

Central Lancashire Online Knowledge (CLoK)

Title	How do we define therapy-resistant Constipation in Children 4-18 years old? A systematic review with meta-narrative synthesis Data extraction
Type	Article
URL	https://clock.uclan.ac.uk/51293/
DOI	##doi##
Date	2024
Citation	Sinopoulou, Vassiliki orcid iconORCID: 0000-0002-2831-9406, Gordon, Morris orcid iconORCID: 0000-0002-1216-5158, Rajindrajith, Shaman, Hathagoda, Wathsala, Rane, Aditi, Sedghi, Anita, Tabbers, Merit, di Lorenzo, Carlo, Saps, Miguel et al (2024) How do we define therapy-resistant Constipation in Children 4-18 years old? A systematic review with meta-narrative synthesis Data extraction. <i>BMJ Paediatrics Open</i> .
Creators	Sinopoulou, Vassiliki, Gordon, Morris, Rajindrajith, Shaman, Hathagoda, Wathsala, Rane, Aditi, Sedghi, Anita, Tabbers, Merit, di Lorenzo, Carlo, Saps, Miguel and Benninga, Marc

It is advisable to refer to the publisher's version if you intend to cite from the work. ##doi##

For information about Research at UCLan please go to <http://www.uclan.ac.uk/research/>

All outputs in CLoK are protected by Intellectual Property Rights law, including Copyright law. Copyright, IPR and Moral Rights for the works on this site are retained by the individual authors and/or other copyright owners. Terms and conditions for use of this material are defined in the <http://clock.uclan.ac.uk/policies/>

How do we define therapy-resistant Constipation in Children 4-18 years old? A systematic review with meta-narrative synthesis

Vassiliki Sinopoulou, Morris Gordon, Shaman Rajindrajith, Wathsala Hathagoda, Aditi Bhupendra Rane, Anita Sedghi, Merit Tabbers, Carlo di Lorenzo, Miguel Saps, Marc Benninga

Abstract

Background

Therapy resistant constipation often is a frustrating clinical entity recognised by the persistence of infrequent and painful bowel movements fecal incontinence and abdominal pain despite intensive treatment. It is important to clearly define therapy resistant constipation before children are subjected to invasive diagnostic and therapeutic procedures.

Aim

To conduct a systematic review determining how pediatric interventional studies define therapy resistant constipation.

Method

We searched CENTRAL, MEDLINE, Embase, WHO ICTR and ClinicalTrials.gov. Studies that included patients with therapy resistant constipation were identified. Data were extracted on criteria used for defining therapy resistant constipation and reported using meta-narrative approach highlighting areas of convergence and divergence in the findings.

Results

A total of 1553 abstracts were screened in duplicate, and 47 studies were included in the review. There were at least 7 definitions used in the paediatric literature to define medically resistant constipation. The term intractable was used in 24 articles and 21 used the term refractory to describe therapy resistant constipation. Out of them only 14 articles have attempted to provide an explicit definition including a predefined time and prior therapy. There were 10 studies without a clear definition for therapy resistant constipation. The duration before being diagnosed as therapy resistant constipation varied from 1 months to 2 years among studies. Seven studies employed the Rome criteria (Rome III or Rome IV) to characterising constipation, while 5 adopted the Rome III and European and North American paediatric societies definition of paediatric gastroenterology, hepatology and nutrition guideline of management of constipation in children.

Conclusion

The current literature has no explicit definition for therapy resistant constipation in children. There is a need for a detailed consensus definition to ensure consistency of future research and to avoid unnecessary, and maybe even harmful, invasive diagnostic and therapeutic interventions.

Key messages

- What is already known on this topic: Childhood therapy-resistant constipation is a common and painful condition, often managed with invasive therapies. However, a consensus definition and diagnosis does not exist.
- What this study adds: The existing literature for interventions on therapy-resistant constipation often does not define it. When it does there is inconsistency around duration of symptoms and previous therapy failure.
- How this study might affect research, practice or policy: This review can lead to a consensus definition and diagnostic criteria for therapy-resistant constipation. In turn, this will aid appropriate management and consistency in future research.

