e-ISSN 2830 5442

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Volume 2 / No. 2

May 2023

www.apghn.com

Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

e-ISSN 2830 5442

Volume 2, No. 2, May 2023

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

EDITORIAL BOARD

COVER ILLUSTRATION

Gryselda Hanafi

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition (APGHN) is the official journal issued by the Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
Contact us: apghnjgai@gmail.com

e-ISSN 2830 5442

Volume 2, No. 2, May 2023

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

TABLE OF CONTENT

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition (APGHN) is the official journal issued by the Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
Contact us: apghnjgai@gmail.com

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Fundoplication in Pediatric Achalasia Patients Undergoing Heller's Myotomy: A Systematic Review

Sarah Susanto[1,2], Brendan O'Connor[3], Warwick J. Teague[3]

[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

[2]University of Melbourne, Melbourne, Australia

[3]Department of Paediatric Surgery, The Royal Children's Hospital Melbourne, Melbourne, Australia

Corresponding author:
Sarah Susanto, M.D.
sarah.susanto19@gmail.com

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.1-17

Citation:
Susanto S, O'Connor B, Teague WJ. Fundoplication in Pediatric Achalasia Patients Undergoing Heller's Myotomy: A Systematic Review. *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(2):1-17.

Abstract:

Background: Achalasia is a rare motility disorder, with the incidence being the lowest among children. The disease is caused by the inability of the LOS to relax and the absence of normal peristalsis of esophagus. Heller's myotomy has been known to be the gold standard management of achalasia, however, reports on postoperative GERD were established in the past. To control the reflux symptoms, fundoplication has been used as an addition to Heller's myotomy. Unfortunately, there has been an inconclusive finding from available studies regarding the need for performing fundoplication. Hence, we aim to determine whether or not the addition of fundoplication to Heller myotomy in achalasia children resulted in better postoperative outcomes and fewer complications of GERD.

Methods: A literature search was carried out in four databases: Medline, EMBASE, Pubmed, and Cochrane Library. The search was limited to publications from 2006 to 2019, English studies, and achalasia patients age 0-18 years old that underwent Heller's myotomy. The exclusion of studies from the primary screening according to title and abstracts and secondary screening on the full text were done according to a priori protocol. Duplicate studies were also eliminated by using reference management software and manually.

Results: A total of 446 studies were retrieved from the search. Preliminary screening based on the eligibility criteria resulted in 21 articles to be included in this review. A total of 410 patients were included in this study, in which 80 underwent HM alone and 330 experienced fundoplication as an adjunct to HM (HMF). There was a higher proportion of asymptomatic patients in the HM group (56.3%) compared to HMF (48.8%). Both groups had a similar rate of complications (HMF 12.1%, HM 10.0%). However, in terms of postoperative GERD, slightly better results were seen among HMF patients (9.7%) than HM (15%).

Conclusion: Fundoplication did not result in better resolution of symptoms, as seen from its percentage of asymptomatic patients. Improvements in postoperative GERD were seen in HMF patients, however, it was deemed as insignificant. The findings suggest that there was a limited benefit in using fundoplication.

Keywords: achalasia, children, fundoplication, GERD, Heller's myotomy

Introduction

Achalasia is a rare motility disorder of the esophagus, with a reported incidence of 0.11 for every 100000 children.[1] Achalasia is the rarest among children younger than 5 years old. This is supported by the fact that for every 100,000 children younger than the age of 16, on average 0.11 to 0.18 develop achalasia every year.[2,3] In fact, only 5% of patients with achalasia report developing symptoms before they reach the age of 15.[1] Patients with achalasia experience difficulty in swallowing, as there is partial or total inability of the lower esophageal sphincter (LOS) muscle to relax, as well as the absence of normally coordinated esophageal peristalsis.[4] This condition hinders the normal downward movement of the food bolus from the esophagus to the stomach, leading to various symptoms such as dysphagia, heartburn, chest pain, regurgitation, and weight loss. As a result, the long-term impact of achalasia includes significant impairment in the quality of life of those affected. A possible etiological explanation for achalasia is that there is a degeneration of the myenteric plexus and vagal nerve fibers of the LOS, which might occur due to autoimmunity or viral infection. However, despite this proposed mechanism, the etiology remains unclear.[5]

While it is known that Heller's myotomy (HM) has been the gold standard for decades in treating achalasia, there are cases in the past that have proceeded to complications.[6] The adverse effects include esophageal perforations and gastroesophageal reflux, with the latter being the most common out of the two. This is due to the widening of the esophageal passageway from the HM, which allows fluid or solids to go downwards and hence upwards as well. Handling the reflux is necessary as it can lead to erosive esophagitis, Barret's esophagus, and even adenocarcinoma of the esophagus.[7] In order to tackle this problem, concurrent anti-reflux procedures have been considered along with HM, and the method of choice is fundoplication in most cases.

Unfortunately, it is still debatable whether or not HM in conjunction with fundoplication should always be done, considering that there are pharmacological anti-reflux treatments that could be given to the patients. There is a possibility that fundoplication exacerbates the obstruction, due to it being done too tightly. In this case, post-operative dysphagia could occur.[8] Despite the probability of it causing adverse effects, the use of fundoplication has been known to provide the best long-term reduction of GERD.[9]

The need to perform fundoplication in order to control GERD on pediatric achalasia patients who received HM is still inconclusive. Enough evidence on the efficacy and safety of fundoplication should be gathered to support its use, and to reduce doubts regarding its benefit. Therefore, this study aims to review whether the addition of

fundoplication in Heller's myotomy patients leads to better improvement in swallowing without the post-operative complications of GERD.

Methods

The systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Study Selection

Four electronic databases have been used for this systematic review as a source of information, which includes Medline (Ovid), EMBASE (Ovid), Pubmed, and Cochrane Library. The keywords used to do the search were achalasia, Heller's myotomy, and children (based on PICO keywords presented in **Table 1**). The search strategy was created by the author and assessed by a librarian who is an expert in the field of literature searching. The most recent search was done on 7 November 2019, and results of each databases were attached in Appendix 2. Limits were applied to the searches in EMBASE only, so that only published articles as well and articles in press that were included to the search results.

Studies from the electronic database searching were exported into MEDLINE format, which resulted in the complete references within an excel sheet. The first screening of the studies was done based on the title and abstracts, according to the PICO components (**Table 1**). The full-text articles were obtained for studies with no abstract in the excel sheet. Another screening was then done through assessing the full-text articles using the inclusion and exclusion criteria as the filter (**Table 2**).

Table 1. PICO keywords

Patients/Population:	Pediatric achalasia patients receiving Heller's myotomy
Intervention/Exposure:	Fundoplication
Comparator:	Without fundoplication
Outcome(s):	Reversal of achalasia symptoms (able to swallow) without the postoperative complications of GERD

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Pediatric achalasia patients 18 years old or younger who received Heller's myotomy	Patients older than 18 years old who did not have achalasia or not treated with Heller's myotomy

Papers with either Heller's myotomy with fundoplication or Heller's myotomy without fundoplication.	Patients solely treated with other surgical interventions for achalasia
Papers with both Heller's myotomy with fundoplication and Heller's myotomy without fundoplication.	Studies without information on the symptoms before and after the surgery
Resolution of achalasia symptoms (able to swallow) without the postoperative complications of GERD	Non-English studies
English studies	Studies published before 2006
Studies published from 2006-2019	Animal/ non-human studies
Human studies	Systematic review and meta-analysis
Cohort or cross-sectional studies	Duplicate publications

Data Extraction

Studies from the four databases that have been screened and fulfil the eligibility criteria were exported to its RIS format and then be imported to EndNote X9. which is a reference management software. Duplicate studies will be eliminated both manually and using the "Find Duplicates" option in the software. After all of the duplicate studies has been eliminated, the articles were independently extracted by the reviewers to obtain certain data. The extraction was done through using Microsoft Excel version 16.31.

Risk of Bias and Quality Assessments

The assessments of the risk of bias and the quality of each paper were done by utilizing the Risk of Bias in Non-randomized Studies- of Interventions (ROBINS-I) tool. The first stage of ROBINS-I is the protocol stage, which contains the PICO component of this systematic review. The next stage focused more on each study being assessed, and it requires the reviewer to analyze the design and PICO of the study. The measurement of study bias was classified as before, at the time, and after the intervention. Responses to each component were either "Yes", "Probably Yes", "No", "Probably No", and "No Information".

Results

The search results from Medline (Ovid), EMBASE (Ovid), Pubmed, and Cochrane resulted in a total of 446 studies. The studies were then screened based on their title and abstract, which then proceeded to full-text screening. The final number of studies that are eligible to be included in the qualitative synthesis is 21. The reasons for

exclusion were provided in detail in the **Figure 1** below and is mainly due to the participants of the studies being older than 18 years old (n= 154).

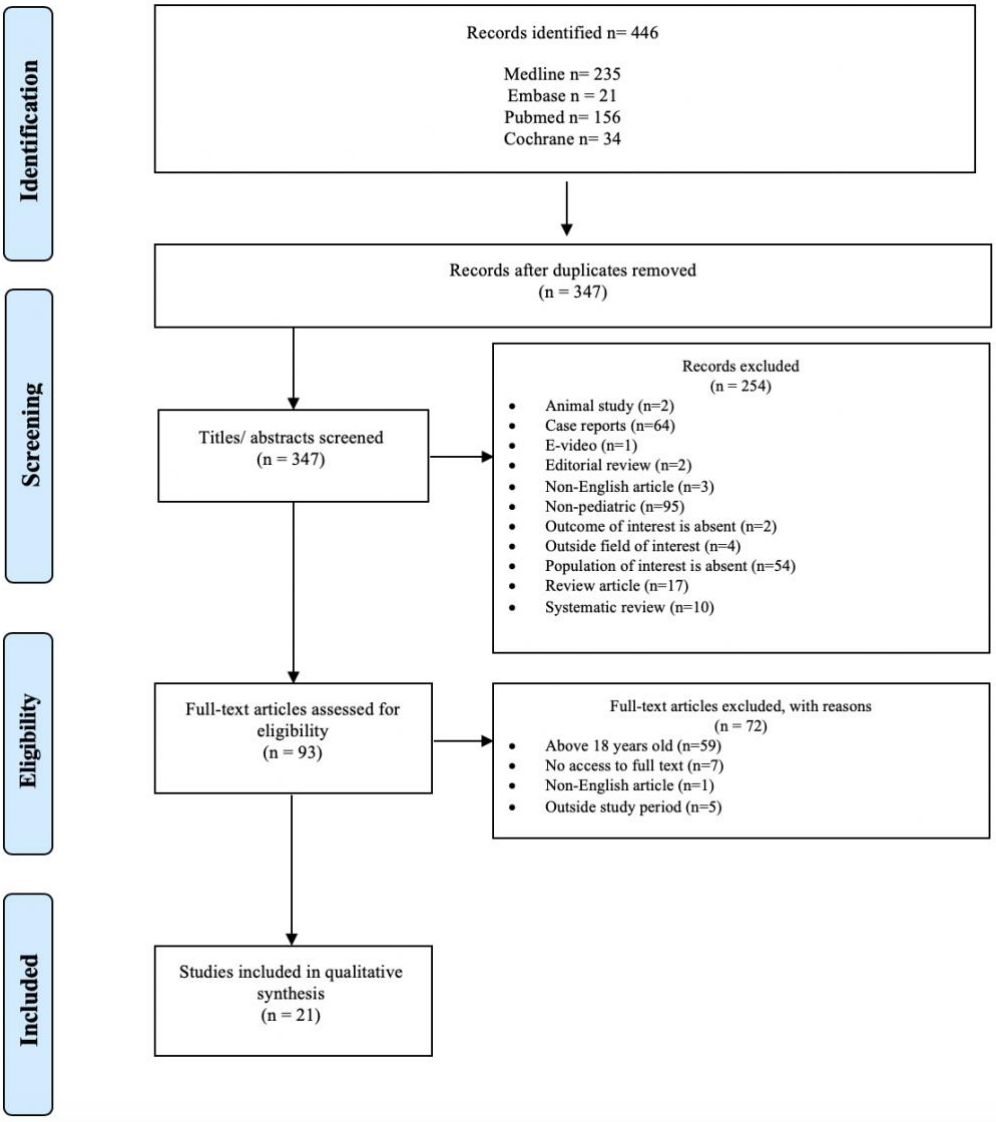

Figure 1. PRISMA flowchart

The study characteristics of all the studies that were included in the analysis were displayed in **Table 3**. The 21 papers consisted of 4 cohort studies (3 retrospective, 1 prospective), 6 cross-sectional studies, and 11 case series. The year of publication ranged from 2007 to 2019, and the span of the study period is from 1990 until 2017. A total of 410 patients were recruited, in which 80 patients underwent HM alone, and 330 underwent HM along with fundoplication. The participants of the included literatures consisted of 260 males and 210 females. However, the data of 60 patients contains those that did not take HM at all, as the studies have failed to mention the gender of secondary HM participants. Furthermore, the gender data also includes

those that were excluded in the study. An average of patients age was not able to be calculated since a subset of the studies provided only the age of diagnosis and not at surgery.

Risk of Bias

The risk of bias assessment using the ROBINS-I tool concluded that the 21 articles had either a low or a moderate risk of bias for all domains. Therefore, an overall judgement of moderate risk was given to every included study, based on the criteria stated in the ROBINS-I guideline.

Primary Outcomes

Among patients of the HMF group, there were 12 (3.6%) relapse cases, and partial improvements of the preoperative achalasia symptoms were seen in 35 (10.6%) patients. Treatment success were denoted in 161(48.8%) patients, where their symptoms completely resolved. In addition, a total of 40 (12.1%) HMF patients began to gain weight. However, postoperative symptoms existed in 41 (12.4%) patients with dysphagia, 32 (9.7%) patients with GERD, and 6 (1.8%) children with vomiting.

Among patients in HM group, 45 (56.3%) of them showed absence of symptoms and partial improvements were seen in 3 (3.8%) patients. Unfortunately, recurrent symptoms occurred in 3 (3.8%) patients, dysphagia still remained in 20 (25.0%) patients, and 12 (15%) patients reported GERD symptoms. Furthermore, 17 (21.3%) patients reported higher body weight compared to before the treatment.
(**Table 4**)

Table 3. Study characteristics of included studies

Author	Study design	Study period	No. of patients	Intervention		Age	Gender
				HM	HMF		
Yu *et al.* (2019)[10]	Cross-sectional	2010 - 2017	30	0	30	13.6 ± 3 [a]	18 males, 12 females
Vandewalle *et al.* (2018)[11]	Case series	January 2007-December 2016	26	0	26	14.4 (11.6-15.5)[a]	16 males, 10 females
Vaos *et al.* (2008)[12]	Retrospective cohort	January 1991-December 2005	15	15	0	9.5 (6.0-13.0) [b]	5 males, 11 females [c]
Garzi *et al.* (2007)[13]	Prospective cohort	January 1997-October 2005	12	0	12	11 (3.5-16.0) [a]	7 males, 5 females
Saliakellis *et al.* (2017)[14]	Cross-sectional	January 1995-December 2012	40	2	38	10 (3.2-17.4) [b, d]	21 males, 27 females [c,d]
Altokhais *et al.* (2016)[15]	Cross-sectional	January 2004-November 2015	6	0	6	7 (2.0-12.0) [a]	2 males, 4 females
Erginel *et al.* (2016)[16]	Case series	1991-2013	20	0	20	3.34 (0.58-17.0)[a, d]	13 males, 9 females [c,d]
Zagory *et al.* (2016)[17]	Case series	September 2004-August 2014	19	1	18	11.6 (0-17) [b, d]	14 males, 9 females [c,d]
Smits *et al.* (2015)[18]	Cross-sectional	January 1990 – December 2013	41	15	26	11.9 (9.3 – 13.8)[a]	52 males, 35 females [c,d]
Caldaro *et al.* (2015)[19]	Retrospective cohort	February 2009-December 2013	9	0	9	10.7 (2-16) [a]	6 males, 3 females
Pachl *et al.* (2014)[20]	Retrospective cohort	May 1999- May 2013	28	18	10	13 (3.2- 17.4) [a]	13 males, 15 females
Esposito *et al.* (2013)[21]	Case series	June 2000 – June 2012	31	0	31	8.4 (5 – 14.9) [a]	18 males, 13 females
Tannuri *et al.* (2010)[22]	Cross-sectional	2000-2009	15	0	15	12.0 (9.0-17.0) [a]	7 males, 8 females
Jung *et al.* (2010)[23]	Case series	1990-2007	17	0	17	7 (0.3- 17) [a]	12 males, 10 females [c]

Corda *et al.* (2010)[24]	Case series	January 1998- June 2008	20	20	0	12 (5-15) [a]	13 males, 7 females
Pastor *et al.* (2009)[25]	Cross-sectional	July 1981- June 2007	20	2	18	12.4 ± 4.8 [a, e]	5 males, 5 females [e]
Askegard-Giesmann *et al.* (2009)[26]	Case series	1999-2005	26	1	25	15 (4-18) [a]	15 males, 11 females
Zhang *et al.* (2009)[27]	Case series	May 1993- October 2005	9	6	3	10.3 (3.0-14.4) [b]	6 males, 7 females [c]
Grabowski *et al.* (2016)[28]	Case series	1997-2014	11	0	11	13 (6-17) [a]	7 males, 4 females
Ashraf *et al.* (2014)[29]	Case series	January 2002- December 2007	10	0	10	8 (infants), 2 (4-year-old) [f]	6 males, 4 females
Adikibi *et al.* (2009)[30]	Case series	2000-2007	5	0	5	12.1 (9.3-14.9)	4 males, 1 female

HM: Heller's myotomy alone; HMF: Heller's myotomy with fundoplication

NR: Not reported

[a]., Age at surgery

[b]., Age at diagnosis

[c]., Data includes excluded patients

[d]., Data of all patients of the study, which also includes those who received initial treatments besides Heller myotomy and fundoplication.

