

Review Article



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Management of the Most Common Functional Gastrointestinal Disorders in Infancy: The Middle East Expert Consensus

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ABSTRACT

The occurrence of functional gastrointestinal disorders (FGIDs) is a formidable challenge for infants, parents, and healthcare professionals. Although data from the Middle East are scarce, experts consider FGIDs a prevalent condition in everyday clinical practice. The new Rome IV criteria revisited the definitions from a clinical perspective to provide a practical and consistent diagnostic protocol for FGIDs. However, the treatment practices for functional disorders vary considerably among Middle Eastern countries, often resulting in mismanagement with unnecessary investigations and treatments. In addition, the role of various treatment modalities, including probiotics such as *Lactobacillus reuteri* DSM 17938, in FGIDs requires further discussion and evaluation. During a consensus meeting, a locally relevant approach for treating common FGIDs such as infant regurgitation, infant colic, and functional constipation was discussed and approved by regional experts. The participants suggested a simplified treatment plan and protocol for general pediatricians and other primary care physicians managing FGIDs. This easy-to-follow standardized protocol will help streamline the initial management of this complex disorder in the Middle East region and even globally.

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Conflict of Interest

Flavia Indrio serves as a Speaker for BioGaiia, Nestlé Nutrition Institute and Danone. Axel Enninger serves as a speaker, member of advisory board Nestlé Nutrition Institute, Speaker, member of advisory board Milupa/Danone, Speaker: infectopharm, abbvie, Nutricia and Author: Thieme, infectopharm. None of the other authors have a conflict of interest.

Keywords: Colic; Constipation; Gastrointestinal diseases; Infant; Middle East; Probiotics; Laryngopharyngeal reflux

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) in infants encompass a variable combination of age-dependent, chronic, or recurrent symptoms not explained by structural or biochemical abnormalities [1]. As a condition that seems to merely exist as patient symptoms and parent interpretations, FGIDs pose a challenge to healthcare professionals, who are typically trained to gather palpable evidence of pathologies [1,2]. However, FGIDs are real for the affected infants and parents, and considering their high prevalence [1], gaining clarity on their diagnosis and treatment is of utmost importance. The Rome III criteria were updated recently to Rome IV with the aim of further refining and accommodating the practical aspects of the FGID diagnostic process [1].

FGID BURDEN

Prevalence estimates of FGIDs show wide variation in the published literature. According to clinical studies, 55% of infants show at least one FGID symptom from birth to 6 months [3]. Infant regurgitation is by far the most common FGID, present in up to 67% of infants and peaking at 4 months of age. Infant colic and functional constipation are also common during infancy, with a prevalence of up to 19% and 27%, respectively. Functional diarrhea is relatively uncommon among the four FGIDs, with a prevalence of up to 7% [1]. Experts from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) conducted a literature review that identified 30 studies that reported the prevalence of FGIDs in infants under 12 months of age and determined the average prevalence of infant regurgitation, colic, and constipation as 30%, 20%, and 15%, respectively [4]. The overall prevalence of FGIDs with the new Rome IV criteria was more or less similar to the rates reported with the Rome III criteria [5,6]. In addition, although FGIDs are generally described as separate entities, as many as 78% of infants with FGIDs may present with more than one disorder, with colic being the most frequent concomitant disorder [7,8].

Although clear estimates from the Middle East and North Africa (MENA) region are lacking, available data point toward a much higher prevalence of FGIDs. In a recent survey of pediatricians from the MENA region, the majority of the participants stated that the prevalence of infant colic <4 months of age exceeded 40% [9]. A survey of Saudi mothers found that their major reasons for changing an infant formula were colic and gas (32%), constipation (23.6%), and gastroesophageal reflux (20.4%) [10].

FGIDs impair infant and parent quality of life and may have a lasting impact on later life. Regurgitation can negatively impact infant quality of life due to food refusal, crying, back arching, and irritability [11]. Frequent regurgitation during infancy increases the risk of heartburn, vomiting, and acid regurgitation at 9 years of age [12]. There are several reports of potential associations between infant colic and later health outcomes, including recurrent abdominal pain, sleep disorders, aggression, fussiness, and migraine [13,14]. Colic and excessive or inconsolable crying can also lead to poor mother-child interactions, postpartum depression, social isolation, parental frustration, exhaustion, and an increased risk of child abuse [15-18].

Table 1. Potential risk factors or associations for functional gastrointestinal disorders [19-21]

• Cesarean delivery
• Preterm delivery
• Neonatal use of antibiotics
• Being an only child
• Being the firstborn child
• Having divorced or separated parents
• Living in an urban area
• Being underweight for age

WHO IS AT RISK OF DEVELOPING FGIDS IN EARLY CHILDHOOD?