Introduction:

Functional constipation is a common gastrointestinal disorder that affects children globally. Based on the available data, it has a pooled prevalence of 9.5%.^[1] Constipation is a frequent cause of emergency department visits.^[2] It can result in substantial use of clinical resources in outpatient departments, particularly among children.^[3] Additionally, constipation can significantly impact public funds through annual health budgets, directly and indirectly.^[4]

Several guidelines describe the management of childhood constipation.^[5-7] Even with optimal management, about 1/3 of children are deemed to have therapy resistant constipation.^[8] Although childhood functional constipation is clearly defined using the Rome criteria, there is no such definition for children not responding to optimal management.^[9] Several authors have defined therapy resistant constipation using the duration of unresponsiveness to medical management varying from 3 months to 2 years without clear consensus.^[5, 10] In addition, clinicians and researchers use the terms “refractory” and “intractable” interchangeably, complicating the definition of therapy resistant constipation.

Therapy resistant constipation has long-term physical and psychological complications.^[11-13] In addition, some children with therapy resistant constipation undergo invasive diagnostic tests such as barium enema, defecography, anorectal and/or colorectal manometry. The majority of these children need (a combination of) oral laxatives, enemas or transanal irrigation. A smaller proportion requires even needs surgical interventions, such as sacral neuromodulation, antegrade continence enema, the formation of diversion stomas and surgical resection of the bowel, or subtotal colectomy, with ileorectal anastomosis, all interventions which have significant morbidity and a high incidence of complications.^[14] Therefore, it is imperative to clearly define therapy resistant constipation to ensure consistent deployment of therapies to this group and consistent understanding of goals and

outcomes of therapies in these circumstances. Against this backdrop, we aimed to conduct a systematic review to determine how interventional studies define the condition and propose a way forward for an internationally accepted definition.

Methods:

A plan for this systematic review was prospectively registered in PROSPERO (CRD42022371846)

Literature search

A literature search was conducted using CENTRAL, MEDLINE, Embase, WHO ICTR and ClinicalTrials.gov and searched for studies meeting the inclusion criteria. Our search strategy was: **“(Intractable OR Refractory OR Non-respons*) AND constipation* AND child*)”**. The age limit was set from 2 to 18 years, and the search was performed in November 2022.

The included studies reference of all Cochrane systematic reviews for constipation in childhood were also hand-searched. The details of the search strategy are given in **Appendix 01**. We followed the preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA 2020 checklist.

Inclusion and exclusion criteria

Inclusion Criteria:

All published papers from January 1995 to October 2022, on intractable/ refractory constipation, in correspondence with the release of the CONSORT statement to the current date, were included.

Type of participants: Patients with therapy resistant constipation, between 4-18 years of age

Types of interventions: Studies that included and compared any form of intervention and dosage of drugs or no intervention

Types of outcomes: Any outcome measures

Exclusion Criteria:

Studies on adults and children younger than four years, non-intractable/ refractory constipation, articles written in non-English languages, opinion pieces, commentaries, editorials, secondary evidence and review articles, and non-interventional works.

Data collection and analysis:Title/abstract and full-text screening

All potential studies were reviewed independently by two authors (AR and WH) for title/abstract screening, followed by full-text screening (AR, WH and AS). Any conflicts were resolved by a fourth author (MG, VS).

Data extraction

All included studies underwent data extraction independently by three authors (AR, WH and AS), and disagreements were resolved by a fourth author (MG, VS).

Data were extracted based on the following headings:

- Definitions for therapy resistant constipation (or descriptions that can be characterised as definitions)
- Reference for the definition (if given)
- Classification of definition as explicit or implicit
- Inclusion criteria for each study
- Exclusion criteria for each study
- Type of study (Randomised clinical trial, non-randomised clinical trial, cross-sectional etc.)
- Age of included children
- Country(ies) of study origin.

All the included studies' characteristics were manually collected and recorded within a database file.

Definition of refractory/intractable constipation

We classified studies based on the type of definition: explicit or implicit. Then identified the most common themes within the definitions.

- Mention of a time frame in the definition
- Mention of Bowel frequency
- Use of Rome Criteria
- Reference
- Interactable/ Refractory or Both
- Previous therapy

Data was reported using a meta-narrative approach, highlighting areas of convergence and divergence in the findings. Meta-narrative review is a relatively new method of systematic review, designed for topics that have been differently conceptualized and studied by different groups of researchers. We followed the RAMESES publication standards for meta-narrative reviews.[15]

Data analysis

All the categorical data were presented as tables and figures, and no numerical data were included in the analysis.

Risk of bias analysis

No risk of bias analysis applicable

The level of bias of the included studies does not affect the definition of intractable constipation, which is the only outcome of interest of this meta-narrative review.

