urine analysis was the most commonly performed test (25%) followed by abdominal radiographs (18%) and blood work (7%). Overall, 26% of patients received enemas with no significant difference between groups ($P=0.89$). The most commonly prescribed laxative was PEG-3350 (Table 2). Groups received similar doses of PEG-3350 (mean = 0.9 g/kg; $P=0.38$).

Primary outcome

Among the children who received guideline congruent therapy the overall failure rate was 34% (75/221; 95% confidence interval [CI]: 0.28, 0.40). Higher treatment failure rates were seen in IBS-C 43% (37/86) versus 28% (38/135) in the FC group; $P=0.02$; 95% CI of the difference: 15% (95% CI: 2%, 27%). Including those who did not receive guideline congruent therapy, treatment failure occurred in 35% (113/322; 95% CI: 0.30, 0.40) of all study participants including 42% (49/118) in the IBS-C group and 31% (64/204) in the FC group; $P=0.07$.

Secondary outcomes

The overall treatment failure rate among children ≥ 4 years of age was 36% (75/211) (Table 2). This was similar to the

Figure 1. Study flow chart of potentially eligible participants.

failure rate in children < 4 years of age (38/111; 34%); $P=0.82$. Similarly, the treatment failure rate did not vary based on administration of guideline congruent therapy in this group of children (34% [47/138] yes versus 38% [28/73] no; $P=0.53$). Of the 204 children with FC, there was no difference in treatment failure rates if they were <4 (24/77; 31%) or ≥ 4 years in age (40/127; 32%); $P=0.96$.

On day 7, the symptoms reported as persisting differed between groups with 45% (53/118) of those classified as having IBS-C reporting ongoing abdominal pain in between bowel movements compared to 22% (44/204) of those classified as FC; $P=0.001$. The overall mean time to symptom improvement was 3.5 ± 2.2 days; this was longer in children classified as having IBS-C (4.0 ± 2.3 days) compared to those classified as FC (3.2 ± 2.1 days); $P=0.006$ (Figure 2).

Overall, 17% (42/322) of study participants had a subsequent health care provider visit within 7 days of the index ED visit and 3% (10/322) had an ED revisit (Table 3). Prior to ED presentation, children classified as having IBS-C were more likely to

have missed school days/daycare (41%; 48/118) compared to children with FC (22%; 45/204); $P=0.001$. Daycare and school absenteeism in the week following the ED visit were similar between groups ($P=0.07$). In the multiple regression model, none of the included variables were significantly associated with the outcome of treatment failure. Classification according to Rome III criteria had an odds ratio of 1.56 (95% CI: 0.97, 2.51).

DISCUSSION

In our cohort of 512 children, only 40% met Rome III diagnostic criteria for FC while 23% had IBS-C and 37% met neither of these definitions. Children with a Rome III diagnosis of IBS-C had higher treatment failure rates when compared to children with FC (43% versus 28%) when using guideline congruent therapy targeting constipation symptoms. However, in regression analysis, after adjustment for known confounders, Rome III classification was not independently associated with treatment failure (odds ratio [OR]: 1.56 [95% CI: 0.97, 2.51]).