Despite a lack of validated risk stratification tool for FGIDs, increased prevalence was observed in only-children, firstborns, and infants with divorced or separated parents [19]. Preterm delivery and neonatal use of antibiotics in the first few months of life were also associated with FGIDs, particularly infant colic and regurgitation. Cesarean delivery and feeding patterns at 1 month of life emerged as risk factors for infant dyschezia and functional diarrhea [20]. Living in an urban area and being underweight for one's age were proposed to be significantly associated with functional constipation (**Table 1**) [21]. It is also interesting to note that male and female infants show a comparable prevalence of FGIDs [7,19] in contrast to the female preponderance seen in older children [22].

CLINICAL PRESENTATION AND DIAGNOSIS OF FGIDS

Common FGIDs such as infant regurgitation, infant colic, dyschezia, functional diarrhea, and functional constipation may start very early in life [1]. A clear objective diagnosis may facilitate the acceptance of an FGID diagnosis by the parents, especially considering the apparent lack of a causative organic pathology [23]. Key diagnostic recommendations per the Rome IV criteria for some of the commonly encountered FGIDs in infants <12 months of age are given below [1]. Since infant diarrhea is a relatively complicated disorder in primary care, the criteria for functional diarrhea are not discussed here.

Infant regurgitation

Infant regurgitation is characterized by gastroesophageal reflux, which is sufficiently high to be visualized. Regurgitation must be differentiated from similar disorders such as vomiting and rumination as well as gastroesophageal reflux disease, which is diagnosed when regurgitation causes complications or contributes to tissue damage or inflammation [1].

An objective diagnosis of infant regurgitation requires **both** of the following criteria in otherwise healthy infants at 3 weeks to 12 months of age [1]:

1. Regurgitation two or more times per day for 3 or more weeks; and
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing.

Infant colic

Infant colic has been described as a behavioral syndrome in infants involving long periods of crying and hard-to-soothe behavior [1].

An objective clinical diagnosis of infant colic requires that the infant meet **all** three of the following criteria [1]:

1. <5 months of age when the symptoms start and stop;
2. Recurrent and prolonged periods of crying, fussing*, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers; and
3. No evidence of failure to thrive, fever, or illness.

*Fussing refers to intermittent distressed vocalization and has been defined as “[behavior] that is not quite crying but not awake and content either.” Infants often fluctuate between crying and fussing, making it difficult to distinguish between the two symptoms in practice.

Functional constipation and dyschezia

Functional constipation is often the result of repeated attempts by a child to withhold feces in an attempt to avoid unpleasant defecation. This withholding behavior leads to stool retention, which leads the colon to absorb more water and create hard stools [1].

A diagnosis of functional constipation in infants requires **1 month of at least two** of the following [1]:

1. Two or fewer defecations per week;
2. History of excessive stool retention;
3. History of painful or hard bowel movements;
4. History of large-diameter stools; and
5. Presence of a large fecal mass in the rectum.

Functional constipation should not be confused with infant dyschezia, which represents poor coordination between increased intra-abdominal pressure and relaxation of the muscular pelvic floor during defecation [1,24]. Infants with dyschezia strain for many minutes, scream, cry, and turn red or purple in the face with each attempt to defecate. They pass stools several times daily rather than demonstrating constipation, characterized by two or fewer defecations per week [1].

The diagnostic criteria for dyschezia in infants <9 months of age are as follows [1]:

1. At least 10 minutes of straining and crying before the successful or unsuccessful passage of soft stools; and
2. No other health problems.

In the majority of infants, the symptoms of dyschezia begin in the first few months of life and resolve spontaneously after 3–4 weeks [1]. Since there is no management for dyschezia except reassurance, we recommend referring the child to a pediatric gastroenterologist to confirm the diagnosis. This entity is not included in the consensus statement.

Functional diarrhea

Functional diarrhea is defined by the daily painless recurrent passage of three or more large unformed stools for 4 or more weeks with onset in the infant, toddler, or preschool years [1]. Considering that the occurrence of chronic or recurrent diarrhea in infancy can be due to many serious organic disorders, the recommended approach to its management is to refer the child to a pediatric gastroenterologist. Hence, we have not included it in this consensus statement.

Although several treatment guidelines and protocols are available for the management of FGIDs in infancy [25-27], certain practical aspects, such as the differential management

of exclusively breastfed infants versus formula-fed infants with FGIDs, remain ambiguous. Moreover, the guidelines do not provide the definitive duration of all arms of the treatment protocols or algorithms. These gaps provide room for individual interpretation and practice and may lead to inconsistent treatment practices among healthcare professionals. The Middle East FGID Consensus meeting was organized to generate a simple, definitive, and practical recommendation for clinicians managing FGIDs in this region.

