ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REVIEW ARTICLE

Review shows that parental reassurance and nutritional advice help to optimise the management of functional gastrointestinal disorders in infants

Silvia Salvatore[1], Abdelhak Abkari[2], Wei Cai[3], Anthony Catto-Smith[4], Sylvia Cruchet[5], Frederic Gottrand[6], Badriul Hegar[7], Carlos Lifschitz[8], Thomas Ludwig[9], Neil Shah[10], Annamaria Staiano[11], Hania Szajewska[12], Suporn Treepongkaruna[13], Yvan Vandenplas (Yvan.Vandenplas@uzbrussel.be)[14]

1.Department of Pediatrics, University of Insubria, Varese, Italy
2.Faculty of Medicine, Unit of Pediatric Gastroenterology, University Hospital Ibn Rochd, University Hassan2, Casablanca, Morocco
3.Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
4.Lady Cilento Children's Hospital, Queensland University of Technology, Brisbane, Australia
5.Institute of Nutrition and Food Technology, University of Chile (INTA), Santiago, Chile
6.Department of Pediatrics, Jeanne de Flandre Children's Hospital, CHU Lille, University of Lille, Lille, France
7.Division of Gastrohepatology, Department of Child Health, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
8.Hospital Italiano, Buenos Aires, Argentina
9.Danone Nutricia Research, Singapore, Singapore
10.Great Ormond Street Hospital, London, UK
11.Department of Translational Medical Science, Section of Pediatrics, University of Naples Federico II, Naples, Italy
12.Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland
13.Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
14.KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Keywords
Constipation, Functional gastrointestinal disorders, Infantile colic, Management, Regurgitation

Correspondence
Professor Yvan Vandenplas, KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1050 Brussel, Belgium.
Tel: +32(0)24775794 |
Fax: +32(0)24775783 |
Email: Yvan.Vandenplas@uzbrussel.be

Received
20 December 2017; revised 21 February 2018; accepted 23 April 2018.

DOI:10.1111/apa.14378

ABSTRACT

Aim: Regurgitation, infantile colic and functional constipation are common functional gastrointestinal disorders (FGIDs) during infancy. Our aim was to carry out a concise review of the literature, evaluate the impact of these common FGIDs on infants and their families, and provide an overview of national and international guidelines and peer-reviewed expert recommendations on their management.

Methods: National and international guidelines and peer-reviewed expert recommendations on the management of regurgitation, infantile colic and functional constipation were examined and summarised.

Results: Regurgitation, infantile colic and functional constipation cause frequent parental concerns, lead to heavy personal and economic costs for families and impose a financial burden on public healthcare systems. Guidelines emphasise that the first-line management of these common FGIDs should focus on parental education, reassurance and nutritional advice. Nutritional advice should stress the benefits of continuing breastfeeding, while special infant formulas may be considered for non-breastfed infants with common FGIDs. Drug treatment is seldom required, with the exception of functional constipation.

Conclusion: By providing complete and updated parental education, reassurance and nutritional advice, healthcare professionals can optimise the management of FGIDs and related symptoms and reduce the inappropriate use of medication or dietary interventions.

INTRODUCTION

Many infants experience at least one symptom of a functional gastrointestinal disorder (FGID) before they reach their first birthday (1). These FGID symptoms are often extremely distressing for the infant and parents, leading to a cascade of infant discomfort and crying, parental anxiety, repeated healthcare consultations and escalating healthcare costs (2). Parents are frequently offered conflicting advice on how to manage FGIDs and

Abbreviations
FGIDs, Functional gastrointestinal disorders; GI, Gastrointestinal.

Key notes

- Regurgitation, infantile colic and functional constipation are common functional gastrointestinal disorders (FGIDs) during infancy, cause frequent parental concerns and heavy personal and economic costs for families and public healthcare systems.
- This review examined the literature and found that guidelines emphasise that the first-line management of these common FGIDs should be parental education, reassurance and nutritional advice, including continued breastfeeding.
- With the exception of functional constipation, drug treatment is seldom required.

their related symptoms, ranging from personal experience, social media exchanges and recommendations for medications that do not have any proven efficacy and could induce adverse reactions, to expert opinions and evidence-based guidelines.

Despite this, we now recognise that the first-line management of the most common FGIDs, particularly infantile colic and regurgitation, should focus on parental education and reassurance and nutritional advice. The latter includes recommendations on feeding volume, frequency, techniques for all infants and considering special formulas with proven effects for formula-fed infants with persisting symptoms. Limiting over-the-counter remedies, frequent inappropriate formula changes and the use of extensive protein hydrolysates or amino acid formulas may lead to more favourable outcomes for the infant and parents and relieve the burden on healthcare systems (2) (Fig. 1).

The aim of this review was to carry out a comprehensive literature overview and evaluate the impact of FGIDs on individuals and society. We also wanted to provide a summary of the international guidelines and expert opinions on nutritional advice that should be offered to parents of both breastfed and formula-fed infants.