Table 1. Baseline clinical characteristics abstracted from chart

Characteristic	Overall Cohort N=322	Functional Constipation N=204	Irritable Bowel Syndrome N=118	P value
Weight – mean, kg (SD)	23.8 (13.3)	22.7 (13.5)	25.6 (12.8)	0.07
Female Gender – No. %	262 (51)	102 (50)	69 (59)	0.09
Age – mean, year (SD)	5.9 (3.6)	5.6 (3.6)	6.5 (3.5)	0.04
Historical findings documented in chart				
Lumpy or hard stools – No. %	188 (58)	125 (61)	63 (53)	0.20
Bulky stools – No. %	39 (12)	26 (13)	13 (11)	0.80
Straining/pain with defecation – No. %	153 (48)	97 (48)	56 (48)	0.99
Abdominal pain or discomfort – No. %	227 (71)	135 (66)	92 (78)	0.03
Bowel movement frequency $\leq$ 2/week	82 (26)	54 (26)	28 (23)	0.59
Decreased intake – No. %	94 (29)	54 (26)	40 (34)	0.16
Fever – No. %	30 (9)	16 (8)	14 (12)	0.23
Blood streaked tinged stools – No. %	42 (13)	29 (12)	17 (14)	0.58
Vomiting – No. %	54 (22)	36 (23)	18 (15)	0.65
Encopresis – No. %	16 (5)	13 (6)	3 (3)	0.13
Duration of Symptoms- Days (Median IQR [‡] : 25,75)	7 (2,24)	5 (2,14)	7 (3,60)	<0.001
Frequency of Symptoms ($\geq$ 1/week) – No. %	192 (60)	113 (55)	79 (67)	0.04
Physical findings documented in chart				
Abdominal distension – No. %	48 (15)	35 (17)	13 (11)	0.14
Abdominal tenderness – No. %	54 (19)	42 (23)	12 (12)	0.03
Abdominal Palpable stool – No. %	88 (27)	61 (30)	27 (23)	0.17
Rectal exam fecal Impaction – No. %	12 (4)	9 (4)	3 (3)	0.39
Anal/perianal Fissure – No. %	28 (9)	20 (10)	8 (7)	0.35
Symptoms Supportive Of IBS-C*				
Bowel Movement Urgency	76 (24)	32 (16)	44 (37)	<0.001
Passing mucous/phlegm	19 (6)	6 (3)	13 (11)	0.003
Tenesmus	120 (37)	53 (26)	67 (57)	<0.001
Emergency Department Discharge Diagnosis				
Constipation	217 (67)	144 (71)	73 (62)	0.07
Abdominal pain/possible constipation	97 (30)	56 (28)	41 (35)	0.11
Anal fissure	8 (3)	4 (2)	4 (3)	0.32

*Part of the questionnaire administered on day 7, those symptoms are not part of the ROME III IBS-C diagnosis however their presence is supportive of IBS-C diagnosis.

[‡]Interquartile ranges, 25th and 75th percentiles.

In our study, 69% of patients had abdominal pain at presentation. Although there was an association between ROME III diagnosis of IBS-C and treatment failure in bivariate analysis, it was not statistically significant in the regression model. The frequency of abdominal pain we report is in keeping with prior ED reports (15,17). However, our study is the first that classifies children evaluated in an ED according to the Rome III criteria. This approach revealed novel findings—only 40% of children met FC diagnostic criteria while 23% had IBS-C. In addition, children with IBS-C were twice as likely to report persistent abdominal pain compared to children classified as FC (45% versus 22%). Although supportive features of IBS-C were

not included in our classification algorithm, they all were significantly more common in children classified as having IBS-C, a finding that strengthens our approach to patient classification. The ROME IV IBS-C criteria (18) now additionally require the persistence of abdominal pain despite the administration of laxative therapy. Applying these criteria to our study cohort reduces the proportion of children meeting IBS-C diagnostic criteria to 15% (49/322).

Given the high failure rate of PEG-3350 therapy in adult patients with IBS-C, it is crucial that alternative therapeutic options be considered in children with IBS-C (8). Although limited evidence is available for the paediatric population,

Table 2. Ancillary testing, treatments and referral/follow-up given

Characteristic	Overall Cohort N=322	Functional Constipation N=204	Irritable Bowel Syndrome-Constipation Subtype N=118	P value*
Ancillary Testing				
Blood work	23 (7)	13 (6)	10 (9)	0.49
Urine	76 (24)	51 (25)	25 (21)	0.42
Abdominal x-ray	54 (17)	36 (18)	18 (15)	0.58
Prescribed laxatives in the ED				
Enema – No. %	83 (26)	53 (26)	30 (25)	0.89
Overall oral laxative use – No. %	274 (85)	174 (86)	100 (85)	0.99
PEG-3350 – No. %	262 (81)	166 (81)	96 (81)	0.99
Lactulose – No. %	8 (3)	6 (3)	2 (2)	0.50
PEG-3350 Dose [‡] g/kg (SD)	0.8 (0.5)	0.9 (0.6)	0.8 (0.5)	0.38
PEG-3350 (minimum 0.4 g/kg)	221 (69)	135 (66)	86 (73)	0.21
Counselling and Education given in the ED				
Dietary modification	221 (69)	138 (68)	83 (70)	0.87
Parent Behaviour modification	45 (14)	29 (14)	16 (14)	0.51
ED education/educational material	119 (37)	74 (36)	45 (38)	0.74
Referral/Follow-up				
Referral indicated in chart	41 (13)	20 (10)	21 (18)	0.04
Follow up documented in the chart	147 (46)	95 (47)	52 (44)	0.66

ED Emergency department.