[e]., Data of patients undergoing Heller's myotomy as initial intervention only

[f]., Age only reported in terms of infants and 4 years old children

Table 4. Postoperative outcomes of included studies with HM only or HMF patients only

Author(s)		Achalasia symptoms				Dysphagia	GERD	Vomiting	Gained weight
		Relapse	Improvement		Asymptomatic				
			Dysphagia	GERD					
Yu *et al.*	HMF	NR	NR		19	10[p]	NR	5	NR
Vandewalle *et al.*	HMF	NR	16	13	NR	10[p]	7	NR	NR
Garzi *et al.*	HMF	NR	N/A		12	NR	NR	NR	12
Saliakellis *et al.*	HMF	NR	NR		15[a]	NR	11	NR	NR
Altokhais *et al.*	HMF	NR	1		5	NR	NR	NR	NR
Erginel *et al.*	HMF	NR	N/A		20	NR	NR	NR	NR
Zagory *et al.*	HMF	NR	NR		14	5	NR	NR	NR
Caldaro *et al.*	HMF	NR	NR		NR	2	1	NR	NR
Esposito *et al.*	HMF	NR	NR		30	5	NR	NR	NR
Tannuri *et al.*	HMF	NR	NR		NR	2	-	NR	NR
Jung *et al.*	HMF	NR	4		10	NR	NR	NR	NR
Pastor *et al.*	HMF	NR	NR		6[b]	3[b]	NR	1[b]	NR
Askegard-Giesmann *et al.*	HMF	7	NR		NR	NR	1	NR	NR
Grabowski *et al.*	HMF	4	NR		6	4	-	NR	11
Ashraf *et al.*	HMF	NR	N/A		10	NR	-	NR	10
Adikibi *et al.*	HMF	NR	1		4	NR	NR	NR	NR
Vaos *et al.*	HM	NR	NR		10	1[p], 13[o]	NR	NR	NR
Corda *et al.*	HM	NR	NR		15	5	-	NR	NR
Smits *et al.*	HM	3	NR		NR	NR	5	NR	NR
	HMF	1	NR		NR	NR	9	NR	NR
Pachl *et al.*	HM	NR	NR		17	NR	1	NR	17
	HMF	NR	NR		7	NR	3	NR	7
Zhang *et al.*	HM	NR	3		3	1	2	NR	NR
	HMF	NR	NR		3	-	-	NR	NR

HM: Heller's myotomy only; HMF: Heller's myotomy along with fundoplication

N/A: Not applicable; NR: Not reported; -: No patients in the category
GERD: Gastroesophageal reflux disease
[p]., Persistent dysphagia; [o]., Occasional dysphagia
[a]., Data of patients undergoing Heller's myotomy as initial intervention only
[b]., Data of patients undergoing Heller's myotomy as their last treatment

Secondary Outcomes

Overall, no deaths were seen among the subjects. The length of hospitalization of HMF patients (4.63 (2.38-14.13) days) is longer compared to those of HM patients (3.5 (2.0-5.0) days). A total of 120 (36.4%) out of 330 patients were able to be followed up to a range mean of 0.25 to 4.42 years postoperatively. In **Table 5** it can be seen that complications within HMF patients were intraoperative mucosal perforation (n= 18 (5.5%)), postoperative gastric perforation (n= 1 (0.3%)), persistence of painful symptoms (n= 3 (0.9%)), dumping syndrome (n= 3 (0.9%)), and inhalation pneumopathy (n= 1 (0.3%)). Other adverse effects include gas bloat syndrome (n= 1 (0.3%)), aspiration during induction of anesthesia (n= 1 (0.3%)), pneumonia (n= 2 (0.6%)), and retrosternal pain (n= 2 (0.6%)). Not only that, in eight cases (2.4%) the Nissen fundoplication was overly tight.

There were a smaller number of complications among HM patients, namely four (5.0%) patients with perforation of the esophageal mucosa during the surgery, one (1.3%) patient who developed esophagitis, and one (1.3%) with pneumonia. Infection also occurred in two (2.5%) patients, one of them was located in the chest and the other one was a local infection of the wound. The average follow-up period was similar to that of HMF patients, which was 0.83 to 5 years. The data of Vaos et al. were excluded from the calculation of the follow-up duration as he provided only the range of years elapsed after the surgery without the average. The included studies managed to follow 32 HM patients.

Table 5. Characteristics of the included studies in regard to follow-up and complications

Author		Complication		Follow-up		Length of hospital stay (days)
		IMP	Others	Duration	No. of patients followed	
Yu *et al.*	HMF	NR	NR	3.6 ± 2.1	12	NR
Vandewalle *et al.*	HMF	1	1[a]	0.81 (0.29-1.75)	NR	NR
Garzi *et al.*	HMF	1	3[b]	NR	12	NR
Saliakellis *et al.*	HMF	NR	NR	NR	NR	NR
Altokhais *et al.*	HMF	-	-	2 (0.5-11)	NR	3.5 (2-7)
Zagory *et al.*	HMF	1	NR	NR	NR	6.5 (1-40)
Caldaro *et al.*	HMF	1	NR	2.58 (1.08-5.25)	NR	6 (3-18)
Esposito *et al.*	HMF	3	NR	0.75-13	31	4 (3-8)
Tannuri *et al.*	HMF	NR	NR	2.69 (0.17-8)	NR	2.5 (1-4)

Jung *et al.*	HMF	NR	8[c]	0.5	17	NR
Pastor *et al.*	HMF	3	1[d]	NR	20	NR
Askegard-Giesmann *et al.*	HMF	2	1[e]	1.7 (0-6.21)	NR	3.5 (1-17)
Grabowski *et al.*	HMF	2	NR	2.5 (1-10)	10	8 (5-13)
Ashraf *et al.*	HMF	NR	NR	0.25	10	NR
Adikibi *et al.*	HMF	-	-	4.42 (0.13-7.58)	5	3 (3-6)
Vaos *et al.*	HM	NR	3[f]	5-15	7	4 (3-6)
Corda *et al.*	HM	3	NR	5.00 (0.67-9.50)	20	3 (1-5)
Smits *et al.*	HM	-	1[g], 1[h]	NR	NR	NR
	HMF	4	2[g], 2[i], 1[h]	NR	NR	NR
Pachl *et al.*	HM	1	NR	0.83 (0-5)	25	3 (1-8)
	HMF	-	NR			
Zhang *et al.*	HM	NR	NR	1.27 (0.17- 4)	5	NR
	HMF	NR	NR		3	NR

NR: Not reported; -: No patients in the category

[a]., Postoperative gastric perforation

[b]., Patients reported persistence of painful symptoms

[c]., Other complications consists of 3 Dumping syndrome patients, 1 patient with inhalation pneumopathy, and 4 patients that had their Nissen fundoplication too tight

[d]., Gas bloat syndrome

[e]., Aspiration during induction of anaesthesia

[f]., Three patients consisting of 1 patient with chest infection, 1 with wound infection, and one with oesophagitis.

[g]., Pneumonia

[h]., Oesophagectomy

[i]., Retrosternal pain

Discussion

Achalasia is a rare motility disorder, especially among children. In managing achalasia, surgical intervention was said to offer a more long-lasting improvements of the symptoms compared to pharmacological treatments. One mode of surgery is HM, which although known as the gold-standard it also has a risk of triggering GERD. To solve the reflux symptoms, a technique of wrapping the fundus of the stomach around the esophagus called fundoplication might be used. However, until now it is still unclear whether the benefits of using fundoplication outweigh its risks. Thus, we aim to review whether fundoplication leads to better improvement in achalasia symptoms along with less postoperative GERD compared to HM alone.

From **Table 4** it can be seen that there were less asymptomatic patients in the HM group (n= 45) compared to HMF (n= 161). However, the number of cases was not

representative of the actual proportion of asymptomatic patients, as the number of patients within each group were different. Therefore, calculations of the percentage were deemed to be more appropriate. After dividing the number of asymptomatic patients reported per children in each group, there was a higher percentage of asymptomatic HM patients (56.3%), compared to HMF (48.8%).

The difference in the number of patients with no persisting symptoms after the operation in both groups can be explained by a possible technical error of the fundoplication, in which it was done too tightly, hence created obstructing symptoms of the esophagus and hinder the recovery.

The difference in the number of asymptomatic patients can also be explained by a higher proportion of patients in the HMF group (33.3%) that underwent preoperative treatments compared to HM (8.8%). A study done by Portale et al. mentioned that patients who had prior treatments with BT injection were less likely to be asymptomatic than those who had not.[31] From all of those studies, 11 HMF patients had previous BT injection while there were no HM patients who underwent treatment with BT.

There was also a difference in the length of follow-up, where the mean was longer in HM patients (0.83-5 years) than HMF (0.25-4.42 years), allowing more asymptomatic HM patients to be noted by the research. Furthermore, only 120 (36%) HMF patients were able to be followed-up as compared to 32 (40%) in HM patients. This finding made it unclear whether the patients that were lost to follow up had an improved condition or not.

Both groups had a similar rate of achalasia symptoms relapse, with 3.8% of patients in the HM group and 3.6% in the HMF group. According to Askegard-Giesmann et al. and Weche et al., the presence of relapse cases among the patients was caused by incomplete myotomy in most cases.[26] As stated above, an overly constricting fundoplication might also contribute to the symptoms relapse in HMF patients, as it adds to the obstruction of the LOS. This can be seen in **Table 5**, where indeed, there were four cases among HMF children where the fundoplication was done with excessive tightness. Reflux symptoms can be triggered in children with no fundoplication but had an adequate myotomy, which can potentially induce stricture due to peptic stricture of the LOS.[32]

On the other hand, partial improvements were seen in more HMF patients (10.6%) as compared to HM (3.8%). This is consistent with the findings of Li et al., although

it was said that the improvement of symptoms post-fundoplication was more specific to reflux-related symptoms such as heartburn and regurgitation.[33]

The rate of persistent or occasional dysphagia was reported approximately twice as much in 20 HM patients (25%) as in 41 HMF patients (12.4%). In order to manage the persistent symptom of dysphagia, esophagectomy might be considered. However, there were a probability of esophageal resection to cause anastomotic leak, as shown in a study by Devaney et al.[34] Therefore, it was suggested by Fernandez-Ananin et al. that esophagectomy should be performed only when the more conservative treatment has failed.[35] In the case of fundoplication types, Frazzoni et al. suggested the use of partial fundoplication instead of total in order to prevent postoperative dysphagia.[9]

GERD occurred in 12 HM patients (15%) and 32 HMF patients (9.7%). The higher percentage of GERD among patients with no fundoplication was as expected, as the aim of using fundoplication was to prevent reflux. In addition, Moore et al. had stated that laparoscopic fundoplication is the gold standard in treating GERD.[7] However, as there was only as much as 5.3% reduction in the incidence of GERD, it suggests that the benefits of using fundoplication was limited.

Both groups in this study had cases of complications. Complications occurred in a similar rate in HMF children (n= 40 (12.1%)) and among HM patients (n= 8 (10.0%)). Madiwale et al. found out that fundoplication in children was associated with a higher incidence of complications, which supported the slightly higher percentage of complications in HMF patients.[36] In addition, it was found that the most common complication in both groups in our study were intraoperative mucosal perforation (IMP) during myotomy. It is important to take into account that HMF children had more preoperative surgical and/or pharmacological interventions, which might have impacted the condition of the patients and made them prone to developing complications.

The limitation of this study is that there was a presence of numerous confounding factors, such as duration of surgery, preoperative treatments, variable patient ages, duration of follow-up. However, this happened due to the included papers being cross-sectional, cohort studies, case control, and case series. Another limitation is the significant difference in the number of patients within both groups, which was inevitable as the included papers were those that suit the eligibility criteria the most. A larger sample size is needed to have a significant number of patients in the study; however, it was unable to be done as most of the studies were single centered as well as achalasia being a rare disease among children. Another limitation was the incompleteness of several data from the papers, however, the most necessary data which was the primary and secondary endpoints were able to be retrieved from all

studies. A potential source of bias of this review was that the literature search was not performed by looking at the references of articles on relevant topic, and grey literatures. However, the search strategy was performed on four databases and developed through the help of an expert librarian. Another potential bias was missing information of the studies, which was stated in the table of results. We were unable to retrieve the full text of 7 articles and exclusion of 4 non-English papers were performed, which might add to potential bias of this paper.

Conclusion

Our results suggested that the HM group was superior to HMF in terms of the primary outcome of symptom resolution, with only a slight improvement of GERD symptoms in children who had fundoplication. Furthermore, patients with fundoplication in our study had also shown more complications intra and postoperatively. Thus, it is important for surgeons to carefully and precisely perform the fundoplication, especially to prevent an excessively tight wrapping and perforation due to the injury the oesophageal mucosa. Future research that uses prospective cohort studies should be performed, as it is able to calculate incidence. RCTs could also be performed through conducting an international multicenter study to gather sufficient number of achalasia patients. Future studies should have only a minimal amount of surgeon who perform the surgeries, in order to prevent the difference of the surgeon's skills to be the confounding factor.

Conflict of Interest

None declared.

Funding Statement

There is no specific grant from any funding agency involved in this study.

References

1. Franklin AL, Petrosyan M, Kane TD. Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management. World J Gastrointest Endosc. 2014;6(4):105-11.https://doi.org/10.4253/wjge.v6.i4.105
2. Marlais M, Fishman JR, Fell JM, Haddad MJ, Rawat DJ. UK incidence of achalasia: an 11-year national epidemiological study. Arch Dis Child. 2011;96(2):192-4.https://doi.org/10.1136/adc.2009.171975
3. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. Lancet. 2014;383(9911):83-93.https://doi.org/10.1016/s0140-6736(13)60651-0
4. Schlottmann F, Patti MG. Esophageal achalasia: current diagnosis and treatment. Expert Rev Gastroenterol Hepatol. 2018;12(7):711-21.https://doi.org/10.1080/17474124.2018.1481748
5. Patel DA, Lappas BM, Vaezi MF. An Overview of Achalasia and Its Subtypes. Gastroenterol Hepatol (N Y). 2017;13(7):411-21
6. Shea GE, Johnson MK, Venkatesh M, Jolles SA, Prout TM, Shada AL, et al. Long-term dysphagia resolution following POEM versus Heller myotomy for achalasia patients. Surg Endosc. 2020;34(4):1704-11.https://doi.org/10.1007/s00464-019-06948-y

7. Moore M, Afaneh C, Benhuri D, Antonacci C, Abelson J, Zarnegar R. Gastroesophageal reflux disease: A review of surgical decision making. World J Gastrointest Surg. 2016;8(1):77-83.https://doi.org/10.4240/wjgs.v8.i1.77
8. Triantafyllou T, Theodoropoulos C, Georgiou G, Kalles V, Chrysikos D, Filis K, et al. Long-term outcome of myotomy and fundoplication based on intraoperative real-time high-resolution manometry in achalasia patients. Ann Gastroenterol. 2019;32(1):46-51.https://doi.org/10.20524/aog.2018.0326
9. Frazzoni M, Piccoli M, Conigliaro R, Frazzoni L, Melotti G. Laparoscopic fundoplication for gastroesophageal reflux disease. World J Gastroenterol. 2014;20(39):14272-9.https://doi.org/10.3748/wjg.v20.i39.14272
10. Yu YR, Rosenfeld EH, Chiou EH, Chumpitazi BP, Fallon SC, Brandt ML. High-resolution manometric guidance during laparoscopic Heller myotomy: Impact on quality of life and symptom severity for children with achalasia. J Pediatr Surg. 2019;54(5):1063-8.https://doi.org/10.1016/j.jpedsurg.2019.01.041
11. Vandewalle RJ, Frye CC, Landman MP, Croffie JM, Rescorla FJ. Clinical factors and high-resolution manometry predicting response to surgery for achalasia in children. J Surg Res. 2018;229:345-50.https://doi.org/10.1016/j.jss.2018.04.027
12. Vaos G, Demetriou L, Velaoras C, Skondras C. Evaluating long-term results of modified Heller limited esophagomyotomy in children with esophageal achalasia. J Pediatr Surg. 2008;43(7):1262-9.https://doi.org/10.1016/j.jpedsurg.2008.02.074
13. Garzi A, Valla JS, Molinaro F, Amato G, Messina M. Minimally invasive surgery for achalasia: combined experience of two European centers. J Pediatr Gastroenterol Nutr. 2007;44(5):587-91.https://doi.org/10.1097/MPG.0b013e318032062f
14. Saliakellis E, Thapar N, Roebuck D, Cristofori F, Cross K, Kiely E, et al. Long-term outcomes of Heller's myotomy and balloon dilatation in childhood achalasia. Eur J Pediatr. 2017;176(7):899-907.https://doi.org/10.1007/s00431-017-2924-x
15. Altokhais T, Mandora H, Al-Qahtani A, Al-Bassam A. Robot-assisted Heller's myotomy for achalasia in children. Comput Assist Surg (Abingdon). 2016;21(1):127-31.https://doi.org/10.1080/24699322.2016.1217352
16. Erginel B, Gun Soysal F, Keskin E, Celik A, Salman T. Early myotomy and fundoplication in achalasia in childhood: a single-centre experience for 22 years. Acta Chir Belg. 2016;116(1):16-8.https://doi.org/10.1080/00015458.2015.1128197
17. Zagory J, Golden J, Demeter N, Nguyễn Y, Ford H, Nguyen N. Heller Myotomy Is Superior to Balloon Dilatation or Botulinum Injection in Children with Achalasia: A Two-Center Review. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2016;26.https://doi.org/10.1089/lap.2015.0435
18. Smits M, van Lennep M, Vrijlandt R, Benninga M, Oors J, Houwen R, et al. Pediatric Achalasia in the Netherlands: Incidence, Clinical Course, and Quality of Life. J Pediatr. 2016;169:110-5.e3.https://doi.org/10.1016/j.jpeds.2015.10.057
19. Caldaro T, Familiari P, Romeo EF, Gigante G, Marchese M, Contini AC, et al. Treatment of esophageal achalasia in children: Today and tomorrow. J Pediatr Surg. 2015;50(5):726-30.https://doi.org/10.1016/j.jpedsurg.2015.02.047
20. Pachl MJ, Rex D, Decoppi P, Cross K, Kiely EM, Drake D, et al. Paediatric laparoscopic Heller's cardiomyotomy: a single centre series. J Pediatr Surg. 2014;49(2):289-92; discussion 92.https://doi.org/10.1016/j.jpedsurg.2013.11.042
21. Esposito D, Maione F, D'Alessandro A, Sarnelli G, De Palma GD. Endoscopic treatment of esophageal achalasia. World J Gastrointest Endosc. 2016;8(2):30-9.https://doi.org/10.4253/wjge.v8.i2.30
22. Tannuri AC, Tannuri U, Velhote MC, Romão RL. Laparoscopic extended cardiomyotomy in children: an effective procedure for the treatment of esophageal achalasia. J Pediatr Surg. 2010;45(7):1463-6.https://doi.org/10.1016/j.jpedsurg.2009.08.023
23. Jung C, Michaud L, Mougenot JF, Lamblin MD, Philippe-Chomette P, Cargill G, et al. Treatments for pediatric achalasia: Heller myotomy or pneumatic dilatation? Gastroenterol Clin Biol. 2010;34(3):202-8.https://doi.org/10.1016/j.gcb.2009.10.022
24. Corda L, Pacilli M, Clarke S, Fell JM, Rawat D, Haddad M. Laparoscopic oesophageal cardiomyotomy without fundoplication in children with achalasia: a 10-year experience: a retrospective review of the results of laparoscopic oesophageal cardiomyotomy without an anti-reflux procedure in children with achalasia. Surg Endosc. 2010;24(1):40-4.https://doi.org/10.1007/s00464-009-0513-4
25. Pastor AC, Mills J, Marcon MA, Himidan S, Kim PC. A single center 26-year experience with treatment of esophageal achalasia: is there an optimal method? J Pediatr Surg. 2009;44(7):1349-54.https://doi.org/10.1016/j.jpedsurg.2008.10.117
26. Askegard-Giesmann JR, Grams JM, Hanna AM, Iqbal CW, Teh S, Moir CR. Minimally invasive Heller's myotomy in children: safe and effective. J Pediatr Surg. 2009;44(5):909-11.https://doi.org/10.1016/j.jpedsurg.2009.01.022
27. Zhang Y, Xu CD, Zaouche A, Cai W. Diagnosis and management of esophageal achalasia in children: analysis of 13 cases. World J Pediatr. 2009;5(1):56-9.https://doi.org/10.1007/s12519-009-0010-9