FUNCTIONAL GASTROINTESTINAL DISORDERS IN EARLY LIFE

During infancy, the structure and function of the gastrointestinal (GI) tract, the nervous system and microbiota are still maturing and this may cause GI signs and symptoms that have no obvious structural or biochemical cause. The occurrence of these principal GI manifestations has been categorised into seven recognised FGIDs (Table 1). The diagnosis of a functional disorder virtually eliminates organic disease as a cause of the symptoms. From birth to 6 months of age, approximately one infant out of two shows at least one FGID or related signs and symptoms (1,3). Regurgitation, infantile colic and functional constipation are the most common FGIDs in infancy, and it has been shown that more than one FGID often coexist in the same infant (3,4). Functional diarrhoea, dyschezia, rumination syndrome and cyclic vomiting syndrome occur less frequently (1,5).

IMPACT ON FAMILY AND SOCIETY

FGID symptoms vary from mild to extremely distressing for the infant and parents and may lead to parental anxiety, poor quality of life, short- and long-term health consequences, shortened duration of full breastfeeding, numerous formula changes and medical consultations and high associated healthcare costs (1,2,6–11) (Table 2).

For example, one observational study used the Parent Child Early Relational Assessment Scale and the Beavers Scale to examine relationships within 32 families whose children cried excessively (12). The researchers found that parent–child, and particularly father–child, interactions were less than optimal, infants were less competent in interacting with their parents and the interaction between the parents was more likely to be dysfunctional than control families where the infant did not cry excessively. Another study revealed an association between infantile colic, symptoms of postpartum maternal depression and insecure mother–child bonding (13).

Thus, any medical consultation needs to both examine the child and assess the family's experiences, how well they are coping and their level of anxiety (14). Healthcare professionals should appreciate that FGIDs in general, and excessive crying in particular, may be extremely distressing for families and can damage the relationships between parents and their children.

ECONOMIC IMPACT

FGIDs and related symptoms have a significant impact on personal and public healthcare expenses. These include the costs of prescribed treatments in countries where residents pay for child healthcare, over-the-counter or home remedies, visits to healthcare professionals and loss of income when parents have to take time off work (2).

In the United States, the total national cost for constipation-related emergency department visits increased by 121% to $1.6 billion between 2006 and 2011 and infants were the most frequent visitors (15). In the United Kingdom, the annual total cost to the National Health Service for infant crying and sleeping problems in the first 12 weeks after birth has been estimated at £65 million (16).

Another study concluded that the total cost of treating FGIDs in infants in England was at least £72.3 million per year in 2014 and 2015 (2). The study also concluded that the number of prescribed medications and over-the-counter remedies that were purchased indicated gaps between treatment guidelines for FGIDs, which emphasise parental reassurance and nutritional advice, and their implementation (2).

DIAGNOSTIC CRITERIA

Internationally agreed diagnostic criteria for FGIDs were first published in 1989 and these Rome criteria have been regularly updated, most recently in 2016 (14) (Table 3).

AETIOLOGY AT A GLANCE

Most parents request information about the cause of their child's symptoms. Providing parents with an easy to understand and complete explanation of the underlying disorder may reduce their anxiety and reinforce their empathy and confidence. However, to provide proper parental education, we need to clarify the interaction between physiological changes during the maturation of the GI tract, the natural evolution of the specific disorder and the parental coping mechanisms. For example, contributory factors for reflux and regurgitation include feeding large amounts of liquid over a short period of time, a short intra-abdominal oesophagus, an obtuse angle of His,