Patient and Public Involvement

No patients were involved in this review

Research Ethics Approval

No ethics approval was required for this work.

Results

A total of 1535 studies were identified upon a search conducted on the 3rd of November 2022, 1466, of which were excluded as they did not meet the inclusion criteria for this review. 69 studies were screened for eligibility. Twenty-five studies were excluded: duplicates (16), opinion pieces (3), and literature/ systematic reviews (3). A total of 47 studies (28 full papers, 16 abstracts and 3 trial registrations) were included and downloaded for data extraction as PDF files. **(Figure 1)**

Description and characteristics of included studies

The 47 studies included in the systematic review comprised of 28 full papers, 3 clinical trial registrations, and 16 abstracts. The year of publication of the studies was from 1996 to 2022. The studies came from diverse geographical regions; from North America, Europe, Asia, Australia, South America. **Supplementary Table 1** provides study characteristics including design, definition of therapy resistant constipation used by the researchers, terminology used to define therapy resistant constipation, duration of treatment before being diagnosed with therapy resistant constipation, and the source of reference.

Definitions of therapy resistant constipation

There were at least 7 clear definitions of therapy resistant constipation for children in the published literature included in this review. Most of these variations are due to the duration of therapeutic interventions before labelling children as having therapy resistant constipation and the terminology used to define therapy resistant constipation. Some of them included refractory constipation: symptoms not responsive to conventional therapy,[16] functional constipation unresponsive to optimal conventional treatment for at least 3 months,[17] chronic constipation not responding to maximum laxative therapy, behavioral therapy, and toilet-training program with duration of symptoms of > 2 years,[18] and all children presenting with chronic constipation and

showing no response to rigorous medical management over a period of 1 month or more.[19] It is important to note that 10 articles had no clear definition at all.

Terminology (Refractory or intractable)

Twenty one (21) studies,[16, 19-37] used the word refractory while 24 studies,[10, 17, 18, 38-58] used the word intractable to describe treatment resistant constipation. Two (2) studies used refractory and intractable interchangeably.[59, 60]

Studies with an explicit definition

Out of 47 studies, 14 studies provided an explicit definition for therapy resistant constipation. The definitions combined varying components such as duration of treatment, specifications of therapy and nature of stools. Among them, duration of medical treatment was the most frequently used component in defining therapy resistant constipation. Of the 47 studies which included duration of treatment as part of the definition, 2 studies considered no responsiveness of 2 years or more to treatment,[18, 53] 3 considered unresponsiveness to treatment more than 12 months,[21, 48, 59] 2 studies considered no responsiveness of 6 months to treatment,[42, 43] 10 studies used duration of treatment more than 3 months,[10, 17, 24, 25, 39, 40, 44, 47, 52, 60] and one study defined therapy resistant constipation as having bowel movement less than 3 per week for at least 2 months prior to diagnosis.[36] **(Figure 2)**

A total of 15 studies defined therapy resistant constipation without reporting treatment duration.[16, 20, 22, 23, 26-28, 35, 37, 38, 41, 45, 46, 54, 61]

Studies with no structured definition

Seven (7) studies used the Rome criteria (in general, even though the Rome criteria does not define it) to define therapy resistant constipation. Among them, one study used the Rome IV criteria without a specific duration of treatment.[22] Five (5) studies, used Rome III criteria with a definitive duration of treatment.[24, 42, 43, 59, 61] One RCT defined therapy resistant constipation fulfilling the Rome IV criteria for 3 or more months.[49] Ten (10) studies did not provide a clear definition for therapy resistant constipation.[17, 29-32, 50, 55-58] **(Figure 2)**

Discussion:

Therapy resistant constipation is a common and formidable challenge in paediatric clinical practice. It is crucial to have a clear and explicit definition of this clinical entity in order to implement appropriate management strategies at an early stage that may improve outcomes. The Rome criteria clearly define functional constipation in infants, toddlers, and children.[9, 62] However, after an extensive review of the existing paediatric literature, we were unable to find a clear definition for therapy resistant constipation for children specially in terms of the duration of unresponsiveness to optimal medical management before being labelled as therapy resistant constipation. Although the National Institute for Clinical Excellence (NICE, UK) has defined therapy resistant constipation, the duration of symptoms of constipation is however not included in their definition.[7] Widely varying definitions found in our review show the lack of consensus among these definitions. We believe that it is imperative to use unambiguous terminology that includes, rigorous criteria of failure, type of therapeutic interventions, and their precise duration in defining therapy resistant constipation.

