Infant formulas for the treatment of functional gastrointestinal disorders: a position paper of the ESPGHAN Nutrition Committee.

Nadja **Haiden**[1], Francesco **Savino**[2], Susan **Hill**[3], Laura **Kivelä**[4], Barbara **de Koning**[5], Jutta **Köglmeier**[6], Veronica **Luque**[7], Sissel J. **Moltu**[8], Lorenzo **Norsa**[9], Miguel **Saenz De Pipaon**[10], Elvira **Verduci**[11], Jiri **Bronsky**[12]

Affiliations:

[1] : Department of Neonatology, Kepler Universityhospital Linz, Austria

[2] : Department of Patologia e cura del bambino "Regina Margherita" Regina Margherita Children Hospital, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Torino, Italy.

[3] : Nutrition and intestinal failure Division, Gastroenterology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK

[4] : Celiac Disease Research Center, Tampere University, Tampere, Finland; Department of Pediatrics, Tampere University Hospital, Tampere, Finland; Children's Hospital, Helsinki University Hospital, Helsinki, Finland; Research Institute, University of Oslo, Oslo, Norway

[5] : Department of pediatric gastroenterology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands

[6] : Unit of Nutrition and Intestinal Failure Rehabilitation, Department of paediatric Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

[7] : Serra Húnter Fellow, Paediatric Nutrition and Development Research Unit, Universitat Rovira i Virgili-IISPV, Spain

[8] : Department of Neonatal Intensive Care, Oslo University Hospital, Norway Pediatric

[9] : Pediatric Hepatology Gastroenterology and Transplantation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy

[10] : Neonatology Hospital La Paz Institute for Health Research – IdiPAZ, (Universidad Autónoma de Madrid), Pº de la Castellana, 261, Madrid 28046, Spain

[11] Metabolic Diseases Unit, Department of Pediatrics, Vittore Buzzi Hospital, University of Milan

[12] : Department of Paediatrics, University Hospital Motol, Prague, Czech Republic

Running title:

Infant formulas for mild functional gastrointestinal disorders

Conflict of interest:

Outside of submitted work: NH received honoraria, speakers fee, congress fee and/or participated in advisory boards of Baxter, Nutricia, Nestlé, Hipp MAM and Medis; FS has received personal lecture fee from Nestlé , Biostime and Junia Pharma; LK has received personal lecture fees from the Finnish Coeliac Society and serves as a member of the advisory committee of the Finnish Coeliac Society; BdK no conflicts of interest; VL participate in industry funded-research and/or consultancy for Nestlé, DGC and BENEO; SJM has received honoraria, speaker fees and/or participated in advisory boards of Baxter, Nutricia and NuMega. She has also received research funding (Formulaid™) from DSM nutritional Products; LN received honoraria, speakers fee, congress fee and/or participated in advisory boards of Takeda, Nestlè, Danone; MSdP received honoraria, speakers fee, congress fee and/or participated in advisory boards of Baxter, Nutrinia, Nutricia, Nestlé and Fresenius; EV received honoraria, speakers fee, congress fee and/or participated in advisory boards of Nutricia, Nutricia Metabolics, Nestlé; JB received honoraria, speakers fee, congress fee and/or participated in advisory boards of AbbVie, MSD, Nutricia, Nestlé and Sanofi; JK, SH have no conflict of interest to declare

Funding:

No funding was obtained for this study.

Corresponding Author:
Prof. Nadja Haiden, M.D., MSc, MBA
Head of Department of Neonatology
Kepler University Hospital
Krankenhausstraße 26-30
4020 Linz
AUSTRIA
nadja.haiden@kepleruniklinikum.at

Abstract

Introduction: Functional gastrointestinal disorders (FGID), such as infant regurgitation, infant colic, and functional constipation, are common and typically physiological phenomena during the early months of an infant's life and account for frequent consultations with pediatricians. Various infant formulas are marketed for their management and are frequently given by parents to infants prior to a medical consultation. However, the evidence supporting their effectiveness is limited and some have altered nutritional compositions when compared to standard formulas. Thus, these products should only be used under medical supervision and upon medical advice. Marketing and over-the-counter sales do not ensure proper medical guidance and supervision. The aim of this position paper is to review the current evidence regarding the safety and efficacy of formulas specifically formulated for addressing regurgitation, colic, and constipation, recognized as FGID. The objective is to provide guidance for clinical management based on the highest quality of available evidence.

Methods: A wide search using Pubmed, MEDLINE, EMBASE and Cochrane Database of Systematic Reviews was performed including the MESH terms infant formula, colic, constipation, regurgitation, reflux, palmitate, lactase, lactose, magnesium, hydrolyzed protein, prebiotics or probiotics. 752 papers were identified and screened. Finally, 72 papers were included in the paper. In the absence of evidence, recommendations reflect the authors' combined expert opinion. Final consensus was obtained by multiple e-mail exchange and meetings of the Nutrition Committee.

Results:

1. For breastfed infants experiencing FGID such as regurgitation, colic, or constipation, transitioning from breastfeeding to commercial formulas is not recommended.
2. In general, whether an infant is breastfed or formula-fed, it's crucial to reassure parents that FGIDs are normal and typically do not necessitate treatment or change to a special formula.
3. Thickened formulas, often termed anti-reflux formulas, may be considered in specific cases of regurgitation.
4. The usage of specialized formulas for infants with colic is not advised due to a lack of clinical evidence.
5. In the case of constipation in infants, the use of formulas enriched with high β-palmitate and increased magnesium content may be considered to soften the stool.

Conclusion:

Generally, there is limited evidence supporting the use of specialized formulas for FGID. Breastfeeding should never be discontinued in favor of formula feeding.

Keywords:

Infant formula, functional gastrointestinal disorders, anti-reflux, infant colic, constipation, regurgitation, anti-colic.

Abbreviations:

AR	anti-reflux
CMPA	cow's milk protein allergy
eHF	extensively hydrolyzed protein formulas
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
MCT	medium chain triglycerides
FGID	Functional gastrointestinal disorders
OFC	oral food challenge
pHF	partially hydrolyzed protein formulas
RCT	randomized controlled trial

What is already known?

- Functional gastrointestinal disorders, such as infant regurgitation, infant colic, and functional constipation, are common and typically physiological phenomena during the early months of an infant's life.

- The infant food industry provides a wide range of formulas designed for managing these mild functional gastrointestinal disorders.

- Despite the widespread use of these formulas, their effectiveness in treating mild functional gastrointestinal disorders remains uncertain.

What is new?

- Weaning from breastfeeding is not advised for infants experiencing any or several functional gastrointestinal disorders. In majority of formula-fed infants, no specific formulas are indicated.

- In breastfed infants with regurgitation, breast milk can be expressed and supplemented with thickening agents and in formula fed infants, industrially thickened infant formulas often referred to as "anti-reflux formulas," or formulas with appropriately added thickeners can be considered in special cases under medical guidance.

- Special anti-colic formulas do not usually benefit infants with colic.

- In cases of infant constipation, considering formulas with high β-palmitate and an elevated magnesium content may be an option to soften stool consistency.

- It is generally not recommended to use formulas for combined functional gastrointestinal disorders.

Disclaimer:
ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of the healthcare provider.

Conflict of interest:

Outside of submitted work: NH received honoraria, speakers fee, congress fee and/or participated in advisory boards of Baxter, Nutricia, Nestlé, Hipp MAM and Medis; FS has received personal lecture fee from Nestlé , Biostime and Junia Pharma; LK has received personal lecture fees from the Finnish Coeliac Society and serves as a member of the advisory committee of the Finnish Coeliac Society; BdK no conflicts of interest; VL participate in industry funded-research and/or consultancy for Nestlé, DGC and BENEO; SJM has received honoraria, speaker fees and/or participated in advisory boards of Baxter, Nutricia and NuMega. She has also received research funding (Formulaid™) from DSM nutritional Products; LN received honoraria, speakers fee, congress fee and/or participated in advisory boards of Takeda, Nestlè, Danone; MSdP received honoraria, speakers fee, congress fee and/or participated in advisory boards of Baxter, Nutrinia, Nutricia, Nestlé and Fresenius; EV received honoraria, speakers fee, congress fee and/or participated in advisory boards of Nutricia, Nutricia Metabolics, Nestlé; JB received honoraria, speakers fee, congress fee and/or participated in advisory boards of AbbVie, MSD, Nutricia, Nestlé and Sanofi; JK, SH have no conflict of interest to declare

Funding:

No funding was obtained for this study.

Introduction

Functional gastrointestinal disorders (FGIDs) may either be idiopathic or result from maladaptive behavioral responses to internal or external stimuli, such as the retention of feces due to painful defecation. It's essential to recognize these disorders as normal physiological variations, generally not requiring medical interventions or treatment [1]. However, despite the often self-resolving nature of these issues, various infant formulas are available for their management. Unfortunately, the evidence supporting the effectiveness of these formulas in alleviating symptoms is frequently limited. Compounding the situation, these formulas are heavily marketed, potentially creating misconceptions among healthcare providers and parents about their therapeutic effects. Moreover, some of these formulas have altered nutritional compositions, including the addition of starches such as bean gum, rice, potato, or corn for thickening purposes. This modified composition may not always be preferable when compared to standard formulas. Thus, these products should only be used under medical supervision and upon medical advice. Marketing and over-the-counter sales do not ensure proper medical guidance and supervision.

The ESPGHAN Nutrition Committee conducted a review, summarization, and evaluation of the most robust evidence concerning infant formulas for FGIDs. This information is documented in this position paper, representing an update to certain sections of previous ESPGHAN societal papers [2] [3] . It is important to note that this paper does not primarily focus on the safety and efficacy of prebiotics and probiotics, synthetic human milk components such as oligosaccharides, or synbiotics, as these ingredients are also used in standard formulas. Instead, the paper concentrates on formulas specifically designed for the treatment of FGID and addresses the following research questions:

1. Do anti-reflux formulas reduce infant regurgitation during the first 6 months of life and what is the evidence of their efficacy versus standard formula?
2. Do anti-colic formulas reduce infant colic and what is the evidence of their efficacy versus standard formula?
3. Do anti-constipation formulas reduce functional constipation during the first 6 months of life and what is the evidence of their efficacy versus standard formula?
4. What modifications in infant formulas improve symptoms of FGID?

Methods

A comprehensive literature search was conducted on Pubmed, MEDLINE, EMBASE and Cochrane Database of Systematic Reviews until April 30th, 2023. The search terms primarily focused on infant formula and its ingredients, including "infant formula," "palmitate," "probiotics", "lactase", "lactose", "magnesium" and "hydrolysed protein" alongside other relevant keywords (anti-reflux formula, anti-colic formula, constipation, regurgitation, infant, functional gastrointestinal disorders). These search terms were combined with subject heading terms related to specific conditions of interest, such as "colic," "regurgitation," "reflux," and "constipation." (Supplement 1) Only studies examining the effectiveness of formulas that included infants up to 6 months of age and written in English were considered for inclusion in this position paper. 752 papers were identified and screened. Finally, 72 papers were included in the paper (Supplement 2).

The findings from the literature search were discussed during face-to-face meetings, involving the members of the ESPGHAN Nutrition Committee. In instances where conclusive evidence was lacking, the recommendations provided are a reflection of the collective expert opinion of the authors. Rigorous discussions took place during multiple meetings of the Nutrition Committee, supplemented by numerous email exchanges. Discussions continued until an unanimous consensus on the wording and a 100% agreement was reached. This position paper presents recommendations for clinicians, which are evidence based where reliable scientific evidence was available. Where evidence was lacking, recommendations are based on best practice according to consensus among the expert authors.

Interventions for the treatment of regurgitation

Diagnostic criteria for infant regurgitation must include both of the following in otherwise healthy infants 3 weeks to 12 months of age [1]:

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

When stomach contents move back into the esophagus, mouth, and/or nose involuntarily, this is called gastroesophageal reflux (GER). The term regurgitation is used when these gastric contents can be visualized [1]. However, it's important to note that GER and regurgitation are normal, physiologic occurrences in infants and do not typically require treatment.

Factors contributing to GER and posseting include increasing drinking volumes during the early months of life, a relatively short esophagus with limited capacity, and the incomplete functional closure of the lower esophageal sphincter (cardia), which allows food pulp to flow back into the esophagus. When GER is associated with symptoms that negatively impact the infant's health or wellbeing, it is referred to as gastroesophageal reflux disease (GERD) [4]. GERD can lead to reflux esophagitis and other symptoms due to prolonged exposure of the

esophageal mucosa to stomach acid. Symptoms of GERD may include food refusal, pain and failure to thrive [4]. Unlike uncomplicated regurgitation, which can often be managed through education, reassurance, and support for parents, GERD requires diagnostic evaluation (e.g., to rule out cow's milk protein allergy= CMPA) and targeted therapy [5] [6]. (Figure 1)

Non- nutritional interventions

Reassurance of parents and family are essential in the management of infant regurgitation [7]. The following points can be addressed when talking to the parents:

- Frequency and Amount: It is normal for infants to posset after feeds, and the frequency can vary from infant to infant. Some infants may spit up more frequently, while others may do it less often.
- Proper Feeding Practices: Simple advice on feeding techniques can help reduce the occurrence of regurgitation. For example, ensuring the infant is positioned upright during feeding, burping them after each feed, and avoiding overfeeding (responding to infant satiety cues) may be beneficial. As a pediatric healthcare provider, check whether feeding frequency, volume and composition, bottle and teat are appropriate to reassure the family.
- Gradual Improvement: As the infant´s digestive system matures, infant regurgitation tends to improve. Many infants outgrow frequent posseting as they reach their first birthday.
- Comfort and Behavior: Most infants with regurgitation are comfortable and show no signs of distress during or after posseting. They continue to feed well and have normal bowel movements. If the infant seems fussy or uncomfortable, or if the infant does not gain weight, it's essential to consult a pediatrician to rule out other potential underlying problems.
- When to Seek Medical Advice: While GER and regurgitation are generally harmless, parents should consult a pediatrician if the infant experiences the following:
    - Poor weight gain or signs of dehydration
    - Frequent projectile vomiting
    - Arching of the back or signs of discomfort during or after feeds
    - Refusal to feed
    - Persistent coughing or wheezing

Nutritional Interventions

Thickening of human milk

Since regurgitation is considered normal, breastfeeding is encouraged. In breastfed infants experiencing frequent regurgitation, thickening of expressed breast milk with thickening agents (such as rice starch, xanthan gum, or carob bean gum) may be considered in cases where parents are distressed (expert opinion). However, there are circumstances where they

should be used with caution: Carob bean gum thickeners are approved for use in infants after 42 weeks post-conception, and xanthan gum as a thickener is only approved for children over 1 year of age due to concerns about the potential occurrence of necrotizing enterocolitis [8, 9]. Presence of regurgitation in a breastfed infant should not be a reason to switch to a formula.

Thickened formulas

Thickened formulas (marketed as so-called anti-reflux, "AR formulas") are promoted for managing regurgitation in infants. These formulas aim to reduce the reflux of stomach contents into the esophagus and minimize associated spitting up by increasing their thickness. Infant formulas can be thickened by adding starch to regular formula or by using already thickened special formulas (AR formula). Rice, potato, and corn starch, carob, or locust bean gum (LBG), xanthan gum, pectin, and soybean polysaccharides have been tested as thickening agents [10]. It's important to note that adding approximately 2% starch (e.g., rice starch or modified corn starch) significantly increases the energy content of the formula, which may lead to overfeeding. Studies indicate that thickened or AR formula is associated with a statistically significant increase in weight gain (additional increment of 3.5–3.7 g/d) compared with standard formula, as observed in four randomized controlled trials (RCTs) involving 265 infants [11]. To avoid overfeeding, it is generally preferred to use low-energy thickeners such as locust bean or guar gum [12, 13]. Thickened formulas create a thicker texture and reduce the frequency of visible reflux episodes with posseting [5, 13-19], but they do not affect gastric emptying time [19]. There is currently no conclusive evidence to recommend one thickening agent over another due to a lack of comparative trials [20]. In general AR formulas are preferred to adding thickening agents to standard formula, because AR- formulas have a controlled homogenous composition and an osmolarity and caloric content similar to standard formula [20]. An overview of 13 randomized controlled trials investigating the efficacy of AR formulas showed a reduction in the daily number of regurgitation episodes from a mean of 5.4 episodes per day to 2.5 episodes per day over a period of 1 to 4 weeks in infants fed rice, corn starch, and locust bean AR-formulas [10]. However, the design of these studies differed significantly in terms of inclusion criteria, research methods, duration of intervention, and the formula and/or thickener tested, making the 50% reduction figure only indicative. Nevertheless, one effect appears to be established, and for this reason the revised "Practical Guidelines" published in 2018 by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) suggest that thickened infant formula may potentially reduce the number of visible regurgitations [5].

Some small RCTs have suggested that a partly fermented formula in combination with a thickener [17] or protein modification may impact on regurgitation episodes. Partially hydrolyzed protein thickened formulas (whey protein, locust bean gum) have reported benefits compared to standard ones in reducing the frequency and severity of regurgitation

[10, 15]. However, the trial enrolled very few children and did not investigate the superiority of protein modification since the formulas are in combination with thickener.

Nutritional interventions in case of suspected CMPA

The prevalence of CMPA in infants experiencing manifestations such as regurgitation FGID is debated, often resolving naturally by around one year of age. For individuals not showing improvement with conventional management, considering CMPA is an option. A trial of a time-limited elimination diet (removed from the mothers' diet if breast feeding and from the infant's diet if on solid food) for 2-4 weeks followed by an Oral Food Challenge (OFC) can be undertaken. For detailed guidance, we recommend referring to the recently published ESPGHAN guidelines on CMPA. [6].

Conclusion:

Some anti-reflux/AR thickened formulas reduce the number of visible regurgitations. There is no evidence that protein hydrolyzation or fermentation offers a further benefit to thickening.

Recommendation:

1. Regurgitation:

- Breastfeeding should not be stopped in infants experiencing regurgitation.
- Both in breastfed and formula fed infants, reassurance of parents should be the first line recommendation.
- Most formula fed infants with regurgitation do not require switching to a specific formula.

2. In cases with regurgitations without other symptoms, if parents experience great distress and could not be reassured:

- In breastfed infants, breast milk can be expressed and supplemented with thickening agents.
- In formula fed infants, industrially thickened infant formulas, commonly known as "anti-reflux formulas," or formulas with appropriately added thickeners can be considered. To avoid overfeeding it is generally preferred to use low-energy thickeners such as locust bean or guar gum.

3. A 2-4 weeks trial of cow's milk protein avoidance may need to be considered in some cases

Interventions for the treatment of infantile colic

Infantile colic also known as “three-month colic,”, is a common functional problem in infants characterized by bloating and flatulence. The incidence of infantile colic varies between 8% to 29% among healthy infants [21, 22]. Typically, colic symptoms reach their peak around six weeks of age and gradually resolve three to four months [23, 24]. Persistent and intense infant crying episodes often lead to parental distress [25, 26]. Moreover, infants affected by colic have a higher risk of developing long-term functional abnormalities, atopic diseases, and psychological issues [27]. In 1954, Wessel introduced a widely accepted definition based on symptoms rather than underlying causes. According to this definition, infantile colic is characterized by crying that lasts for at least three weeks, occurring on more than three days per week, and lasting for more than three hours per day [28].

More recently, the description of infantile colic has been included in the Rome IV criteria for functional gastrointestinal disorders [1, 29, 30]:

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 reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers

3. No evidence of infant failure to thrive, fever, or illness

The etiology of infantile colic remains uncertain but is likely to be multifactorial. A combination of psychological, behavioral, and biological factors, including food hypersensitivity, gut microbiota composition, and dysmotility, or gastrointestinal-related causes such as CMPA, GER or motility disorders of the gastrointestinal tract are believed to contribute to its development [1]. Recent studies have indicated that the immaturity of the infant gut and the composition of gut microbiota may play a role in the pathophysiology of infantile colic, potentially surpassing the impact of the infant’s dietary composition [31]. Alterations in gut microbiota have been implicated in functional gastrointestinal disorders such as colic, with several studies noting an increase in pathogenic bacteria like E. coli, Klebsiella, and Proteobacteria, as well as a decrease in beneficial bacteria such as Lactobacilli and Bifidobacteria [32]. Furthermore, recent research by Rhoads et al. suggests that gut inflammation and dysbiosis could independently contribute to colic development regardless of feeding mode [33]. Various theories and speculations have been proposed to explain the causes of infantile colic, including negative maternal experiences during pregnancy, infant adaptation difficulties in transitioning to postnatal life, heightened perception of painful intestinal contractions due to increased visceral afferents, gaseous abdominal distension and food intolerances, among others [34, 35]. However, in the case of colicky infants, breastfeeding should not be discontinued or switched to formula. Furthermore, parents should be reassured about the physiological nature of infant colic.

Non- nutritional interventions

Several therapeutic recommendations exist for the management of infantile colic, although their efficacy lacks scientific evidence. These recommendations include gentle abdominal massage, warm baths, creating a calm environment during breastfeeding/feeding, minimizing sensory overload, using special positioning techniques such as the “tiger in the tree” position, and administering teas containing fennel, caraway, or simethicone as a pain-relieving agent. It is worth noting that fennel has raised concerns due to potential toxicity risks [36, 37]. It is also important to highlight that none of these remedies are supported by scientific evidence [38]. Alongside these interventions, counseling and providing reassurance to parents about the functional nature of the symptoms, as well as practicing carrying and cradling the infant during episodes of crying, have been shown to be effective in the treatment of mild infantile colic [39].

Nutritional interventions

Formulas with reduced lactose content

Special infant formulas with reduced lactose content have been on the market for the treatment of infantile colic for a while. This approach was based on the hypothesis that colicky infants have an increased lactose malabsorption as indicated by higher breath H_2 production in the fasting state which could contribute to colic symptoms [40]. There have not been dedicated studies exclusively focusing on formulas solely with reduced lactose content as a modification. Supplementation with lactase drops demonstrated effectiveness in alleviating infant colic in an RCT involving 162 patients [41] in both breastmilk and formula fed infants, potentially facilitating the lactose digestion. These results confirmed earlier studies [42-44]. However, these trials did not utilize currently used stringent definition of colic as per Rome criteria [1] and had a small sample size.

Formulas with combined modifications of composition

In some anti-colic formulas, reduced lactose content is combined with partially or extensively hydrolyzed protein with or without medium chain triglycerides (MCT). Hydrolyzed protein is believed to facilitate a more rapid gastrointestinal passage, suggesting that infants with colic may experience improvement when given these formulas. An industry-driven RCT involving 275 infants compared a new formula containing partially hydrolyzed whey proteins (pHF), low levels of lactose, prebiotic oligosaccharides, and a high content of beta-palmitic acid with a standard formula along with simethicone [45]. Although the study formula was effective in reducing colicky symptoms as evidenced by a reduction in crying episodes after 14 days from 3.32 ($\pm$2.06, standard formula) to 1.76 ($\pm$ 1.60, study formula; $p<0.0001$) episodes per day, the combination of several factors in the formula made it difficult to determine which specific component was responsible for the observed improvement A more recent double-blind, placebo-controlled trial involving an alpha-lactalbumin-enriched (alpha-lactalbumin is the human milk dominant whey protein that was increased to improve the aminogram while

reducing the total protein content) and probiotic-supplemented formula did not show a reduction in crying duration [46]. There is no evidence that adding MCT has any additional effect on colic symptoms.

Formulas with hydrolyzed protein

There is only weak evidence for the use of hydrolyzed protein in colic. A small industry-driven single arm study with a pHF showed improvement of mild gastrointestinal symptoms [47]. However, the lack of a control group does not allow us to conclude whether the improvement was due to the formula composition or to a placebo effect combined with the physiological improvement expected with infant's maturation. Small non-industry driven RCTs suggested a possible effect of extensively hydrolyzed protein in reducing the duration of crying in a primary care setting [48, 49]. Furthermore, two extensively hydrolyzed casein formulas with different compositions were found to be equally effective in managing colicky symptoms associated with protein sensitivity [50]. In a double-blind crossover study, colicky infants were subjected to a challenge involving both a standard cow´s milk formula and an extensively hydrolyzed casein formula, confirming that removing cow´s milk formula from the infants' diet led to symptom improvement [51].

However, according to a Cochrane review the reported benefits of partially or extensively hydrolyzed protein formulas for colic are weak due to small sample sizes, industry-driven trials and with a significant risk of bias [52]. Where studies did report some benefit, this was not large enough to be clinically significant.

Formulas with Probiotics

Probiotics have shown potential in influencing the composition of gut microbiota, which could have implications for colic symptoms [53]. The evidence for the treatment of infant colic with Lactobacillus reuteri DSM 17938 appears promising to reduce colic in breastfed infants [54]. In recent years, several "anti-colic" formulas enriched with probiotics with or without prebiotics have been introduced to the market. However, most of the probiotics and prebiotics used in formulas lack sufficient clinical evidence to fully support their use in treating infant colic and there are no RCTs showing clinically significant efficacy. On the other hand, one RCT did not find a favorable effect of this probiotic strain in infants with colic compared to healthy controls when fed a partially hydrolyzed protein formula (pHF) with reduced lactose content and Lactobacillus reuteri DSM 17938 [55].

Formulas containing beta-palmitate

Anti-colic formulas often contain additional components such as structurally modified vegetable oils with enhanced fat absorption, such as β-palmitate, or pregelatinized potato starch.

The potential reduction of colic through the addition of β-palmitate (SN-2-palmitate) has been subject to limited study. In most cases, interventions involved multiple nutritional modifications concurrently, including partially hydrolyzed protein SN-2-palmitate formula enriched with fructo- and galacto-oligosaccharides [45, 56]. Generally, these interventions resulted in a decrease in episodes of crying and colic frequency. However, due to the composite nature of these interventions, the beneficial effect cannot be solely attributed to β-palmitate. Only one double-blind RCT, examining the isolated effect of SN-2-palmitate on infant crying, reported a significant difference in crying time at 12 weeks of age [57]. A recent Cochrane review conducted by Gordon et al. in 2018 explored the effectiveness of dietary modifications, such as partially hydrolyzed whey proteins, low levels of lactose, prebiotic oligosaccharides, and a high β-palmitate content in the treatment of infantile colic [52]. However, the review also highlighted the presence of limited and biased evidence in this field, mainly due to the very small sample sizes in the studies and significant limitations such as methodological flaws (e.g., the absence of data before washout), poor study quality, and potential conflicts of interest. [52].

Formulas containing other sources of protein

As an alternative to cow's milk-based formulas, various protein sources have been examined for their effects in colicky infants. An industry-driven RCT tested a goat milk-based formula but did not find any improvement in fussiness and colic, in contrast to cow's milk-based formula [58]. The use of soy-based formulas was suggested for colicky infants in the past, but there is insufficient evidence to support their use. As a result, these formulas are currently not recommended by the ESPGHAN Nutrition Committee [6, 52, 59-61].

The effectiveness of anti-colic formulas is not well-established, primarily due to evidence coming from small-scale studies with methodological weaknesses [62, 63]. The evidence supporting dietary changes for the treatment of colic in infants is also limited. Therefore, caution should be exercised when considering these interventions, and further research is needed to determine their true efficacy [52].

Nutritional interventions in case of suspected CMPA

In the differential diagnosis of infantile colic, CMPA can be considered as a potential contributing factor, along with other possible conditions. However, there is currently insufficient data to support the notion that infant colic occurs solely as a single manifestation of CMPA [6]. For infants presenting with crying and irritability, there is insufficient data to recommend a time-limited cow's milk elimination diet for 2-4 weeks followed by an OFC [6]. In cases where treatment for infant colic, fulfilling Rome IV clinical research criteria, is being

considered, and where CMPA is suspected based on additional symptoms like regurgitation, vomiting, diarrhea, food refusal, dysphagia, constipation, anal fissures, perianal rash, or blood loss, a time-limited elimination diet for 2-4 weeks can be tried, which should be followed by an OFC. Clinical manifestations of CMPA are predominantly cutaneous (70-75%), and less frequently gastrointestinal (13-34%) and respiratory (1-8%) [6]. For further clarification we refer the reader to the recently published ESPGHAN guidelines on CMPA [6].

Conclusion:

There are currently insufficient data on the benefits and efficacy of "anti-colic formulas" or soy protein formulas or other formulas with modified content in colicky infants.

Recommendation:

Breastfeeding should not be stopped in infants with colic and parents should be reassured that infant colic is natural.

Low-lactose, partially hydrolyzed protein formula, extensively hydrolyzed protein formulas and formulas supplemented in pre- or probiotics have shown insufficient evidence to be recommended.

Soy protein formulas have failed to show any efficacy in colic treatment and are not recommended.

The use of "anti-colic formulas" or other formulas with modified content is generally not recommended in infants having colic.

Interventions for the treatment of constipation

Functional constipation in infants is characterized by the presence of dry hard stool that can lead to painful bowel movements [29]. With a prevalence of up to 27% it is a common issue in infancy and has multiple underlying factors [29]. While structural-anatomic, endocrine, or metabolic causes are uncommon, they should be ruled out using a system of red-flags before attributing stool problems to functional causes. The diagnosis of functional constipation in infants is based on the Rome IV criteria, which require the presence of at least two of the following for 1 month [1]:

- Defecation frequency ≤2 times per week
- Excessive stool retention
- Painful hard bowel movement
- Sizable fecal mass in the rectum
- Stools with large diameter

Non-nutritional interventions

Non-nutritional interventions can be used in managing constipation in infants although evidence from prospective RCTs is missing. Ensuring adequate hydration, regular physical activity, such as 'tummy time' (period during the day an infant spends awake and, on their stomach), and gently massaging the infant's tummy in a clockwise motion can be considered and may provide relief to the infant. Additionally, communicating with a pediatrician for guidance and monitoring the infant's progress is essential for effective management of constipation which is also addressed in the respective ESPGHAN guidelines [64].

Nutritional interventions

Formulas designed for infants with constipation come in various compositions, which may include partially hydrolyzed protein, β-palmitate, or higher levels of magnesium or lactose.

Formulas containing lactose and magnesium

In the case of infants with habitual constipation who are not breastfed, research indicates that using standard infant formula containing lactose as the primary carbohydrate has demonstrated effectiveness when compared to formulas with another carbohydrate source [65]. Lactose, even if not fully absorbed in the gut, can exhibit a prebiotic effect by supporting the growth of beneficial bacteria [66]. Unhydrolyzed lactose is metabolized by anaerobic microorganisms, leading to an osmotic laxative effect through increased water secretion and enhanced luminal retention [67, 68]. However, there is a lack of data on formulas with elevated lactose content as a sole measure. In a small crossover trial involving 30 infants experiencing constipation, it was observed that incorporating three times the usual lactose content along with a one-third increase in magnesium content compared to conventional formula led to increased stool water content and alleviated constipation symptoms in term-born, formula-fed infants [69].

Magnesium plays a physiological role in promoting water secretion from the intestinal mucosa, which leads to a softer stool consistency. Infant formulas containing elevated levels of magnesium, typically ranging between 8–9 mg/100ml as opposed to the approximately 5mg/100ml in conventional formulas, have demonstrated positive effects on stool frequency, composition, and the reported quality of life as perceived by parents and safety issues have not been reported nor suspected [69-71]. A small industry-sponsored RCT involving 89 infants using a pHF with increased magnesium concentration (25%) compared to a routine intact protein cow's milk-based infant formula, demonstrated improvements in stool consistency and frequency by influencing gastrointestinal motility in constipated infants [72]. Due to the increased amount of magnesium compared to the placebo formula, the improvement cannot be attributed to the partially hydrolyzed protein. Furthermore, the certainty of evidence is low due to poor study design and limited patient numbers in these studies.

Formulas containing beta-palmitate

β-palmitate (SN-2-palmitate), a component naturally present in human milk, plays a significant role in softening stool consistency by reducing the formation of insoluble calcium [73]. Data from 21 studies indicated that the inclusion of a high SN-2-palmitate fat blend, with a greater proportion of palm oil in the SN-2 position (a configuration typical in human milk), in infant formulas might result in short-term effects on stool consistency, leading to softer stools [74]. However, an earlier study found that higher levels of β-palmitate, when combined with pHF and added prebiotics, did not significantly improve stool consistency or defecation frequency in constipated infants compared to standard formula [75].

Nutritional interventions in case of suspected CMPA

In cases where patients do not respond to conventional therapies for constipation, CMPA should be considered. In such instances, a time-limited elimination diet lasting 2-4 weeks can be initiated, followed by an OFC [6]. We refer the reader to the recently published ESPGHAN guidelines on CMPA [6]

Conclusion:

Formulas with higher content of magnesium or β-palmitate can be effective to improve stool consistency but there is insufficient evidence to support their routine use for infants with constipation. There is no evidence that protein hydrolyzation offers any additional benefit.

Recommendation:

Both in breastfed and formula fed infants, non-nutritional interventions should be used as first line treatment.

Breastfeeding should not be stopped in infants with functional constipation.

The use of formulas with high β-palmitate or with a higher content of magnesium may be considered in selected cases to soften the stool.

Interventions for the treatment of combined FGIDs

There is a growing interest in the development of infant formulas that aim to alleviate combined FGIDs, defined as the presence of various FGID simultaneously, such as regurgitation, infantile colic, and constipation. To achieve this, multiple modifications have been implemented in formulas, including reducing lactose content, increasing magnesium levels, incorporating partially hydrolyzed protein, and adding prebiotics and/or probiotics. However, the current body of evidence consists mainly of observational studies, and there is a lack of prospective RCTs. As a result, a definitive assessment of the actual efficacy of these infant formulas cannot be made at this time. Further research is needed to better understand

the potential benefits and effectiveness of these modified formulas in addressing multiple gastrointestinal symptoms in infants [76]. Also in cases with combined FGIDs, CMPA should be considered. In such instances, a time-limited elimination diet lasting 2-4 weeks can be initiated, followed by an OFC [6]. We refer the reader to the recently published ESPGHAN guidelines on CMPA [6]

Conclusion:

There are currently insufficient data on the benefits and efficacy of formulas for the use in combined functional gastrointestinal disorders.

Recommendation:

Breastfeeding should not be stopped in infants experiencing any or several mild functional gastrointestinal disorders.

The use of formulas for combined functional gastrointestinal disorders is generally not advised.

Conclusion

Infant formulas designed for FGID are specifically formulated for the exclusive or partial nutrition of infants with specific medical conditions. It is crucial to emphasize that these formulas should only be used under the guidance and supervision of physicians or healthcare professionals. In certain cases of significant regurgitation, the use of thickened feeds may be considered. The evidence for formulas with altered composition as hydrolyzed protein or reduced lactose to treat infant colic is insufficient. Soy formulas or formulas with pre or probiotics have failed to show any efficacy to treat infantile colic. Infant formulas with high β-palmitate or with higher magnesium content may be effective in softening stool in selected infants with constipation. Regardless of the functional gastrointestinal disorder, discontinuing breastfeeding is not advised. It is always recommended to seek advice from healthcare professionals for proper guidance and supervision.

Legend Tables and Figures

Table 1: Overview of the efficacy of Formulas for the use in functional gastrointestinal disorders (FGID).

Figure 1.: Definitions and differences between gastroesophageal reflux, regurgitation and gastroesophageal reflux disease [1]

Figure 2: Recommendations for infant formulas with claims for use in regurgitation, colic, constipation and combined functional symptoms

Supplemental Material 1: Summary of the literature review

References:

1. Zeevenhooven, J., I.J. Koppen, and M.A. Benninga, *The New Rome IV Criteria for Functional Gastrointestinal Disorders in Infants and Toddlers.* Pediatr Gastroenterol Hepatol Nutr, 2017. **20**(1): p. 1-13.
2. Aggett, P.J., et al., *Antireflux or Antiregurgitation Milk Products for Infants and Young Children: A Commentary by the ESPGHAN Committee on Nutrition.* Journal of Pediatric Gastroenterology and Nutrition, 2002. **34**(5).
3. Tabbers, M.M., et al., *Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN.* J Pediatr Gastroenterol Nutr, 2014. **58**(2): p. 258-74.
4. Sherman, P.M., et al., *A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population.* Am J Gastroenterol, 2009. **104**(5): p. 1278-95; quiz 1296.
5. Rosen, R., 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**(3): p. 516-554.
6. Vandenplas, Y., et al., *An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy.* J Pediatr Gastroenterol Nutr, 2023.
7. Vandenplas, Y., et al., *Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies.* Acta Paediatr, 2016. **105**(3): p. 244-52.
8. Beal, J., et al., *Late onset necrotizing enterocolitis in infants following use of a xanthan gum-containing thickening agent.* J Pediatr, 2012. **161**(2): p. 354-6.
9. Woods, C.W., et al., *Development of necrotizing enterocolitis in premature infants receiving thickened feeds using SimplyThick(R).* J Perinatol, 2012. **32**(2): p. 150-2.
10. Salvatore, S., et al., *Thickened infant formula: What to know.* Nutrition, 2018. **49**: p. 51-56.
11. Horvath, A., P. Dziechciarz, and H. Szajewska, *The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials.* Pediatrics, 2008. **122**(6): p. e1268-77.
12. Tounian, P., et al., *Effectiveness and Tolerance of a Locust Bean Gum-Thickened Formula: A Real-Life Study.* Pediatr Gastroenterol Hepatol Nutr, 2020. **23**(6): p. 511-520.
13. Vandenplas, Y., et al., *A clinical trial with an "anti-regurgitation" formula.* Eur J Pediatr, 1994. **153**(6): p. 419-23.
14. Xinias, I., et al., *Cornstarch thickened formula reduces oesophageal acid exposure time in infants.* Dig Liver Dis, 2005. **37**(1): p. 23-7.
15. Vandenplas, Y., et al., *Double-blind comparative trial with 2 antiregurgitation formulae.* J Pediatr Gastroenterol Nutr, 2013. **57**(3): p. 389-93.
16. Infante Pina, D., et al., *Prevalence and dietetic management of mild gastrointestinal disorders in milk-fed infants.* World J Gastroenterol, 2008. **14**(2): p. 248-54.
17. Bellaiche, M., et al., *Safety and Tolerance of a Novel Anti-Regurgitation Formula: A Double-Blind, Randomized, Controlled Trial.* J Pediatr Gastroenterol Nutr, 2021. **73**(5): p. 579-585.

18. Vandenplas, Y., T. Devreker, and B. Hauser, *A Double-Blinded, Prospective Trial with A New Formula in Distressed and Regurgitating Infants.* The Open Nutrition Journal, 2008. **2**(1): p. 48-50.
19. Moukarzel, A.A., H. Abdelnour, and C. Akatcherian, *Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER.* J Clin Gastroenterol, 2007. **41**(9): p. 823-9.
20. Barbieur, J., E.I. Levy, and Y. Vandenplas, *Efficacy and safety of medical and nutritional management of gastroesophageal reflux in formula-fed infants: a narrative review.* Curr Opin Pediatr, 2022. **34**(5): p. 503-509.
21. Lucassen, P.L., et al., *Systematic review of the occurrence of infantile colic in the community.* Arch Dis Child, 2001. **84**(5): p. 398-403.
22. Wolke, D., A. Bilgin, and M. Samara, *Systematic Review and Meta-Analysis: Fussing and Crying Durations and Prevalence of Colic in Infants.* J Pediatr, 2017. **185**: p. 55-61.e4.
23. Brazelton, T.B., *Crying in infancy.* Pediatrics, 1962. **29**: p. 579-88.
24. Lucas, A. and I. St James-Roberts, *Crying, fussing and colic behaviour in breast- and bottle-fed infants.* Early Hum Dev, 1998. **53**(1): p. 9-18.
25. Despriee Å, W., et al., *Prevalence and perinatal risk factors of parent-reported colic, abdominal pain and other pain or discomforts in infants until 3 months of age - A prospective cohort study in PreventADALL.* J Clin Nurs, 2022. **31**(19-20): p. 2784-2796.
26. Bellaiche, M., et al., *Assessment of the severity of infant crying and its impact on parents: Development and validation of the ColiQ Questionnaire in France.* Arch Pediatr, 2021. **28**(4): p. 264-272.
27. Savino, F., et al., *A prospective 10-year study on children who had severe infantile colic.* Acta Paediatr Suppl, 2005. **94**(449): p. 129-32.
28. Wessel, M.A., et al., *Paroxysmal fussing in infancy, sometimes called colic.* Pediatrics, 1954. **14**(5): p. 421-35.
29. Benninga, M.A., et al., *Childhood Functional Gastrointestinal Disorders: Neonate/Toddler.* Gastroenterology, 2016.
30. Drossman, D.A. and W.L. Hasler, *Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction.* Gastroenterology, 2016. **150**(6): p. 1257-61.
31. Camilleri, M., et al., *Exploring hypotheses and rationale for causes of infantile colic.* Neurogastroenterol Motil, 2017. **29**(2).
32. Hofman, D., et al., *Faecal Microbiota in Infants and Young Children with Functional Gastrointestinal Disorders: A Systematic Review.* Nutrients, 2022. **14**(5).
33. Rhoads, J.M., et al., *Infant Colic Represents Gut Inflammation and Dysbiosis.* J Pediatr, 2018. **203**: p. 55-61.e3.
34. Wurmser, H., et al., *Association between life stress during pregnancy and infant crying in the first six months postpartum: a prospective longitudinal study.* Early Hum Dev, 2006. **82**(5): p. 341-9.
35. St James-Roberts, I., et al., *Infant crying and sleeping in London, Copenhagen and when parents adopt a "proximal" form of care.* Pediatrics, 2006. **117**(6): p. e1146-55.
36. Fewtrell, M., et al., *Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition.* J Pediatr Gastroenterol Nutr, 2017. **64**(1): p. 119-132.

37. Agency, E.M. and E.o.M.f.H. Use, *Committee on Herbal Medicinal Products (HMPC) assessment report on Foeniculum vulgare miller.*, in *EMEA/HMPC/137426/2006*, EMEA, Editor. 2008.
38. Biagioli, E., et al., *Pain-relieving agents for infantile colic.* Cochrane Database Syst Rev, 2016. **9**(9): p. Cd009999.
39. Akhnikh, S., et al., *The excessively crying infant: etiology and treatment.* Pediatr Ann, 2014. **43**(4): p. e69-75.
40. Moore, D.J., T.A. Robb, and G.P. Davidson, *Breath hydrogen response to milk containing lactose in colicky and noncolicky infants.* J Pediatr, 1988. **113**(6): p. 979-84.
41. Narang, M. and D. Shah, *Oral lactase for infantile colic: a randomized double-blind placebo-controlled trial.* BMC Pediatr, 2022. **22**(1): p. 468.
42. Kearney, et al., *A trial of lactase in the management of infant colic.* Journal of Human Nutrition and Dietetics, 1998. **11**(4): p. 281-285.
43. Kanabar, D., M. Randhawa, and P. Clayton, *Improvement of symptoms in infant colic following reduction of lactose load with lactase.* Journal of Human Nutrition and Dietetics, 2001. **14**(5): p. 359-363.
44. Ahmed, M., et al., *Clinical efficacy of lactase enzyme supplement in infant colic: a randomised controlled trial.* J Pak Med Assoc, 2018. **68**(12): p. 1744-7.
45. Savino, F., et al., *Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula.* Eur J Clin Nutr, 2006. **60**(11): p. 1304-10.
46. Dupont, C., et al., *Alpha-lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance.* Eur J Clin Nutr, 2010. **64**(7): p. 765-7.
47. Huang, Y., et al., *The Effects of a Partially Hydrolyzed Formula with Low Lactose and Probiotics on Mild Gastrointestinal Disorders of Infants: A Single-Armed Clinical Trial.* Nutrients, 2021. **13**(10).
48. Lucassen, P.L., et al., *Infantile colic: crying time reduction with a whey hydrolysate: A double-blind, randomized, placebo-controlled trial.* Pediatrics, 2000. **106**(6): p. 1349-54.
49. Arikan, D., et al., *Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic.* J Clin Nurs, 2008. **17**(13): p. 1754-61.
50. Jakobsson, I., et al., *Effectiveness of casein hydrolysate feedings in infants with colic.* Acta Paediatr, 2000. **89**(1): p. 18-21.
51. Forsyth, B.W., *Colic and the effect of changing formulas: a double-blind, multiple-crossover study.* J Pediatr, 1989. **115**(4): p. 521-6.
52. Gordon, M., et al., *Dietary modifications for infantile colic.* Cochrane Database Syst Rev, 2018. **10**: p. CD011029.
53. Indrio, F., et al., *Health Effects of Infant Formula Supplemented with Probiotics or Synbiotics in Infants and Toddlers: Systematic Review with Network Meta-Analysis.* Nutrients, 2022. **14**(23).
54. Savino, F., et al., *Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial.* Pediatrics, 2010. **126**(3): p. e526-33.
55. Turco, R., et al., *Efficacy of a partially hydrolysed formula, with reduced lactose content and with Lactobacillus reuteri DSM 17938 in infant colic: A double blind, randomised clinical trial.* Clin Nutr, 2021. **40**(2): p. 412-419.

56. Savino, F., et al., *"Minor" feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides.* Acta Paediatr Suppl, 2003. **91**(441): p. 86-90.
57. Litmanovitz, I., et al., *Reduced crying in term infants fed high beta-palmitate formula: a double-blind randomized clinical trial.* BMC Pediatr, 2014. **14**: p. 152.
58. He, T., et al., *Goat Milk Based Infant Formula in Newborns: A Double-Blind Randomized Controlled Trial on Growth and Safety.* J Pediatr Gastroenterol Nutr, 2022. **75**(2): p. 215-220.
59. Agostoni, C., et al., *Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition.* J Pediatr Gastroenterol Nutr, 2006. **42**(4): p. 352-61.
60. Hill, D.J. and C.S. Hosking, *Infantile colic and food hypersensitivity.* J Pediatr Gastroenterol Nutr, 2000. **30 Suppl**: p. S67-76.
61. Cohen-Silver, J. and S. Ratnapalan, *Management of infantile colic: a review.* Clin Pediatr (Phila), 2009. **48**(1): p. 14-7.
62. Infante, D., O. Segarra, and B.L. Luyer, *Dietary treatment of colic caused by excess gas in infants: biochemical evidence.* World J Gastroenterol, 2011. **17**(16): p. 2104-8.
63. Veitl V, B.A., Böckler H-M, Helm K, Kafka C, Lamme W, Müller H, Wells JK, *Akzeptanz, Toleranz und Wirksamkeit von milupa Comformil bei Säuglingen mit kleineren Ernährungs- und Verdauungsproblemen.* Journal für Ernährungsmedizin, 2000. **2**(4): p. 14-20.
64. Tabbers, M.M., et al., *Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN.* Journal of Pediatric Gastroenterology and Nutrition, 2014. **58**(2).
65. Hyams, J.S., et al., *Effect of infant formula on stool characteristics of young infants.* Pediatrics, 1995. **95**(1): p. 50-4.
66. Szilagyi, A., *Review article: lactose--a potential prebiotic.* Aliment Pharmacol Ther, 2002. **16**(9): p. 1591-602.
67. Laforgia, N., et al., *[Significance of lactose breath test in the newborn].* Minerva Pediatr, 1995. **47**(10): p. 433-6.
68. Roggero, P., et al., *Sugar absorption in healthy preterm and full-term infants.* J Pediatr Gastroenterol Nutr, 1986. **5**(2): p. 214-9.
69. Infante, D.D., et al., *Modification of stool's water content in constipated infants: management with an adapted infant formula.* Nutr J, 2011. **10**: p. 55.
70. Xinias, I., et al., *A Synbiotic Infant Formula with High Magnesium Content Improves Constipation and Quality of Life.* Pediatr Gastroenterol Hepatol Nutr, 2018. **21**(1): p. 28-33.
71. Benninga, M.A. and Y. Vandenplas, *The Magnesium-Rich Formula for Functional Constipation in Infants: a Randomized Comparator-Controlled Study.* Pediatric Gastroenterology, Hepatology & Nutrition, 2019. **22**(3): p. 270.
72. Fabrizio, V., et al., *Softer More Frequent Stools in Infants With Difficult Stooling Fed Hydrolyzed Protein Formula With Added Prebiotics: Randomized Controlled Trial.* Front Pediatr, 2022. **10**: p. 894626.
73. Havlicekova, Z., et al., *Beta-palmitate – a natural component of human milk in supplemental milk formulas.* Nutrition Journal, 2015. **15**(1).
74. Bronsky, J., et al., *Palm Oil and Beta-palmitate in Infant Formula: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition*

(ESPGHAN) Committee on Nutrition. J Pediatr Gastroenterol Nutr, 2019. **68**(5): p. 742-760.
75. Bongers, M.E., et al., *The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial.* Nutrition Journal, 2007. **6**(1): p. 8.
76. Vandenplas, Y., et al., *An Observational Real-Life Study with a New Infant Formula in Infants with Functional Gastro-Intestinal Disorders.* Nutrients, 2021. **13**(10).

Figure 1.: Definitions of and differences between gastroesophageal reflux, regurgitation and gastroesophageal reflux disease [5]

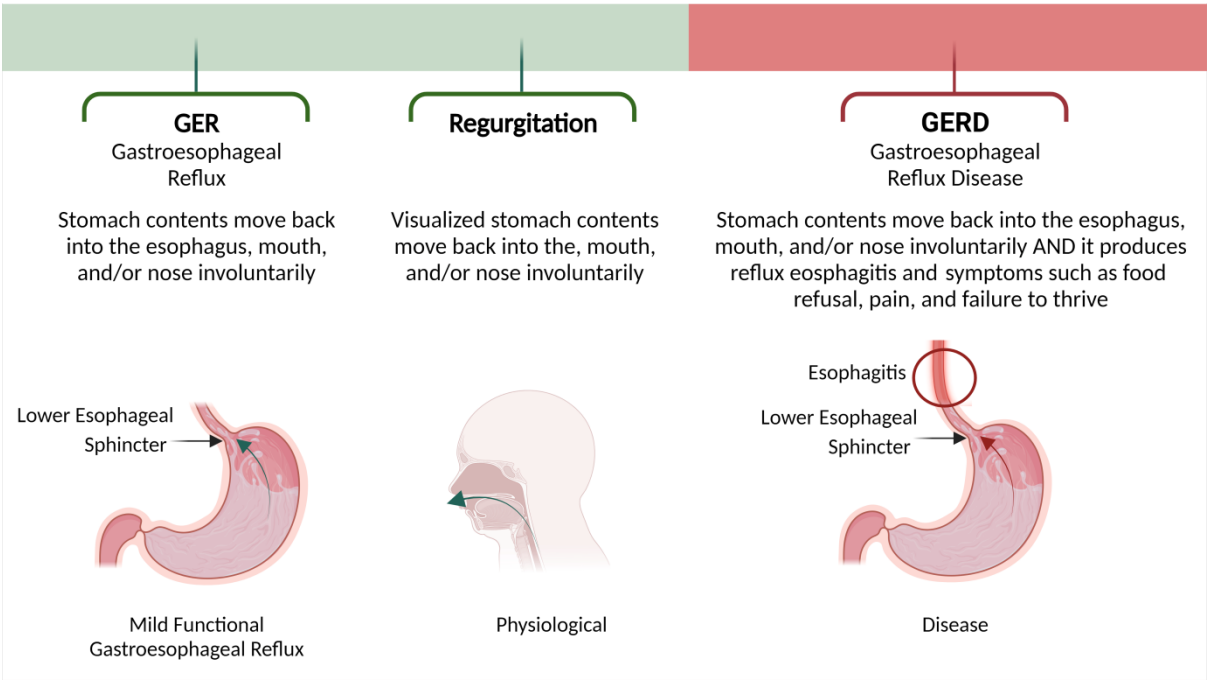

Figure 2: Recommendations for infant formulas with claims for use in regurgitation, colic, constipation and combined functional gastrointestinal symptoms

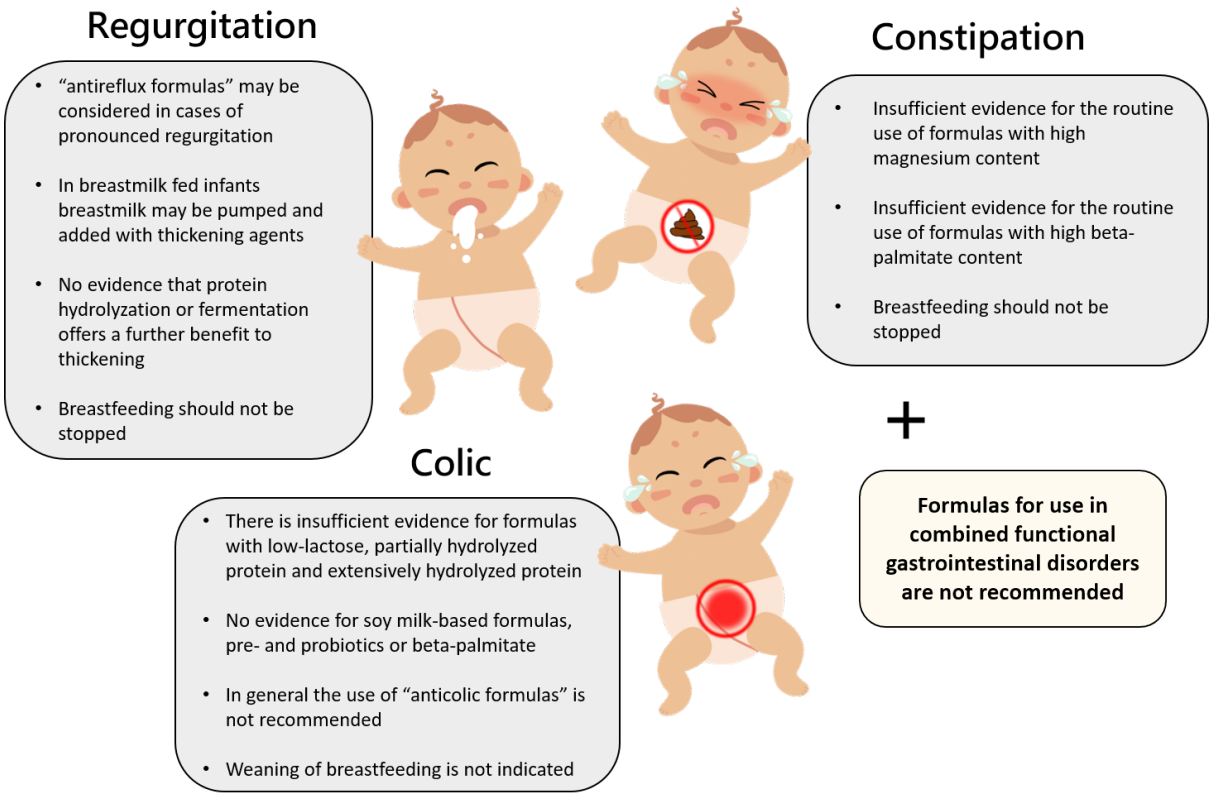

Table 1: Overview of the efficacy of formulas for the use in functional gastrointestinal disorders (FGID).

Formulas	Symptoms of FGID	Ingredients of formulas	Efficacy
"Anti-reflux formulas"	Regurgitation - ≥ 2 times/day for ≥3 weeks - No aspiration, failure to thrive, feeding difficulties, apnea, gulping	Rice, potato, and corn starch, carob, or locust bean gum, xanthan gum, pectin, and soybean polysaccharides Fermentation, protein hydrolyzation	- Reduction in the number of visible regurgitations - no evidence that protein hydrolyzation or fermentation offers a further benefit to thickening.
"Anti-colic formulas"	Infantile colic - <5 months of age when the symptoms start and stop - Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers - No evidence of infant failure to thrive, fever, or illness	Higher beta-palmitate content Lower lactose content Partially hydrolyzed or extensively hydrolyzed protein Lactobacillus reuteri DSM 17938	- No proven efficacy for soymilk-based formulas, pre- and probiotics or beta-palmitate - Insufficient evidence for low-lactose, partially hydrolyzed formulas, extensively hydrolyzed formulas
Formulas for the use in constipation	Constipation - Defecation frequency ≤ 2 times/week - Stool retention - Painful bowel movement - Sizable fecal mass in the rectum - Stools with large diameter	Higher lactose content Higher magnesium content Higher beta-palmitate content Partially hydrolyzed protein	- Insufficient evidence for formulas with high magnesium content - Insufficient evidence for formulas with high beta-palmitate content - No evidence for protein hydrolyzation
Formulas for use in combined FGID	Flatulence, colic and/or constipation	Lower lactose Galacto-oligosaccharides (GOS) or fructo-oligosaccharides (FOS)	- No proven efficacy