28. Grabowski A, Korlacki W, Pasierbek M, Pultorak R, Achtelik F, Ilewicz M. Pediatric achalasia. Single-center study of interventional treatment. Prz Gastroenterol. 2017;12(2):98-104.https://doi.org/10.5114/pg.2016.64845
29. Ashraf MN, Kayani MSB, Khan MN. Early childhood achalasia cardia: A local experience. Pakistan Journal of Medical and Health Sciences. 2014;8:744-6
30. Adikibi BT, MacKinlay GA, Munro FD, Khan LR, Gillett PM. Intraoperative upper GI endoscopy ensures an adequate laparoscopic Heller's myotomy. J Laparoendosc Adv Surg Tech A. 2009;19(5):687-9.https://doi.org/10.1089/lap.2008.0156
31. Portale G, Costantini M, Rizzetto C, Guirroli E, Ceolin M, Salvador R, et al. Long-term outcome of laparoscopic Heller-Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. J Gastrointest Surg. 2005;9(9):1332-9.https://doi.org/10.1016/j.gassur.2005.10.001
32. Weche M, Saad AR, Richter JE, Jacobs JJ, Velanovich V. Revisional Procedures for Recurrent Symptoms After Heller Myotomy and Per-Oral Endoscopic Myotomy. J Laparoendosc Adv Surg Tech A. 2020;30(2):110-6.https://doi.org/10.1089/lap.2019.0277
33. Li ZT, Ji F, Han XW, Yuan LL, Wu ZY, Xu M, et al. Role of fundoplication in treatment of patients with symptoms of hiatal hernia. Sci Rep. 2019;9(1):12544.https://doi.org/10.1038/s41598-019-48740-x
34. Devaney EJ, Lannettoni MD, Orringer MB, Marshall B. Esophagectomy for achalasia: patient selection and clinical experience. Ann Thorac Surg. 2001;72(3):854-8.https://doi.org/10.1016/s0003-4975(01)02890-9
35. Fernandez-Ananin S, Fernández AF, Balagué C, Sacoto D, Targarona EM. What to do when Heller's myotomy fails? Pneumatic dilatation, laparoscopic remyotomy or peroral endoscopic myotomy: A systematic review. J Minim Access Surg. 2018;14(3):177-84.https://doi.org/10.4103/jmas.JMAS_94_17
36. Madiwale MV, Sahai S. Nissen fundoplication: a review of complications for the pediatrician. Clin Pediatr (Phila). 2015;54(2):105-9.https://doi.org/10.1177/0009922814540205

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Comparison of PUCAI Score in Mesalazine-Treated Children with Ulcerative Colitis

Nadia Chairunnisa[1], Juwita Pratiwi[1], Ninung Rose Diana[1]

[1]Department of Pediatrics, Gastroenterohepatology Division, Medical University of Diponegoro, Semarang, Indonesia

Corresponding author:
Ninung Rose Diana, M.D.
roseadhiani@yahoo.co.id

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.18-24

Citation:
Chairunnisa N, Pratiwi J, Diana NR. Comparison of PUCAI Score in Mesalazine-Treated Children with Ulcerative Colitis. *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(2):18-24.

Abstract:

Background: Ulcerative colitis is a chronic idiopathic inflammatory bowel disease (IBD) characterized by intestinal inflammation confined to the superficial mucosal layer. Mesalazine, a 5-aminosalicylic acid (5-aminosalicylic, or 5-ASA) compound, is most often used as first-line therapy for mild to moderate ulcerative colitis. *The* Pediatric Ulcerative Colitis Activity Index (PUCAI) is a non-invasive multi-item measure that has been shown to be valid, reliable, and responsive to short-term changes in several clinical trials and cohort studies. Therefore, this study aims to compare the PUCAI scores in children with ulcerative colitis who received mesalazine therapy to those who did not.

Methods: We performed a retrospective database analysis of 12 patients, who were diagnosed with ulcerative colitis at Dr. Kariadi General Hospital, Semarang, Indonesia in a span of 1 year. We included all cases of pediatric patients with ulcerative colitis, then we divided them into 2 groups, the group receiving mesalazine therapy and the group who did not. We monitored the development of PUCAI scores before and after treatment.

Results: The number of samples in this study was 12 samples. All sample data were taken based on data from pediatric gastroenterohepatology patients diagnosed with colitis ulcerative based on pathology anatomy results, who were treated in the pediatric ward of RSUP Dr. Kariadi Semarang. From the result of the paired t-test, there was a significant decrease in PUCAI score in patients who received Mesalazine, ($p = 0.007$), while those who did not receive mesalazine, did not show any significant decrease in PUCAI score.

Conclusion: Ulcerative colitis (UC) is a chronic relapsing inflammatory condition. UC is often treated with mesalazine as the first-line treatment. The use of the PUCAI score is an appropriate tool to determine the progression of this disease. Based on the data obtained, the administration of mesalazine therapy in children with ulcerative colitis can improve PUCAI scores compared to children who do not receive mesalazine therapy.

Keywords: mesalazine, ulcerative colitis, PUCAI score

Introduction

Ulcerative colitis is a chronic idiopathic inflammatory bowel disease (IBD) characterized by intestinal inflammation confined to the superficial mucosal layer. It may involve the rectum only, the distal colon, or the entire colon, usually contiguously. The classic symptoms of ulcerative colitis include bloody diarrhea, urgency, and tenesmus. Mesalazine, a 5-aminosalicylic acid (5-aminosalicylic, or 5-ASA) compound, is most often used as first-line therapy for mild to moderate ulcerative colitis. However, the precise mechanism of action of mesalazine is still poorly elucidated. It is believed to exert a negative effect on the cyclooxygenase and lipoxygenase pathways, thereby reducing the formation of pro-inflammatory prostaglandins and leukotrienes. Peroxisome proliferator-activated gamma-receptors are also involved in colonic inflammation and have been identified as targets of 5-ASA action. Furthermore, mesalazine may have antioxidant properties that reduce tissue injury and play a role in the inhibition of T cell activation and proliferation.[1,2]

Oral mesalazine compounds have been shown to be effective in inducing and maintaining remission in patients with ulcerative colitis. Mesalazine exerts a therapeutic effect through local topical activity on the inflamed mucosa. Oral mesalazine in its unchanged form is almost completely absorbed by the small intestine, with very little of the intact drug reaching the large intestine. Therefore, the main objective of the various formulations currently available in the market is to optimize drug delivery to the affected colon and minimize systemic absorption. This promotes maximum therapeutic efficacy at the lowest possible dose, which in turn reduces side effects.[3,4]

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a non-invasive multi-item measure that has been shown to be valid, reliable, and responsive to short-term changes in several clinical trials and cohort studies. The PUCAI has been proven to have excellent correlation with the invasive Mayo score, physician global assessment, and colonoscopy appearance.[5,6] Therefore, this study aims to compare the PUCAI scores in children with ulcerative colitis who received mesalazine therapy to those who did not.

Methods

We performed a retrospective database analysis of 12 patients, who were diagnosed with ulcerative colitis at Dr. Kariadi General Hospital, Semarang, Indonesia in a span of 1 year. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Committee. We included all cases of pediatric patients with ulcerative colitis, then we divided them into 2 groups, the group receiving mesalazine therapy and the group who did not. We monitored the

development of PUCAI scores before and after treatment. Statistical data was collected and analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Co.). Shapiro-Wilk analysis was used to determine the normality of the data and continued with a paired t-test to compare PUCAI scores before and after therapy. The data is significant if $p < 0.05$.

Results

The number of samples in this study was 12 samples. All sample data were taken based on data from pediatric gastroenterohepatology patients diagnosed with colitis ulcerative based on pathology anatomy results, who were treated in the pediatric ward of RSUP Dr. Kariadi Semarang. Characteristics of the data are in the table below (**Table 1**).

Table 1. Baseline characteristics of children with ulcerative colitis

Characteristics	Frequency
Gender, n (%)	
Boys	7 (41.7)
Girls	5 (58.3)
Age (years) *	7.2±3.9
Pre-treatment PUCAI score*	40.8±18.5
Post-treatment PUCAI score*	5.0±9.2
Length of treatment (days) *	180.0±33.8
Mesalazine therapy, n (%)	
Yes	9 (75)
No	3 (25)

***Data presented in Mean±Standard Deviation. PUCAI: Pediatric Ulcerative Colitis Activity Index.**

Based on the baseline characteristics data, our patients were predominantly boys (41.7%), with mean age of 7.2±3.9 years. The mean pre- and post- treatment PUCAI score were 40.8±18.5 and 5.0±9.2. Nine patients (75%) received mesalazine therapy while the other 3 patients did not. The mean duration of treatment was 180.0±33.8 days.

Shapiro-Wilk analysis was not significant ($p>0.05$) for pre-and post-treatment PUCAI score in both groups, indicating a normal distribution of those data. We then continued with paired-t test to evaluate the changes of PUCAI score pre-and post-treatment in both mesalazine and non-mesalazine group. (**Table 2**)

Table 2. Data normality test

Treatment		p
Pre	Mesalazine	0.85
	Non- mesalazine	1.000
Post	Mesalazine	0.97
	Non- mesalazine	1.000

From the result of the paired t-test, there was a significant decrease in PUCAI score in patients who received Mesalazine, (p = 0.007), while those who did not receive mesalazine, did not show any significant decrease in PUCAI score.(**Table 3**)

Table 3. Comparison of PUCAI score between mesalazine and non-mesalazine

Variables	PUCAI score		p-value
	Pre- treatment	Post- treatment	
Mesalazine	35 (10-75)	0	**0.007***
Non- Mesalazine	38 (20-65)	26 (10-25)	0.213

Discussion

Ulcerative colitis (UC) is a disease with a less heterogeneous phenotype than Crohn's disease (CD) but it still poses many unique challenges. The incidence of pediatric-onset UC, which constitutes roughly 15% to 20% of all UC, ranges from 1 to 4/100,000/year in most North American and European regions. It is extensive in 60% to 80% of all cases and twice as often as in adults. Since disease extent has been consistently associated with disease severity, it is not surprising that children with UC more often require hospitalization for an acute severe exacerbation (25%–30% over 3–4 years) and more often to undergo colectomy for medically refractory disease (up to 30%–40% in a 10-year follow-up), although lower colectomy rates have also been reported.[7]

It is mandated that the rapidly emerging novel therapies for inflammatory bowel diseases (IBDs) be evaluated in the clinical trial setting. Robust outcome measures are of utmost importance in determining the outcome of these trials. No single clinical or biochemical parameter consistently reflects activity of intestinal inflammation and, thus, multi-attribute measures of disease activity have been developed. Although other Crohn's disease (CD) activity indices have been used, the Crohn's Disease Activity Index (CDAI) is generally accepted as the standard clinical outcome measure in adult CD trials. Meanwhile, The Pediatric Crohn's Disease Activity Index (PCDAI) has become the most accepted disease activity measurement in childhood CD. [7]

In 2007, a Pediatric Ulcerative Colitis Activity Index (the PUCAI) was developed and validated using prospectively enrolled cohorts of children with UC. The PUCAI score

which lacks of invasive parameters, is suitable for longitudinal use in clinical trials and for determining the timely introduction of second-line therapy in severe acute UC.

The feasibility of using PUCAI in an outpatient clinical practice setting is also excellent. Over 96% of visits contained all six required components to calculate a PUCAI. The test-retest reliability of the PUCAI was also quite good. This study extends the foundational work completed by Turner, et al by including large sample size and diversity of practice sites (approximately 2000 patients from 35 centers). The PUCAI differentiated very well among the four PGA-based disease severity categories, with a fairly distinct separation between disease categories. The PUCAI change scores also differentiated well among different categories (no change, small, moderate, large) of change in PGA. A small change in PUCAI (indicated with a 10-point change) gave a sensitivity and specificity of approximately 80%.[8]

5-ASA acts topically on the colonic mucosa but is rapidly absorbed if ingested. As such. this drug is usually bound to an inactive carrier in order to prevent early absorption and metabolism within the small bowel. The covalent bond will be cleaved by bacterial diazoreductases, releasing the active form into the colon. Sulfasalazine, olsalazine and balsalazide are known to utilize this mechanism to ensure a more precise drug delivery to the colon. Meanwhile, another formulation of ASA, a pH-sensitive acrylic coated 5-ASA, works by delaying the release of its active compound until luminal pH of 7 in the distal bowel. This allows a bolus of 5-ASA to be released in the terminal ileum and proximal colon. Asacol and salofalk are known to employ this method. Latest formulations, such as Apriso and Lialda, utilize both a pH-sensitive acrylic layer to delay 5-ASA release and a coating of lipophilic and hydrophilic excipients to extend release throughout the colon.[9,10]

Four small pediatric clinical trials and a few retrospective studies confirmed that 5-ASA is effective for inducing remission in mild to moderate UC in children, achieving endoscopic remission in 27% after 12 weeks. There are no pediatric trials evaluating combined oral and rectal 5-ASAs, nor the effectiveness of 5-ASA in maintaining remission. The Cochrane meta-analysis showed a trend that suggest better benefit of the newer 5-ASA preparations (in terms of both efficacy and minimizing adverse effects) over sulfasalazine for inducing remission, but sulfasalazine was superior for maintaining remission. In contrast, the recent meta-analysis showed no difference in both inducing and maintaining remission. One pediatric double-blinded randomized clinical trial (RCT) showed that olsalazine 30 mg/ kg/ day induced a clinical response in 39% versus 79% with sulfasalazine 60 mg/ kg/ day after 3 months in 56 children with mild to moderate UC. Results from another pediatric trial suggested equivalent efficacy of mesalazine and sulfasalazine in maintaining remission in either UC or Crohn's colitis. A dedicated meta-analysis comparing the efficacy of sulfasalazine

versus newer 5-ASA included 20 RCTs and showed no major differences of efficacy and adverse events.[9]

In this study, it was shown that mesalazine therapy could significantly reduce PUCAI scores in children with ulcerative colitis. Several studies have shown that administering mesalazine to mild to moderate pediatric UC has low effectiveness. But the intention-to-treat 35% remission rate at week 6 is consistent with published data from other studies. Clinical remission in adults has been reported in only 28–46% of active patients. Comparisons between adult and pediatric results, however, are not straightforward. A PUCAI-defined remission is more difficult to achieve as compared with a Mayo-defined remission, used in the aforementioned adult trials. A Mayo-defined remission may still allow some blood in the stool. Pediatric data to benchmark our results are scarce. A small trial with only 15 patients in the 5-ASA arm had a similar PUCAI-defined remission rate of 35% at 8 weeks. Another pediatric trial found a PUCAI-defined remission rate of 40% in the standard-dose and 48% in the high-dose mesalazine groups, slightly higher than in our study.[6] However, that trial included a higher proportion of children with mild disease [25% of children in our trial versus ~50% in the aforementioned study]. A North American pediatric registry found that only 31% of children with UC treated with 5-ASA at disease onset were in steroid-free remission and had no treatment escalation at 1 year.[10]

According to the ESPGHAN-ECCO [European Society for Paediatric Gastroenterology Hepatology and Nutrition and European Crohn's and Colitis Organization] guidelines, 5-ASA is the first-line treatment in mild-moderate pediatric UC. However, pediatric gastroenterologists should be aware of the fact that patients may need to change to second-line treatment especially in children with PUCAI score of > 45 on day 3. Some studies show that mesalazine therapy takes 2–3 weeks for adequate response, as such, a lack of response by 3 weeks should trigger a change in treatment. This is consistent with our study which showed that the average treatment for ulcerative colitis was more than 3 weeks.[10]

Conclusion

Ulcerative colitis (UC) is a chronic relapsing inflammatory condition. UC is often treated with mesalazine as the first-line treatment. The use of the PUCAI score is an appropriate tool to determine the progression of this disease. Based on the data obtained, the administration of mesalazine therapy in children with ulcerative colitis can improve PUCAI scores compared to children who do not receive mesalazine therapy.

Conflict of Interest

None declared.

Funding Statement

There is no specific grant from any funding agency involved in this study.

References

1. Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A, et al. Rural and Urban Residence During Early Life is Associated with Risk of Inflammatory Bowel Disease: A Population-Based Inception and Birth Cohort Study. Am J Gastroenterol. 2017;112(9):1412-22.https://doi.org/10.1038/ajg.2017.208
2. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology. 2017;152(2):313-21.e2.https://doi.org/10.1053/j.gastro.2016.10.020
3. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3):343-56.e3.https://doi.org/10.1016/j.cgh.2017.06.016
4. Gundersen MD, Goll R, Fenton CG, Anderssen E, Sørbye SW, Florholmen JR, et al. Fibrosis Mediators in the Colonic Mucosa of Acute and Healed Ulcerative Colitis. Clin Transl Gastroenterol. 2019;10(10):e00082.https://doi.org/10.14309/ctg.0000000000000082
5. Gordon IO, Agrawal N, Willis E, Goldblum JR, Lopez R, Allende D, et al. Fibrosis in ulcerative colitis is directly linked to severity and chronicity of mucosal inflammation. Aliment Pharmacol Ther. 2018;47(7):922-39.https://doi.org/10.1111/apt.14526
6. Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative Colitis and Crohn's Disease Have Similar Burden and Goals for Treatment. Clin Gastroenterol Hepatol. 2020;18(1):14-23.https://doi.org/10.1016/j.cgh.2019.07.005
7. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114(3):384-413.https://doi.org/10.14309/ajg.0000000000000152
8. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis-An Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;67(2):292-310.https://doi.org/10.1097/mpg.0000000000002036
9. Christensen B, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, et al. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. Clin Gastroenterol Hepatol. 2017;15(10):1557-64.e1.https://doi.org/10.1016/j.cgh.2017.02.016
10. Santha SL, Shankar PR, Pan A, Schoen B, Kugathasan S, Sauer CG. Mucosal Healing in Clinical Practice: A Single-Center Pediatric IBD Experience. Inflamm Bowel Dis. 2017;23(8):1447-53.https://doi.org/10.1097/mib.0000000000001176

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Infantile Hyperchylomicronemia Due to A Novel GPIHBP1 Disease-Causing Variant Presenting with Milky Blood: A Rare Case Report

Iman Marzouq[1], Basant Elbanna[1], Sabine Schröder[2], Kornelia Tripolszki[2], Aida M. Bertoli-Avella[2], Aml Mahfouz[1]

[1] Paediatric Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

[2] CENTOGENE GmbH, Rostock, Germany

Corresponding author:
Basant Elbanna
b_abdelazim14@alexmed.edu.eg

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.25-31

Citation:
Marzouq I, Elbanna B, Schröder S, Tripolszki K, Bertoli-Avella AM. Mahfouz A. Infantile Hyperchylomicronemia Due to A Novel GPIHBP1 Disease-Causing Variant Presenting with Milky Blood: A Rare Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2023;2(2):25-31.