Terminology of therapy resistant constipation

Several studies have used the term intractable,[10, 17, 18, 38-58] while others have used the term refractory.[16, 19-37] It is interesting to note that some studies have used both terms.[59, 60] Although, it's clear that both terms are being used in the definition of medically unresponsive constipation, the literature shows no agreement on the terminology and use the terms refractory and intractable loosely and interchangeably. It is important for researchers and healthcare professionals to come to a consensus on the terminology used to describe therapy resistant constipation as it helps to understand the pathophysiology, recognize symptomatology, use the correct diagnostic tools, compare treatment regimens, and design clinical trials.

Time frame of therapy resistant constipation

It is also evident that there is no clear agreement among studies on the duration of medical treatment before children are deemed to be considered as therapy resistant constipation. Among the studies that provided an explicit definition for therapy resistant constipation, there is no definitive time duration that can be used as a benchmark. Most studies with an explicit definition seem to believe that symptoms must persist for at least three months to meet the criteria for therapy resistant constipation,[10, 17, 39, 40, 52, 60] while some studies have set a longer time frame of 12 (4/47) [21, 33, 48, 59] or 24 months (2/47),[18, 53] respectively. Among those studies that do offer an explicit definition, there is still no consensus about how long symptoms need to persist in order to be considered as therapy resistant.

Studies with no clear definition for therapy resistant constipation

We also found that a significant number of studies have not attempted to clearly define medically unresponsive constipation.[29-32, 50, 51, 55-58] In those studies, there was no clear identification of duration of medical unresponsiveness. Although beyond the scope of defining the therapy resistant constipation, some studies which had not clearly defined the unresponsiveness have reported outcomes of major surgical interventions as treatments for children. We believe this is one of the reasons that demands an internationally accepted definition for medically unresponsive constipation in children. Other reasons why we need a standard definition include, harmonizing research in this important disease entity, and identify epidemiological and pathophysiological nuances related to refractory/intractable constipation.

Studies that used the variations of Rome criteria to define therapy resistant constipation

The Rome criteria do not provide a clear definition for therapy resistant constipation. However, we found that a notable proportion of studies (10 out of 47) have utilised the Rome criteria to describe

refractory constipation. One study implemented the Rome IV criteria without specifying a duration,[22] four (4) studies employed the Rome III/IV criteria with a specific duration.[34, 35, 38, 61] Three (3) studies employed Rome III criteria[42, 43, 59] and one study used Rome IV criteria [49] with specific duration. Among the studies that established a duration, some considered a period of 6 months or longer,[42, 43] one study used a period of 12 months,[59] while others required the fulfilment of the Rome III/IV criteria for a minimum of 3 months of treatment.[24, 49] It is evident that researchers look upon the Rome process to have a definition for medically unresponsive constipation. This reinforces the importance of having a clear and consistent definition for medically refractory constipation in future iterations of the Rome criteria to ensure the high quality and validity of research findings on childhood constipation as well as optimal care for those with severe unresponsive constipation .

Studies with description with prior medical therapy

Eleven studies with an explicit definition have considered prior medical therapy before being considered as therapy resistant constipation. These therapies include maximum doses of osmotic and stimulant laxatives, and extensive behavioral therapy and toilet training.[16, 18, 21, 23, 28, 35, 37, 46, 47, 59, 60] All 3 guidelines published by NICE, ESPGHAN/NASPGHAN, and Indian Academy of Paediatrics have defined the standard management.[5-7] High dose polyethylene glycol is used to evacuate the rectal fecal mass as the first step and rectal enemas and suppositories are used when there is poor response to polyethylene glycol. All 3 guidelines agreed polyethylene glycol-based therapy as the first line maintenance therapy for childhood constipation and stimulant laxatives are added when there is a poor response. Therefore, we believe that there should be consensus on the choice of drugs, their dosages, the order of usage of different laxatives, both oral and rectal laxatives, and the duration of therapy. The recommended therapy in these guidelines can

be used as a steppingstone in defining the optimal medical intervention before being labelled as therapy resistant constipation.