METHODS

For the development of a regional consensus, 14 leading experts from Bahrain, Iran, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, and United Arab Emirates convened a meeting. A structured quantitative method was employed to facilitate the discussion and reach a consensus [28]. Statements were prepared before the consensus meeting based on local clinical practice and discussions with experts from the region. Before the vote, each statement was extensively discussed within the group and amended. All group members voted anonymously, and a 10-point scale was used to quantify the consensus (0=strongly disagree to 9=fully agree). A vote of 6 or greater meant “agreement,” while a vote of 9 was considered an expression of stronger agreement than a vote of 6. Consensus was considered achieved if more than 75% of the votes were 6, 7, 8, or 9.

CONSENSUS RECOMMENDATIONS

This expert discussion focused on managing FGIDs in healthy term infants <12 months of age. FGIDs in preterm infants, toddlers, or older children were not discussed in this opinion. The experts agreed that FGIDs are a frequently encountered challenges in everyday clinical practice despite the apparent lack of formal epidemiology figures from the region. There is consensus that a concerted effort is needed to estimate the burden of FGIDs in the region. As with any functional disorder, parental and caregiver reassurance, counseling, support, and education are integral aspects of the management of infantile FGIDs [1]. The risk stratification of FGIDs has been discussed as a potential tool to help identify and prevent the disorder in at-risk infants. The experts also opined that the role of allergy in FGIDs and its management is a separate topic in itself and beyond the scope of this discussion.

Infant regurgitation

Warning signs such as severe vomiting, irritability, crying, fussiness, feeding problems, atopic dermatitis, constipation, diarrhea, failure to thrive, hematemesis, back arching, neurological abnormalities, and/or neurodevelopmental delay should be ruled out as a first step in the management of infant regurgitation [25,29]. Considering the evidence of probiotics offering a better gastric emptying rate and other potential benefits in the treatment of regurgitation [30,31], the experts opined that a trial of a thickened formula with added *Lactobacillus reuteri* DSM 17938 may be an option for the management of infant regurgitation (**Table 2, Fig. 1**).

Infant colic

The experts discussed available evidence for the management of infant colic, including clinically significant data for the probiotic *L. reuteri* DSM 17938 (**Table 3**) [32-35]. There was a strong consensus within the group that this specific probiotic strain is an option for

Table 2. Expert consensus on infant regurgitation

No.	Consensus statements based on expert opinion	Consensus*
1	A thickened formula is recommended for formula-fed infants with regurgitation after ruling out alarm signs.	87%
2	In the absence of alarm signs, trial of a thickened formula with <i>Lactobacillus reuteri</i> DSM 17938 can be considered the first-line therapy for 2–4 weeks.	80%
3	Exclusively breastfed infants with regurgitation should not be overfed; mothers should continue breastfeeding and be offered feeding advice.	100%
4	Experts agree with the Rome Working Committee’s decision to leave “troublesome” symptoms out of the new Rome IV criteria (due to difficulty defining “troublesome” in infancy”).	100%

*Proportion of votes ≥6; consensus was reached if >75% of the working group members voted in favour of each question.