*Comparing those with FC. versus IBS-C.

[‡]PEG dose: Whenever possible, parent report was used to calculate dose/kg. If not available, chart documentation was used. If dose unknown they were not considered to be adequately treated.

Figure 2. Reverse Kaplan–Meier score for persistence of symptoms to day 7. Log Rank test $P=0.002$. FC Functional constipation; IBS Irritable Bowel syndrome-constipation subtype.

therapies can include dietary modification (addition of soluble fibres or eliminating fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) (19) and cognitive

behavioural therapy. Pharmacologics (e.g., antidepressants, prosecretory agents) are reserved for severe cases (19,20). While these complex therapeutic approaches are unlikely to be performed by most ED physicians (21), accurately differentiating FC from IBS-C might help prognosticate response to therapy, enable the provision of more disease-specific anticipatory guidance and early referral for appropriate follow-up.

We had several limitations to our study. Patients were identified retrospectively through chart review and ROME III questionnaire, treatment, and outcome data were gathered 7 days after the visit, which can introduce selection, recall, and treatment bias. There is no validated outcome scale available for use so we adopted a scale previously used in similar settings (15,16). Additionally, our data collection tools focused on classifying children as having IBS-C or FC, consequently 191 children were classified as ‘other’ primarily due to the brief symptom interval in this group of children, which often did not achieve the two months duration required to assign a diagnosis of IBS-C or FC. In our study, it was difficult to differentiate between acute impaction and chronic constipation, which can require alternative treatment modalities. However, it is challenging to differentiate these two entities without performing a digital rectal examination, which is unwarranted in most cases. We only followed patients up to 7 days postindex ED visit and

Table 3. Outcomes according to Rome III criteria classification

Characteristic	Overall Cohort N=322	Functional Constipation N=204	Irritable Bowel Syndrome-Constipation Subtype N=118	P value
Primary Outcome:				
Overall treatment failure	113 (35)	64 (31)	49 (42)	0.07
Treatment failure in children treated with guideline congruent therapy n=221	75 (34)	38 (28)	37 (43)	0.02
Secondary Outcomes:				
In children ≥ 4 years in age				
Overall treatment failure n=211	75 (36)	40 (32)	35 (42)	0.13
Treatment failure in children treated with guideline congruent therapy n=138	47 (34)	22 (28)	25 (42)	0.07
In children < 4 years in age				
Overall treatment failure n=111	38 (34)	24 (31)	14 (41)	0.31
Treatment failure in children treated with guideline congruent therapy n=83	28 (34)	16 (29)	12 (44)	0.15
Persistent Symptoms Breakdown				
Same symptoms as when brought in	109 (34)	67 (33)	42 (36)	0.62
Less than 1 BM every other day	86 (27)	51 (25)	35 (30)	0.36
Pain/difficulty passing stools	84 (26)	46 (23)	38 (32)	0.06
Any abdominal pain in between BM	97 (30)	44 (22)	53 (45)	<0.001
Any symptom improvement	269 (84)	175 (86)	94 (80)	0.15
Return Visits				
To any health care provider	42 (17)	25 (12)	17 (14)	0.58
ED revisits	10 (3)	6 (3)	4 (3)	0.82
Daycare and Work Absenteeism				
Missed school/daycare	93 (29)	45 (22)	48 (41)	<0.001
Missed school/daycare last 7 days	60 (19)	32 (16)	28 (24)	0.07
Missed work	62 (19)	35 (17)	27 (23)	0.21

Total number of children ≥ 4 or < 4 years in age who received guideline congruent therapy.

BM Bowel movement; ED Emergency department.

the outcomes could have changed if longer follow-up data was available.

CONCLUSION

Many children diagnosed with FC in an ED meet IBS-C criteria. ROME III classification of IBS-C is associated with higher treatment failure rates regardless of treatment adequacy or age compared to those with FC. However, after adjustment for other known confounders, this association was not statistically significant. Further prospective studies need to clarify association of ROME classification, therapeutic interventions, and outcomes.

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