Previous literature on defining therapy resistant constipation

A previous systematic review analyzing adult literature has also attempted to define pharmacologically therapy resistant constipation in adults. In this study 61 papers were reviewed to define pharmacologically therapy resistant constipation. Similar to our findings they also found the terminology of severe, refractory, and intractable interchanging being used without consensus. In addition, the duration of therapy for constipation prior to be labelled as therapy resistant varied from 6-12 months with some studies not specifying the duration but only mentioning several years.[63]

Strengths and limitations

This review has several strengths. We searched a number of data-bases to identify the relevant literature and included all possible papers as well as abstracts which had defined therapy resistant constipation. We identified articles which had both explicit as well as implicit definitions, therefore were able to understand the components that are needed to scientifically define therapy resistant constipation. It was decided not to restrict inclusion of the articles based on the quality assessment as that had no implication on the definition of therapy resistant constipation. A limitation of our study is that we excluded articles published in non-English languages where we could have missed some of the definitions. However, observing the trends of definitions used in articles published in English language, it is unlikely that this would affect the overall conclusions of the present article.

It is important to establish consensus on a definition for this clinical paradigm. As many aspects of the different definitions given in the literature directly inform the choice of therapeutic goals for patients, professionals, and researchers, clarity on these definitions will directly inform such

practice. It is possible that this research has uncovered a spectrum of overlapping but distinct clinical presentations. It is also possible that a single consensus is needed with other incomplete understandings of this clinical phenomenon as identified in our findings, rejected by the clinical community. It is therefore vital as a future and relatively urgent research goal to reach such an international consensus. The most appropriate method to achieve this would be through either a roundtable or Delphi process.

Conclusions

We conclude by stating although there is a significant literature on therapy resistant constipation in children; however, there is no consensus definition in terms of the terminology, the maximum medical treatment and duration of maximum medical intervention before identifying as having medically unresponsive constipation. It is crucial to clearly define therapy resistant constipation in children as it significantly impacts the management and outcome and can prevent unnecessary and potentially harmful further investigations and invasive treatment. It is important to establish a consensus and incorporate this definition into guidelines and criteria to ensure consistency in treatment.

Data sharing statement: Any materials used for this review will be shared upon request from the authors

Contribution of authors:

Vassiliki Sinopoulou: Designed and developed, screened, extracted, resolved conflicts, contributed to writing and editing, advised on, approved the final version prior to submission

Morris Gordon: Designed and developed, resolved conflicts, contributed to writing and editing, advised on, approved the final version prior to submission

Shaman Rajindrajith: Contributed to writing and editing, advised on, approved the final version prior to submission

Wathsala Hathagoda: Screened, extracted, contributed to writing and editing, approved the final version prior to submission

Aditi Bhupendra Rane: Screened, extracted, contributed to writing and editing, approved the final version prior to submission

Anita Sedghi: Screened, extracted, contributed to writing and editing, approved the final version prior to submission

Merit Tabbers: Contributed to writing and editing, advised on, approved the final version prior to submission

Carlo di Lorenzo: Advised on, approved the final version prior to submission

Miguel Saps: Advised on, approved the final version prior to submission

Marc Benninga: Contributed to writing and editing, advised on, approved the final version prior to submission

Funding: There was no funding for this review. Authors provided their time voluntarily.

Competing interests statement:

Vassiliki Sinopoulou: No relevant interests

Morris Gordon: No relevant interests

Shaman Rajindrajith: No relevant interests

Wathsala Hathagoda: No relevant interests

Aditi Bhupendra Rane: No relevant interests

Anita Sedghi: No relevant interests

Merit Tabbers: No relevant interests

Carlo di Lorenzo: No relevant interests

Miguel Saps: Abbvie, Ironwood and IQVIA consultant

Marc Benninga: Consultant for HIPPI, Danone, FrieslandCampina, United Pharmaceuticals,

Norgine, Coloplast, Wellspect, Mallinckrodt, Allergan

Figure 1. PRISMA flow chart

Figure 2. Schematic representation of the contents of the definitions, or other related details, for therapy resistant constipation by the included studies'