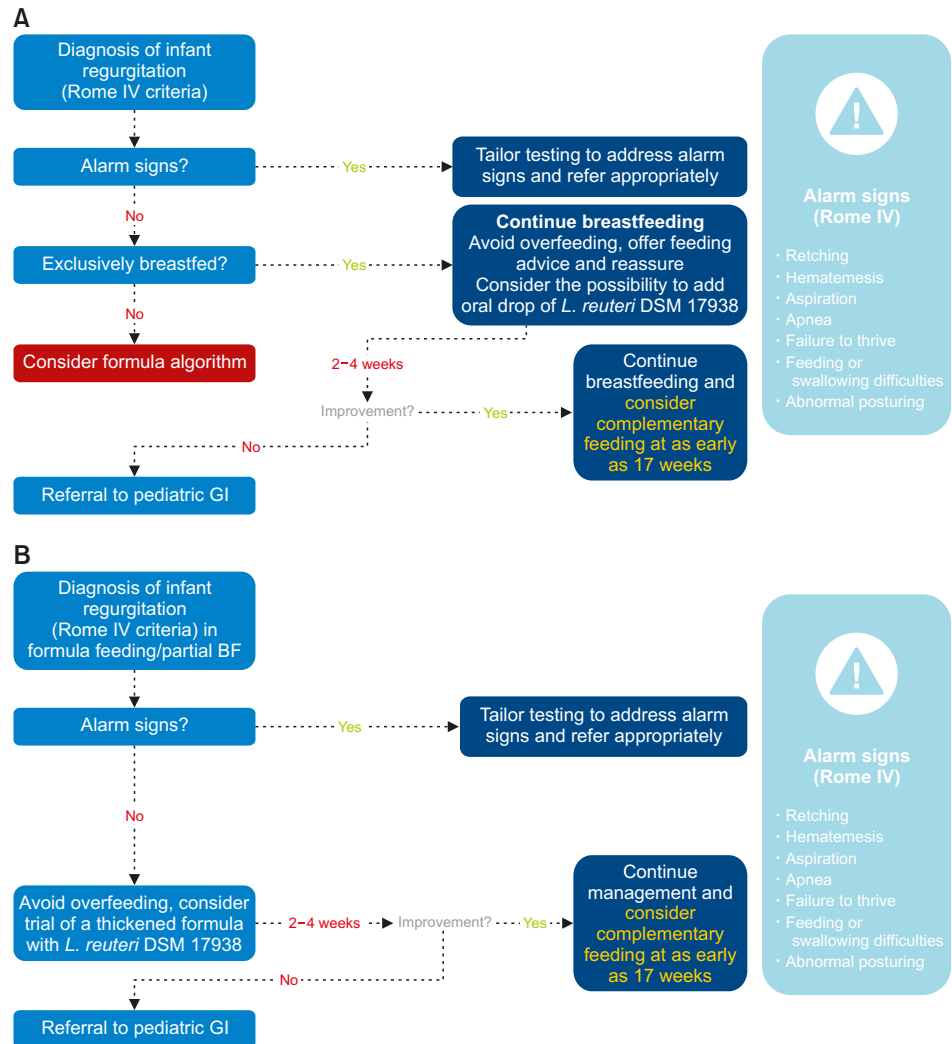


Fig. 1. (A) Management algorithm for infant regurgitation in breastfed infants. (B) Management algorithm for infant regurgitation in formula-fed infants. GI: gastroenterology, BF: breastfeeding.

the management of infant colic (Table 4, Fig. 2). The experts felt that the role of lactose avoidance in infant colic is debatable because of the lack of clinical evidence and should not be recommended as a routine treatment.

Functional constipation

The experts recommended the early administration of oral laxatives for the management of functional constipation. Considering the limited available evidence and proven safety profile

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Table 3. Review of *Lactobacillus reuteri* DSM17938 trials on crying time* in colicky infants

Publication	Included trials	Age	Difference (95% CI)	p-value
Anabrees et al., 2013 [32]	Savino et al., 2007 Savino et al., 2010 Szajewska et al., 2013	Up to 5 months	-56.0 (-59.92 to -52.15)	<0.00001
Urbańska et al., 2014 [33]	Savino et al., 2010 Szajewska et al., 2013 Sung et al., 2014	Up to 5 months	-43.32 (-67.62 to -19.02)	0.005
Xu et al., 2015 [34]	Savino et al., 2010 Szajewska et al., 2013 Roos et al., 2013 Sung et al., 2014 Mi et al., 2015	Up to 5 months	-45.83 (-59.45 to -32.2)	0.0001
Dryl and Szajewska, 2018 [35]	Savino et al., 2010 Szajewska et al., 2013 Mi et al., 2015 Chau et al., 2015	Up to 6 months	-59.31 (-69.59 to -49.03)	<0.00001

CI: confidence interval.

*Mean daily crying time (minutes) at day 21 vs. control.

Table 4. Expert consensus on infant colic

No.	Consensus statements based on expert opinion	Consensus*
1	The addition of <i>Lactobacillus reuteri</i> DSM 17938 to infant formula can be considered for infants with colic.	86%
2	In the absence of alarm signs, the trial of a formula with <i>L. reuteri</i> DSM 17938 might be recommended as the first-line treatment for 4–6 weeks for infants with colic.	79%
3	Breastfed infants with colic should continue to receive breastfeeding. (Adding <i>L. reuteri</i> DSM 17938 for 4 weeks together with parental reassurance is highly recommended.)	85%
4	Experts agree to the Rome IV Working Committee's decision to revise the diagnostic criteria for infant colic (removal of Wessel's rule of 3's; removal of the term "paroxysmal").	100%
5	There is no evidence to support lactose avoidance or restriction in infantile colic.	100%

*Proportion of votes ≥6; consensus was reached if >75% of the working group members voted in favour of each question.

