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Pediatric Aspects of Nutrition Interventions for Disorders of Gut-Brain Interaction

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Dietary factors may play an important role in the generation of symptoms in children with disorders of gut-brain interaction (DGBIs). Although dietary modification may provide successful treatment, there is a relative paucity of controlled trials that have shown the effectiveness of dietary interventions. This study is a narrative review that explores the existing literature on food and pediatric DGBIs. The following have been shown to be beneficial: (i) in infants with colic, removing cow's milk from the infant's diet or from the maternal diet in those who are breastfed; (ii) in infants with regurgitation, adding thickeners to the formula or removing cow's milk protein from the infant's diet or the maternal diet in those who are breastfed; and (iii) in children with pain-predominant DGBIs, using soluble fiber supplementation or a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet. In children with functional constipation, there is no evidence that adding fiber is beneficial. Given that most dietary interventions include restriction of different foods in children, a thoughtful approach and close follow-up are needed.

Am J Gastroenterol 2022;117:995–1009. https://doi.org/10.14309/ajg.0000000000001779

INTRODUCTION

Disorders of gut-brain interaction (DGBIs) are very common in children (1–5). Food may have an important role in the generation of symptoms, and therefore, dietary modification may provide successful treatment (1,6–9). The pathophysiology of food-induced problems in DGBIs in children is complex and multifactorial and includes several behavioral (psychological and social) and biological factors (physiological effects of diet, food intolerance, gut microbiome, visceral hypersensitivity, central and peripheral sensitization, and dysmotility) (1,10). This study is an expert narrative review that addresses the relevant information regarding the role of food and pediatric DGBIs.

METHODS

This narrative review was performed after doing an extensive review of the literature on dietary interventions in pediatric DGBIs using PubMed (2,3). Controlled and uncontrolled trials, systematic reviews, meta-analyses, and review articles were identified. The authors discussed, reviewed, and summarized the identified references to achieve consensus on the provided recommendations. This review will focus only on specific dietary interventions (food) in those pediatric DGBIs in which dietary interventions have been studied in controlled trials.

INFANT COLIC

Infant colic has been described as a behavioral syndrome of early infancy involving long periods of crying and hard-to-soothe behavior (7,10,11). It affects somewhere between 4% and 28% of infants worldwide and usually resolves by the age of 5 months (10).

The etiopathogenesis of infant colic remains undefined (10). Several factors can contribute to its manifestation including excessive gas production, dysbiosis, gut inflammation, alterations in motility, food intolerance or allergy, and enteric nervous system immaturity and behavioral factors (7,10,12,13).

Dietary therapies for children with colic

Most dietary interventions have focused on either changing the infant's formula in non-breastfed infants or changing the maternal diet on those babies that are exclusively breastfed (10) (Tables 1 and 2; Figure 1).

Non-breastfed infants. Modifications to the infant formula involve changing the carbohydrate (hypothesizing that malabsorption of lactose may lead to increased gas production, fussiness, and crying) or changing the protein content or type (hypothesizing that colic is secondary to intolerance or allergy) (10). Decreasing the lactose content has not been shown to produce a difference in symptom reduction (7,14–16). Attempts to alter the protein intake have included either modifying the amount of protein or modifying its type by using specialized formulas (soy-based, partially hydrolyzed, extensively hydrolyzed, amino acid-based/elemental, the addition of prebiotics, etc.) (7,10).

1. Modifying the amount of protein: Double-blind randomized controlled trial (RCT) studies have failed to show a difference in the amount of crying (7,17).
2. Soy-based formulas: They may reduce symptoms of colic (18). However, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition stated recently that there is insufficient

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Received January 10, 2022; accepted April 9, 2022; published online April 13, 2022