References

1. Koppen IJN, Vriesman MH, Saps M, et al. Prevalence of Functional Defecation Disorders in Children: A Systematic Review and Meta-Analysis. *J Pediatr*. 2018;198:121-30 e6.
2. MacGeorge CA, Simpson KN, Basco WT, Jr., et al. Constipation-Related Emergency Department Use, and Associated Office Visits and Payments Among Commercially Insured Children. *Acad Pediatr*. 2018;18(8):952-6.
3. Rouster AS, Karpinski AC, Silver D, et al. Functional Gastrointestinal Disorders Dominate Pediatric Gastroenterology Outpatient Practice. *J Pediatr Gastroenterol Nutr*. 2016;62(6):847-51.
4. Choung RS, Shah ND, Chitkara D, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. *J Pediatr Gastroenterol Nutr*. 2011;52(1):47-54.
5. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58(2):258-74.
6. Yachha SK, Srivastava A, Mohan N, et al. Management of Childhood Functional Constipation: Consensus Practice Guidelines of Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. *Indian Pediatr*. 2018;55(10):885-92.
7. Constipation in children and young people: diagnosis and management [Internet]. Royal College of Obstetricians and Gynaecologists. 2010 [cited 26th May 2020]. Available from: <https://www.nice.org.uk/guidance/cg99/evidence/full-guidance-pdf-245466253>.
8. van Ginkel R, Reitsma JB, Buller HA, et al. Childhood constipation: longitudinal follow-up beyond puberty. *Gastroenterology*. 2003;125(2):357-63.
9. Hyams JS, Di Lorenzo C, Saps M, et al. Functional Disorders: Children and Adolescents. *Gastroenterology*. 2016;10.1053/j.gastro.2016.02.015.
10. Nurko S, Garcia-Aranda JA, Guerrero VY, et al. Treatment of intractable constipation in children: experience with cisapride. *J Pediatr Gastroenterol Nutr*. 1996;22(1):38-44.
11. van der Plas RN, Benninga MA, Staalman CR, et al. Megarectum in constipation. *Arch Dis Child*. 2000;83(1):52-8.
12. van Dijk M, Benninga MA, Grootenhuis MA, et al. Prevalence and associated clinical characteristics of behavior problems in constipated children. *Pediatrics*. 2010;125(2):e309-17.
13. Ranasinghe N, Devanarayana NM, Benninga MA, et al. Psychological maladjustment and quality of life in adolescents with constipation. *Arch Dis Child*. 2017;102(3):268-73.
14. Baaleman DF, Vriesman MH, Lu PL, et al. Long-Term Outcomes of Antegrade Continence Enemas to Treat Constipation and Fecal Incontinence in Children. *J Pediatr Gastroenterol Nutr*. 2023;77(2):191-7.
15. Wong G, Greenhalgh T, Westhorp G, et al. RAMESES publication standards: meta-narrative reviews. *BMC Med*. 2013;11:20.
16. Bonilla S, Nurko S, Rodriguez L. Long-term Use of Bisacodyl in Pediatric Functional Constipation Refractory to Conventional Therapy. *J Pediatr Gastroenterol Nutr*. 2020;71(3):288-91.
17. Koppen IJ, Kuizenga-Wessel S, Voogt HW, et al. Transanal Irrigation in the Treatment of Children With Intractable Functional Constipation. *J Pediatr Gastroenterol Nutr*. 2017;64(2):225-9.
18. Yik YI, Cain TM, Tudball CF, et al. Nuclear transit studies of patients with intractable chronic constipation reveal a subgroup with rapid proximal colonic transit. *J Pediatr Surg*. 2011;46(7):1406-11.
19. Redkar RG, Mishra PK, Thampi C, et al. Role of rectal myomectomy in refractory chronic constipation. *Afr J Paediatr Surg*. 2012;9(3):202-5.