Table 5. Expert consensus on functional constipation

No.	Consensus statements based on expert opinion	Consensus*
1	In the absence of alarm signs, trial of a formula with <i>Lactobacillus reuteri</i> DSM 17938 might be considered for 2–4 weeks in infants <6 months of age with functional constipation.	62%
2	Mothers of breastfed infants with constipation should be given education and reassurance and encouraged to continue breastfeeding.	100%
3	The experts recommend early administration of oral laxatives.	92%
4	The experts agree with the Rome IV Working Committee's decision to differentiate functional constipation from infantile dyschezia.	88%

*Proportion of votes ≥6; consensus was reached if >75% of the working group members voted in favour of each question.

[36,37], there was a weak recommendation for the management of functional constipation using the probiotic *L. reuteri* DSM 17938, which did not meet the consensus criteria (Table 5). Although this indication differs from that stated in the ESPGHAN and NASPGHAN guidelines, the experts opined that the latest scientific evidence points toward the potential benefits of *L. reuteri* DSM 17938 in the management of functional constipation [38]. Hence, the panel concluded that while the main treatment for functional constipation remains oral laxatives, *L. reuteri* DSM 17938 is the most studied strain to date and a viable option if a probiotic is being considered in combination with oral laxatives for the treatment of this FGID.

DISCUSSION

Pharmacotherapy is not recommended for the management of FGIDs such as infant regurgitation and colic due to a lack of evidence and the potential risk of adverse events [26,39,40]. Potential conservative treatments for regurgitation include upright positioning after meals and thickened feedings. Evidence is limited for positioning [41-45], and even

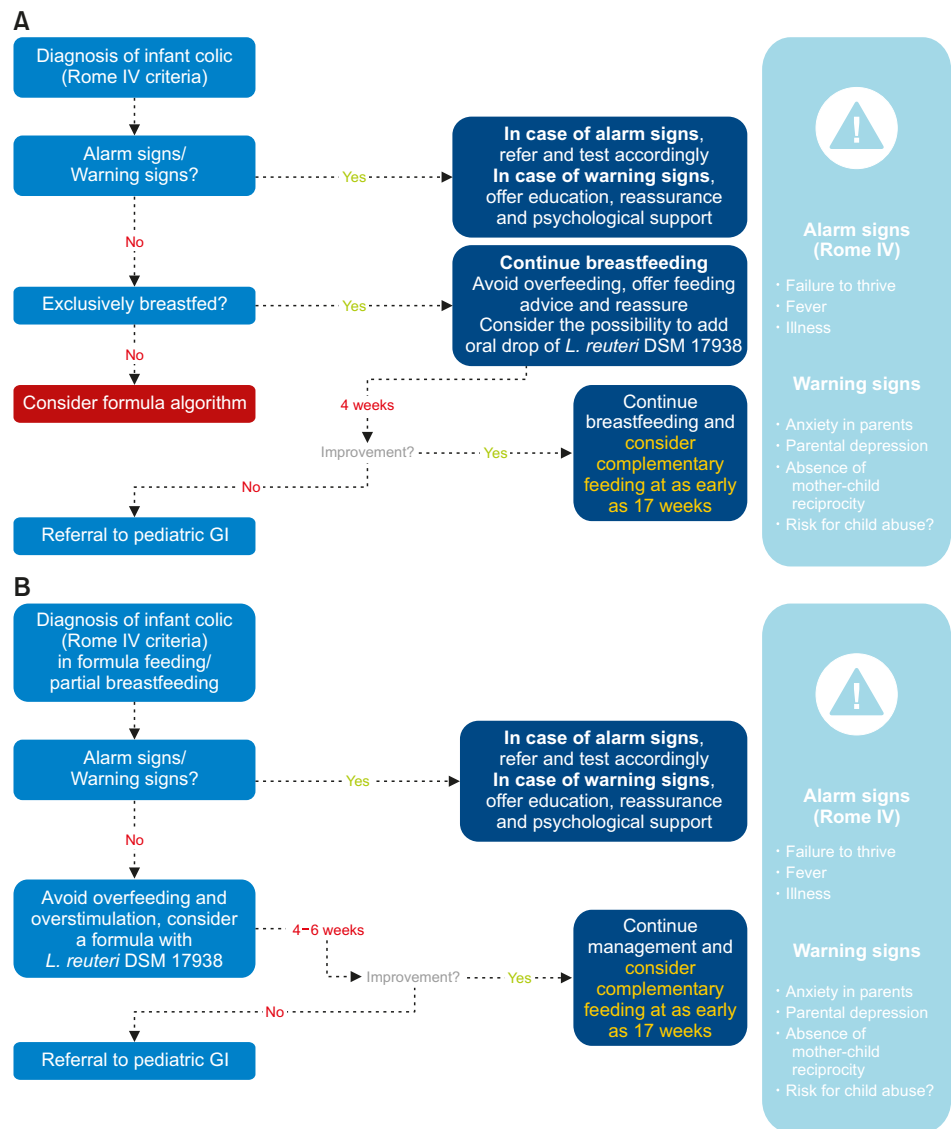


Fig. 2. (A) Management algorithm for infant colic in breastfed infants. (B) Management algorithm for infant colic in formula-fed infants. GI: gastroenterology.

considering the possible benefits, positioning and elevating the head of the crib are not recommended by ESPGHAN, NASPGHAN, or the American Academy of Pediatrics because of the risk of sudden infant death syndrome [26,46,47]. Thickened feedings and antiregurgitation formulas, especially those with digestible carbohydrates, can decrease regurgitation in healthy infants without interfering with their nutrition [48,49].

The first step in the management of colic is to rule out important warning signs such as severe vomiting, back arching, gastrointestinal bleeding, failure to thrive, abdominal distention, bloating, and any other signs of further organic causes [25]. Evidence from several randomized controlled trials and systematic reviews supports the use of a particular probiotic supplement (*L. reuteri* DSM 17938) to reduce infant crying due to colic (Table 3) [32-35].

It is important to rule out serious disorders such as Hirschsprung's disease and cystic fibrosis in infants presenting with constipation. The goal of treatment is to facilitate painless defecation until a regular defecation pattern is restored and the cycle of pain and hard stools is broken [1,25]. Nonstimulant laxatives such as polyethylene glycol (PEG), lactulose, or Milk of Magnesia may be considered for the initial management of functional constipation [1]. PEG should be considered in infants older than 6 months of age [25]. There is limited published information on the treatment of infant constipation with probiotics; however, it is considered safe in infancy [1,36,37]. Experts agree that constipation in infancy is a relatively more difficult and serious disorder since it may be the manifestation of a serious medical/organic disorder. A simple protocol and treatment flowchart for functional constipation was deemed counterproductive by the participating experts; therefore, it was not included in this paper.

Available evidence suggests that colic, constipation, and regurgitation may be associated with cow's milk allergy (CMA), which must be excluded [50-52]. Readers are recommended to always consider the possibility of CMA in an infant presenting with FGID and, in case of a possible allergic etiology, follow an accepted management guideline for CMA.

CONCLUSION

Regularly updated tools such as the Rome IV criteria will be of great assistance in the clinical diagnosis of FGIDs in infancy. As a next step, we developed a simple and practical treatment protocol for primary care physicians and general pediatricians, who are usually the initial point of contact for the parents of infants with FGIDs. With the right utilization of the latest Rome criteria and our treatment plan, we hope that clinicians in our region will be empowered to provide a positive diagnosis and follow it up with a unified and effective treatment strategy for patients suffering from these challenging disorders in early life.

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REFERENCES

1. Benninga MA, Nurko S, Faure C, Hyman PE, St James Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2016;150:1443-55.e2.
[PUBMED](#) | [CROSSREF](#)
2. Thompson WG. The road to Rome. *Gastroenterology* 2006;130:1552-6.
[PUBMED](#) | [CROSSREF](#)
3. Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, et al. Gastrointestinal symptoms in infancy: a population-based prospective study. *Dig Liver Dis* 2005;37:432-8.
[PUBMED](#) | [CROSSREF](#)
4. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. *J Pediatr Gastroenterol Nutr* 2015;61:531-7.
[PUBMED](#) | [CROSSREF](#)
5. Zwiener R, Robin S, Keller C, Hyman PE, Nurko S, Saps M, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers according to the Rome IV criteria. *Gastroenterology* 2017;152:S649.
[CROSSREF](#)

6. Robin SG, Keller C, Zwiener R, Hyman PE, Nurko S, Saps M, et al. Prevalence of pediatric functional gastrointestinal disorders utilizing the Rome IV criteria. *J Pediatr* 2018;195:134-9.
[PUBMED](#) | [CROSSREF](#)
7. van Tilburg MA, Hyman PE, Walker L, Rouster A, Palsson OS, Kim SM, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J Pediatr* 2015;166:684-9.
[PUBMED](#) | [CROSSREF](#)
8. Bellaiche M, Oozeer R, Gerardi-Temporel G, Faure C, Vandenplas Y. Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life. *Acta Paediatr* 2018;107:1276-82.
[PUBMED](#) | [CROSSREF](#)
9. Indrio F, Miqdady M, Al Aql F, Haddad J, Karima B, Khatami K, et al. Knowledge, attitudes, and practices of pediatricians on infantile colic in the Middle East and North Africa region. *BMC Pediatr* 2017;17:187.
[PUBMED](#) | [CROSSREF](#)
10. AlFaleh K, AlLuwaimi E, AlJefri S, ALOsaimi A, Behaisi M. Infant formula in Saudi Arabia: a cross sectional survey. *Kuwait Med J* 2014;46:328-32.
11. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. *World J Gastroenterol* 2004;10:1795-7.
[PUBMED](#) | [CROSSREF](#)
12. Martin AJ, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002;109:1061-7.
[PUBMED](#) | [CROSSREF](#)
13. Savino F, Castagno E, Bretto R, Brondello C, Palumeri E, Oggero R. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatr Suppl* 2005;94:129-32.
[PUBMED](#) | [CROSSREF](#)
14. Romanello S, Spiri D, Marcuzzi E, Zanin A, Boizeau P, Riviere S, et al. Association between childhood migraine and history of infantile colic. *JAMA* 2013;309:1607-12.
[PUBMED](#) | [CROSSREF](#)
15. Radesky JS, Zuckerman B, Silverstein M, Rivara FP, Barr M, Taylor JA, et al. Inconsolable infant crying and maternal postpartum depressive symptoms. *Pediatrics* 2013;131:e1857-64.
[PUBMED](#) | [CROSSREF](#)
16. Botha E, Joronen K, Kaunonen M. The consequences of having an excessively crying infant in the family: an integrative literature review. *Scand J Caring Sci* 2019;33:779-90.
[PUBMED](#) | [CROSSREF](#)
17. Akman I, Kuşçu K, Ozdemir N, Yurdakul Z, Solakoglu M, Orhan L, et al. Mothers' postpartum psychological adjustment and infantile colic. *Arch Dis Child* 2006;91:417-9.
[PUBMED](#) | [CROSSREF](#)
18. Riih  H, Lehtonen L, Huhtala V, Saleva K, Korvenranta H. Excessively crying infant in the family: mother-infant, father-infant and mother-father interaction. *Child Care Health Dev* 2002;28:419-29.
[PUBMED](#) | [CROSSREF](#)
19. Chogle A, Velasco-Benitez CA, Koppen IJ, Moreno JE, Ram rez Hern ndez CR, Saps M. A population-based study on the epidemiology of functional gastrointestinal disorders in young children. *J Pediatr* 2016;179:139-43.e1.
[PUBMED](#) | [CROSSREF](#)
20. Salvatore S, Baldassarre ME, Di Mauro A, Laforgia N, Tafuri S, Bianchi FP, et al. Neonatal antibiotics and prematurity are associated with an increased risk of functional gastrointestinal disorders in the first year of life. *J Pediatr* 2019;212:44-51.
[PUBMED](#) | [CROSSREF](#)
21. Walter AW, Hovenkamp A, Devanarayana NM, Solanga R, Rajindrajith S, Benninga MA. Functional constipation in infancy and early childhood: epidemiology, risk factors, and healthcare consultation. *BMC Pediatr* 2019;19:285.
[PUBMED](#) | [CROSSREF](#)
22. Chitkara DK, Rawat DJ, Talley NJ. The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. *Am J Gastroenterol* 2005;100:1868-75.
[PUBMED](#) | [CROSSREF](#)
23. Koppen IJ, Nurko S, Saps M, Di Lorenzo C, Benninga MA. The pediatric Rome IV criteria: what's new? *Expert Rev Gastroenterol Hepatol* 2017;11:193-201.
[PUBMED](#) | [CROSSREF](#)
24. Bell  R, Cond  M. Functional gastrointestinal disorders in newborns: nutritional perspectives. *Pediatr Med Chir* 2018;40:10-3.
[PUBMED](#) | [CROSSREF](#)

25. Vandenplas Y, Hauser B, Salvatore S. Functional gastrointestinal disorders in infancy: impact on the health of the infant and family. *Pediatr Gastroenterol Hepatol Nutr* 2019;22:207-16.
[PUBMED](#) | [CROSSREF](#)
26. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018;66:516-54.
[PUBMED](#) | [CROSSREF](#)
27. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014;58:258-74.
[PUBMED](#) | [CROSSREF](#)
28. CDC Evaluation Research Team. Gaining consensus among stakeholders through the nominal group technique [Internet]. Atlanta (GA): CDC; 2018 [cited 2019 Mar 13]. Available from: <https://www.cdc.gov/healthyyouth/evaluation/pdf/brief7.pdf>
29. Moore DM, Rizzolo D. Sandifer syndrome. *JAAPA* 2018;31:18-22.
[PUBMED](#) | [CROSSREF](#)
30. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. *J Pediatr* 2008;152:801-6.
[PUBMED](#) | [CROSSREF](#)
31. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Filannino A, Cavallo L, et al. *Lactobacillus reuteri* accelerates gastric emptying and improves regurgitation in infants. *Eur J Clin Invest* 2011;41:417-22.
[PUBMED](#) | [CROSSREF](#)
32. Anabrees J, Indrio F, Paes B, AlFaleh K. Probiotics for infantile colic: a systematic review. *BMC Pediatr* 2013;13:186.
[PUBMED](#) | [CROSSREF](#)
33. Urbańska M, Szajewska H. The efficacy of *Lactobacillus reuteri* DSM 17938 in infants and children: a review of the current evidence. *Eur J Pediatr* 2014;173:1327-37.
[PUBMED](#) | [CROSSREF](#)
34. Xu M, Wang J, Wang N, Sun F, Wang L, Liu XH. The efficacy and safety of the probiotic bacterium *Lactobacillus reuteri* DSM 17938 for infantile colic: a meta-analysis of randomized controlled trials. *PLoS One* 2015;10:e0141445.
[PUBMED](#) | [CROSSREF](#)
35. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch Med Sci* 2018;14:1137-43.
[PUBMED](#) | [CROSSREF](#)
36. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. *Lactobacillus reuteri* (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. *J Pediatr* 2010;157:598-602.
[PUBMED](#) | [CROSSREF](#)
37. Olgaç MAB, Sezer OB, Özçay F. [Comparison of probiotic and lactulose treatments in children with functional constipation and determination of the effects of constipation treatment on quality of life]. *Çocuk Sağlığı Hastalık Derg* 2013;56:1-7. Turkish.
38. Kubota M, Ito K, Tomimoto K, Kanazaki M, Tsukiyama K, Kubota A, et al. *Lactobacillus reuteri* DSM 17938 and magnesium oxide in children with functional chronic constipation: a double-blind and randomized clinical trial. *Nutrients* 2020;12:225.
[PUBMED](#) | [CROSSREF](#)
39. 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. *J Pediatr* 2009;154:514-20.e4.
[PUBMED](#) | [CROSSREF](#)
40. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994;94:29-34.
[PUBMED](#)
41. Orenstein SR. Prone positioning in infant gastroesophageal reflux: is elevation of the head worth the trouble? *J Pediatr* 1990;117(2 Pt 1):184-7.
[PUBMED](#) | [CROSSREF](#)
42. Orenstein SR, Whittington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. *N Engl J Med* 1983;309:760-3.
[PUBMED](#) | [CROSSREF](#)

43. Bagucka B, De Schepper J, Peelman M, Van de Maele K, Vandenplas Y. Acid gastro-esophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. *Acta Paediatr Taiwan* 1999;40:298-301.
[PUBMED](#)
44. Tobin JM, McCloud P, Cameron DJ. Posture and gastro-oesophageal reflux: a case for left lateral positioning. *Arch Dis Child* 1997;76:254-8.
[PUBMED](#) | [CROSSREF](#)
45. Loots C, Kritas S, van Wijk M, McCall L, Peeters L, Lewindon P, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. *J Pediatr Gastroenterol Nutr* 2014;59:237-43.
[PUBMED](#) | [CROSSREF](#)
46. Eichenwald EC; COMMITTEE ON FETUS AND NEWBORN. Diagnosis and management of gastroesophageal reflux in preterm infants. *Pediatrics* 2018;142:e20181061.
[PUBMED](#) | [CROSSREF](#)
47. Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and other sleep-related infant deaths: evidence base for 2016 updated recommendations for a safe infant sleeping environment. *Pediatrics* 2016;138:e20162940.
[PUBMED](#) | [CROSSREF](#)
48. 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.
[PUBMED](#) | [CROSSREF](#)
49. Bosscher D, Van Caillie-Bertrand M, Van Dyck K, Robberecht H, Van Cauwenbergh R, Deelstra H. Thickening infant formula with digestible and indigestible carbohydrate: availability of calcium, iron, and zinc in vitro. *J Pediatr Gastroenterol Nutr* 2000;30:373-8.
[PUBMED](#) | [CROSSREF](#)
50. Pensabene L, Salvatore S, D'Auria E, Parisi F, Concolino D, Borrelli O, et al. Cow's milk protein allergy in infancy: a risk factor for functional gastrointestinal disorders in children? *Nutrients* 2018;10:1716.
[PUBMED](#) | [CROSSREF](#)
51. Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics* 1983;71:268-71.
[PUBMED](#)
52. Sopo SM, Arena R, Scala G. Functional constipation and cow's-milk allergy. *J Pediatr Gastroenterol Nutr* 2014;59:e34.
[PUBMED](#) | [CROSSREF](#)