Abstract:

Background: Familial hyperchylomicronemia is a very rare autosomal recessive disorder and the most severe type of pediatric hyperlipidemia. The purpose of this case report is to enhance clinician's insight on the diagnosis and management plan in the case of infantile hyperchylomicronemia presenting with milky blood.

Case: We reported a 2-month-old infant with familial chylomicronemia syndrome. The patient was 'accidentally' diagnosed by the observation of milky blood. Exome sequencing revealed a homozygous likely pathogenic GPIHBP1 variant (NM_178172.5:c.193T>C p.(Cys65Arg)) confirming the diagnosis. He was treated with low-fat diet, a formula rich in medium-chain triglycerides and fenofibrates. After 4 days, his serum triglycerides decreased markedly. Fenofibrates were stopped at the age of one year and his serum triglycerides were maintained at low level with dietary measures. No complications occurred during two years follow-up period.

Discussion: Clinical manifestations of familial chylomicronemia syndrome start in early life with a very high level of hypertriglyceridemia and with monogenetic etiology, in contrast to multifactorial chylomicronemia syndrome that starts in adulthood, with proposed polygenic etiology. The main treatment of familial chylomicronemia syndrome is dietary fat restriction to less than 15% of the total caloric intake and medium-chain triglycerides which can bypass the chylomicron pathway of fat metabolism.

Conclusion: The main challenge in this case was the early diagnosis to protect the patient against serious complications. The mainstay of therapy is low-fat diet and medium-chain triglycerides. This case illustrates the relevance of establishing a timely genetic diagnosis and treatment.

Keywords: chylomicronemia, GPIHBP1, milky blood, medium-chain triglycerides, fenofibrates

Introduction

Familial hyperchylomicronemia is a very rare autosomal recessive disorder.[1] Chylomicrons transport dietary fat in the circulation and very-low density lipoproteins (VLDL) transport endogenous triglycerides. Triglycerides are cleared from the circulation by lipoprotein lipase (LPL). Normally chylomicrons are cleared from the circulation by three to four hours after a meal.[2] The chylomicronemia syndrome (CS) may be due to monogenic (familial chylomicronemia syndrome (FCS)) or polygenic etiology.[1, 2] FCS is due to mutation in the LPL gene or cofactors responsible for regulation of its activity.[1] Clinical presentation includes milky blood, hepatomegaly, xanthoma, lipemia retinalis, and acute pancreatitis.[1] The main treatment of FCS is dietary fat restriction to less than 15% of the total caloric intake and medium chain triglycerides.[1, 2]

Case

A two-month-old infant born to a first cousin marriage was exclusively breastfed since birth. He had two older healthy siblings. He presented to us at the emergency ward with parental concern of irritability. Physical examination revealed low-grade fever, unexplained irritability, anthropometric measures were average to age, lax abdomen, no organomegaly nor xanthomas, and fundus examination was negative for lipemia retinalis. Milky blood was reported during blood sampling (**Figure 1**). Subsequent laboratory investigations are shown in **Table 1**. The results of lipid electrophoresis are shown in **Table 2**.

Figure 1. Milky blood presenting in the case

Given the very high level of serum triglycerides, fasting hyperchylomicronemia and after exclusion of secondary causes (normal liver, renal function, thyroid profile, and random blood sugar), the possible diagnosis of FCS was suggested. He was admitted on intravenous fluids and formula rich in medium-chain triglycerides (MCT), he received fenofibrates 40 mg orally and omega-3 fatty acids. His symptoms improved after two days. His serum triglycerides markedly decreased (1197 mg/dL) after 4 days and he was discharged. Upon introduction of breastfeeding (25%) concomitantly with MCT formula (75%) for 1 week, serum triglyceride level increased again (3906

mg/dL). Thus, breastfeeding was stopped and continued with MCT formula, fibrates and omega-3 fatty acids. Lipid profile for all tested family members was normal. On follow-up visits, he was maintained on low-fat diet and same management. He acquired normal developmental milestones. At one year of age, fenofibrate therapy was stopped and the therapy was continued low-fat diet, MCT formula, and omega-3 fatty acids. His follow-up serum triglyceride level did not exceed 1000 mg/dL for two years period and without any complications.

Table 1. Initial laboratory investigations

Parameters	Result	Reference range[3, 4]
White blood cells	15.64	(5.5-17) 10^3/ uL
Hemoglobin	9.5!	(10.6-13.7) g/ dL
Platelet count	646	(150-500) 10^3/ uL
ALT	12	Up to 45 U/L
Urea	11	(10-50) mg/dL
BUN	5	(6-23) mg/dL
Creatinine	0.22	(0.2-0.4) mg/dL
Total cholesterol	119	Up to 200 mg/dL
Triglycerides	20364*	Up to 200 mg/dL
HDL-Cholesterol	8	More than 35 mg/dL
LDL-Cholesterol	48	Up to 140 mg/dL
TSH	4.8	(1.7-9.1) uIU/ml
Free T4	1.2	(0.8-2) ng/dL

*very high triglycerides level, !normocytic normochromic anemia

Table 2. Results of lipid electrophoresis

Parameters	Result	Reference range[3, 4]
Alpha Lipoprotein	1 %	22-46 %
Pre Beta Lipoprotein	49%	Up to 27%
Beta Lipoprotein	3%	47-71%
Chylomicrons	47%	Absent

To identify the cause of chylomicronemia, DNA was extracted from dried blood spot (DBS) on filter card (CentoCard ®). Exome sequencing was performed as previously described, using the Twist Human Core Exome Plus Kit and sequencing on an Illumina platform to obtain at least 20x coverage depth for >98% of the targeted bases.[5] An inhouse (CENTOGENE) bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling, annotation, and comprehensive variant filtering was applied. The analysis revealed a homozygous missense variant in the GPIHBP1 gene: NM_178172.5:c.193T>C, p.(Cys65Arg). This result confirmed the clinical diagnosis of monogenic FCS. The detected variant is extremely rare (not present in any public database), and the in-silico tools predict that this variant is damaging. In CENTOGENE's bio-databank, this GPIHBP1 variant

has been detected in two additional patients from Egypt, presenting with a similar phenotype. The variant is classified as likely pathogenic according to the ACMG-ClinGen established criteria.

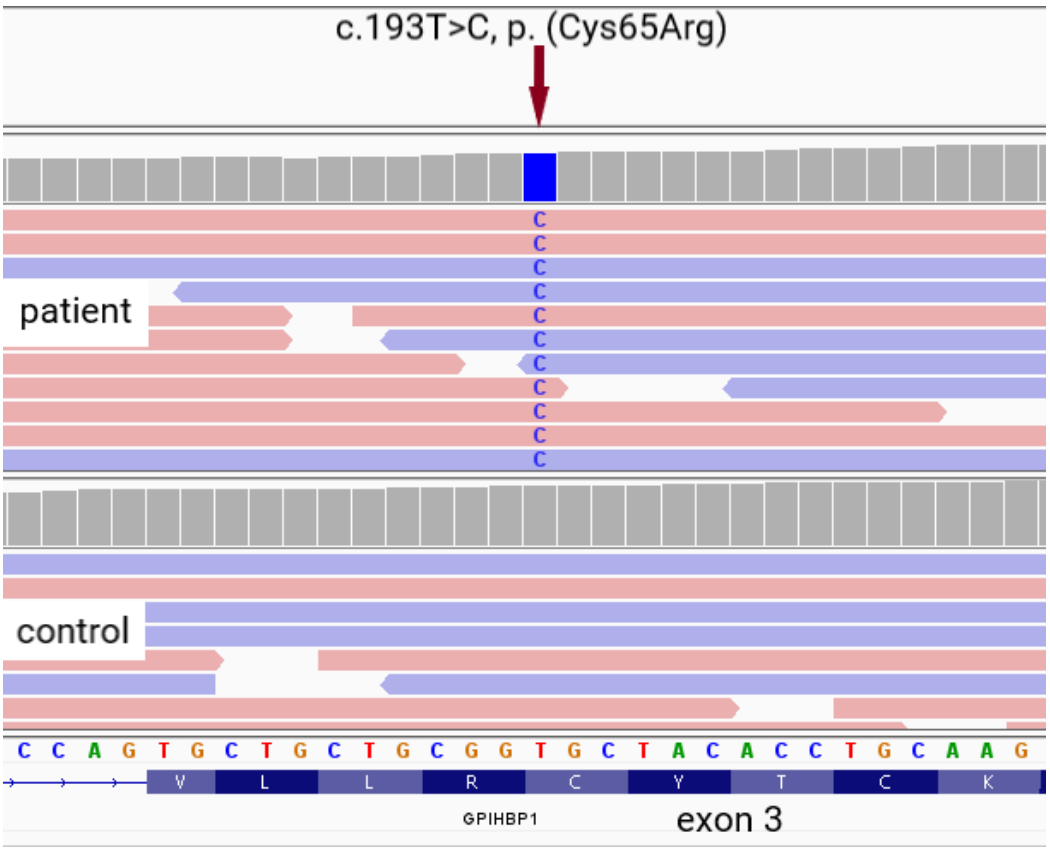

Figure 2. Bam file showing the GPIHBP1 (NM_178172.5:c.193T>C p.(Cys65Arg)) variant indicated with arrow. Total read count with the variant is 113 (variant allele frequency: 100%). Visualized by the Broad Institute Integrative Genomics Viewer.

Discussion

We present the case of an Egyptian patient with an early clinical and genetic diagnosis of familial Chylomicronemia Syndrome (FCS). Timely medical treatment was implemented with favorable response and absence of clinical complications.

Clinical manifestations of FCS start in early life with a very high level of hypertriglyceridemia and with monogenetic etiology, in contrast to multifactorial chylomicronemia syndrome that starts in adulthood, with proposed polygenic etiology.[2] The studied case had very high hypertriglyceridemia (> 20000 mg/dL), with fasting chylomicronemia in early infancy. A genetic diagnosis was established by exome sequencing and the detection of a rare homozygous likely pathogenic variant in GPIHBP1, c.193T>C p.(Cys65Arg). Previous case studies reported missense and loss of function variants (nonsense, deletions, duplications, splicing) in the same gene, with 51 variants registered in Human Gene Mutation Database (HGMD). Several authors have reported missense variants affecting the same Cys65 residue detected in our case. Olivecrona et al.[6] reported three siblings with mutations involving cysteines in the Ly6 domain of GPIHBP1 (Cys65Ser and Cys68Gly). Also, Franssen et al.[7] reported a young boy with the variant Cys65Tyr, suggesting that these residues are relevant for the protein function.

FCS can present with nonspecific symptoms such as fever and irritability.[8] Milky blood can be detected during blood sampling, as reported in the current case.[1] Similar findings were reported by Mo Kyung Jung et al.[8], Nehal M. El-koofy et al.[9], N. El Idrissi Slitine et al[10], and Shwetha Kuthiroly et al.[11]. Other clinical presentations include eruptive xanthoma, lipemia retinalis and hepatomegaly.[11, 12, 13, 14] The most serious complication in FCS is the development of acute pancreatitis.[11,14] Other clinical complications include chylothorax, cerebral thrombophlebitis, lipid encephalopathy.[11, 13, 15, 16] The studied case presented only with irritability and milky blood with no hepatomegaly, xanthoma, lipemia retinalis nor pancreatitis. The prevention of these complications is likely due to the early diagnosis and treatment.

The main treatment of FCS is dietary fat restriction to less than 15% of the total caloric intake and medium-chain triglycerides which can bypass the chylomicron pathway of fat metabolism.[1, 2] High doses of omega-3 fatty acids (4–6 gram eicosapentaenoic acid (EPA) or doxosahexaenoic acid (DHA) daily) can reduce the production of VLDL and size of chylomicrons. It can also activate LPL lipolysis by apo C3 inhibition.[1] Lipid-lowering drugs as fibrates, nicotinic acid and statins are not Food and Drug Administration (FDA) approved for use in pediatrics younger than 18 years of age. Their use in marked hypertriglyceridemia is of little effect.[1] Lipid apheresis can be used in severe hypertriglyceridemia.[1] The studied case was treated with low-fat diet, medium-chain triglycerides, fibrates, and omega-3 fatty acids. Although it is

recommended not to stop breastfeeding[17], our attempts to breastfeeding were unsuccessful as reported previously by Callum J et al.[13] and Nehal M. El-koofy et al.[9]

Conclusion

We present a young patient clinically diagnosed with FCS, and genetically confirmed by exome sequencing with a novel likely pathogenic variant in GPIHBP1. We highlight the importance of early disease detection and treatment to prevent severe complications such as cerebral complications and acute pancreatitis. Screening of hyperchylomicronemia could be considered as part of the newborn screening program.

Conflict of Interest

Sabine Schröder, Kornelia Tripolszki, Aida M. Bertoli-Avella are employees of CENTOGENE GmbH.

Funding Statement

The authors confirm that the presented case study did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgement

The authors would like to thank the Alexandria University Children's Hospital nursing staff for providing the needed care.

References

1. Brahm AJ, Hegele RA. Chylomicronaemia--current diagnosis and future therapies. Nat Rev Endocrinol. 2015;11(6):352-62.https://doi.org/10.1038/nrendo.2015.26
2. Goldberg RB, Chait A. A Comprehensive Update on the Chylomicronemia Syndrome. Front Endocrinol (Lausanne). 2020;11:593931.https://doi.org/10.3389/fendo.2020.593931
3. Bain BJ, Bates I, Laffan MA. Dacie and lewis practical haematology e-book: Elsevier Health Sciences; 2016.
4. Rifai N. Tietz textbook of clinical chemistry and molecular diagnostics-e-book: Elsevier Health Sciences; 2017.
5. Trujillano D, Oprea GE, Schmitz Y, Bertoli-Avella AM, Abou Jamra R, Rolfs A. A comprehensive global genotype-phenotype database for rare diseases. Mol Genet Genomic Med. 2017;5(1):66-75.https://doi.org/10.1002/mgg3.262
6. Olivecrona G, Ehrenborg E, Semb H, Makoveichuk E, Lindberg A, Hayden MR, et al. Mutation of conserved cysteines in the Ly6 domain of GPIHBP1 in familial chylomicronemia. J Lipid Res. 2010;51(6):1535-45.https://doi.org/10.1194/jlr.M002717
7. Franssen R, Young SG, Peelman F, Hertecant J, Sierts JA, Schimmel AW, et al. Chylomicronemia with low postheparin lipoprotein lipase levels in the setting of GPIHBP1 defects. Circ Cardiovasc Genet. 2010;3(2):169-78.https://doi.org/10.1161/circgenetics.109.908905
8. Jung MK, Jin J, Kim HO, Kwon A, Chae HW, Kang SJ, et al. A 1-month-old infant with chylomicronemia due to GPIHBP1 gene mutation treated by plasmapheresis. Ann Pediatr Endocrinol Metab. 2017;22(1):68-71.https://doi.org/10.6065/apem.2017.22.1.68
9. El-koofy NM, Abdo YA, El-Fayoumi D, Esmael AF, Elmonem MA, Ezzeldin Z. Management strategy and novel ophthalmological findings in neonatal severe hypertriglyceridemia: a case report and literature review. Lipids in Health and Disease.

2021;20(1):38.https://doi.org/10.1186/s12944-021-01464-2
10. El Idrissi Slitine N, Bennaoui F, Louachama O, Habibi L, Fdil N, Tali A, et al. Lipoprotein Lipase (LPL) Gene Mutation: A First Report in Children. International Journal of Pediatrics. 2017;5(10):5839-42.https://doi.org/10.22038/ijp.2017.25461.2163
11. Kuthiroly S, Yesodharan D, Radhakrishnan N, Ganapathy A, Mannan AU, Hoffmann MM, et al. Lipoprotein Lipase Deficiency. Indian J Pediatr. 2021;88(2):147-53.https://doi.org/10.1007/s12098-020-03305-z
12. Sustar U, Groselj U, Khan SA, Shafi S, Khan I, Kovac J, et al. A homozygous variant in the GPIHBP1 gene in a child with severe hypertriglyceridemia and a systematic literature review. Frontiers in Genetics. 2022;13.https://doi.org/10.3389/fgene.2022.983283
13. Wilson CJ, Priore Oliva C, Maggi F, Catapano AL, Calandra S. Apolipoprotein C-II deficiency presenting as a lipid encephalopathy in infancy. Ann Neurol. 2003;53(6):807-10.https://doi.org/10.1002/ana.10598
14. Aycan Z, Berberoğlu M, Ocal G, Altundas N, Adiyaman P, Evliyaoğlu O. Neonatal diabetes with hyperchylomicronemia. Indian J Pediatr. 2002;69(12):1087-9.https://doi.org/10.1007/bf02724395
15. Onci Es S, Lamzouri O, Bouchlarhem A, Haddar L, Mohammed A, mimouni H, et al. A very rare case of chylomicronemia revealed by cerebral thrombophlebitis in a 4-month-old infant. Ann Med Surg (Lond). 2022;75:103276.https://doi.org/10.1016/j.amsu.2022.103276
16. Millichap J. Apolipoprotein C-II Deficiency with Encephalopathy. Pediatric Neurology Briefs. 2003;17(7). https://doi.org/10.15844/pedneurbriefs-17-7-8
17. Rohrs HJ, Berger S. Pediatric lipid disorders in clinical practice. Medscape [Internet] Accessed. 2016;10

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Crohn's Disease in Children: A Case Report

Nicodemus[1], Nuraini Irma Susanti[2]
[1]Pediatric Intensive Care Unit, Mayapada Hospital, South Jakarta, Indonesia
[2] Pediatric Gastroenterologist, Mayapada Hospital, South Jakarta, Indonesia

Corresponding author:
Nicodemus, M.D.
nicodemus_suwandy92@yahoo.com
nicodemus_suwandy@yahoo.co.id

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.32-45

Citation:
Nicodemus, Susanti NI. Crohn's Disease in Children: A Rare Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2023;2(2):32-45.