20. Tang V, Sunku B, Flores A. Experience of lubiprostone use in children with refractory constipation and colonic dysmotility *Journal of Pediatric Gastroenterol Nutrition*. 2009;49:e51-2.
21. Bellomo-Brandao MA, Arruda VPA, Bustorff-Silva JM, et al. Long-term outcomes in children with refractory constipation treated by conservative therapy or by antegrade continence enema procedure (ACE). *Journal of Pediatric Gastroenterology and Nutrition*. 2018;67:e448.
22. Omar A, Alghfeli H, Miqdady M, et al. Colonic transit marker studies are a useful diagnostic tool and intervention for education which can impact on management of children with chronic refractory constipation. *Journal of Pediatric Gastroenterol Nutrition*. 2021;72:e557.
23. Heitmann PT, Wiklendt L, Thapar N, et al. Characterization of the colonic response to bisacodyl in children with treatment-refractory constipation. *Neurogastroenterol Motil*. 2020;32(8):e13851.
24. Campos G, Lomazi E, Sandy N, et al. Refractory constipation: rates of success. *Journal of Pediatric Gastroenterol Nutrition*. 2019;68:e443.
25. Puoti MG, Ives M, Curry J, et al. Multidisciplinary assessment of paediatric chronic refractory constipation. *Journal of Pediatric Gastroenterol Nutrition*. 2019;68:e416.
26. Arbizu RA, Nurko S, Heinz N, et al. Prospective evaluation of same day versus next day colon manometry results in children with medical refractory constipation. *Neurogastroenterol Motil*. 2017;29(7).
27. van der Wilt AA, van Wunnik BP, Sturkenboom R, et al. Sacral neuromodulation in children and adolescents with chronic constipation refractory to conservative treatment. *Int J Colorectal Dis*. 2016;31(8):1459-66.
28. Gonzalez R, Lopez-Herce J, Garcia A, et al. Neostigmine in the treatment of refractory constipation in critically ill children. *J Pediatr Gastroenterol Nutr*. 2011;53(2):224-6.
29. Motion J, Barclay A, Bradnok T, et al. Prucalopride for treatment refractory constipation in children: a single tertiary centre experience. *Journal of Pediatric Gastroenterol Nutrition*. 2022;74:e429.
30. Carr B, Barrett M, Wild L, et al. Quantifying and predicting benefit from pediatric sacral nerve stimulation for severe constipation and fecal incontinence. *Journal of the American College of Surgeons*. 2017;225:S-155-S6.
31. Zacur GM, Watts L, Ezell G, et al. Increased occurrence of high amplitude propagating contractions on next day colon manometry for refractory pediatric constipation. *Neurogastroenterology and Motility* 2021;33:44.
32. van der Wilt AA, Groenewoud HHM, Benninga MA, et al. Cost-effectiveness of sacral neuromodulation for chronic refractory constipation in children and adolescents: a Markov model analysis. *Colorectal Dis*. 2017;19(11):1013-23.
33. Ribeiro AF. RBR-7mry33 Surgical aperture for irrigation of the bowel in children with Constipation Brazil: Registro Brasileiro de Ensaio Clinicos; 2018 [Available from: <https://ensaiosclinicos.gov.br/rg/RBR-7mry33>]
34. Kajbafzadeh AM. IRCT20111229008554N4 Intrarectal electromotive botulinum toxin type A administration in children with refractory constipation: Iranian Registry of Clinical Trials; 2018 [Available from: <https://en.irct.ir/trial/28186>].
35. van Wunnik BP, Peeters B, Govaert B, et al. Sacral neuromodulation therapy: a promising treatment for adolescents with refractory functional constipation. *Dis Colon Rectum*. 2012;55(3):278-85.
36. Redkar RG, Raj V, Bangar A, et al. Role of ano rectal myomectomy in children with chronic refractory constipation. *Afr J Paediatr Surg*. 2018;15(1):31-5.
37. Gomez-Suarez RA, Gomez-Mendez M, Petty JK, et al. Associated Factors for Antegrade Continence Enemas for Refractory Constipation and Fecal Incontinence. *J Pediatr Gastroenterol Nutr*. 2016;63(4):e63-8.

38. Christison-Lagay ER, Rodriguez L, Kurtz M, et al. Antegrade colonic enemas and intestinal diversion are highly effective in the management of children with intractable constipation. *J Pediatr Surg*. 2010;45(1):213-9; discussion 9.
39. Gupta A, Basson S, Borrelli O, et al. Surgically treated intractable constipation in children evaluated with colonic manometry. *J Pediatr Surg*. 2020;55(2):265-8.
40. Kuizenga-Wessel S, Koppen IJN, Zwager LW, et al. Surgical management of children with intractable functional constipation; experience of a single tertiary children's hospital. *Neurogastroenterol Motil*. 2017;29(5).
41. Baaleman DF, Vriesman MH, Lu P, et al. A pilot study comparing outcomes and experience with three-dimensional and high-resolution anorectal manometry in children with functional constipation. *Gastroenterology*. 2022;162:S-949.
42. Ng SKK, Tsui SY, Chung LY, et al. Application of High-resolution Anorectal Manometry in Children with Intractable Constipation. *Hong Kong Journal of Paediatrics*. 2014;19:194-5.
43. Kajbafzadeh AM, Sharifi-Rad L, Nabavizadeh B, et al. Intrarectal Electromotive Botulinum Toxin Type A Administration in Children With Intractable Constipation: A Randomized Clinical Trial. *Am J Gastroenterol*. 2020;115(12):2060-7.
44. Wessel S, Koppen IJ, Wiklendt L, et al. Characterizing colonic motility in children with chronic intractable constipation: a look beyond high-amplitude propagating sequences. *Neurogastroenterol Motil*. 2016;28(5):743-57.
45. Levitt MA, Martin CA, Falcone RA, Jr., et al. Transanal rectosigmoid resection for severe intractable idiopathic constipation. *J Pediatr Surg*. 2009;44(6):1285-90; discussion 90-1.
46. Haddad M, Clarke S, Fell JM. Percutaneous Endoscopic Colostomy of the Left Colon: A New Technique for the Management of Intractable Chronic Constipation. *Pediatric Endosurgery & Innovative Techniques*. 2002;6(3):207-10.
47. Mousavi SA, Karami H, Rajabpoor AA. Intractable chronic constipation in children: outcome after anorectal myectomy. *Afr J Paediatr Surg*. 2014;11(2):147-9.
48. Rawat DJ, Haddad M, Geoghegan N, et al. Percutaneous endoscopic colostomy of the left colon: a new technique for management of intractable constipation in children. *Gastrointest Endosc*. 2004;60(1):39-43.
49. Rego RMP. RBR-344jq8 Assessment of applicability and results of nerve electrical stimulation in the treatment of children with intractable constipation Brazil: Registro Brasileiro de Ensaio Clinicos; 2018 [updated 13 March 2018. Available from: <https://ensaiosclinicos.gov.br/rg/RBR-344jq8>.
50. Bellomo-Brandao MA, Collares EF, da-Costa-Pinto EA. Use of erythromycin for the treatment of severe chronic constipation in children. *Braz J Med Biol Res*. 2003;36(10):1391-6.
51. Koppen IJ, Thompson BP, Ambeba EJ, et al. Segmental colonic dilation is associated with premature termination of high-amplitude propagating contractions in children with intractable functional constipation. *Neurogastroenterology and Motility*. 2017;29(10):1-9.
52. Monjaraz ET, Carrillo MJ, Pena R, et al. High resolution anorectal manometry in children with difficult-to-treat (intractable) constipation and fecal incontinence. *Journal of Pediatric Gastroenterology and Nutrition*. 2017;67:S44.
53. Hynes M, Yik YL, Veysey D, et al. Gastrointestinal Transit Patterns Identified in Children with Intractable Chronic Constipation using Scintigraphy: Experience of Over 1000 Cases. *Gastroenterology*. 2017;152:S 515.
54. Youssef NN, Barksdale Jr E, Griffiths JM, et al. Management of intractable constipation with antegrade enemas in neurologically intact children. *J Pediatr Gastroenterol Nutr*. 2002;34(4):402-5.
55. Menakaya J, Giles C, Williams A, et al. Combination trans-anal irrigation package improves treatment compliance in children with intractable constipation and faecal incontinence *Archives of Disease in Childhood*. 2022;107:A-109.

56. Vriesman MH, Lu PL, Diefenbach KA, et al. Sacral nerve stimulation versus antegrade continence enema treatment for children with intractable constipation and fecal incontinence *Gastroenterology*. 2018;154:S-561.
57. Valitutti F, Rybak A, Saliakellis E, et al. Colonic manometry parameters can predict the outcome of the surgical ostomy formation in children with intractable constipation. *Digestive and Liver Disease*. 2016;48:E254.
58. Koppen IJ, Wiklendt L, Yacob D, et al. Impaired postprandial colonic response in the presence of coordinated propagating colonic contractions suggests an extrinsic neuropathy in children with intractable functional constipation. *Gastroenterology*. 2017;152(5):S649-S50.
59. Arruda VPA, Bellomo-Brandao MA, Bustorff-Silva JM, et al. Refractory functional constipation: clinical management or appendicostomy? *J Pediatr (Rio J)*. 2020;96(2):210-6.
60. Noviello C, Nobile S, Romano M, et al. Functional constipation or redundancy of the colon? *Indian J Gastroenterol*. 2020;39(2):147-52.
61. Van Der Wilt AA, Breukink SO, Han IJ, et al. Sacral neuromodulation in adolescents with constipation refractory to conservative treatment. *Colorectal Disease*. 2014;16:35.
62. Benninga MA, Faure C, Hyman PE, et al. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. *Gastroenterology*. 2016;10.1053/j.gastro.2016.02.016.
63. Soh AYS, Kang JY, Siah KTH, et al. Searching for a definition for pharmacologically refractory constipation: A systematic review. *J Gastroenterol Hepatol*. 2018;33(3):564-75.