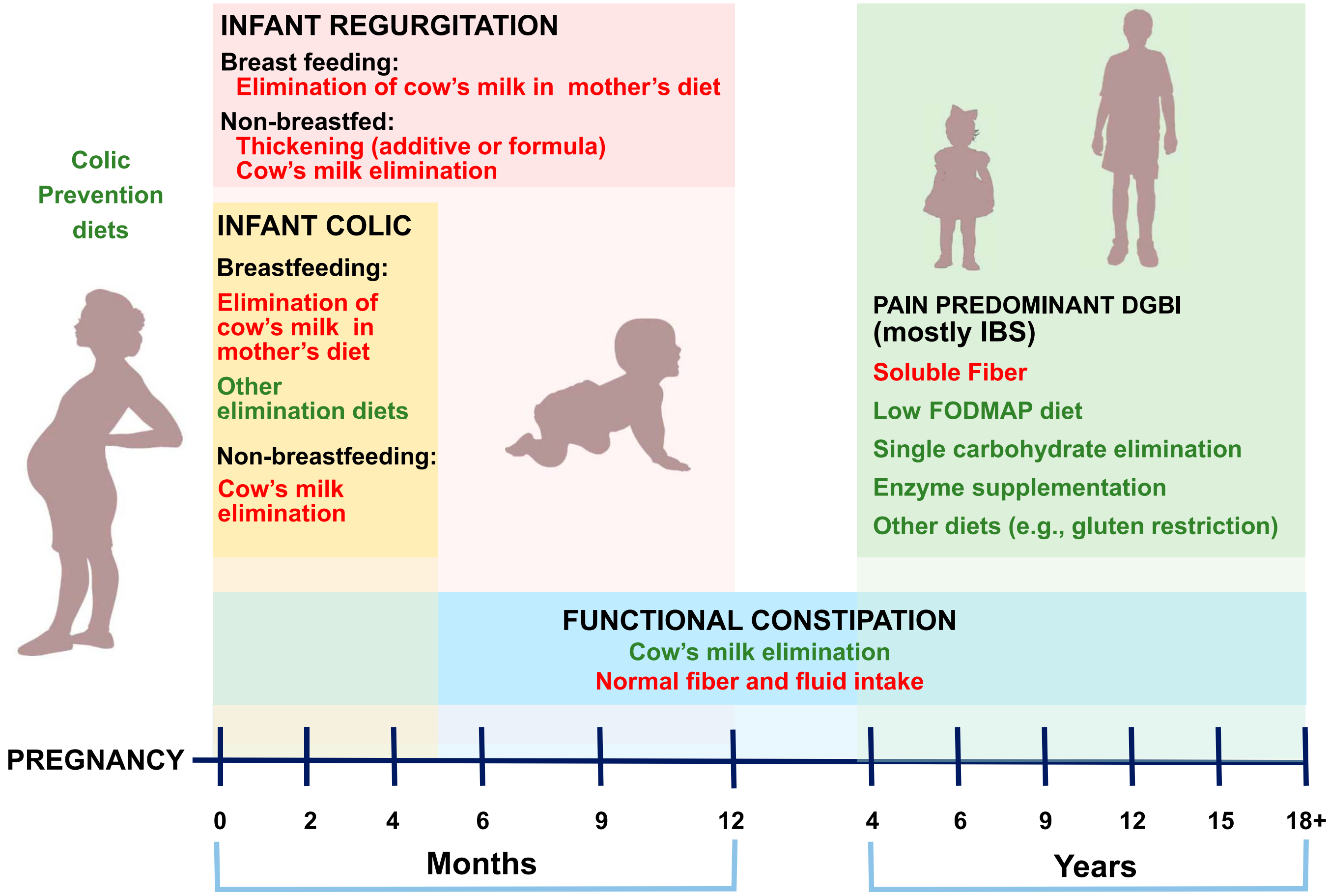

Figure 1. Specific dietary interventions for pediatric disorders of gut-brain interaction (DGBIs). Specific DGBIs are placed according to the age of presentation. Evidence-based dietary interventions are shown in red. Those with some information are shown in green. IBS, irritable bowel syndrome.

evidence to support the use of soy formulas for colic. In addition, owing to concerns regarding a cross-over allergy to cows' milk protein and their estrogen content, it is recommended that soy-based formulas should not be given to infants (19).

3. Hypoallergenic formulas: Studies have shown conflicting results (7,20–24). Recent systematic reviews and meta-analyses that have included more than 15 RCTs and 1,200 infants have concluded that although there is insufficient evidence to recommend dietary modifications in all infants with colic, a 2–4-week elimination diet may be indicated in more severe cases, given the possibility of an underlying cow's milk allergy (CMA) (2,7,10,21,22).

Breastfed infants. Breastfeeding should be continued. Mothers often alter their diet in an attempt to settle their infant, commonly by reducing intake of dairy and intestinal gas-producing foods, especially pulses/legumes, onion, garlic, cruciferous vegetables, wheat, and rye.

There is some experimental evidence on the association between maternal intake of cow's milk and crying in colicky infants (11,25), and several studies have demonstrated a reduction in colic when breastfeeding mothers consumed a hypoallergenic diet (26,27). A recent trial randomized breastfeeding mothers of babies with colic to either a low fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAP) diet or a regular Australian diet and showed a significant reduction in crying time for the low-FODMAP group (20).

It is important to note that other nondietary interventions such as education or medication may be as or more effective than dietary changes (28,29).

Prevention of infant colic. There are no available RCTs evaluating whether maternal avoidance of cow's milk or other dietary interventions during pregnancy or after delivery will prevent colic. Studies have failed to show a protective effect of maternal diets during pregnancy on infant development of allergic problems, including CMA (30). A recent RCT demonstrated that a combination of fermented formula with galacto-oligosaccharides and fructo-oligosaccharides modestly decreased the incidence of infant colic (8%), but more information is needed before this can be recommended (31).

INFANT REGURGITATION

Infant regurgitation is one of the most frequent DGBIs in children with a prevalence of about 20% (2,8,32,33). Gastroesophageal reflux (GER) is a normal physiologic event that occurs multiple times a day and manifests itself as infant regurgitation (8,34). GER can evolve into a pathologic entity, gastroesophageal reflux disease (GERD), when it becomes troublesome and symptomatic or is associated with esophageal damage or extraesophageal problems (8,35).

Factors that contribute to the more frequent physiologic reflux in an infant include a combination of large fluid intake, a shorter esophagus, a small stomach size and capacity resulting in faster gastric distention and increased intragastric pressure, frequent feedings per day, an exclusively liquid diet, high fluid intake per kilogram per day, and a supine position that predisposes to a common immersion of the gastroesophageal junction, compounded by a small esophageal capacity to hold fluids (2,8,36–42). The type of diet can also affect esophageal and gastric functions (37,38). Breastfed infants have less regurgitation in comparison with formula-fed children (38), and hypoallergenic formulas have been shown to decrease reflux events and enhance gastric emptying in comparison with regular infant formulas (8).

Dietary therapies for infants with regurgitation

Treatment of infant regurgitation should be tailored to the child's clinical presentation, psychosocial circumstances, and underlying pathophysiological mechanisms (2,8) (Tables 1 and 2 and Figure 1). No medications are necessary, and multiple RCTs have shown that proton pump inhibitors are not effective in controlling the regurgitation or irritability, they increase adverse events and should not be given to children with infant regurgitation (2,8,43,44). The treatment of infant regurgitation includes mostly conservative measures.

Reduction of the ingested volume of formula. Although there are no RCTs, frequent feedings of smaller volumes for age while maintaining an appropriate total daily amount of formula or breast milk to meet the child's nutritional needs are often recommended (8,36,37,45).

Thickening. The next consideration, especially if there is inadequate weight gain, includes formula thickeners (8,37,46). Thickening decreases visible regurgitation and therefore provides increased calories, and it has an impact on achieving parental reassurance (46). The impact on nonregurgitation symptoms is less clear (8,36,37,47,48).

There are 2 main approaches to thickening: (i) home thickening of a standard formula (which is usually less expensive) or (ii) commercially available thickened formulas (46).

Thickeners that have been added to formulas include cereal, cornstarch, bean gum, fiber, soybean polysaccharides, and other commercial products (46). Care should be taken when adding thickeners because the osmolarity and viscosity of the formulas may change to nonrecommended levels (46). One study reported that a heaping tablespoon of starch added a quantity between 3.6 g and 4.6 g (49). This is well above the regulatory limit for starch in antiregurgitation formulas; it increases formula osmolarity and provides an additional 20 calories per 100 mL. Furthermore, overthickening results in a higher viscosity, requiring an increased sucking effort and/or a crosscut nipple to flow through (46). No one particular thickening agent is more effective than another.

There have been safety concerns regarding the high levels of inorganic arsenic in rice cereal, which may cause neurotoxicity and increase long-term cancer risk. In April 2016, the US Food and Drug Administration proposed a limit of 100 parts per billion for inorganic arsenic in infant rice cereal, which corresponds to a level proposed by the European Commission for rice destined for the production of food for young children. The relatively large volume of rice cereal needed to thicken infant formulas puts this patient population more at risk for high arsenic levels. Despite the warning, thickening with rice cereal does have some advantages over other cereals, including its high solubility, low cost, and successful long-term use. Prospective studies are underway to try to better clarify these issues. Cereal cannot be used to thicken breast milk because of the presence of amylases.

There are other commercial thickeners such as xanthan gum-based, carob-based, and cornstarch-based thickeners that can be used to thicken breast milk (50). Concerns have been raised about the risk of thickeners in infants, including arsenic exposure, necrotizing enterocolitis, dehydration, decreased intake, and constipation, and these concerns sometimes limit their use (50). Whenever a thickener is used, clinical follow-up is needed to ensure that patients tolerate the degree of thickening with adequate improvement in symptoms and minimal adverse effects.

Commercially prepared thickened formulas are at times preferred because they usually have better viscosity, digestibility, and nutritional balance (46). Commercial antiregurgitation (AR) formulas have a controlled composition with thickening components less than 2 g/100 mL for starch and 1 g/100 mL for carob bean gum and a caloric content that is similar to a standard formula (46). Locust bean gum increases viscosity more than other thickening agents, but there is no clinical evidence that it is superior to other additives (51).

There are 2 types of commercial formulas—AR "regular" formulas or "comfort" formulas. While the first is positioned to reduce regurgitation in the "happy spitter," the second is positioned in the management of the infant presenting with regurgitation and distress. These comfort formulas contain partially hydrolyzed proteins and are reduced in lactose content (36). A thickened extensive hydrolysate may be effective, independent of the cause of the symptoms, but does not make a precise diagnosis of CMA, given other effects on esophageal and gastric physiology (36,52).

Elimination of cow's milk protein. GER and CMA may both occur in the first year of life. Differentiating between troublesome GER symptoms, GERD, and CMA may be challenging because the symptoms overlap. The association of CMA with GERD has been reported in 16%–56% of cases with persistent gastrointestinal symptoms and suspicion of GERD (52). It has also been reported that CMA can induce GER (53). Elimination of cow's milk may significantly improve reflux symptoms, esophageal clearance, and baseline indirect parameters of esophageal function and mucosal integrity (53).

Elimination of cow's milk protein has been achieved either with the use of extensively hydrolyzed or amino acid-based formulas or with the elimination of cow's milk protein intake in mothers of breastfed infants (52). When the symptoms are due to allergy, extensively hydrolyzed formula reduces GER symptoms and vomiting frequency (usually within 2 weeks), and reintroduction causes recurrence of symptoms (8,36,52,53). In non-breastfed infants with suspected CMA, formulas with cow's milk-based extensively hydrolyzed proteins can be tried as the first choice, rice hydrolysates are the second option, and amino acid-based formulas should be reserved for more severe clinical reactions (52). There are no specific RCTs that evaluate extensively hydrolyzed or amino acid-based formulas for regurgitation. In breastfed infants, elimination can be achieved if the mother eliminates all dairy ingestion including casein and whey products (8,36,52).

Given the similarity of the symptoms between infants with severe regurgitation and CMA and the difficulty in making the diagnosis, a trial of a minimum of 2 weeks with an extensively hydrolyzed formula or amino acid-based formulas or avoidance

Table 1. Summary of dietary interventions for children with disorders of gut-brain interaction

Category	Study	Design	Population sample size	Findings
Infant colic				
Decrease lactose	Miller et al. (14)	RCT crossover trial with two 1-wk periods. Comparison of breast milk treated with lactase or with placebo	15 infants with colic (6.5 ± 2.2 wk)	The mean (+SE) duration of crying and fussing during the period of treatment with lactase (225 + 22 min/24 h) did not differ significantly from that during treatment with placebo (185 + 25 min/24 h).
	Stahlberg et al. (15)	RCT crossover study comparing breast milk or cow's milk (treated and untreated with lactase) treated with 1 wk each	10 infants with colic (11.9 ± 8.4 wk)	No difference in symptoms was observed when comparing groups.
	Kanabar et al. (16)	RCT crossover trial comparing a formula preincubated with lactase vs control. 10 d and 5 d washout and 10 d crossover	46 formula-fed or breastfed infants with colic (range 3–13 wk)	Significant decrease in breath hydrogen production (45% vs 26%; CI 12.9%–44.4%) but no significant reduction in symptoms.
		Other comments		3 studies found no difference (14–16).
Change of protein in the formula	Dupont et al. (17).	RCT comparing an experimental formula (enriched with a-lactalbumin, supplemented with probiotics, reduced in protein and lactose content, and thickened with cornstarch) vs control diet for 1 mo	66 formula-fed infants with colic (<12 wk)	No difference in crying time as compared with a control group,
	Savino et al. (119)	RCT comparing a partially hydrolyzed formula with oligosaccharides and a standard formula with simethicone for 14 d	267 infants with colic (mean 1.39 ± 0.84 mo)	Both reduced colic episodes at 7 d (partially hydrolyzed formula: from 5.99 + 1.84 to 2.47 + 1.94 episodes; vs standard formula from 5.41 + 1.88 to 3.72 + 1.98 episodes; 95% CI 95% −0.7 to −1.8; $P < 0.001$); effects were greater in the hydrolyzed plus oligosaccharides group at 2 wk in favor of the whey hydrolysate formula. This difference was significant after 2 wk (partially hydrolyzed: 1.76 + 1.60 vs 3.32 + 2.06 episodes in standard formula) ($P < 0.001$).
	Turco et al. (24)	RCT comparing a partially hydrolyzed formula with reduced lactose content and Lactobacillus reuteri DSM 17938 (L. reuteri) (group A) to a standard formula (group B). Intervention 4 wk. Follow-up 8 wk	247 infants with colic (<4 mo) Group A: 124 Group B: 117	Mean daily crying time at 28 d was significantly lower in group B when compared with group A (104.7 min [87–122.4] vs 146.4 min [129.2–163.7]); treatment effect −41.8 (95% CI: −66.5 to −17.1; $P = 0.001$).
		Other comments		RCTs (10,18), systematic reviews (7,11), and meta-analyses show equivocal results (10)
Change of diet in mothers	Estep et al. (120)	Baseline 3–5 d. Interruption of breastfeeding and a temporary substitution with an amino acid-based formula for 4–8 d	6 breastfed infants (mean age 20.5 d, range 15–48 d)	Effective in controlling the colic within 1 or 2 d; however, this intervention could have negative effects on mother-infant interaction and the long-term continuation of breastfeeding and is not recommended.
	Jakobsson et al. (26)	Elimination of cow's milk in mothers for a week. In those who responded, there were 2 challenges with cow's milk given to mothers over 2 d in a double-blind crossover trial	66 breastfeeding mothers of infants with colic (mean age 2.6 wk; range 1–12 wk)	Colic disappeared in 35/66 mothers and reappeared after 2 challenges in 35%.
	Hill et al. (27)	RCT comparing low-allergen maternal diet (elimination of dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish) with a diet containing potential allergens for 7 d	90 breastfeeding mothers of infants with colic (mean 5.7 ± 1.1 wk; range: 2.9–8.6 wk)	35/47 of infants (74%) responded (reduction in cry/fuss duration of 25%) to a low-allergen maternal diet, compared with 16/43 of infants (37%) with a maternal diet containing potential allergens ($P < 0.001$).

Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
	Iacovou et al. (20)	RCT comparing low FODMAP diet with a regular Australian diet for 7 d	14 breastfeeding mothers of babies with colic (mean age 6.3 wk; range 3.3–8.7 wk)	Mean crying-fussing durations were 91 min/d in 7 controls compared with 269 min/d in colicky infants ($P < 0.0001$), which fell by median 32% during the low FODMAP diet compared with 20% during the typical Australian diet ($P = 0.03$).
	Taubman et al. (28)	RCT crossover trial comparing education vs a maternal elimination diet, if breastfed or on cow's milk elimination diet. Each intervention was for 9 d	20 infants with colic. Mean age education group 5.4 ± 2.2 wk. Mean age maternal elimination 6.5 ± 1.8 wk	Infants whose parents were given information and support experienced a more rapid reduction in crying time. The group receiving counseling (n = 10) had a decrease in crying from 3.21 ± 1.10 to 1.08 ± 0.70 h/d ($P = 0.001$). The crying in the group that received dietary changes (n = 10) decreased from 3.19 ± 0.69 to 2.03 ± 1.07 h/d ($P = 0.01$), a level still greater than twice normal. The decrease in those receiving counseling was faster and greater than that of those given dietary changes ($P < 0.02$). In the second phase, those who received counseling still showed a significant decrease in crying from 2.09 ± 1.07 to 1.19 ± 0.60 h/d ($P = 0.05$).
	Oggero et al. (29)	RCT comparing low-allergen diet (hydrolyzed formula or milk elimination in mothers) (group A) vs normal with the addition of dicyclomine (group B) for 30 d	120 formula-fed or breastfed infants with colic (mean 6.8 wk, range 3–12 wk). Group A 60 (44 formula-fed). Group B 45 formula-fed, 15 breastfed	In breastfed infants, there was no difference in comparing groups (improvement 62 vs 65%). Among formula-fed ones, there was significant improvement in those using dicyclomine (53%; $P < 0.01$)
		Other comments		RCTs (10,18), systematic reviews (7,11), and meta-analyses show equivocal results (10)
Prevention of infant colic	Vandenplas et al. (31)	RCT comparing infant formula with short-chain and long-chain oligosaccharides + fermented formula (scGOS/lcFOS + FER), compared with only fermented formula or scGOS/lcFOS with no fermented formula. Younger than 28 d and followed for 17 wk	432 healthy non-breastfed infants (median age 4 d, range 0–28 d)	The fermented formula with scGOS/lcFOS + FE decreased the incidence of infant colic (8%) compared with short chain GOS-long chain FOS (20%) or fermented formula (20%) alone. There was also a reduction in crying episodes per day (median 2.64 vs 3.38 crying episodes, $P = 0.030$).
Infant regurgitation				
Smaller and frequent feedings	Jadcherla et al. (40)	Symptomatic dysphagic neonates underwent evaluation for suspected GER using pH-impedance methods. Comparisons were made between the first, second, and third postprandial hour	35 neonates (mean 30 ± 4.9 wk)	There were decreased amounts of gastroesophageal reflux (GER) events with more frequent feedings, longer feeding duration, and slower feeding rate. Prolonged feeding duration was significantly associated with decreased total, nonacid GER, and Bolus Clearance Time (BCT) ($P < 0.03$). Significant positive correlations ($P < 0.05$) were detected between feeding flow rate vs frequency of total, nonacid GER, and BCT. Significant positive correlation ($P = 0.002$) was noted between feeding volume and BCT. BCT decreased with each hourly interval (ANOVA $P < 0.05$)

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Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
Thickening of formula by adding cereal, cornstarch, or other products	Salvatore et al. (46)	Meta-analysis of 14 RCTs with a parallel or crossover design that compared thickened formula with either carob-bean gum (7 trials), cornstarch (3 trials), rice starch (2 trials), cereal (1 trial), and soy fiber (I trial) with standard formula	877 infants with regurgitation (birth to 24 mo)	There was a significant decrease in regurgitation in those with thickened formula; this ranged from 0.6 to 1.8 episodes per day in a pooled analysis of 369 infants (47). However, there does not seem to be a positive effect on other nonregurgitation-related symptoms, such as irritability, improved sleeping, cough, and choking (8,36,46,47). No particular thickening agent was shown to be more effective than another (46).
		Other comments		Systematic reviews and multiple controlled trials have shown that, compared to the standard formula, adding thickening agents to a formula may result in a significant decrease in the prevalence of regurgitation (8,47).
Use of commercially available thickened antiregurgitation formulas	Hegar et al. (45)	RCT comparing standard formula (group A) vs home-thickened formula (group B) vs commercially thickened with bean gum (group C) for 1 mo	Infants with regurgitation (n = 60; mean age 47.1 ± 17.7)	The regurgitation decreased significantly in the 3 groups ($P <$ 0.0005). The largest decrease was in group C (−4.2 + 2.1/d), but it did not differ between groups.
	Savino et al. (121)	RCT comparing of formulas containing partially hydrolyzed whey protein, modified vegetable oil with a high beta-palmitic acid content, prebiotic oligosaccharides, and starch given for 14 d	168 infants with regurgitation	The thickened formula with partially hydrolyzed whey showed significantly reduced regurgitation by 1.1 and 1.3 episodes per day after 7 and 14d compared with a standard formula.
	Vandenplas et al. (48)	RCT comparing antiregurgitation formula with nonhydrolyzed protein, locust bean gum, or whey hydrolysate locust bean gum	115 infants with regurgitation (mean age 9.1 wk, range 2 wk–5 mo)	Showed a significant decrease in regurgitation in both groups, which decreased from 8.25 to 2.32 in the nonhydrolyzed group and to 1.89 in the hydrolyzed group, $P = 0.001$.
		Other comments		In a recent systematic review there was a significant reduction ($P < 0.05$) in the daily number of episodes of regurgitation in infants who were fed rice, corn, and locust bean gum AR formula from a mean of 5.4 to 2.5 episodes per day over a period of 1–4 wk (46).
Comparison between home thickening vs commercial formulas	Penna et al. (122)	Case-controlled study giving antiregurgitation (AR) formula vs homemade thickening with cornstarch for 4 mo	100 infants with regurgitation (neonates to 12 mo)	There was no difference ($P > 0.05$) in regurgitation when comparing both arms. Overall, the regurgitation disappeared after 3 mo in a slightly higher percentage of infants (52% vs 40%) who were fed AR formulas ($P > 0.05$).
Elimination of cow's milk protein	Omari et al. (53)	Elimination of cow's milk protein (mothers of breastfed infants eliminated cow's milk, soy, and eggs from their diets, while non-breastfed infants switched to an aminoacid based formula) for 3 d. Those who responded were then followed by an RCT to 2 rechallenges with or without cow's milk protein for 7 d	50 infants with regurgitation and pain (mean age 13 ± 7 wk)	Fourteen infants (28%) were diagnosed with cow's milk allergy (CMA). In the group with CMA, elimination diet significantly improved reflux symptoms (difference in the IGERDQ score of −8; $P < 0.003$), esophageal clearance (difference of −14 min; $P = 0.05$), % acid exposure (difference in −2% pH time < 4%; $P = 0.04$), and baseline indirect parameters of esophageal function and mucosal integrity.

Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
		Other comments		There are no RCTs evaluating extensively hydrolyzed or amino acid-based formulas. When modified diets have been used, it has been shown that vomiting frequency decreases significantly (usually within 2 wk) after the elimination of cow's milk protein from maternal diet, and reintroduction causes recurrence of symptoms (8,36,52,53)
Pain-predominant DGBIs				
Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet	Chumpitazi et al. (79)	RCT crossover trial comparing low FODMAP diet vs traditional American childhood diet (TACD) × 48 h	33 children with IBS (mean age 11.5 3.0 yr; range 7–17 yr)	Less frequent abdominal pain occurred during a low FODMAP diet (1.1 + 0.2 [SEM] episodes per day vs 1.7 + 0.4 in the traditional American childhood diet: TACD); $P < 0.05$. Compared with baseline (1.4 + 0.2), children had fewer daily abdominal pain episodes during the low FODMAP diet ($P < 0.01$) but more episodes during the TACD ($P < 0.01$).
	Dogan et al. (80)	RCT comparing a low FODMAP diet vs general protective standard dietary advice × 2 mo	60 children with IBS (mean age 13.4 ± 2.6; range 6–18 yr)	The mean decrease in VAS pain score after 2 mo of diet was 3.80 ± 1.10 in the low-FODMAP group vs 2.03 ± 1.03 in the standard group ($P < 0.05$).
	Boradyn et al. (81)	RCT comparing a low FODMAP diet vs National Institute for Health and Care Excellence (NICE) guidelines diet x 4 wk.	27 children (mean age of 8.2; range 4–12 yr of age) with functional abdominal pain	There was no improvement vs baseline in abdominal symptoms noted in the low FODMAP diet group (abdominal pain intensity 1.18 [0.79–2.32] before and 1.29 [0.46–1.54] after). Those on a NICE diet (n = 14) vs baseline did have a significant decrease in abdominal symptoms (1.45 [0.64–1.86] before and 0.56 [0.32–0.68] after; $P = 0.001$); however, there was no overall difference at the end of the study comparing both groups.
Fiber supplementation	Feldman et al. (88)	RCT comparing soluble corn fiber (10 g) with placebo: 2 wk baseline, followed by 2 wk of intervention	52 children with functional abdominal pain (mean 9.3 yr, range 5–15 yr)	Children taking a soluble corn fiber (10 g) showed a greater improvement in pain 13/26 (50%) vs 7/26 (27%) controls ($P < 0.04$).
	Christensen et al. (87)	RCT comparing ispaghula husk (5 mL) BID vs placebo for 7 wk	40 children with functional abdominal pain (range 3–15 yr)	There was no difference in the number of episodes of abdominal pain.
	Romano et al. (90)	RCT comparing partially hydrolyzed guar gum (5 g/d)	60 children with functional abdominal pain disorders (mean age 12.8 yr; 8–16 yr)	Those on fiber had a higher response (43 vs 5%; $P = 0.025$). It was also more effective in reducing clinical symptoms with modification of the Birmingham IBS score (median 0 ± 1 vs 4 ± 1, $P = 0.025$) in intensity of abdominal pain assessed with the Wong-Baker Face Pain Rating Score and in normalization of bowel habit evaluated with the Bristol Stool Scale (40% vs 13.3%, $P = 0.025$).

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Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
	Horvath et al. (89)	RCT comparing glucomannan (2.52 g/d) vs placebo for 4 wk	84 children with functional abdominal pain (mean age 7–17 yr) (11.3 ± 2.5 yr)	Treatment success was similar in the glucomannan (n = 41) and placebo (n = 43) groups with no pain (12/41 vs 6/43), respectively (RR = 2.1, 95% CI: 0.87–5.07), and treatment success (23/41 vs 20/43; RR = 1.2, 95% CI: 0.79–1.83).
	Shulman et al. (91)	RCT comparing psyllium (6 or 12 g based on age) vs placebo: 2 wk baseline followed by 6 wk of intervention	86 children with IBS (mean 13.3 + 3 yr; range 7–18 yr)	Those on psyllium had a significant reduction in the frequency of abdominal pain (mean reduction of 8.2 + 1.2 after receiving psyllium vs mean reduction of 4.1 + 1.3 after receiving placebo; $P = 0.03$).
		Other comments		Of 5 RCTs, 3 have shown an improvement in abdominal pain (88,90,91) while 2 did not show any benefit (87,89). Those which demonstrated benefit provided ≥5 g/d of soluble fiber.
Lactose challenge studies	Lebenthal et al. (82)	RCT of three 6-wk crossover periods of baseline diet and milk intake, chocolate cow's milk or chocolate soy milk.	38 children with functional abdominal pain (range 6–14 yr)	No significant difference with 14/38 having worsening of pain with lactose-containing diet challenge vs 11/38 having worsening of pain on nonlactose-containing formula. The elimination of lactose did not affect the overall frequency of improvement in recurrent abdominal pain. In addition, the recovery rate from recurrent abdominal pain was similar in both lactose absorbers and nonabsorbers independent of dietary restrictions.
	Dearlove et al. (83)	RCT comparing a lactose-containing drink or placebo for 2 wk	39 children with abdominal pain (mean age 10.6 ± 2.6 yr): 21 received lactose and 18 placebo	There was no difference in the number of children claiming relief from the placebo or lactose-containing preparation and no relationship with the results of the lactose breath test.
	Gremse et al. (123)	RCT crossover design comparing lactose-hydrolyzed or lactose-containing milk for 14 d.	30 children (3–17 yr) with abdominal pain	There was a significant increase in abdominal pain experienced by study participants during the lactose ingestion period when compared with the lactose-free period.
Fructose-free diet	Wirth et al. (85)	RCT comparing a fructose-restricted diet vs no dietary intervention for 2 wk.	103 children with abdominal pain (3–16 yr, median 88.8 yr): 51 fructose-restricted and 52 controls.	Significant decrease in the pain score from a median 5.5 to 4 in those on fructose-restricted diet vs no significant change in the other group B (5.3 to 5). There was no difference in pain frequency.
Lactase administration	Medow et al. (86)	RCT crossover trial giving lactase (vs placebo) tablets before a lactose challenge for 2 wk	18 children with lactose intolerance (11.4 ± 4.3 yr)	Those on lactase had a significant decrease in clinical symptoms including bloating, diarrhea, abdominal pain, and flatulence.
Functional constipation				
Extra fluid intake	Young et al. (98)	RCT comparing 3 groups: 50% increase in water intake, hyperosmolar (>600 mOsm/L) supplemental fluid and normal fluid intake for 3 wk	108 children, 2–12 yr	There was similar stool frequency for the 3 groups. There were no other differences.

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Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
Fiber	Chmielewska et al. (109)	RCT comparing glucomannan (2.52 g/dL) vs placebo for 4 wk	80 children with constipation (mean age 6.1 ± 3.3 yr, range 3–16)	No difference in treatment success comparing both groups (56% vs 58%; $P > 0.99$ 95% CI 0.95 0.6–1.4). No difference in stool frequency or presence of abdominal pain.
	Karagiozoglou-Lampoudi et al. (108)	RCT comparing physician advice to increase fiber with intervention by a dietitian	86 children with constipation (mean age 4.4 yr, range 1–11 yr)	There was improved fiber consumption and a long-term adherence (1 mo) to a high-fiber diet when constipated children and their parents were guided by either a pediatrician or a dietician. However, the study did not provide information on whether an increase in dietary fiber was related to an improvement in symptoms of constipation.
	Ustundag et al. (110)	RCT comparing hydrolyzed guar gum vs lactulose for 4 wk	61 patients (age 4–16 yr)	BM frequency increased from 4.0 ± 0.7 to 5.0 ± 1.7 in the guar gum group and from 4.0 ± 0.7 to 6.0 ± 1.1 in the lactulose group ($P < 0.05$) but no difference between groups.
	Kokke et al. (111)	RCT comparing different fiber mixtures vs lactulose for 8 wk	147 children with constipation (mean age 5.5; range 1–12 yr).	No difference was observed in defecation frequency (7 times per week in the fiber group vs 6 in the lactulose group; $P = 0.48$) and fecal incontinence (9/42 vs 5/55 patients, $P = 0.084$; stool consistency was lower in the lactulose group, $P = 0.01$).
	Quitadamo et al. (112).	RCT comparing a mixture of fiber (acacia fiber, psyllium fiber, and fructose) vs PEG base solutions for 8 wk	100 children with constipation (mean age SD: 6.5 2.7 yr)	77.8% of children treated with fiber and 83% of children treated with PEG had improved ($P = 0.788$). The mean BM frequency was 5.6 + 1.9 vs 5.8 + 2.0; $P = 0.621$.
	Castillejo et al. (114)	RCT comparing cocoa husk supplementation vs placebo for 4 wk	56 children with constipation (mean 6.6) (2.3 yr; 3–10 yr)	The total colonic transit time decreased in the cocoa group by 45.4 + 38.4 h and by 8.7 + 28.9 h in the placebo group ($P = 0.15$). At the end of the intervention, 41.7% and 75.0% of the patients who received cocoa husk supplementation or placebo, respectively, reported having hard stools ($P = 0.17$). No difference was found in improvement in defecation frequency between the intervention and placebo groups (6.16 + 3.35 vs 5.08 + 2.1 BM per week; $P = 0.7$).
		Other comments		A meta-analysis of 8 studies (9) including 615 children with functional constipation evaluated the effect of glucomannan (109), hydrolyzed guar gum vs lactulose (110) (61 patients), Fructo-oligosaccharides (124), and different fiber mixtures (111,112) compared with other laxatives or placebo. None of the included studies found a difference in success or improvement of defecation parameters compared with either laxative treatment or placebo.

SPECIAL SECTION

Table 1. (*continued*)

Category	Study	Design	Population sample size	Findings
Cow's milk elimination	Iacono et al. (125)	RCT crossover trial comparing cow's milk vs soy for 2 wk	65 children with constipation (34.6 + 17.1 mo; 11–72 mo)	68% responded while on soy milk. The response was confirmed by a double-blind challenge with cow's milk. Response was defined as 8 or more BM during the treatment period.
	Dehghani et al. (126)	RCT comparing cow's milk-free diet vs cow's milk diet for 4 wk	70 patients with constipation were included (mean 4.6 ± 2.7 yr, 1–13 yr).	There was an 80% vs 47% response when comparing cow's milk-free diet vs control; in 42% of responders, constipation returned after challenge with cow's milk.
		Other comments		A recent meta-analysis showed that children on cow's milk-free diet had a significantly higher defecation frequency and softer stools compared with those receiving a diet containing cow's milk (9). These variables changed significantly after 8 wk of an oligoantigenic diet (96).

BM, bowel movement; CI, confidence interval; PEG, polyethylene glycol; RCT, randomized controlled trial; RR, relative risk; GOS, galacto-oligosaccharides; FOS, fructo-oligosaccharides; lcFOS, long chain fructo-oligasaccharides; scGOS, small chain galacto-oligosaccharides; FER, fermented.

of cow's milk by breastfeeding mothers may be indicated in infants who have not responded to conventional therapies.

PAIN-PREDOMINANT DISORDERS OF GUT-BRAIN INTERACTION

The pediatric pain-predominant DGBIs affect approximately 13.5%–15.8% of children worldwide (3,54,55). There are several inter-related factors playing a role in an individual, including psychosocial distress, visceral hypersensitivity, gut microbiome, and diet (3,6,56–70). Diet is an important perceived inducer of gastrointestinal symptoms in children with DGBIs, and 92%–93% of those with irritable bowel syndrome identify at least 1 type of food trigger which exacerbates their symptoms (57,58) and a higher median number of foods causing gastrointestinal symptoms (58,59).

Children with food-induced symptoms report reduced daily intake of overall calories, fat, and lactose (57) and use several coping strategies including consuming smaller portions, modifying foods, not eating even when hungry, and avoiding offending foods (57–59). In children with irritable bowel syndrome, an increasing number of self-perceived food culprits are associated with more severe gastrointestinal symptoms such as more frequent abdominal pain episodes; increased pain intensity; decreased quality of life, including interference with school performance, sports, and social activities; and psychosocial abnormalities (somatization, anxiety, and functional disability) (58,59).

Several pathophysiologic mechanisms may play a role in symptom generation. For example, in children with functional dyspepsia, the feeling of bloating, fullness, and nausea correlates with the amount of gastric food retention (62,63). However, a strong relationship between gastric accommodation abnormalities and meal-induced gastrointestinal symptoms has not been identified (71).

The type of food, in particular carbohydrates, may also affect symptom generation (65). There are several factors associated with symptom generation with carbohydrates including (i) the amount ingested, (ii) ingestion with a meal, (iii) small intestinal enzymatic activity (e.g., disaccharidases), (iv) consuming the carbohydrate with microorganisms capable of metabolizing it, (v) the gut microbiome, and (vi) other host factors such as visceral hypersensitivity (6). Several large studies have identified biopsy-based disaccharidase deficiencies in children with DGBIs (66,67,72,73). However, currently missing in those with identified disaccharidase deficiencies are evaluations of specific postprandial gastrointestinal symptoms or responses to dietary therapies.

The gut microbiome composition of children also differs from that of adults and is dependent on dietary intake and other environmental factors (69,74). Growing evidence suggests that it plays a role within the paradigm of food-induced gastrointestinal symptoms (75). It has also been shown that subsequent changes in gut microbiome composition after a dietary challenge may also relate to food-induced symptoms (70).

Dietary therapies for children with pain-predominant DGBI

Although not supported by RCT evidence, given a relationship of symptoms to gastric emptying, clinical practice recommendation for children with functional dyspepsia is often to administer a low-fat diet and frequent meals (3) (Tables 1 and 2 and Figure 1).

Low FODMAP diet. FODMAP carbohydrates include fructose, lactose, fructo-oligosaccharides (e.g., inulin), galacto-oligosaccharides, and polyols (76). Uncontrolled studies have identified improvement using a low FODMAP diet in children with pain-predominant DGBIs ranging from 50% to 79% (77,78). Two RCTs have identified amelioration of gastrointestinal symptoms using a low FODMAP diet vs either traditional diet or general protective standard diet (79,80). A small RCT did not identify a difference in abdominal pain frequency comparing a low FODMAP diet vs a National Institute for Health and Care Excellence diet (which also restricts fermentable carbohydrates) (81).

Single carbohydrate restriction. Lactose restriction is often used and is supported by several uncontrolled studies. However, most

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Table 2. Expert recommendations for dietary interventions for children with DGBIs

Infant colic	
Non-breastfed infants	There is limited evidence that using hypoallergenic formulas provide improvement. In intractable patients, a 2–4-wk trial of eliminating cow's milk protein may be indicated (10).
Breastfed infants	Breastfeeding should be continued. There is limited evidence that shows that using hypoallergenic diets in mother's produce decreased colic in infants. There is limited evidence that shows that elimination of other dietary compounds including FODMAPs from the maternal diet may be effective. In intractable patients, a 2-wk trial of eliminating cow's milk protein from mother's diet may be tried (2,10,26,27).
Infant regurgitation	
	Avoid overfeeding.
	Use smaller and more frequent feeding.
Non-breastfed infants	Thickening: Thickening of formula has been shown to be effective to decrease regurgitation, but its effect on nonregurgitation symptoms is not clear (8,36,52,53). Feedings can be thickened with the addition of nutritional supplements such as cereal, cornstarch, bean gum, fiber, soybean polysaccharides or the use of commercially available formulas. No thickening method has been shown to be more effective than another. Commercially available formulas have a controlled composition that maintains approved levels of viscosity, osmolality, and caloric density. When thickeners are added at home, exact instructions need to be given to caregivers to avoid complications.
	Elimination of cow's milk protein: There is limited information that elimination of cow's milk protein by changing the formula can be effective. However, in those children with cow's milk intolerance, an elimination diet is effective. Given the difficulty to establish which patients have cow's milk protein intolerance, in intractable patients, a 2–4-wk trial of eliminating cow's milk protein with the use of a hypoallergenic formula (extensively hydrolyzed or amino acid-based formula in formula-fed) may be tried (8,36,52,53). Thickened formulas are usually reserved for "happy" spitters, and formulas with protein changes for those infants with distress.
Breastfed	Cow's milk elimination: Elimination of cow's milk protein in breastfeeding mothers has been shown to be effective. A 2–4-wk trial of withdrawal of all dairy products, including casein and whey, from the mother's diet is recommended (8,36,52,53).
Pain-predominant DGBIs	
Irritable bowel syndrome/functional abdominal pain	There is evidence to support fiber supplementation using a soluble fiber (e.g., psyllium) with a dosage >5 g/d (88,90,91). There is limited evidence that the use of a low FODMAP diet may be effective (79). The evidence for a low FODMAP diet is stronger than for lactose or fructose-only restriction. Limited evidence supports the use of lactase enzyme supplementation.
Functional constipation	
	No evidence that a high-fiber diet is beneficial (9,127,128) In intractable infants, a cow's milk-free diet may be beneficial particularly in preschool children and in children with a personal or family history of atopy or with a previous diagnosis of cow's milk protein allergy (9,115,128).
Important considerations	
	Avoid nutritional deficiencies. Before prescribing a restrictive diet, a careful evaluation of the patient is needed to avoid the induction or exacerbation of maladaptive responses, disordered eating, or avoidant and restrictive disorders (118).

DGBI, disorder of gut-brain interaction; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyol.

RCTs evaluating lactose challenges in children with pain-predominant DGBIs have been negative (82,83).

Several pediatric uncontrolled studies suggest that a fructose-restricted diet may be helpful (84). One prospective RCT compared a two-week fructose-restricted diet vs no dietary intervention (85). Those on the fructose-restricted diet had less severe pain without a decrease in pain frequency (85).

Enzyme supplementation. Administering lactase tablets before a lactose challenge decreased bloating, diarrhea, abdominal pain, and flatulence (86).

Fiber supplementation. Five fiber supplementation RCTs, each using different fibers and/or amounts, have been conducted (87–91). The 3 RCTs which demonstrated improvement in gastrointestinal symptoms provided ≥5 g per day of soluble dietary fiber.

Nonceliac gluten sensitivity. A study to determine the prevalence of nonceliac gluten sensitivity in children with pain-predominant DGBIs found that of 1,114 children without celiac disease or wheat allergy, 96% did not have a correlation of symptoms with gluten ingestion (92). Of the remaining 36 children with potential gluten sensitivity, only 11 (comprising <1% of the entire cohort) ultimately met double-blind placebo-controlled criteria for gluten sensitivity (92). Controlled long-term gluten-free diet studies in children with DGBIs without celiac disease or wheat allergy remain to be completed. In addition, studies related to whether fructans rather than gluten induce symptoms in children with DGBIs with suspected nonceliac gluten sensitivity remain to be completed (92).

FUNCTIONAL CONSTIPATION

Functional constipation is a common condition in all pediatric age groups with a worldwide prevalence that varies from 3.0% to 14.4% (1–5,55,93). Although a clear explanation for this variation is lacking, dietary factors, different toileting behaviors, and other cultural-dependent differences in parent-child interactions may be contributing.

Defecation frequency and stool consistency of young infants are influenced by their feeding mode. Breastfed infants pass more frequent and softer stools than formula-fed infants, and breastfeeding is considered to prevent constipation (94,95). During infancy feeding, changes such as the transition from breastfeeding to formula feeding or the introduction of solid foods often trigger the onset of functional constipation (95).

The pathophysiology of constipation is multifactorial. Common factors include diet, physical activity, psychological disorders, colonic sensorimotor disturbances, and pelvic floor dysfunction (2,94–96).

Dietary therapies for children with functional constipation

Many healthcare professionals recommend dietary changes as a first step in the management of children with constipation (94) (Tables 1 and 2 and Figure 1).

Fluid intake. Insufficient fluid intake or excessive fluid loss due to severe diarrhea, vomiting, or fever may lead to the hardening of stools (97). This applies particularly to infants, who are more susceptible to dehydration because of their small body weight and high turnover of fluids. Increasing fluid intake may soften stools. However, most colonic fluids are not ingested from the diet but are the result of intestinal secretion, and only a small portion of the fluids present in the colon are retained in the stools. One RCT assessing extra fluid intake in children with functional constipation showed insufficient evidence for a beneficial effect (98). Therefore, current pediatric guidelines for functional constipation do not recommend increasing fluid intake (94,99). An exception should be made for the extra fluid that is required for certain medications to be taken, such as polyethylene glycol. Indeed, a higher defecation frequency was reported in children treated with polyethylene glycol during a period of high fluid intake, as compared with a period with lower fluid intake (100).

Westernized diet. The highest prevalence of childhood constipation is found in Western countries and the lowest in Asian countries (5). These data might suggest a potential role for the Western-type diet (i.e., high in saturated fat, sugar, dairy, and processed food and low in dietary fiber) (101). The Western diet is correlated with higher rates of overweight/obesity, although there are conflicting results on the association between excessive body weight and constipation in children (102). Therefore, the potential contributions of the Western diet on constipation need to be further defined.

Fat intake. Olive oil is sometimes recommended to act as a lubricant and stool softener in infants and toddlers with constipation. However, triglycerides are almost completely absorbed in the small intestine and are therefore not likely to affect stool consistency or colonic transit. Therefore, except for children with malabsorption, olive oil does not reach the colon to be able to exert a laxative effect (103).

Fiber intake. Fiber is an essential nutrient in the human diet that is crucial for human health (103–105). Several studies from all parts of the world have shown that children consume an insufficient amount of dietary fiber (94,105,106). However, RCTs and meta-analyses have failed to show a benefit to the addition of fiber compared with placebo or laxatives (9,94,105,107–114).

A number of new prebiotic-fiber combinations provide some promising results. Further well-designed high-quality RCTs are needed before additional fiber intake can be recommended (9). Adding certain fibers to the diet may increase abdominal pain and flatulence, but the symptoms often decrease after several days. Sometimes gaseousness can be reduced by switching to another fiber supplement (9).

Cow's milk avoidance. Scientific evidence regarding a causal relationship between functional constipation and CMA is controversial. In those who may have food allergy-related constipation, studies show that there is an increase in both rectal mast cell density and spatial interactions between mast cells and nerve fibers that correlate with anorectal motor abnormalities (96).

A review of 10 studies reported that a diet free from cow's milk resulted in an improvement in functional constipation in 28%–78% of children, with the first 3 years of life being the most affected age group (115). Meta-analysis evaluating cow's milk-free diet showed a significant effect of the cow's milk-free diet on treatment success and a significant improvement in stool frequency and consistency. The effect is particularly seen in preschool children and in children with a personal or family history of atopy or with a previous diagnosis of cow's milk protein allergy. The current European and North American pediatric gastroenterology society functional constipation guidelines recommend that a 2- to 4-week trial of cow's milk avoidance should be reserved for children who do not respond to conventional treatment (94).

ADDITIONAL PEDIATRIC CONSIDERATIONS

Although dietary interventions may be helpful, it should be noted that using them for the management of DGBIs can have inadvertent side effects. Given the importance of nutrition in child growth and development, care to provide sufficient calories and nutrients when making dietary changes is paramount. This applies not only to restrictive diets where specific nutrients are being eliminated (116) but also when nutritional supplementation is being added, such as when a formula is being thickened. Given the varying nutritional needs based on the age and sex of children, a registered dietitian with pediatric expertise is an integral member of the healthcare team.

Besides malnutrition, dietary advice needs to take into account the child's psychosocial context. Young children are essentially completely dependent on caregivers for their dietary intake. Parental control of dietary intake diminishes as the child increases in age and reaches adolescence. Interventions, particularly in adolescents, should consider taking into account the child's perceived needs.

It should be noted that abnormal eating (e.g., excessive caloric restriction) can lead to debilitating GI symptoms. Given the need to consider a normal adaptive response to avoid foods that are perceived to trigger DGBI symptoms, determining when eating behaviors become disordered in a child, in particular an adolescent, can be challenging (117). Therefore, a careful assessment of the child and family's situation and dietary intake needs should be performed before dietary interventions are recommended. The recommendations to start a restrictive diet may be inappropriate when excessive food restriction is already taking place (117,118).

Recent information also suggests that there is overlap between patients with avoidance restrictive feeding disorder and DGBI both in adults and adolescents (118). In a recent study of pediatric patients with DGBIs aged 6–18 years, avoidance restrictive feeding disorder symptoms were present in 23%, and most frequently motivated by fear of aversive consequences, similar to findings in adults (118). Currently, there are no simple methods to differentiate between both, and the approach to treatment is different (117,118).

CONFLICTS OF INTEREST

Guarantor of the article: Samuel Nurko, MD, MPH.
Specific author contributions: S.N., M.A.B., T.S., and B.P.C.: planning of the article, drafting the article, and reviewing and approving the final draft of the article.
Financial support: None to report.
Potential competing interests: M.A.B.: Consultant for Danone, FrieslandCampina, Sensus, United Pharmaceuticals and HIPP; B.P.C.: Receives royalties from the Rome Foundation for the use of the modified Bristol Stool Scale for Children; T.S.: No disclosures; S.N.: Consultant for Allergan and IHS.

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SPECIAL SECTION