Abstract:

Background: Crohn's disease in children is a chronic inflammatory bowel disease (IBD). The incidence of this disease has tended to increase in recent decades. This case report aimed to increase clinician insight into Crohn's disease.

Case: We reported a case of Crohn's disease, one of the inflammatory bowel disease (IBD) type in a 16-year-old boy. The patient came with complaints of loose stools without mucus and blood, accompanied by heartburn, nausea, vomiting, and decreased appetite. The patient had a history of changes in defecation patterns in the last 4 months and decreased appetite and weight loss in the last 1 month. There was epigastric tenderness on physical examination. Inflammatory markers and fecal calprotectin values were increased. Gastrointestinal endoscopy results found pangastritis and pancolitis with histopathological examination showing results appropriate to IBD. The patient received corticosteroid methylprednisolone 1 mg/kg/day as induction therapy and experienced improvement in symptoms and laboratory results after 7 days of therapy.

Discussion: There are characteristic differences between Crohn's disease and ulcerative colitis. A definite diagnosis is made by endoscopy and histopathological examination. The current goal of Crohn's disease therapy is no longer limited to improving symptoms or optimizing growth and development, but also targeting the improvement of the gastrointestinal mucosa. Remission induction therapy can be carried out with exclusive enteral nutrition or corticosteroids which are gradually reduced.

Conclusion: This case report increases clinician insight into the characteristics, approaches to IBD diagnosis, and remission induction therapy in Crohn's disease in children.

Keywords: Crohn's disease, inflammatory bowel disease, pediatric

Introduction

Inflammatory bowel disease (IBD) is a chronic disease condition causing problems in children, such as growth and developmental disorders. Inflammatory bowel disease includes Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease involves the entire digestive tract from mouth to anus, while ulcerative colitis affects the colon. The incidence and prevalence of IBD are increasing, and 20-30% of cases occur before the age of 20 years.[1] Inflammatory bowel disease that occurs in children tends to be more progressive and aggressive than in adults. Crohn's disease is more common in children than ulcerative colitis with a male-to-female ratio of 1.8:1.[2] In recent decades, there has been an increase in cases of Crohn's disease in children. It is estimated that 10% of patients with Crohn's disease are diagnosed before the age of 17 years.[3] Data on IBD in children in Asian countries show variations, as in Singapore there has been a 10-fold increase from 0.23 to 2.28 per 100,000 population in the last 20 years.[4] Meanwhile in Korea, the incidence of IBD in children increased from 0.86 to 3.33 per 100,00 population, with an increase of 0.67 to 2.78 for Crohn's disease in children and 0.19 to 0.56 for ulcerative colitis in children.[5] Along with developments, the goals of therapy has changed from initially only relieving and controlling symptoms to now improving the mucosa (mucosal healing). This case report aimed to increase clinician insight into diagnosing and providing adequate management of pediatric patients with IBD, especially Crohn's disease.

Case

A 16-year-old boy, weight 65 kg and height 169 cm came to the Emergency Room with complaints of weakness, loose stools for 2 days before admission to the hospital accompanied by nausea and vomiting for more than 10 times, and abdominal pain in the pit of the stomach for 1 day before admission to the hospital. The patient has had a history of intermittent diarrhea for 4 months before admission to the hospital. When the patient had diarrhea, the frequency could be up to 10 times a day with the consistency varying from liquid to dregs. The average duration of diarrheal episodes lasted 1 week, interspersed with diarrhea-free episodes for 1 week, and then diarrhea returned. Recurrent diarrhea was experienced intermittently and accompanied by a stomach feeling twisted. There was no mucus or blood in the patient's stool. The patient also experienced anorexia and lost 5 kg of weight in the last 1 month. From the physical examination, the patient was fully conscious, vital signs were within normal limits, and abdominal tenderness was found in the epigastric region. Laboratory results showed leucocytosis (25.2 thousand/uL) with eosinophilia (58%) and increased C-reactive protein (CRP 48.45 mg/L). Blood sedimentation rate (ESR) was normal and IGRA was negative. The results of the stool analysis showed occult blood (+) and increased fecal calprotectin (137.6). No leukocytes, amoebas, or bacteria were found in the patient's feces. The stool culture was negative. The patient was admitted to the hospital with a normal soft diet, received fluid infusion, and was

treated medically with anti-emetics, proton pump inhibitors (PPI), probiotics, and broad-spectrum antibiotics.

Diagnostic endoscopy was performed on the patient. From the esophagoduodenoscopy and colonoscopy result, it can be concluded the patient had severe pangastritis and pancolitis (**Figure 1** and **Figure 2**).

Tissue biopsies were performed from the antrum, corpus, duodenum, caecum, and ascending colon to the rectum. The results of the anatomic histopathological examination of the gastric section were active chronic gastritis, non-atrophic, non-dysplastic USS grade IV, stage 0, and H.pylori was not found. Interpretation of histopathological anatomy from the duodenum to the rectum showed non-specific duodenitis, active chronic colitis, and proctitis with moderate to severe degree of activity.

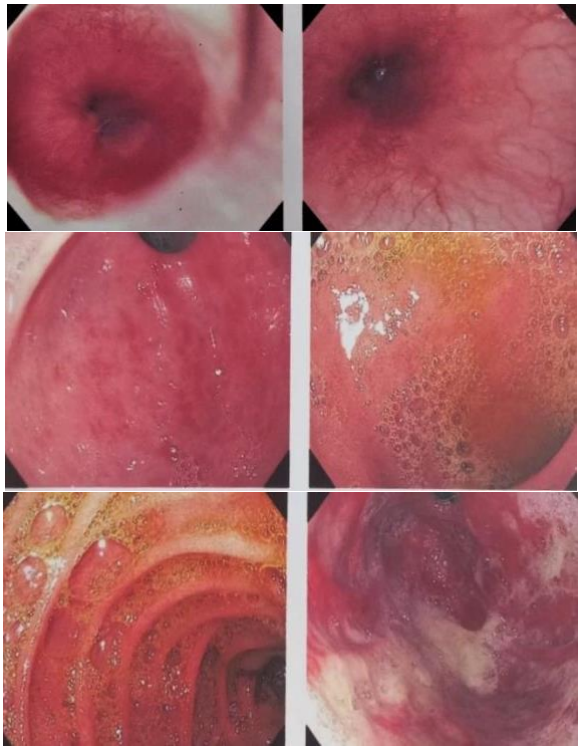

Figure 1. Esophagogastroduodenoscopy (EGD) of the patient showing diffuse hyperemic mucosa of the fundus, corpus, antrum, and pyloric with moderate edema.

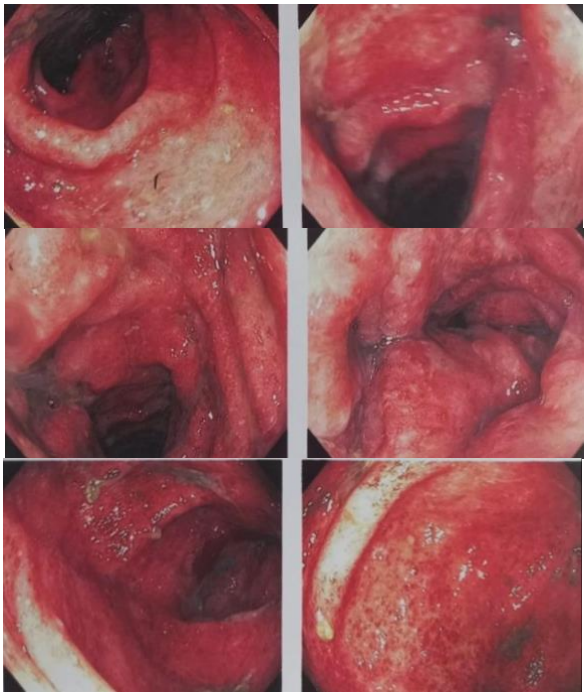

Figure 2. Colonoscopy of the patient showing diffuse erosive hyperemic mucosa of the ascending, transverse, descending colon, caecum, rectum and sigmoid.

Overall, it can be concluded that the picture found supports IBD with severe inflammation from the stomach to the rectum with a moderate-severe degree of activity and a chronic picture of crypt distortion in the caecum to the ascending colon. In all preparations, no dysplasia was found. Based on history, physical examination, laboratory results, and endoscopy results the patient was diagnosed with pangastritis and pancolitis e.c IBD e.c Crohn's disease. The patient tried to be given an enteral nutrition but the tolerance was not good because there was nausea and profuse vomitting. Enterall nutrition is still given in combination with total parenteral nutrition (TPN) to meet nurtitional needs. The patient received methylprednisolone 1 mg/kg/day intravenously. After 7 days of receiving steroid, the patient showed improvement in symptoms with laboratory evaluation results showing improvement in CRP to normal. The patient was allowed to discharge with oral methylprednisolone 1 mg/kg/day for 1 week which was planned to be reduced gradually according to further clinical evaluation (tapering dose).

Discussion

Inflammatory bowel disease (IBD) is an immune-mediated disease. Children with IBD show a more severe degree of disease than adults. Among pediatric IBD patients, 44% require surgery at some point, and 29% have one or more relatives with IBD.[6] A family history of IBD is often found in patients with Crohn's disease who are diagnosed before the age of 11 years.[7] The causes and pathogenesis of IBD are remain unknown. The disease is thought to involve multiple genetic components at more than 200 loci. The genes associated with IBD are broadly related to the immune response. Several genetic defects lead to impaired intestinal epithelial function or predispose to adaptive and humoral immune responses. Overall, the interaction between genetics, the immune system, and the gastrointestinal microbiota environment play an important role in the occurrence of Crohn's disease and the ongoing inflammatory process.[8] In Korean children with Crohn's disease, the IL23R gene and its variants are associated with progression to stenosis.[9] Crohn's disease in children in Asia predominantly affects the ileocolonic with the most common inflammatory phenotype.[10]

IBD in children has a variety of symptoms, both gastrointestinal and extra-intestinal symptoms. Early symptoms of patients with IBD include abdominal pain, diarrhea, and blood in the stools which are frequent manifestations[11]. In ulcerative colitis, the most common manifestations are abdominal pain and bloody diarrhea, whereas, in Crohn's disease, the manifestations are diarrhea, abdominal pain, weight loss, growth retardation, and anorexia.[1] Growth retardation has been reported in up to 20% of children with Crohn's disease and growth failure in up to 44% of children younger than the age of 6 years with IBD.[12] In our patients found abdominal pain in the pit of the stomach, symptoms of diarrhea recurrent and intermittent in which there is no visible blood, weight loss, and anorexia. The nutritional status of the patient is still good.

Some important aspects in the management of pediatric IBD in Asia are early diagnosis and referral by increasing the ability of general practitioners and public awareness, making the right diagnosis, and ruling out other diagnoses, especially infections and gastrointestinal tuberculosis (TB) where this can cause colitis and mimic Crohn's disease, and cost-effective therapy strategies. As TB is endemic in Asia, ruling out TB needs to be considered as an initial step in establishing a diagnosis.[13] In our patient, there were no leukocytes, bacteria, or amoebas in the patient's stool and the IGRA examination results were negative so the possibility of infection and intestinal TB could be ruled out.

In most children with IBD, especially Crohn's disease, inflammatory markers are increased so laboratory tests are needed including complete peripheral blood, CRP, ESR, kidney function, liver function (SGOT/SGPT, albumin), fecal calprotectin, and

stool analysis and culture. The possibility of infection must be ruled out by examination of a stool culture. The use of fecal calprotectin as an indicator of IBD is increasing. Calprotectin is significantly associated with mucosal inflammation in pediatric IBD and may be a major marker of inflammation.[14] Fecal calprotectin can also be used for disease monitoring.[15] In our patient, found leukocytosis accompanied by increased markers of inflammation (CRP 44.35 mg/L), stool analysis possitive of occult blood with increased fecal calprotectin, and negative stool culture. This supports the diagnosis of IBD.

Radiological imaging in pediatric IBD includes ultrasonography (USG), computed tomography (CT-scan), and magnetic resonance enterography (MRE). Ultrasonography can be used to visualize characteristics of Crohn's disease such as bowel thickening, dilatation, strictures, presence or absence of abscesses, fistulas, or inflammation of the mesentery. CT scan and MRI can be used to find out other abnormalities that may accompany or cause symptoms similar to IBD. The American College of Radiology (ACR) mentions that for pediatric patients with suspected Crohn's disease, CT-enterography and MRE examinations are equally good. Nevertheless, a definite diagnosis of IBD must be established by endoscopic examination of the gastrointestinal tract accompanied by histopathological examination.

Gastrointestinal endoscopy should be performed in all cases with suspected IBD and multiple histological biopsies taken from all parts of the gastrointestinal tract to differentiate Crohn's disease from ulcerative colitis.16 Total colonoscopy with ileum intubation, upper gastrointestinal endoscopy, multiple biopsies and exploration of the bowel are recommended as diagnostic procedures.17 The difference between Crohn's disease and ulcerative colitis is sometimes not clearly defined. Involvement of almost the entire digestive tract with a wide distribution of inflammation and the presence of granulomas makes the diagnosis more suggestive of Crohn's disease than ulcerative colitis. In our patient, endoscopic results found pangastritis and pancolitis which indicated involvement of almost the entire digestive tract accompanied by a wide distribution of inflammation.

Complete comparison of Crohn's disease and ulcerative colitis is presented in **Table 1**.

Table 1. Comparison of the characteristics of Crohn's disease and ulcerative colitis[1]

Characteristics	Crohn's disease	Ulcerative Colitis
Gender	boy > girl	boy = girl
Symptoms and signs	Abdominal pain, diarrhea, anorexia, weight loss, growth failure	Massive bloody diarrhea, abdominal pain
Location	Mouth to anus, involving all layers of the mucosa - serosa	Colon, involving only the mucosa
Endoscopic findings	Segmental distribution, aphthous ulcers, deep ulcers, cobble stones, strictures, fistulas	Diffuse and continuous erythema
Histological Findings	Pathognomonic non-caseating granuloma, ileitis	Cryptitis, crypt abscess, distal Paneth cell metaplasia
Radiological findings	Skip area, rigid stenotic segment	Colonic dilatation in toxic megacolon

Based on the history, symptom characteristics, laboratory results, endoscopy results, and histopathological examination results, the diagnosis of Crohn's disease was made in our patient.

Initially, the goals of IBD therapy in children were to relieve symptoms, optimize growth, and improve the patient's quality of life. To achieve these, tight control of inflammation is essential. However, the new paradigm of the current goal of IBD therapy in children is to achieve mucosal healing.[18] (**Figure 3** and **Table 2**). Achievement of mucosal healing is associated with better long-term outcomes.[19] Normal histological features are the main focus of current therapy. In Asia, the goals of Crohn's disease therapy in children include normal growth, absence of disability, and improvement of quality of life, as well as mucosal healing as a long-term goal of therapy.[20] However, in some parts of Asia Pacific with limited resources, it may not be possible to achieve the goal of endoscopic mucosal healing.

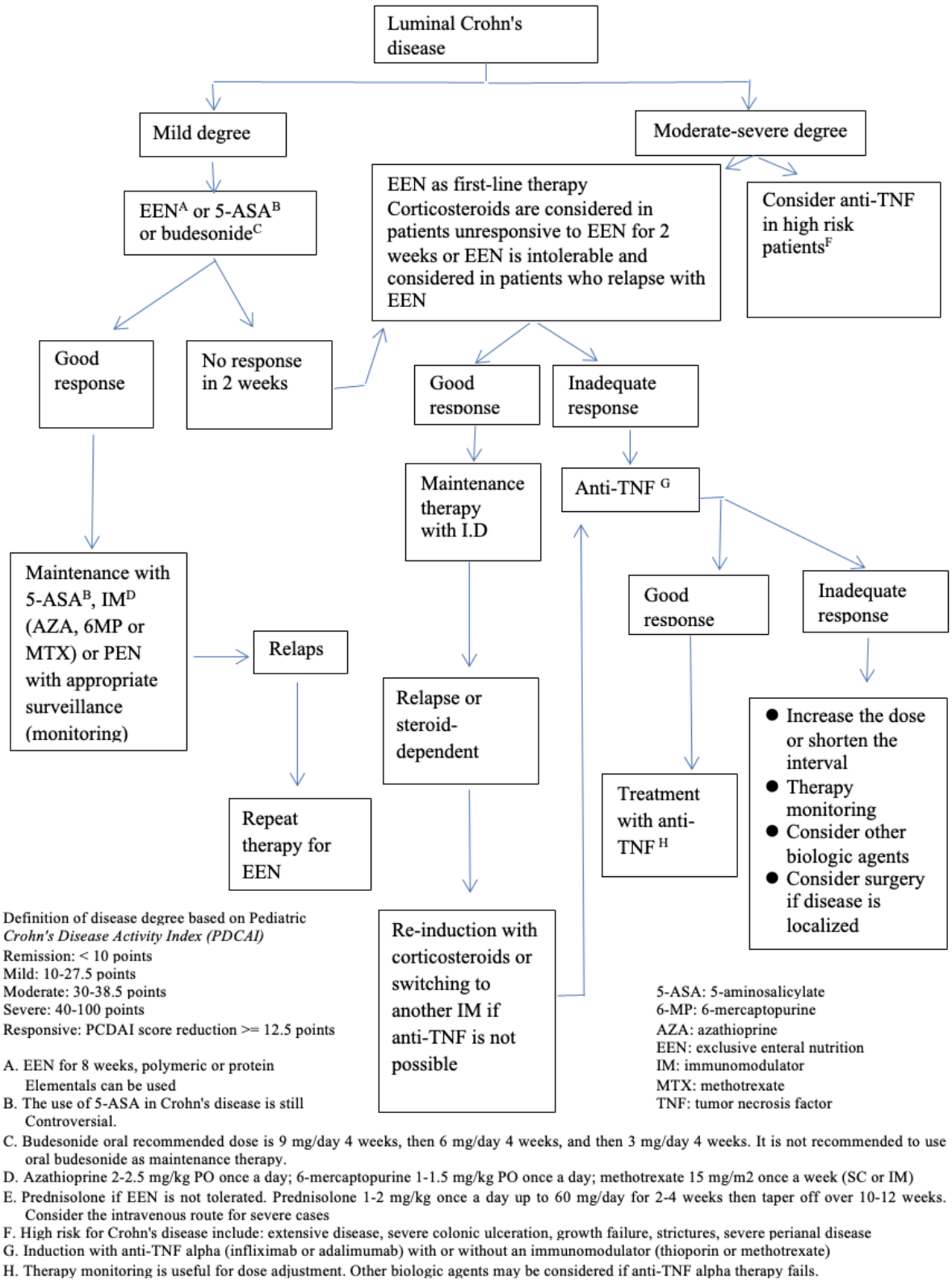

Figure 3. Management of pediatric Crohn's disease in Asia.[21]

Table 2. Treatment recommendations for pediatric inflammatory bowel disease (PIBD) in Asia.[21]

1. Induction Therapy

1.1 Gastrointestinal infections and other causes of diarrhea, especially gastrointestinal TB, need to be ruled out before diagnosing IBD in Asian children.