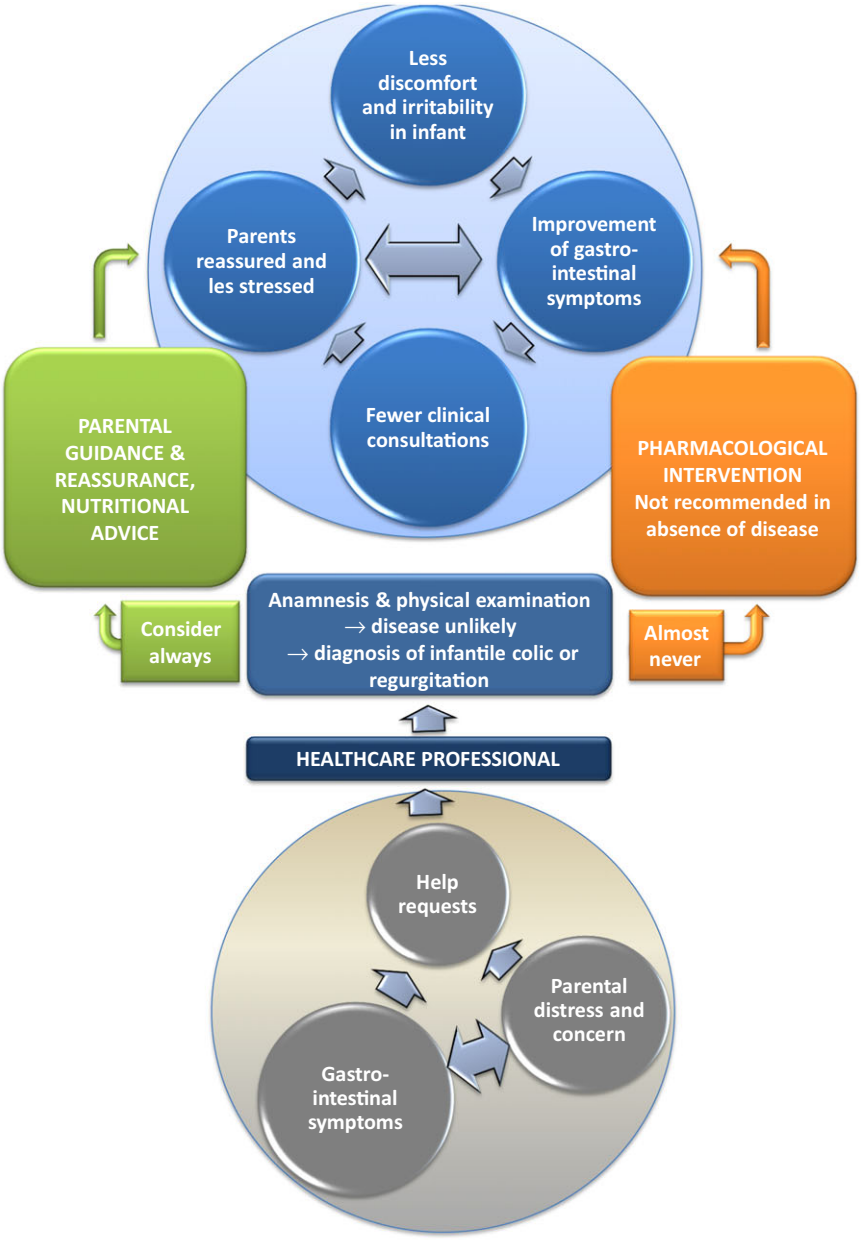

Figure 1 Infants' gastrointestinal symptoms can be distressing for parents and represent a frequent reason for consultations with healthcare professionals.

Table 1 Functional gastrointestinal disorders and prevalence (1,14)

Category	Reported worldwide prevalence (%)
1. Infant regurgitation	30–67
2. Infant colic	5–20
3. Functional constipation	3–27
4. Functional diarrhoea	6–7
5. Cyclic vomiting syndrome	3.4
6. Infant dyschezia	2.4
7. Infant rumination syndrome	1.9

feeding in horizontal position and the position of the infant after feeding (17).

There are gastrointestinal and behavioural hypotheses for infantile colic (18,19). Gastrointestinal hypotheses involve immaturity of the gut function, dysmotility, imbalance of the intestinal microbiota, changes in gut hormones and food hypersensitivities or allergies. For example, the behavioural hypotheses include inadequate maternal–infant interaction, maternal anxiety and a difficult infant temperament. Being aware that crying does not always indicate pain would make caregivers feel less inadequate and scared that their child has a disease.

Table 2 Impact of functional gastrointestinal disorders and related symptoms on family life, and short- and long-term well-being

In the first months after birth, FGIDs and related signs and symptoms have been reported in studies to be more frequently associated with:

- Tiredness and fatigue in mothers (41)
- Postpartum maternal depressive symptoms (42)
- Suboptimal social and emotional behaviour of mothers during feeding (43)
- Premature breastfeeding cessation (7)
- Frequent infant formula changes (44)
- Insecure mother–child attachment (13)
- Suboptimal mother–child, father–child and mother–father interaction (12)
- Loss of parental working days (10)
- Infantile abuse and shaken baby syndrome (45,46)

In the long term, FGIDs and related signs and symptoms have been found to be more frequently associated with:

- Family distress and less satisfactory family life in individual studies with follow-up to 3 years and school age (6,47)
- Children being perceived as fragile by their mothers at 3.5 years of age (48)
- Abdominal pain, or related FGIDs in individual studies at 4, 8, 10 and 13 years follow-up, respectively (9,10,49,50)
- Sleeping problems in individual studies with 3 and 10 years of follow-up, respectively (6,50)
- Behavioural problems such as difficulty with emotional regulation, frequent temper tantrums, or a more impulsive cognitive style in individual studies with 3, 4, 8 and 10 years of follow-up, respectively (6,49–52)

Hypotheses for functional constipation include a family predisposition and dietary factors, such as calcium soaps in the stools and insufficient fibre and liquid intake (20,21).

MANAGEMENT OF REGURGITATION

Regurgitation is very common in infancy and usually improves spontaneously in the first year after birth. Therefore, the main management goal is to provide effective parental reassurance and symptom relief while avoiding complications (Table 4) (14).

If infants have frequent and troublesome regurgitation, a complete medical history and physical examination with anthropometry need to be performed to rule out warning signs of organic disease. Physiological regurgitation should not be diagnosed in infants with vomiting and poor weight gain (22,23).

MANAGEMENT OF INFANTILE COLIC

Caring for a child with infantile colic can be extremely challenging and in most cases its management should concentrate on helping parents to cope with their child's excessive crying (14) (Table 5). Parents can be reassured that crying peaks at about 4–6 weeks after birth and then steadily diminishes until 12 weeks (4,24). If there is no evidence of cows' milk protein allergy or warning signs of organic disease, the feeding technique should be evaluated and the caregivers should be reassured and supported (22).

Although food allergies are frequently associated with GI manifestations, the link between food allergies and infantile colic is unlikely in the absence of other symptoms of atopy (24).

A data meta-analysis of individual participants concluded that Lactobacillus reuteri DSM17938 was effective and could be recommended for breastfed infants with infantile colic, but there were insufficient data to reach conclusions for formula-fed infants with infantile colic (25).

MANAGEMENT OF FUNCTIONAL CONSTIPATION

The goal for treating functional constipation is to restore a regular defecation pattern and to prevent relapses (Table 6). Parental reassurance and follow-up laxatives may still be required if an organic condition, such as Hirschsprung's disease or cystic fibrosis, is excluded and there are no accompanying signs, such as failure to thrive, intermittent diarrhoea or abdominal distension (22).

Table 3 Diagnostic criteria for infant regurgitation, infantile colic and functional constipation in infancy

Infant regurgitation	Infant colic	Functional constipation
Must include both of the following in otherwise healthy infants 3 weeks to 12 months of age: 1. Regurgitation 2 or more times per day for 3 or more weeks 2. No retching, haematemesis, aspiration, apnoea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing	Must include all of the following: 1. An infant who is <5 months of age when the symptoms start and stop 2. Recurrent and prolonged periods of infant crying, fussing, or irritability that occur without obvious cause and cannot be prevented or resolved by caregivers 3. No evidence of failure to thrive, fever or illness	Must include 1 month of at least 2 of the following in infants up to 4 years of age: 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 5. Presence of a large faecal mass in the rectum

Adapted from Benninga et al., 2016 (14).

Table 4 Excerpt of current recommendations for the management of infant regurgitation

Recommendation	Reference
Parental education and reassurance as the first line of management	
• Provide information on:	• Expert group review (22)
• The natural history of regurgitation (even in breastfed infants)	• NICE (2015) (53)
• Correct formula preparation (in formula-fed infants)	
• Impact of overfeeding on symptoms	
• Despite possible benefits of positioning in the treatment of reflux, no position other than supine is recommended for infants due to the risk of sudden infant death syndrome (SIDS)	• NASPGHAN/ESPGHAN (54) • NICE (2015) (53)
Nutritional management	
• Regurgitation is not a reason to stop breastfeeding	• Expert group review (23)
• Correct the frequency and volume of feeds, if necessary	• NICE (2015) (53)
• Thickened or anti-regurgitation formula decreases overt regurgitation and can be considered in persisting and distressing symptoms or in infants with poor growth because of regurgitation	
• In case of frequent regurgitation associated with marked distress:	• NICE (2015) (53)
• In breastfed infants: Ensure that a person with appropriate expertise and training carries out a breastfeeding assessment	
• In formula-fed infants (stepped-care approach):	
▫ Review the feeding history	
▫ Reduce the feed volumes if excessive for the infant's weight	
▫ Offer a trial of smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk)	
▫ Offer a trial of thickened 'anti-regurgitation' formula (e.g. formula containing rice starch, corn starch, locust bean gum or carob bean gum)	
• Modify feeding volumes and frequency according to age and weight to avoid overfeeding	• NASPGHAN/ESPGHAN (54)
• Consider thickened feeding (or anti-regurgitation formula) to treat visible regurgitation/vomiting to improve comfort of the infant and offer additional reassurance to the family	
• In formula-fed infants who are suspected of gastro-oesophageal reflux disease but fail to respond to optimal non-pharmacological treatment, consider a 2–4 week trial of extensively hydrolysed protein-based (or amino-acid-based) formula (as milk protein sensitivity could be the cause)	
Pharmacological therapy	
• No pharmacological recommendation for the treatment of crying/distress or visible regurgitation in otherwise healthy infants	• NASPGHAN/ESPGHAN (54)
• Do not recommend antacids/alginates to be used for chronic treatment of infants with gastro-oesophageal reflux disease	
• Proton pump inhibitors should be prescribed only when there is a clear diagnosis of gastro-oesophageal reflux disease and, whenever possible, the lowest doses should be prescribed for the shortest length of time possible	
• There is no indication for drug treatment in 'happy spitters' or in infants without troublesome regurgitation	• Expert group review (22)
• Proton pump inhibitors do not decrease infant regurgitation, crying or fussiness and should not be empirically started	
• When frequent regurgitation associated with marked distress continues despite the nutritional management:	• NICE (2015) (53)
• In breastfed and formula-fed infants: Consider alginate therapy for a trial period of 1–2 weeks	
• If the alginate therapy is successful continue with it, but try stopping it at intervals to see if the infant has recovered	
• Do not offer acid-suppressing drugs, such as proton pump inhibitors or Histamine-2 receptor antagonists, to treat overt regurgitation in infants and children occurring as an isolated symptom	
• Do not offer metoclopramide, domperidone or erythromycin to treat gastro-oesophageal reflux disease without seeking specialist advice and taking into account their potential to cause adverse events	

PHARMACOLOGICAL MANAGEMENT OF FGIDS IN EARLY LIFE

The parents of children with FGIDs are understandably keen to find a quick and easy solution, such as a pill that will lead to rapid symptom relief (26). In addition, changes in society changes have raised parents' expectations for instant solutions, which results in healthcare professionals being placed under enormous pressure to act and to investigate or prescribe pharmacological products. This often results in infants undergoing unnecessary investigations and medical treatment, which do not offer any significant improvements (22).

A review published in 2016 concluded that there was some evidence to support pharmacological interventions for constipation and rectal dis-impaction as the first-line therapy (27). However, pharmacological therapy appears to offer no benefit for other FGIDs that occur early in life (28).

Despite the lack of drug benefits, and the emphasis on parental and nutritional support in the guidelines, there is still widespread overuse of medical management in FGIDs such as regurgitation and infantile colic (26,27,29).

A survey among general paediatricians in Italy found little adherence to the guidelines for children with gastro-oesophageal reflux symptoms issued by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. The survey reported that 56% of general paediatricians prescribed proton pump inhibitors for infants with unexplained crying

Table 5 Excerpt of current recommendations for the management of infantile colic

Recommendation	Reference
Parental education and reassurance as the first line of management	

• Provide information on:
  • Signs of hunger and fatigue
  • Family structure and regularity
  • The self-limiting nature of the condition
• There is insufficient evidence to recommend swaddling and other caregiving interventions in all infants
• Evidence too limited to recommend herbal products such as fennel and peppermint
	• Expert group review (22)

• Reassure parent that:
  • Infantile colic is usually a transitory phase
  • Soothing strategies such as holding the baby through the crying episode may be helpful
• Encourage parent to:
  • Look after their own well-being, ensuring access of support network
  • Continue breastfeeding where possible
	• NICE, 2017 (55)

Nutritional management	
• Besides parental education and reassurance, nutritional management of infant colic should be the first choice • In selected breastfed infants with excessive irritability and crying, lactating mothers may be advised to exclude dairy products for 2–4 weeks and then reintroduce them • For selected formula-fed infants, the use of extensively hydrolysed infant formula may help • If cow's milk protein allergy is not a potential cause, partially hydrolysed formula with lactose-reduced or lactose-free and containing prebiotics or probiotics may contribute to a reduction in crying time • One double-blind, placebo-controlled trial showed a significant decrease in infantile colic within 1 week of intervention with a partial hydrolysate, with high beta-palmitate and a specific prebiotic mixture of galacto- and fructo-oligosaccharides • In selected breastfed infants, *L. reuteri* DSM 17938 may decrease infantile colic although there is insufficient data to recommend *L. reuteri* DSM 17938 in all colicky infants	• Expert group review (22)
Pharmacological therapy	
• Pharmacological therapy (e.g. proton pump inhibitors, simethicone) is not effective, and may cause serious adverse reactions	• Expert group review (22)

and, or, irritability and 38% prescribed them for infants with uncomplicated recurrent regurgitation and vomiting (30). According to a systematic review and meta-analysis from 2015, there is no benefit in using any kind of proton pump inhibitors for crying and irritable infants (31).

A study from New Zealand published in 2017 concluded that off-label prescribing of proton pump inhibitors for infants was relatively common. For example, 5.2% of children born in 2012 received a proton pump inhibitor before their first birthday and the majority of infants who received these drugs were not diagnosed with severe gastro-oesophageal reflux disease (29).

Conversely, the side effects of acid inhibitors have been extensively reported. One review of children up to 18 years of age reported that at least 23% of patients treated with histamine receptor 2 antagonists experienced side effects, as did 34% of those treated with proton pump inhibitors (32). Concerns have been raised with regard to the impact of proton pump inhibitors on the gut microbiome and the association between using proton pump inhibitors and small bowel bacterial overgrowth in children (33,34). There is sparse evidence for the efficacy of other medication, such as pain relieving agents, prokinetic drugs or over-the-counter remedies such as simethicone for treating infantile colic (28,35–38). However, parents of infants with colic are very likely to decide what medication they give their children without advice from their doctor (39,40).

PRAGMATICALLY MANAGING FGIDS IN EARLY LIFE

Parental education and reassurance are the cornerstones for managing infant colic, constipation and regurgitation. Nutritional advice, such as feeding techniques, volume and frequency, is also recommended.

Based on the current guidelines and expert reviews (Tables 4–6), the most relevant recommendations for the pragmatic management of FGIDs in primary care can be summarised as follows:

Parental reassurance

1. Nutritional advice should stress the benefits of breastfeeding and appropriate support should be offered whenever necessary. Parents should be aware that breastfeeding provides the most ideal nutrition for infants.
2. Overfeeding infants may exacerbate their symptoms and should be avoided.
3. Colic and regurgitation are temporary problems during the first months of life and then they spontaneously resolve.
4. Pharmacological approaches are not necessary for infantile colic and regurgitation and could harm infants. Gastric acid inhibitors or prokinetic drugs have been shown to have side effects, such as an increased rate of infection, and are mostly ineffective for these conditions.

Table 6 Excerpt of current recommendations for the management of functional constipation in infants and toddlers

Recommendation	Reference
Parental education and reassurance as the first line of management	
• Provide information on normal infant defecation patterns	• Expert group review (22)
Nutritional management	
• Continue breastfeeding; evaluation after 2–4 weeks	• NASPGHAN/ESPGHAN (56)
• Verify proper formula preparation for formula-fed infants	
• Harder stools are frequent in infants fed with formulas containing vegetable oil rich in palmitate in the stereospecific numbering (Sn) positions Sn-1 and Sn-3, favouring calcium soaps	• Expert group review (22)
• In some infants, constipation is related to the intake of cow's milk protein although there is no consensus that extensively hydrolysed formula is indicated for constipated infants since constipation as single manifestation of cow's milk allergy is extremely rare	
• Juices containing sorbitol, such as prune, pear and apple juices, decrease constipation but may risk unbalanced nutrition and early introduction of complementary foods and lead to diarrhoea or abdominal pain	
• Lactulose may be considered for functional constipation, but may cause flatulence	
• Do not use dietary interventions alone as first-line treatment for idiopathic constipation	• NICE (2010)(57)
• Treat constipation with laxatives and a combination of	
• Behavioural interventions	
• Dietary modifications to ensure a balanced diet and sufficient fluids are consumed	
Pharmacological therapy	
• Polyethylene glycol may be considered for functional constipation for infants over 6 months of age	• Expert group review (22)
• Rectal treatment with glycerine suppository should be restricted to provide acute relief in functional constipation	
• Evidence does not support the use of enemas, or (oral) mineral oil as this risks lipoid pneumonia due to aspiration	
• Offer the following oral medication regimen for dis-impaction if indicated:	• NICE (2010) (57)
• Polyethylene glycol 3350 + electrolytes, using an escalating dose regimen as the first-line treatment.	
• Adjust the dose of polyethylene glycol 3350 + electrolytes according to symptoms and response. As a guide for children and young people who have had dis-impaction, the starting maintenance dose might be half the dis-impaction dose	
• Add a stimulant laxative if polyethylene glycol 3350 + electrolytes does not work	
• Substitute a stimulant laxative if polyethylene glycol 3350 + electrolytes are not tolerated by the child or young person. Add another laxative such as lactulose or docusate if stools are hard	
• Continue medication at maintenance dose for several weeks after regular bowel habit is established – this may take several months. Children who are not toilet trained should remain on laxatives until toilet training is well established. Do not stop medication abruptly, but gradually reduce the dose over a period of months in response to stool consistency and frequency. Some children may require laxative therapy for several years. A minority may require on-going laxative therapy	

Functional regurgitation

1. Regurgitation is almost never a reason to stop breastfeeding.
2. A thickened anti-regurgitation infant formula may reduce persistent regurgitation in non-exclusively breastfed infants and help to reassure parents. Alginates, extensively hydrolysed protein or amino acid formulas are not indicated for uncomplicated infantile regurgitation.

Infantile colic

1. Probiotics, specifically Lactobacillus reuteri DSM 17938, have been reported to be of potential benefit for exclusively breastfed infants with infantile colic.
2. Limited data suggest formula-fed infants with infantile colic could benefit from a partial hydrolysate with prebiotics and beta-palmitate or a synbiotic formula with reduced lactose and partially hydrolysed protein. However, there is insufficient evidence to recommend the routine use of these kinds of formula.
3. Gastric acid inhibitors have been shown to have side effects and have been demonstrated to be ineffective in infantile colic if the crying is unrelated to gastro-oesophageal reflux disease.

Functional constipation

1. Constipation is rare in breastfed infants and alternative causes of constipation should be considered. Some breastfed infants defecate less than once a week.
2. Nutritional advice may not be sufficient for non-exclusively breastfed infants with functional constipation and laxatives may be required as the first-line treatment. Limited data suggest infants with hard and infrequent stools could benefit from a formula with a partial whey hydrolysate, a formula containing a

mixture of prebiotics and a high level of beta-palmitate and, or, a formula with high magnesium content, but within normal ranges. However, there is insufficient evidence to recommend the routine use of these formulas.

CONCLUSION

FGIDs and related symptoms present a common burden in infancy, as they have a negative impact on the short-term and long-term health outcomes of the infants, reduce families' quality of life and increase healthcare system costs. The optimal management of FGIDs in infancy should start with parental education and reassurance, accompanied by proper nutritional guidance. It is unlikely that any pharmacological intervention will be necessary once an organic cause of the symptoms has been excluded. However, pharmacological therapies are often misused, unnecessary and may cause adverse effects. Breastfeeding should be recommended and supported, even when infants display persistent and severe FGIDs. In non-breastfed infants, special formulas may be considered if reassurance and advice on nutrition, based on the proper volume and frequency of milk intake, fail. FGIDs often lead to a vicious cascade of distressed infants, concerned parents, increased medical consultations, over-prescribing and use of over-the-counter medication, resulting in escalating healthcare costs.

By offering appropriate advice and reassurance to parents, healthcare professionals can help to disrupt this cascade and restore harmony, by reducing infants' distress, alleviating parental anxiety and improving the quality of life for the family while protecting healthcare budgets.

COMPETING INTERESTS

TL is an employee of Nutricia Research. The other authors have no conflicts of interest to declare.

FUNDING

This study did not receive any specific funding.

References

1. 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.
2. Mahon J, Lifschitz C, Ludwig T, Thapar N, Glanville J, Miqdady M, et al. The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. *BMJ Open* 2017; 7: e015594.
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.
4. Vandenplas Y, Ludwig T, Bouritius H, Alliet P, Forde D, Peeters S, et al. Randomised controlled trial demonstrates that fermented infant formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides reduces the incidence of infantile colic. *Acta Paediatr* 2017; 106: 1150–8.
5. van Tilburg MAL, 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.
6. Rautava P, Lehtonen L, Helenius H, Sillanpää M. Infantile colic: child and family three years later. *Pediatrics* 1995; 96: 43–7.
7. Howard CR, Lanphear N, Lanphear BP, Eberly S, Lawrence RA. Parental responses to infant crying and colic: the effect on breastfeeding duration. *Breastfeed Med* 2006; 1: 146–55.
8. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, Palacios J, Jaen D, Ribeiro H, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. *Nutr* 2013; 29: 184–94.
9. Partty A, Kalliomaki M, Salminen S, Isolauri E. Infant distress and development of functional gastrointestinal disorders in childhood: is there a connection? *JAMA Pediatr* 2013; 167: 977–8.
10. Indrio F, Di Mauro A, Riezzo G, Cavallo L, Francavilla R. Infantile colic, regurgitation, and constipation: an early traumatic insult in the development of functional gastrointestinal disorders in children? *Eur J Pediatr* 2015; 174: 841–2.
11. van den Berg MM, van Rossum CH, de Lorijn F, Reitsma JB, Di Lorenzo C, Benninga MA. Functional constipation in infants: a follow-up study. *J Pediatr* 2005; 147: 700–4.
12. Räihä 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.
13. Akman I, Kusçu 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.
14. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2016; 150: 1443–5.
15. Sommers T, Corban C, Sengupta N, Jones M, Cheng V, Bollom A, et al. Emergency department burden of constipation in the United States from 2006 to 2011. *Am J Gastroenterol* 2015; 110: 572–9.
16. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child* 2001; 84: 15–9.
17. Lightdale JR, Gremse DA. Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics* 2013; 131: e1684–95.
18. Savino F. Focus on infantile colic. *Acta Paediatr* 2007; 96: 1259–64.
19. Shamir R, St James-Roberts I, Di Lorenzo C, Burns AJ, Thapar N, Indrio F, et al. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. *J Pediatr Gastroenterol Nutr* 2013; 57(Suppl 1): S1–45.
20. Pijpers M, Bongers MEJ, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. *J Pediatr Gastroenterol Nutr* 2010; 50: 256–68.
21. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol* 2006; 101: 2401–9.
22. Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, et al. Functional gastro-intestinal disorder

algorithms focus on early recognition, parental reassurance and nutritional strategies. *Acta Paediatr* 2016; 105: 244–52.
23. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, 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). *J Pediatr Gastroenterol Nutr* 2009; 49: 498–547.
24. Nocerino R, Pezzella V, Cosenza L, Amoroso A, Di Scala C, Amato F, et al. The controversial role of food allergy in infantile colic: evidence and clinical management. *Nutrients* 2015; 7: 2015–25.
25. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, et al. Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis. *Pediatrics* 2018; 141: pii: e20171811.
26. Saps M, Di Lorenzo C. Pharmacotherapy for functional gastrointestinal disorders in children. *J Pediatr Gastroenterol Nutr* 2009; 48(Suppl 2): S101–3.
27. Salvatore S, Barberi S, Borrelli O, Castellazzi A, Di Mauro D, Di Mauro G, et al. Pharmacological interventions on early functional gastrointestinal disorders. *Ital J Pediatr* 2016; 42: 68.
28. Scarpato E, Quitadamo P, Roman E, Jojkic-Pavkov D, Kolacek S, Papadopoulou A, et al. Functional gastrointestinal disorders in children: a survey on clinical approach in the mediterranean area. *J Pediatr Gastroenterol Nutr* 2017; 64: e142–6.
29. Blank M-L, Parkin L. National study of off-label proton pump inhibitor use among new zealand infants in the first year of life (2005–2012). *J Pediatr Gastroenterol Nutr* 2017; 65: 179–84.
30. Quitadamo P, Miele E, Alongi A, Brunese FP, Di Cosimo ME, Ferrara D, et al. Italian survey on general pediatricians' approach to children with gastroesophageal reflux symptoms. *Eur J Pediatr* 2015; 174: 91–6.
31. Gieruszczak-Białek D, Konarska Z, Skórka A, Vandenplas Y, Szajewska H. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. *J Pediatr* 2015; 166: 767–70.e3.
32. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. *Br J Clin Pharmacol* 2015; 80: 200–8.
33. Jackson MA, Goodrich JK, Maxan M-E, Freedberg DE, Abrams JA, Poole AC, et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut* 2016; 65: 749–56.
34. Cares K, Al-Ansari N, Macha S, Zoubi N, Zaghloul H, Thomas R, et al. Short article: risk of small intestinal bacterial overgrowth with chronic use of proton pump inhibitors in children. *Eur J Gastroenterol Hepatol* 2017; 29: 396–9.
35. Biagioli E, Tarasco V, Lingua C, Moja L, Savino F. Pain-relieving agents for infantile colic. *Cochrane Database Syst Rev* 2016; 9: CD009999.
36. Lucassen P. Colic in infants. *BMJ Clin Evid* 2010; 2010: 0309.
37. 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.
38. Harb T, Matsuyama M, David M, Hill RJ. Infant colic-what works: a systematic review of interventions for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2016; 62: 668–86.
39. Oshikoya KA, Senbanjo IO, Njokanma OF. Self-medication for infants with colic in Lagos, Nigeria. *BMC Pediatr* 2009; 9: 9.
40. Headley J, Northstone K. Medication administered to children from 0 to 7.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Eur J Clin Pharmacol* 2007; 63: 189–95.
41. Kurth E, Kennedy HP, Spichiger E, Hösli I, Stutz EZ. Crying babies, tired mothers: what do we know? A systematic review *Midwifery* 2011; 27: 187–94.
42. Vik T, Grote V, Escribano J, Socha J, Verduci E, Fritsch M, et al. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatr* 2009; 98: 1344–8.
43. Keefe MR, Kotzer AM, Froese-Fretz A, Curtin M. A longitudinal comparison of irritable and nonirritable infants. *Nurs Res* 1996; 45: 4–9.
44. Nevo N, Rubin L, Tamir A, Levine A, Shaoul R. Infant feeding patterns in the first 6 months: an assessment in full-term infants. *J Pediatr Gastroenterol Nutr* 2007; 45: 234–9.
45. Barr RG. Crying as a trigger for abusive head trauma: a key to prevention. *Pediatr Radiol* 2014; 44(Suppl 4): S559–64.
46. Simonnet H, Laurent-Vannier A, Yuan W, Hully M, Valimahomed S, Bourennane M, et al. Parents' behavior in response to infant crying: abusive head trauma education. *Child Abuse Negl* 2014; 38: 1914–22.
47. Brown M, Heine RG, Jordan B. Health and well-being in school-age children following persistent crying in infancy. *J Paediatr Child Health* 2009; 45: 254–62.
48. Forsyth BW, Canny PF. Perceptions of vulnerability 3 1/2 years after problems of feeding and crying behavior in early infancy. *Pediatrics* 1991; 88: 757–63.
49. Canivet C, Jakobsson I, Hagander B. Infantile colic. Follow-up at four years of age: still more 'emotional'. *Acta Paediatr* 2000; 89: 13–7.
50. 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* 2005; 94: 129–32.
51. Neu M, Robinson J. Infants with colic: their childhood characteristics. *J Pediatr Nurs* 2003; 18: 12–20.
52. Santos IS, Matijasevich A, Capilheira MF, Anselmi L, Barros FC. Excessive crying at 3 months of age and behavioural problems at 4 years age: a prospective cohort study. *J Epidemiol Community Health* 2015; 69: 654–9.
53. National Institute for health and care excellence. *Gastro-oesophageal reflux disease in children and young people: diagnosis and management*. London: NICE, 2015.
54. 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). *J Pediatr Gastroenterol Nutr* 2018; 66: 516–54.
55. National Institute for health and care excellence. *Colic, infantile*. London: NICE, 2017.
56. 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.
57. National Institute for health and care excellence. *Constipation in children and young people: diagnosis and management*. London: NICE, 2010.