1.2 EEN is recommended in the induction and re-induction phases as the therapy of choice in Asian children who have just been diagnosed with Crohn's disease or relapse cases who are not high-risk factors.

1.3 EEN is not recommended for induction therapy in complicated Crohn's disease, including strictures, intestinal penetration, and perianal disease.

1.4 In children with Crohn's disease who do not tolerate or respond to EEN after 2-4 weeks, oral corticosteroids should be considered.

1.5 In areas where resources are limited and where EEN is not available, 5-ASA may be considered as induction therapy in mild Crohn's disease.

1.6 EEN is not recommended as induction therapy in Ulcerative Colitis.

1.7 Oral 5-ASA preparations are recommended as first-line therapy for mild to moderate ulcerative colitis.

1.8 Corticosteroids are recommended as the treatment of choice in moderate to severe ulcerative colitis

1.9 Biologic agents may be considered as first-line therapy in high-risk pediatric Crohn's disease and second-line therapy for steroid-refractory ulcerative colitis or patients with ASC.

2. Maintenance Therapy

2.1 Corticosteroids are not recommended as maintenance therapy in pediatric IBD.

2.2 Partial enteral nutrition may be considered as adjunctive therapy to immunomodulators to prolong remission in pediatric Crohn's disease patients with luminal disease without fistulas or strictures.

2.3 In ulcerative colitis, 5-ASA monotherapy is recommended in maintaining remission in children with mild disease. In children with frequent relapses on 5-ASA or corticosteroid-dependent maintenance therapy, AZA is recommended as maintenance therapy.

3. Immunomodulator

3.1 AZA is recommended as first-line maintenance therapy for Crohn's disease and ulcerative colitis

3.2 Where NUDT15 genotyping and TPMT enzyme assay are not available, it is recommended that complete peripheral blood count and liver enzymes should be monitored weekly. After the AZA dose is fixed, monitoring can be paused for up to three months. Complete peripheral blood count and liver enzymes are still required although NUDT15 genotyping and TPMT enzyme assay are available.

3.3 Routine screening for EBV prior to starting thiopurine therapy is not recommended

3.4 MTX may be considered in Crohn's disease both as main maintenance therapy and as replacement therapy in cases of intolerance and non-response to thiopurines.

3.5 TAC may be considered as a short-term agent in cases of steroid-refractory ulcerative colitis as well as replacement therapy in ASC.

4. Biologic

4.1 The use of biologic agents, IFX and ADA is recommended in inducing and maintaining remission in chronic luminal Crohn's disease despite adequate immunosuppressant therapy or steroid refractoriness. In addition, biologic agents should be used as primary induction and maintenance therapy in severe luminal disease and active perianal disease.

4.2 In ulcerative colitis, both IFX and ADA are indicated in steroid-dependent and refractory cases, as well as for active or recurrent disease despite adequate 5-ASA and thiopurine therapy.

4.3 The main considerations for using biologic agents in the Asia Pacific region are the very expensive price, limited materials, and the potential risk of infection, especially TB.

5-ASA: 5-aminosalicylic acid; ADA: adalimumab; ACS: acute severe colitis; AZA: azathioprine; EBV: Epstein Barr Virus; IBD: inflammatory bowel disease; IFX: infliximab; MTX: methotrexate; EEN: exclusive enteral nutrition NUDT-15: nudix hydrolase 15; TAC: tacrolimus; TB: tuberculosis.

The use of antibiotics needs to be considered in patients with Crohn's disease because of the possibility of bacterial overgrowth or to prevent infections that can worsen.[18] In a randomized control trial (RCT) of pediatric patients, it was stated that giving the combination of antibiotics azithromycin and metronidazole during the induction period was more effective in improving symptoms than the metronidazole group alone.[22] The fecal calprotectin values decreased significantly in the group that received the combination antibiotic. Our patient has been administered with broad-spectrum combination antibiotics.

The specific management of Crohn's disease in children is to start giving nutrition and steroids as the initiation of therapy. Exclusive enteral nutrition (EEN) is recommended using a complete liquid formula as a food source for the initial 6-8 weeks.[18] The selection of polymeric formula nutrition can be considered the first choice. In a study by Kadim M et al.,[23] it is stated that giving EEN is as effective as corticosteroids for inducing Crohn's disease remission in children, but giving EEN is more recommended because of its better mucosal healing effect and there are no long-term side effects on growth. A study in Southeast Asia shows that after using EEN for 8 weeks, 91% of children with Crohn's disease achieved remission with significant weight gain and improvement of inflammatory markers and PCDAI scores.[24] A study by Chan et al.,[25] in Malaysia, also shows that EEN is as effective as primary induction therapy in new cases and re-induction in relapsed cases of Crohn's disease in children.

The use of EEN as an induction therapy for Crohn's disease in children is especially relevant in Asia where the incidence of infectious diarrhea is high and there is concern over the use of biologic agents in TB endemic areas.[26] In cases where the diagnosis of Crohn's disease is uncertain, EEN is an appropriate choice to avoid the side effects of immunosuppressants and is also an effective therapy in the Asian child population.[27] The use of nasogastric tube is worth considering so that EEN can be given adequately and avoid rejection. The side effects of EEN administration are diarrhea and vomiting. Crohn's Disease exclusion diet (CDED), a diet rich in complex carbohydrates and low in animal fat with a moderate amount of fiber has been shown to be effective in inducing remission in children with Crohn's disease. When compared to EEN alone, CDED added with partial EEN therapy provides better tolerance and patient acceptance, and induces more remissions in children with mild-moderate Crohn's disease.[28]

In pediatric Crohn's disease patients, oral corticosteroids are effective at inducing remission.[29] If EEN is not effective after 2-4 weeks of administration or is not well tolerated, then systemic corticosteroids should be given. The initial dose of prednisolone follows the patient's weight (weight-dependent) and should be tapered immediately when clinical improvement is achieved, a maximum of 4 weeks after

initiation of therapy. In general, oral prednisolone or prednisone may be given once a day at a dose of 1 mg/kg/day (maximum 40 mg per day) and may be increased to 1.5 mg/kg/day (maximum 60 mg per day) if the response to therapy with an initial dose of 1 mg/kg/day is not satisfactory.[18] For children weighing more than 40 kg, an initial dose of budesonide can be given 9-12 mg once a day for 6 weeks. A dose of up to 12 mg may be given during the first 4 weeks.[30] Then it is gradually lowered as follows: 6 mg once a day for 2 weeks and 3 mg once a day for 2 weeks. The total duration of budesonide administration from initiation to tapering down is 10-12 weeks. If oral administration is not well tolerated, intravenous steroid administration is an option. Ideally, EEN should be given, but in our patient the tolerance was not good because there was severe vomitting. Because enteral nutrition could not be fulfilled properly, steroid was given. For induction therapy, the patient was given methylprednisolone 1 mg/kg/day. An intravenous route is an option because the patient had symptoms of nausea and vomiting. The patient felt improvement in clinical symptoms and CRP significantly after 7 days of receiving corticosteroids, then he was allowed to discharge with oral methylprednisolone 1 mg/kg/day for 1 week which was planned to be tappering down gradually according to further clinical evaluation during outpatient check-up. (**Table 3**)

Table 3. Laboratory work up result.

Laboratory Workup	Result		Unit
	Before steroid treatment	After steroid treatment	
Hemoglobin	17.3	15.3	g/dL
Hematocrit	53	46	%
Erythrocytes	6.4	5.6	Million/uL
Leucocytes	25.2	12.8	Thousand/uL
Thrombocytes	280	421	Thousand/uL
Basophil	1	0	%
Eosinophil	58	3	%
Neutrophil	28	87	%
Lymphocytes	8	5	%
Monocytes	7	5	%
CRP	48.45	0.67	mg/dL
Procalcitonin	N/A	< 0.05	ng/mL
IGRA-TB	Negative	N/A	N/A
Fecal calprotectin	137.6	N/A	N/A
Fecal analysis	Occult blood (+)	N/A	N/A
Fecal culture	Negative	N/A	N/A

N/A: not available

Stenosis as a complication of Crohn's disease is frequently found in Asian children[31]. Therapy using Biologic agents is recommended as initial therapy in children with stenosis without prestenotic dilatation. However, in resource-limited settings where biologic agents are not readily available, endoscopic or surgical dilation should be considered.[32] Indications for surgery in pediatric Crohn's disease include strictures, stenosis, obstructive symptoms, and perianal fistula.[33] Surgery also needs to be considered in children who are entering puberty where the growth of bone age decreases in the range of 6-12 months despite optimal medical and nutritional therapy. There were no signs of obstruction or complications in our patient, so no operative management was required.

Conclusion

Crohn's disease belongs to the category of IBD involving the entire upper and lower digestive tract. This disease can cause complications such as growth and development disorders in children. Crohn's disease can be differentiated from ulcerative colitis by several characteristics. Calprotectin fecal examination, gastrointestinal endoscopy, and histopathological examination results are necessary in all cases of suspected IBD. The current goals of Crohn's disease therapy are to achieve optimal growth, eliminate or reduce symptoms, and achieve the mucosal repair. Exclusive enteral nutrition or corticosteroids is the main pillar in the management of Crohn's disease in the induction phase.

Conflict of Interest

None declared

Funding Statement

There is no specific grant from any funding agency involved in this study.

References

1. Oliveira SB. Diagnosis and management of inflammatory bowel disease in children. BMJ. 2017; 357:2083. https://doi.org/10.1136/bmj.j2083
2. Moon JS. Clinical aspects and treatments for pediatric inflammatory bowel disease. Pediatr Gastroenterol Hepatol Nutr. 2019;22(1):50-6. https://doi.org/10.5223/pghn.2019.22.1.50
3. Ghione S, Sarter H, Fumery M, Armengol-Debeir L, Savoye G, Ley D, et al Dramatic increase in incidence of ulcerative colitis and Crohn's disease [1988-2011]: a population-based study of French adolescents. Am J Gastroenterol. 2018;113:265–72. https://doi.org/10.1038/ajg.2017.228
4. Ong C, Aw MM, Liwanag MJ, Quak SH, Phua KB. Rapid rise in the incidence and clinical characteristics of pediatric inflammatory bowel disease in a South-East Asian cohort in Singapore, 1994-2015. J Dig Dis. 2018;19:395-403. https://doi.org/10.1111/1751-2980.12641
5. Hong SJ, Cho SM, Choe BH, Jang HJ, Choi KH, Kang B, et al. Characteristics and incidence trends for pediatric inflammatory bowel disease in Daegu-Kyungpook province in Korea: a multi-center study. J Korean Med Sci. 2018;33:e132. https://doi.org/10.3346/jkms.2018.33.e132
6. Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Friedler VN, Rosenbach Y, et al. Incidence of bowel surgery and associated risk factors in pediatric-onset Crohn's disease. Inflamm Bowel Dis. 2016;22:2917-23.https://doi.org/10.1097/MIB.0000000000000937

7. Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Treuren WV, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15(3):382-92. https://doi.org/10.1016/j.chom.2014.02.005
8. Morgan XC, Kabakchiev B, Waldron L, Tyler AD, Tickle TL, Milgrom R, et al. Associations between host gene expression, the mucosal microbiome, and clinical outcome in the pelvic pouch of patients with inflammatory bowel disease. Genome Biol. 2015;16(1):67. https://doi.org/10.1186/s13059-015-0637-x
9. Hong J, Yang HR, Moon JS, Chang JY, Ko JS. Association of IL23R variants with Crohn's disease in Korean children. Front Pediatr. 2019;7:472. https://doi.org/10.3389/fped.2019.00472
10. Arai K, Kunisaki R, Kakuta F, Hagiwa S, Murakoshi T,Yanagi T, et al . Phenotypic characteristics of pediatric inflammatory bowel disease in Japan: results from a multicenter registry. Intest Res. 2020;18:412-420. https://doi.org/10.5217/ir.2019.00130
11. Ashton JJ, Ennis S, Beattie RM. Early-onset pediatric inlammatory bowel disease. Immunol Allergy Clin North Am. 2019;39(1):63–79. https://doi.org/10.1016/S2352-4642(17)30017-2
12. Aloi M, Lionetti P, Barabino A,Guariso G, Costa S, Fontana M, et al. Phenotype and disease course of early-onset pediatric inflammatory bowel disease. Inflamm Bowel Dis 2014;20:597–605. https://doi.org/10.1097/01.MIB.0000442921.77945.09
13. Banerjee R, Pal P, Mak JWY, Ng SC. Challenges in the diagnosis and management of inflammatory bowel disease in resource-limited settings in Asia. Lancet Gastroenterol Hepatol. 2020;5:1076–88. https://doi.org/10.1016/S2468-1253(20)30299-5
14. Holtman GA, Lisman-van Leeuwen Y, Reitsma JB, Berger MY. Noninvasive Tests for Inflammatory Bowel Disease: A Meta-analysis. Pediatrics 2016;357. https://doi.org/10.1542/peds.2015-2126
15. Saha A, Tighe MP, Batra A. How to use faecal calprotectin in management of paediatric inflammatory bowel disease. Arch Dis Child Educ Pract Ed .2016; 101: 124–28. https://doi.org/10.1136/archdischild-2014-307941
16. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. The ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58: 795–806. https://doi.org/10.1097/MPG.0000000000000239
17. Anupindi SA, Podberesky DJ, Towbin AJ, Courtier J, Gee MS, Darge K, et al. Pediatric inflammatory bowel disease: imaging issues with targeted solutions. Abdom Imaging. 2015;357:975-92. https://doi.org/10.1007/s00261-015-0423-y
18. Van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical management of pediatric crohn's disease: an ECCO-ESPGHAN guideline update. Journal of Chrohn's and Collitis. 2021;171-194. https://doi.org/10.1093/ecco-jcc/jjaa161
19. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bryant RV, D'Haens G, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324–38. https://doi.org/10.1038/ajg.2015.233
20. Turner D, Riccuito A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organisation for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160:1570-1583. https://doi.org/10.1053/j.gastro.2020.12.031
21. Lee WS, Arai K, Alex G, Treepongkaruna S, Kim KM, Choong CL, et al. Medical management of pediatric inflammatory bowel disease (PIBD) in the Asia Pasific Region: A position paper by the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) PIBD working group. JGHF. 2023. https://doi.org/10.1111/jgh.16097
22. Levine A, Kori M, Kierkus J, Boneh RS, Sladek M, Escher JC, et al. Azithromycin and metronidazole versus metronidazole-based therapy for the induction of remission in mild to moderate paediatric Crohn's disease: a randomised controlled trial. Gut. 2019;68:239–47. https://doi.org/10.1136/gutjnl-2017-315199
23. Kadim M. Efektivitas pemberian nutrisi enteral eksklusif terhadap induksi remisi penyakit crohn. Sari Pediatri. 2019;21(1):57-65. http://dx.doi.org/10.14238/sp21.1.2019.57-65
24. Ong C, Lim PT, Logarajah V, Liwanag MJ, Ang BX, Cher Y, et al. Exclusive enteral nutrition with concomitant early thiopurine use was effective in maintaining steroid-free remission in a Southeast Asian cohort of children with Crohn's disease. BMC Gastroenterol. 2018;18:185. https://doi.org/10.1186/s12876-018-0907-7
25. Chan KJ, Song ZL, Chew KS, Ng RT, Taib SHW, Lee WS. Exclusive enteral nutrition is effective and feasible as primary induction and re-induction therapy in Asian children with Crohn's disease. J Paediatr Child Health. 2021;57:239-245. https://doi.org/10.1111/jpc.15184
26. Hisamatsu T. Enteral nutrition in the biologic era: learn from yesterday, live for today, hope for tomorrow.

Intest Res. 2020;18:139-140. https://doi.org/10.5217/ir.2019.09192
27. Kang Y, Park S, Kim SY, Koh H. Therapeutic efficacy of exclusive enteral nutrition with specific polymeric diet in pediatric Crohn's disease. Pediatr Gastroenterol Hepatol Nutr. 2019;22:72–9. https://doi.org/10.5223/pghn.2019.22.1.72
28. Levine A, Wine E, Assa A, Boneh RS, Shaoul R, Kori M, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. Gastroenterology. 2019;157:440–50. https://doi.org/10.1053/j.gastro.2019.04.021
29. Chan KJ, Song ZL, Chew KS, Ng RT, Taib SHM, Lee WS. Exclusive enteral nutrition is effective and feasible as primary induction and re-induction therapy in Asian children with Crohn's disease. J Paediatr Child Health. 2021;57:239-245. https://doi.org/10.1111/jpc.15184
30. Kuenzig ME, Rezaie A, Kaplan GG, Otley AR, Steinhart AH, Griffiths AM, et al. Budesonide for the induction and maintenance of remission in Crohn's Disease: systematic review and meta-analysis for the Cochrane Collaboration. J Can Assoc Gastroenterol. 2018;1:159–73. https://doi.org/10.1093/jcag/gwy018
31. Wang XQ, Xiao Y, Xu X, Yu Y, Shan CY, Guo L, et al. Study of disease phenotype and its association with prognosis of paediatric inflammatory bowel disease in China. BMC Pediatr. 2018;18:229. https://doi.org/10.1186/s12887-018-1212-x
32. Carnovale C, Maffioli A, Zaffaroni G, Mazhar F, Battini V, Mosini G, et al. Efficacy of tumour necrosis factoralpha therapy in paediatric Crohn's disease patients with perianal lesions: a systematic review. Expert Opin Biol Ther. 2020;20:239-251. https://doi.org/10.1080/14712598.2020.1718096
33. Lee WS, Arai K, Alex G, Treepongkaruna S, Kom KM, Choong CL, et al. Management and monitoring of pediatric inflammatory bowel disease (PIBD) the Asia Pasific Region: A position paper by the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) PIBD working group: Surgical management, disease monitoring and special considerations. https://doi.org/10.1111/jgh.16097

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Literature Review

Pediatric Gastroesophageal Reflux Disease (GERD): A Literature Review

Farahdina Shahnaz[1], Yuda Satrio Wicaksono[1], Himawan Aulia Rahman[1]

[1]Gastrohepatology Division, Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Yuda Satrio Wicaksono, M.D.
yudasatriow@gmail.com

Published:
31st May 2023

DOI:
https://doi.org/10.58427/apghn.2.2.2023.46-60

Citation:
Shahnaz F, Wicaksono YS, Rahman HA. Pediatric Gastroesophageal Reflux Disease (GERD). *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(2):46-60.

Abstract:

Background: Gastroesophageal reflux disease (GERD) is a condition where stomach contents reflux into the esophagus, causing discomfort and complications. It is most prevalent in infants (26.9%) and lesser in children under 10 (3.2%) and over 10 years old (10.1%).

Discussion: GERD is caused by frequent relaxations of the lower esophageal sphincter (LES), allowing stomach contents to escape into the esophagus. Symptoms vary with age, with infants experiencing regurgitation and irritability, while older children may have heartburn and nausea. Diagnosis requires differentiating GERD from similar conditions and may involve various tests, though their primary use lacks sufficient evidence. Nonpharmacological treatments include positioning, thickened feeding, reducing feeding volume but increasing frequency and possibly eliminating cow's milk protein. Pharmacological treatments include Proton Pump Inhibitors (PPIs), and Histamine Receptor Antagonists (H2RAs), though their efficacy varies. Prokinetics are generally not recommended due to lack of evidence. If all these treatments fail, anti-reflux surgery such as fundoplication can be considered.

Conclusion: The hallmark of GERD is the presence of esophagitis during endoscopy. However, Barrett's esophagus is rare in pediatric GERD patients. Factors indicating a worse prognosis include early onset age, an initial GERD diagnosis and the need for PPI at initial diagnosis.

Keywords: P

Introduction

Gastroesophageal reflux is defined as retrograde passage of gastric contents into the esophagus. Gastroesophageal reflux disease (GERD) occurs when the process leads to troublesome symptoms and complications.[1-3] Meanwhile, refractory GERD is defined when GERD does not respond to optimal treatment after 8 weeks.[3] In infants, infrequent gastroesophageal reflux is often physiological and does not cause symptoms or complications. Preterm infants are at risk for gastroesophageal reflux

due to their physiological immaturity of the lower esophageal sphincter, disrupted esophageal peristalsis, relatively abundant milk intake, and slower gastric emptying.[1]

Earlier study found that the prevalence of GERD symptoms was 26.9% (95% confidence interval [CI] 20.1–33.7, I 2¼ 6.83) and ranged from 23.1% to 40.0% in infants aged 0-18 months.[4] A study in Singapore reported that the highest prevalence of GERD in infants was 26.5% at age 6 weeks. The prevalence declined to 7.7% at 3 months, 2.6% at 6 months and 1.1% at 12 months.[5] In children, the prevalence of weekly GERD symptoms was lower in aged <10 years old than in ≥10 years old (3.2% and 10.1% respectively).[4]

Pathophysiology

The lower esophageal sphincter plays a role in the pathophysiology of GERD in children. The lower esophageal sphincter (LES) constitutes the major component of the anti-reflux barrier.[1] The LES is located at the gastroesophageal junction and relaxes during swallowing so that food and liquid will directly go into stomach.[6]

The most common pathophysiology of GERD is the transient LES relaxation. Transient LES relaxation occurs when LES pressure relaxes independently of swallowing, hence allows it to the level of intragastric pressure. Normally this process allows gas releasing into the esophagus. Transient LES relaxation can be stimulated by increased intraesophageal pressure when the patient is crying, gastric distension, and respiratory disease. However, frequent transient LES relaxation serves opportunities for stomach contents into the esophagus and cause GERD symptoms.[7] The normal LES pressure is 5–20 mm Hg and is 4 mm Hg or more above intragastric pressure. Normally, the LES pressure remains slightly higher than that of the lower GI tract to prevent stomach contents escape to the esophagus. During peristalsis, this lower sphincter will relax. If this sphincter relaxes to the level of gastric pressure or a pressure of 0–2 mm Hg, a retrograde passage of gastric contents into the esophagus will occur.[1,6]

The other components of antireflux barrier are the crural ligament, the angle of His, and the phrenoesophageal ligament.[1] The angle of His is located between the esophagus and the great curvature of the stomach and allows one-way movement of food and liquid into the stomach. This angle is larger in infants, providing stomach contents escape and worsen the GERD symptoms. The GERD symptoms also worsen in right-sided sleeping positions, hence increasing the angle of His, esophageal acid exposure and reduces esophageal clearance.[6]

Most of the gastroesophageal reflux episodes are caused by the transient relaxation of the lower esophageal sphincter due to postprandial gastric distension. Moreover, an

increased intraabdominal pressure or delayed gastric emptying will also lead to gastroesophageal reflux, even if the lower esophageal sphincter pressure was normal.[1,6]

Clinical Manifestation

Clinical manifestations of GERD in infants and children vary with age. In infants, gastroesophageal reflux often occurs at birth. This reflux might be worse after oral intake or when the infant is in a recumbent position.[1] These infants present with gastroesophageal reflux yet still able to thrive well with no symptoms nor complications are called happy spitters.[1,2]

Presenting symptoms in infants and young children are presented as regurgitation, irritability, crying episodes, feeding difficulty, gagging, failure to thrive, sleep difficulties.[1,2] In infants, clinical presentations of GERD may also present with extra-oesophageal symptoms such as coughing, choking, wheezing and, rarely, apnoea.[2] A spasmodic torsional dystonia with arching of the back and neck, lifting up of the chain, and rigid opisthotonic posturing is highly indicating GERD in infants and is called Sandifer Syndrome.[1]

Clinical presentations in older children and adolescents are similar to those in adults such as chronic regurgitation, nausea, heartburn, retrosternal or epigastric pain, dysphagia, nocturnal pain, and sour burps. These symptoms might be extra-oesophageal including chronic cough, wheezing, recurrent pneumonia, sore throat, hoarseness, halitosis, chronic sinusitis, laryngitis or dental erosions.[1,2] Children aged <12 years old often present with anorexia, nausea, vomiting, abdominal pain, and food refusal.[2](**Table 1**) There are several red flags that prompts further investigation in children with GERD, presented in **Table 2**.

Table 1. Symptoms related with GERD in infants and children from 0-18 years old[3]

Symptoms	Signs
General - Discomfort/irritability* - Failure to thrive - Feeding refusal - Dystonic neck posturing (Sandifer syndrome)	**General** - Dental erosion - Anemia
Gastrointestinal - Recurrent regurgitation with/without vomiting - Heartburn/chest pain† - Epigastric pain† - Hematemesis - Dysphagia/odynophagia	**Gastrointestinal** - Esophagitis - Esophageal stricture - Barret esophagus

Airway - Wheezing - Stridor - Cough - Hoarseness	**Airway** - Apnea spells - Asthma - Recurrent pneumonia with aspiration - Recurrent otitis media

*A single manifestation of excessive irritability and pain is unlikely to be related to GERD.
†Typical symptoms of GERD in older children

Table 2. Red Flag Symptoms that prompts further investigation[3]

Symptoms and signs	Notes
General	
- Weight loss	- Suggesting a variety of conditions, including systemic infection
- Lethargy	
- Fever	
- Excessive irritability/pain	
- Dysuria	- Suggesting urinary tract infection
- Onset of regurgitation/vomiting > 6 months or increasing/persisting > 12-18 months of age	- Late onset as well as symptoms increasing or persisting after infancy, may suggest diagnosis other than GERD
Neurological	
- Bulging fontanel/increasing head circumference	- May suggest raised ICP (meningitis, brain tumour, hydrocephalus)
- Seizures	
- Macro / microcephaly	
Gastrointestinal	
- Persistent forceful vomiting	- Indicates hypertrophic pyloric stenosis in infants < 2 months old
- Nocturnal vomiting	- May suggest increase ICP
- Bilious vomiting	- Suggests intestinal obstruction (Hirschsprung, intestinal atresia, volvulus)
- Hematemesis	- Suggests serious bleeding from upper GI tract; possibly GERD associated
- Chronic Diarrhea	- May suggest food protein-induced gastroenteropathy
- Rectal bleeding	- Indicative of multiple condition (bacterial gastroenteritis, IBD, food protein induced gastroenteropathy)
- Abdominal distension	- Indicative of obstruction, dysmotility, anatomic abnormalities

NSAID = non-steroidal anti-inflammatory drugs.

Differential Diagnosis

When considering the differential diagnosis of gastroesophageal reflux disease (GERD) in pediatric patients, several other conditions might come to mind due to the similarity of symptoms. (**Table 3**)

Eosinophilic esophagitis, a chronic immune disease, might be considered as it can present with difficulty swallowing, stomach pain, heartburn, and the sensation of food getting stuck in the throat. Inflammation, irritation, or erosion of the lining of the stomach, as seen in gastritis or gastric ulcers, could also present with similar symptoms to GERD. Peptic ulcer disease, which involves ulcers in the stomach or first part of the small intestine, is another condition that can mimic GERD symptoms.

Further investigation is often required to distinguish between these conditions and ensure an accurate diagnosis.

Table 3. Differential Diagnosis of Gastroesophageal Reflux Disease*

GI obstruction	**Metabolic**	**Other GI disorder**
- Pyloric stenosis - Malrotation with volvulus - Intussusception - Hirschsprung disease - Antral/duodenal web - Foreign body - Incarcerated hernia - Superior mesenteric artery syndrome	- Galactosemia - Hereditary fructose intolerance - Uric cycle defect - Acidemia (amino / organic) - Fatty acid oxidation disorder - Metabolic Acidosis - Congenital Adrenal hyperplasia/adrenal crisis	- Achalasia - Gastroparesis - Gastroenteritis - Peptic ulcer - Eosinophilic esophagitis - Food allergy - IBD - Pancreatitis - Appendicitis
Neurologic	**Cardiac**	**Infectious**
- Hydrocephalus - Subdural hematoma - Intracranial haemorrhage - Intracranial mass	- Heart failure - Vascular ring - Autonomic dysfunction	- Sepsis / meningitis - UTI - Upper / lower airway infection - Otitis media - Hepatitis
Toxic	**Renal**	**Others**
- Lead poisoning - Other toxins	- Obstructive uropathy - Renal insufficiency	- Cyclic vomiting syndrome - Rumination syndrome

*Adapted from the ESPGHAN/NASPGHAN 2009 GERD guidelines.

Diagnostic Approach

The diagnosis of GERD in infants and children is established based on clinical manifestations and strengthened by additional diagnostic examinations. These additional diagnostic tests are used to rule out other differential diagnoses of GERD.[3](**Figure 1 and Figure 2**)

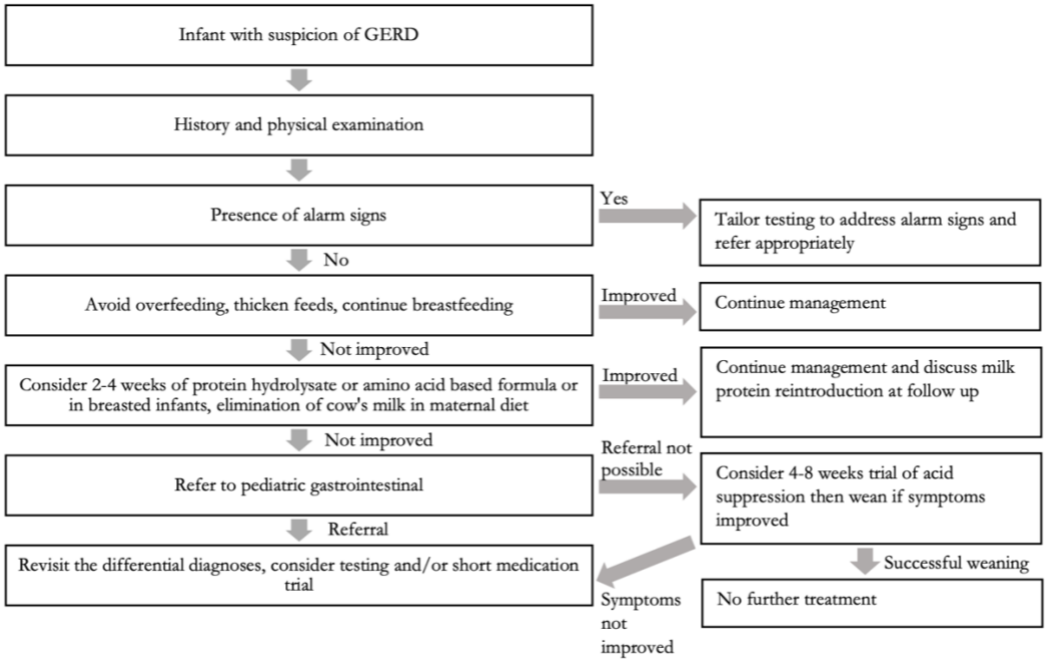

Figure 1. Diagnostic and therapeutic algorithm for reflux in infants

Upper GI Contrast Study

Upper GI contrast study evaluation is used in the evaluation of infants and children with alarm signs or patients with symptoms that are unresponsive to therapies and are needed to be evaluated for anatomic abnormalities. This test is able to rule out other conditions that mimic or predispose to GERD such as hiatal hernia, malrotation, pyloric stenosis, duodenal web, duodenal stenosis, antral web, esophageal narrowing, achalasia, and esophageal stricture. This test is also used in evaluating patients who have had anti-reflux surgery yet still suffers persistent typical or atypical reflux symptoms.[3] Upper GI contrast study will differentiate an obstructing fundoplication with esophageal stasis from a slipped or loose fundoplication.[3] However, there are no sufficient evidences that report the use of upper GI contrast study as the primary diagnosis modality for GERD in infants and children.[3]

Ultrasonography

There is no evidence that support ultrasonography as the primary diagnostic test of GERD in infants and children. The sensitivity of this test is about 95% with a specificity of 11% if performed for 15 minutes post-prandially, compared to the 24-

hour esophageal pH test. Ultrasound is highly user-dependent and esophageal wall thickness does not correlate with esophagitis, therefore, it is not useful for diagnosis of GERD.[6] This test is used to rule out other conditions that mimic GERD such as pyloric stenosis and hiatal hernia.[3]

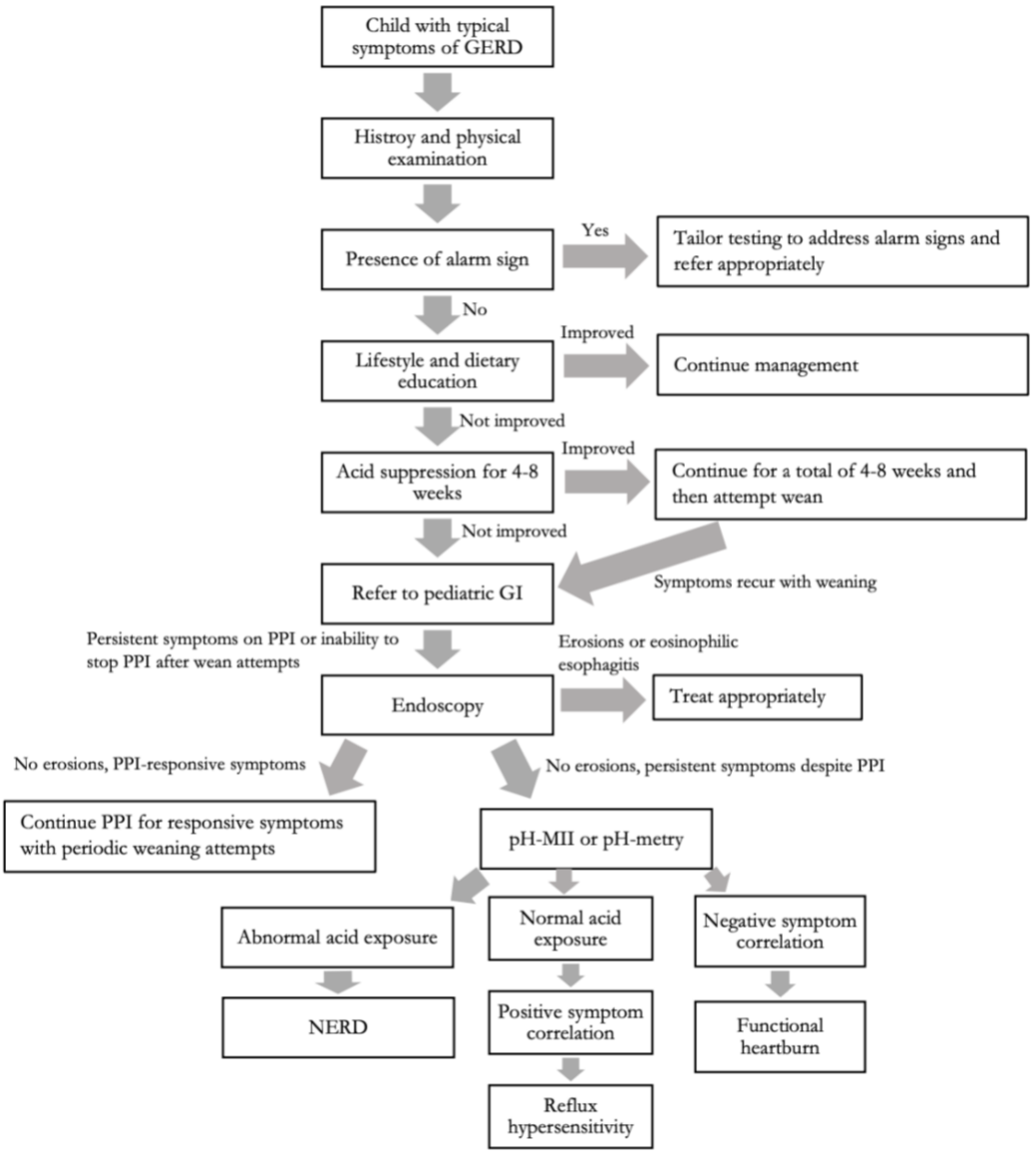

Figure 2. Diagnostic and therapeutic algorithm for reflux in older children

Esophago-gastro-duodenoscopy (EGD) with/without biopsy

EGD serves in establishing diagnosis of erosive esophagitis, eosinophilic esophagitis, and other diagnosis that mimic GERD characteristics. Visible breaks found in esophageal mucosa are defined as erosive esophagitis, meanwhile, eosinophilic

esophagitis is suspected when multiple concentric rings, linear furrow, and small white eosinophilic exudates were found during EGD.[3]

Patients with GERD will likely to have erosive esophagitis findings in EGD as much as 15% to 71%.[3] Visible endoscopic erosions found during EGD will confirm the diagnosis of GERD. EGD is also used in evaluating children with extra-esophageal symptoms with 8% of these patients may have eosinophilic esophagitis.[3] However, normal findings in endoscopy does not rule out the possibility of GERD. GERD might still be present in the absence of erosions of histological abnormalities.

EGD also serves in the evaluation of patients with alarm symptoms, complications of GERD (such as strictures and Barrett esophagus), other conditions predisposing to GERD, and other conditions that mimic GERD manifestations.[3]

Biomarkers

Pepsin is considered to help establish the diagnosis of extraesophageal reflux disease. However, there is insufficient data to support routine use of this biomarker. Pepsin positive were found in almost one-third control patients. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of pepsin to diagnose GERD were of 72%, 71%, 58%, and 82%, respectively. Earlier studies compared the salivary pepsin with the results from pH-MII testing, yet the result had limited sensitivity due to lack of cut-off use. [3,7] Pepsin measured in bronchoalveolar lavage (BAL) and middle ear fluid also showed lack of sensitivity.[3,7]

Manometry or motility studies

There has not any evidences yet to support manometry for the diagnosis of GERD in infants and children. Manometry might be used in the evaluation of GERD etiology. High-resolution of manometry with impedance may rule out esophageal motility disorders in patients whose symptoms are similar to GERD such as esophageal achalasia.[3]

Scintigraphy

The sensitivity and specificity of scintigraphy were only 69% and 78%. Gastric scintigraphy is useful in the evaluation of impaired gastric emptying which might be a risk factor for GERD.[3] It is may also reveals tracer in the bronchi, indicating pulmonary aspiration. Gastric scintigraphy is indicated when GERD manifestations do not respond to therapies and other diagnoses are considered. [3]

Proton pump inhibitor (PPI) trials

Initially PPI was used as a diagnostic test with a consideration that diagnosis of GERD was determined if the symptoms responded to PPI. However, this could not be

applied to infants since none of the trials showed symptoms reduction compared to placebo.[6] In older children and adolescents, a 4 to 8 week of PPI trial can be used as a diagnostic test for GERD.[6] There has not yet adequate evidences to support the use of PPI as a diagnostic test for extra-esophageal symptoms.[3]

pH-Metry/wireless pH recording

Earlier study measured Reflux Index (RI), a percentage of time that pH<4 using pH-metry to establish pathological GERD (abnormal was defined when pH <4 for >10% for infants <1 years old and 5% infants>1 year). The authors found that using history and physical examination as the gold standard for the diagnosis of GERD, RI had a sensitivity and specificity 50% and 82%.[3] However, this test has some limitations. Lack of a gold standard for comparison makes it inconvenient to differentiate GERD and GER using pH-metry. [3] pH-metry is also inadequate to diagnose extra-esophageal symptoms. [3] The appropriate time to consider a symptom correlated with reflux is still debated. [3]

When the pH-MII is not available, pH-metry can be considered in the evaluation of GERD. pH-metry is helpful to correlate symptoms with acid reflux episodes, particularly in differentiating NERD from other acid disorders. pH-metry can also be considered in the evaluation of acid therapy dosage in patients with persistent symptoms or esophagitis in high-risk patients (e.g., esophageal atresia or patients with neurological impairment).

An alternative to pH probe monitoring, wireless pH recording has been introduced as this test is more convenient to some patients. The wireless recording device is clipped to the esophagus, hence, there is no need to have a catheter in the nose. Children with developmental delay or patients with exercise induced GERD will benefit with this test. This wireless device is able to record pH changes for a minimum of 48 hours, yet other studies reported its ability to record up to 5 days. Studies in children have found that the results using this wireless device are comparable to those with pH probe monitoring that underwent simultaneously. Some complications such as esophageal tears, chest pain, and device failure have reported in 0% to 15% of patients.

pH-Impedance monitoring (pH-MIII)

There are some advantages of pH-MII compared to pH-based testing. It is able to detect: 1) refluxate with pH <4 and pH >4, 2) full column refluxate, 3) liquid and gas reflux, and 4) drops in esophageal pH due to reflux versus swallow-related drops in pH. pH-MII also showed a high sensitivity compared to pH-metry in the detection of reflux episodes, specifically the non-acid reflux episodes. [3] Nevertheless, there are still some limitations to this test. pH-MII is not available in all medical centers. The

reference range is also limited due to lack of true control patients. Moreover, there is no pediatric studies yet that show the results of pH-MII can affect the clinical outcomes. [3]

Despite of its limitations, there are some indications for pH-MII in the evaluation of GERD: 1) to evaluate patients with normal endoscopy in order to give appropriate therapy, 2) as a diagnostic test in symptomatic patients who take acid suppression due to its ability to assess the level of non-acid reflux, 3) as a preferrable test to assess the reflux episodes in predominant postprandial events that would be missed by a solely pH-metry, 4) to clarify the role of acid and non-acid reflux in the etiology of esophagitis and other conditions suggestive for GERD. However, there is no adequate evidence to support the pH-MII as a single technique for the diagnosis of GERD in infants and children. [3]

Nonpharmacological treatment

Positioning

Various baby positions have been studied to reduce the frequency of GERD. A study in premature infants showed a significantly reduced number of episodes of reflux in the left lateral decubitus position compared to the right lateral position.[8] Another study in infants placed on an anti-reflux bed (elevation 45 degrees) significantly decreased the parameters and symptoms of regurgitation.[9] However, this method should be strictly observed to prevent infant from rolling over to the lower leg area and compressing on its airway. One other study showed that positioning infant on its right side for one hour after drinking would accelerate gastric emptying and after that it was tilted to the left to reduce gastroesophageal reflux.[10] Up until now, there is not any certain position that is the most effective in reducing gastroesophageal reflux symptoms.

Thickened feeding

Thickened feeding is done by adding a thickening agent to infant formula to increase the thickness of the liquid. Adding thickeners may give benefit to the patient by: reducing vomiting and visible regurgitations per day, increased number of days without regurgitation, and reducing symptoms of crying and irritability.[11] Thickened feeding is recommended to be used for treating GERD patients with visible regurgitation / vomiting. Suggested thickeners to be used are cereal based thickeners (e.g. rice starch, corn starch) and commercial thickeners (e.g. xanthum gum).[3] There are no evidence-based suggestion that suggest a superior thickening agent compared to other.[12]

Reduction of ingested volume

Smaller, more frequent feeding may help by reducing the load of work for the digestive system in pediatric patients. More frequent feeding with lower volume has been shown to reduce reflux index in preterm and term infants. It is suggested to avoid overfeeding by increasing feeding frequency and volume for age and weight, while maintaining the recommended total daily amount. [3]

Elimination of cow's milk protein

There are no conclusive evidence that suggest elimination of cow's milk protein can help with GERD symptoms, though it has been documented in infants with cow's milk protein allergy vomiting frequency decrease significantly after elimination of cow's milk protein in their diet.[13] Reduced vomiting frequency usually happens after 2 weeks of elimination, and reintroduction causes recurrence of symptoms.[13] A trial of using hydrolyzed formula or amino acid based formula should be considered considering the symptoms of GERD and CMPA are identical, especially for those who did not respond to conventional GERD therapy.[3]

Pharmacological Treatment

Antacids and alginates

Antacids and alginates are agents that are designed to neutralize acid, typically containing sodium/potassium bicarbonate, aluminum salt, magnesium salts, or calcium salts. These agents are typically used to treat symptoms related to acid disorder such as heartburn or dyspepsia. Some studies have provided a data about alginates efficacy in treating GERD symptoms.[14] It was found that alginates treatment provides a significant reduction in GERQ-R score compared to those who were not given alginates.[14] Regurgitation incidence is also significantly reduced in the treatment group compared to the control group.[14] In another study, it was also found that alginate reduce the number of vomiting / regurgitation in 24 hours period at 2 weeks of treatment, although the mean frequency of episode didn't differ significantly between 2 groups.[15] Safety on the use of short term alginates shows no significant side effects, while long-term use of antacids may lead to increased aluminum plasma concentration in infants. Antacid are contraindicated in children with renal impairment due to risk of developing hypercalcemia, alkalosis, and renal failure.[3] However, the evidence for these studies ranged from low to very low quality. Therefore, the use of antacids and alginates is not recommended in infants and children with GERD.

Proton Pump Inhibitor and Histamine Receptor Antagonists

Several studies have evaluated the use of multiple proton pump inhibitors (omeprazole, lansoprazole, esomeprazole and pantoprazole) for treating GERD symptoms in pediatric patients.[13,16-19] No study has compared the efficacy between the

PPIs mentioned. All studies in infant population showed that PPI did not fare better than placebo when comparing the outcome (GERQ-Q score, crying/irritability, regurgitation frequency). Several studies have assessed the use of H2RA for treating GERD in pediatric patients. These agents include ranitidine, cimetidine and nizatidine. Cimetidine has been shown to reduce regurgitation and vomiting after 4-8weeks of therapy.[20] However, there are no evidence that suggests an improvement on the symptoms experienced (crying / distress, heartburn, colic) over placebo. Two other studies showed a reduced endoscopic and histologic evidence of esophagitis when treating with H2RA.[21,22] When comparing PPI to H2RA, 2 studies has been done and shows no significant difference in symptom severity (crying/distress, chest pain) between groups. Endoscopic evidence also showed no difference between the 2 groups.[23,24] (**Table 4 and Table 5**)

Although showing not enough evidence on the efficacy, it must be noted that most of the studies are of low-quality evidence and the subject has not been explored extensively enough. Experts opinions based on the adult literature recommends PPIs as the first line therapy above H2RA due to better ability of reducing acid production.[3]

Table 4. Pediatric recommended dose for PPIs[3]

Drugs	Recommended Dose	Maximum Dose
Omeprazole	1-4 mg/kg/day	40 mg
Lansoprazole	2 mg/kg/day	30 mg
Esomeprazole	10 mg/day (<20kg BW) or 20 mg/day (>20kg BW)	40 mg
Pantoprazole	1-2 mg/kg/day	40 mg

Table 5. Pediatric recommended dose for H2RAs[3]

Drug	Recommended Dose	Maximum Dose
Ranitidine	5-10 mg/kg/day	300 mg
Cimetidine	30-40 mg/kg/day	800 mg
Nizatidine	10-20 mg/kg/day	300 mg
Famotidine	1 mg/kg/day	40 mg

Prokinetics

Cisapride, a serotonergic agent that facilitates the release of acethylcholine in the myenteric plexus, is known to reduce the frequency of gastroesophageal reflux. However, due to serious cardiac side effects, this drug has been withdrawn and should only be used by strict in clinical trials with the supervision of a pediatric gastroenterologist. There is not enough evidence for other prokinetics such as

domperidone, metoclopramide, erythromycin, and azithromycin benefits when used for treating GERD, all while exhibiting a worse adverse effect. Baclofen has been shown to reduce the frequency of transient lower esophageal sphincter relaxation, reduces acid reflux, and also accelerates gastric emptying.[25] This finding is consistent with previous existing adult literature.[26] Baclofen side effects includes dyspeptic symptoms, drowsiness, and dizziness. Baclofen can be considered as choice of treatment before surgery when other pharmacological treatment has failed.

Surgical Treatment

Anti-reflux surgery was usually considered when all other options has failed to show any progress on the patient. Fundoplication is done by wrapping the fundus of the gaster around the esophagus. Fundoplication benefits GERD patient by increasing the baseline of lower esophageal sphincter pressure and decreasing the number of transient lower esophageal sphincter relaxation. Data from adult studies has shown an approximately 95% patient satisfaction with chronic GERD with a curative rate of 85%-93% on all cases.[27] A systematic review of pediatric literature, anti-reflux surgery shows a good success rate (median of 86%) in terms symptoms relief.[28] It is suggested that anti reflux surgery may be considered in chronic pediatric GERD patients that presents a life-threatening complication (e.g. recurrent pneumonia) which has failed all other non-surgical treatment.[3]

Prognosis

Three studies follow up patient with chronic GERD from age 12 months to >5 years and none develop Barrett's esophagus at follow-up. Prognostic factors that may contribute to worse outcome are age of onset <5 years and the need of PPI treatment at the time of initial diagnosis.

Conflict of Interest

None declared.

References

1. Leung AK, Hon KL. Gastroesophageal reflux in children: an updated review. Drugs in context. 2019;8. https://doi.org/10.7573/dic.212591
2. Poddar U. Gastroesophageal reflux disease (GERD) in children. Paediatrics and international child health. 2019;39(1):7-12. https://doi.org/10.1080/20469047.2018.1489649
3. Rosen R, Vandenplas Y, Singendonk M, Cabana M, Di Lorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Journal of pediatric gastroenterology and nutrition. 2018;66(3):516. https://doi.org/10.1097/MPG.0000000000001889
4. Singendonk M, Goudswaard E, Langendam M, van Wijk M, van Etten-Jamaludin F, Benninga M, et al. Prevalence of gastroesophageal reflux disease symptoms in infants and children: a systematic review. Journal of Pediatric

Gastroenterology and Nutrition. 2019;68(6):811-7. https://doi.org/10.1097/MPG.0000000000002280
5. McLoughlin VZ, Suaini NH, Siah K, Loo EX, Pang WW, Chong YS, et al. Prevalence, risk factors and parental perceptions of gastroesophageal reflux disease in Asian infants in Singapore. Annals of the Academy of Medicine, Singapore. 2022;51(5):263-71. https://doi.org/10.47102/annals-acadmedsg.2021411
6. Friedman C, Sarantos G, Katz S, Geisler S. Understanding gastroesophageal reflux disease in children. Jaapa. 2021;34(2):12-8. https://doi.org/10.1097/01.JAA.0000731488.99461.39
7. Sintusek P, Mutalib M, Thapar N. Gastroesophageal reflux disease in children: What's new right now? World Journal of Gastrointestinal Endoscopy. 2023;15(3):84
8. Omari TI, Rommel N, Staunton E, Lontis R, Goodchild L, Haslam RR, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145(2):194-200.https://doi.org/10.1016/j.jpeds.2004.05.026
9. Vandenplas Y, De Schepper J, Verheyden S, Devreker T, Franckx J, Peelman M, et al. A preliminary report on the efficacy of the Multicare AR-Bed in 3-week-3-month-old infants on regurgitation, associated symptoms and acid reflux. Arch Dis Child. 2010;95(1):26-30.https://doi.org/10.1136/adc.2008.156497
10. van Wijk MP, Benninga MA, Dent J, Lontis R, Goodchild L, McCall LM, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151(6):585-90, 90.e1-2.https://doi.org/10.1016/j.jpeds.2007.06.015
11. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. Pediatrics. 2008;122(6):e1268-e77. https://doi.org/10.1542/peds.2008-1900
12. Salvatore S, Savino F, Singendonk M, Tabbers M, Benninga MA, Staiano A, et al. Thickened infant formula: What to know. Nutrition. 2018;49:51-6. https://doi.org/https://doi.org/10.1016/j.nut.2017.10.010
13. Winter H, Kum-Nji P, Mahomedy SH, Kierkus J, Hinz M, Li H, et al. Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo-controlled treatment-withdrawal study in infants 1–11 months old with symptomatic GERD. Journal of pediatric gastroenterology and nutrition. 2010;50(6):609-18.https://doi.org/10.1097/MPG.0b013e3181c2bf41
14. Ummarino D, Miele E, Martinelli M, Scarpato E, Crocetto F, Sciorio E, et al. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. Journal of pediatric gastroenterology and nutrition. 2015;60(2):230-5. https://doi.org/10.1097/MPG.0000000000000521
15. Miller S. Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastroesophageal reflux. Current medical research and opinion. 1999;15(3):160-8. https://doi.org/10.1185/03007999909114087
16. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. The Journal of pediatrics. 2009;154(4):514-20. e4. https://doi.org/10.1016/j.jpeds.2008.09.054
17. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. The Journal of pediatrics. 2013;163(3):692-8. e2. https://doi.org/10.1016/j.jpeds.2013.05.007
18. Hussain S, Kierkus J, Hu P, Hoffman D, Lekich R, Sloan S, et al. Safety and efficacy of delayed release rabeprazole in 1-to 11-month-old infants with symptomatic GERD. Journal of pediatric gastroenterology and nutrition. 2014;58(2):226-36. https://doi.org/10.1097/MPG.0000000000000195
19. Moore DJ, Tao BS-K, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. The Journal of pediatrics. 2003;143(2):219-23. https://doi.org/10.1067/S0022-3476(03)00207-5
20. Cucchiara S, Gobio-Casali L, Balli F, Magazzu G, Staiano A, Astolfi R, et al. Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study. Journal of pediatric gastroenterology and nutrition. 1989;8(2):150-6
21. Orenstein S, Blumer J, Faessel H, McGuire J, Fung K, Li B, et al. Ranitidine, 75 mg, over-the-counter dose: pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux. Alimentary pharmacology & therapeutics. 2002;16(5):899-907.https://doi.org/10.1046/j.1365-2036.2002.01243.x
22. Simeone D, Caria MC, Miele E, Staiano A. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. Journal of pediatric gastroenterology and nutrition. 1997;25(1):51-5
23. Cucchiara S, Minella R, Iervolino C, Franco M, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Archives of Disease in Childhood. 1993;69(6):655-9

24. Ummarino D, Miele E, Masi P, Tramontano A, Staiano A, Vandenplas Y. Impact of antisecretory treatment on respiratory symptoms of gastroesophageal reflux disease in children. Diseases of the Esophagus. 2012;25(8):671-7. https://doi.org/10.1111/j.1442-2050.2011.01301.x
25. Omari TI, Benninga MA, Sansom L, Butler RN, Dent J, Davidson GP. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. The Journal of pediatrics. 2006;149(4):468-74. e2. https://doi.org/10.1016/j.jpeds.2006.05.029
26. Tolia V, Gilger MA, Barker PN, Illueca M. Healing of erosive esophagitis and improvement of symptoms of gastroesophageal reflux disease after esomeprazole treatment in children 12 to 36 months old. Journal of pediatric gastroenterology and nutrition. 2010;51(5):593-8. https://doi.org/10.1097/MPG.0b013e3181ddcf11
27. Slater BJ, Dirks RC, McKinley SK, Ansari MT, Kohn GP, Thosani N, et al. SAGES guidelines for the surgical treatment of gastroesophageal reflux (GERD). Surgical Endoscopy. 2021;35:4903-17. https://doi.org/https://doi.org/10.1007/s00464-021-08625-5
28. Mauritz FA, van Herwaarden-Lindeboom MY, Stomp W, Zwaveling S, Fischer K, Houwen RH, et al. The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review. Journal of Gastrointestinal Surgery. 2011;15:1872-8. https://doi.org/10.1007/s11605-011-1644-1

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

www.apghn.com

Volume 2 / No. 2
May 2023

ISSN 2830-5442

Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition