UNIVERSITY OF NAPLES FEDERICO II

PH.D. PROGRAM IN

CLINICAL AND EXPERIMENTAL MEDICINE

CURRICULUM IN TRANSLATIONAL PEDIATRIC SCIENCES

XXX Cycle

(Years 2014-2017)

Chairman: Prof. Gianni Marone

PH.D. THESIS

Insights on Functional Gastrointestinal Disorders in Children: Pathogenesis, Prevalence, and Clinical Management

TUTOR

Prof. Annamaria Staiano

PH.D. STUDENT

Dr. Elena Scarpato

INDEX

❖ **Chapter 1**
Background and Aims of the Study Project **Page 4**

❖ **Chapter 2**
The origins of Functional Gastrointestinal Disorders

2.1 *Exploring hypotheses and rationale for causes of infantile colic* **Page 7**
Publication **Page 11**

❖ **Chapter 3**
Definition and diagnosis of Functional Gastrointestinal Disorders: the Rome Criteria and the Optimization of Clinical Trials

3.1 The Mediterranean-European Area Project on Functional Gastrointestinal Disorders

3.1.1 *Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area* **Page 22**
Publication **Page 25**

3.1.2 *Functional Gastrointestinal Disorders: Prevalence study in Children and Adolescents in the Mediterranean part of Europe* **Page 30**
Publication **Page 33**

3.2 *Functional Chronic Constipation: Rome III Criteria versus Rome IV Criteria* **Page 40**
Publication **Page 42**

3.3 *Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique.* **Page 55**
Publication **Page 58**

❖ **Chapter 4**
Treating Functional Gastrointestinal Disorders

4.1 *Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants* **Page 68**
Publication **Page 71**

❖ **Chapter 5**

Conclusive Remarks **Page 77**

❖ **Chapter 6**

References **Page 78**

❖ **Chapter 7**

Other Publications **Page 84**

❖ **Chapter 8**

Curriculum Vitae **Page 96**

Chapter 1

- Background and Aims of the Study Project –

Functional gastrointestinal disorders (FGIDs) include a combination of chronic or recurrent gastrointestinal symptoms not explained by known biochemical or structural abnormalities (1). FGIDs are multifactorial conditions and several pathophysiological mechanisms appear to contribute to their onset. The most widely accepted pathophysiological hypothesis is the "biopsychosocial model" that involves interactions between an altered physiology (e.g., GI motility disturbances, and visceral hyperalgesia), and psychosocial factors that, via the gut-brain axis, cause the occurrence of GI symptoms in genetic susceptible subjects. However, the precise pathogenetic mechanism leading to the onset of FGIDs has not yet been clarified.

Due to the lack of specific markers, FGIDs are currently diagnosed according to the Rome criteria. The Rome criteria are intended as a guide for the clinician, since they provide a standardized definition and classification for FGIDs. The first meeting of the paediatric working team was held in Rome in 1997, seven years after the publication of the first classification for adult FGIDs, and led to the drafting of the first paediatric classification (1); since then, the Rome criteria have been regularly updated (2, 3).

In accordance to the Rome criteria, FGIDs can be divided into two main groups: FGIDs of the neonate/toddler, and FGIDs of the child/adolescent (Table 1). The advantage of using the Rome criteria in the clinical practice is that they allow a "positive" approach to the patient, avoiding unnecessary tests to rule out an organic cause, with a consequent beneficial effect on both patient's health and healthcare costs. In fact, FGIDs are associated with significant costs: only in the US, from 1997 to 2009, the number of discharges with a primary diagnosis of FGIDs has risen, and the total mean cost per discharge increased from $6.115 to $18.058 (4). In addition, a recent study from Hoekman et al. confirmed that FGIDs, and in particular functional abdominal pain disorders, represent a huge economic burden for the society, with an estimated annual cost/patient of €2.512,

with half of the costs consisting of inpatient/outpatient healthcare use, and one-fourth of the costs related to parental productivity loss (5).

One of the difficulties in the clinical management of FGIDs is that usually, due to the severity and recurrence of the GI symptoms, there is a reluctance of the family to accept a "positive" diagnosis. This leads to a continue searching for an organic cause by consulting multiple referrals and looking for additional investigations. This kind of approach is unfavourable, not only in terms of costs, but especially for the patient's perspective. In fact, it has been demonstrated that the execution of several negative clinical tests and non-acceptance of medical reassurance tend to perpetuate the disease in the child (6).

Another problem related to the management of FGIDs is that, in spite of the Rome criteria, diagnostic approach to FGIDs still varies widely among different countries, due to several factors, including cultural customs. Currently, in many countries the diagnosis of FGIDs is still considered an exclusion diagnosis, inferred after several inappropriate investigations and medical visits, with high burden in terms of patient's anxiety and healthcare costs, due to the abovementioned reasons.

Over the last years, interest in the study and recognition of FGIDs in children has increased. Nevertheless, despite some promising developments, more research is needed to further understand the pathophysiology and treatment of these conditions that remain one of the great challenges in modern paediatric gastroenterological practice.

Given these premises, the main aims of the present Ph.D. thesis were:

1. to evaluate the current diagnostic-therapeutic approach to FGIDs;

2. to define the prevalence of FGIDs in the Mediterranean part of Europe;

3. to improve and standardize clinical trials in FGIDs.

Table 1. Rome IV classification of Childhood Functional Gastrointestinal Disorders

FUNCTIONAL GASTROINTESTINAL DISORDERS: NEONATE AND TODDLER
Infant regurgitation
Infant rumination syndrome
Cyclic vomiting syndrome
Infant colic
Functional diarrhea
Infant dyschezia
FUNCTIONAL GASTROINTESTINAL DISORDERS: CHILD AND ADOLESCENT
Functional nausea and vomiting disorders
Cyclic vomiting syndrome
Functional nausea and functional vomiting
Rumination syndrome
Aerophagia
Functional abdominal pain disorders
Functional dyspepsia
Irritable bowel syndrome
Abdominal migraine
Functional abdominal pain-not otherwise specified
Functional defecation disorders
Functional constipation
Nonretentive faecal incontinence

Chapter 2

- The origins of Functional Gastrointestinal Disorders –

2.1 *Exploring hypotheses and rationale for causes of infantile colic*

Infantile colic (IC) is one of the most frequent FGIDs of the neonate/toddler, with an estimated prevalence ranging from 5% to 28%, accounting for 10–20% of all the paediatric visits of infants aged 2 weeks to 3 months (7). IC is characterized by paroxysms of irritability and inconsolable crying and typically presents in the second or third week after birth, with a peak at 5–8 weeks of age; it usually resolves spontaneously by 4 months of age. Currently, diagnosis of IC is based on the Rome IV criteria, that include all of the following, in infants from birth to 5 months of age: a) paroxysms of irritability with fussing or crying that start and stop without obvious causes; b) symptoms lasting ≥3 hours/day and occur ≥3 days a week for at least 1 week; c) no failure to thrive.

Infantile colic is usually benign and self-limiting, in fact an organic cause for the clinical manifestations is found in less than 5% of the infants (8). Pathogenesis of IC, as most FGIDs, is still unclear and has been associated with different factors, such as allergy to cow's milk proteins, alterations in gut hormones and intestinal microflora, behavioral problems (e.g. parental anxiety), increasing maternal age, and maternal smoking (9). It has also been hypothesized that IC represents the last stage of the physiological "crying curve" of the development of healthy infants (7). Taking into account all these factors, it is not surprising that actual therapeutic options for IC are non-specific and not driven by substantial data.

Since there is still an unmet clinical need, as current treatments are not efficacious, we decided to review the literature on the current management of IC, including nutritional options, prebiotics, probiotics, and synbiotics.

Nutritional Modifications

The literature regarding nutritional changes in IC management is extensive, with numerous studies evaluating the efficacy of hydrolysed formulas in bottle-fed infants, or low-allergen maternal diets in

breastfed infants. Several studies demonstrated an effect of hydrolysate milk on infant distress and crying time (10-12). Nevertheless, for all these studies the level of evidence is low, due to weak methods, unclear randomization procedure, incomplete reporting of the data, or unmasked blinding. For this reason, the recommendation is to avoid changes in the type of formula, if the child is thriving. However, based on clinical reasoning, in a selected subset of formula-fed infants (e.g. children with atopy), a trial with a hypoallergenic formula may be an effective treatment for IC (13, 14). In addition, the use of a low-lactose or a high-fibre formula is not supported by evidence of sufficient quality, while soy-based formulas are not recommended during the first 6 months of life due to the high phytoestrogens content that may affect long- term reproductive health (15)

Pharmacological Approaches to IC

Several medications have been proposed for the treatment of IC, such as simethicone, dicyclomine hydrochloride, or cimetropium bromide. However, due to the uncertain efficacy for the management of IC, and considering the reported side effects for some of them (e.g. dyspnea, respiratory collapse, apnoea, and asphyxia reported for dicyclomine), pharmacological treatment is not recommended for the management of colicky infants.

Behavioral Approaches to IC

Manipulation of the vertebral column is not recommended, due to the lack of evidence on effectiveness and safety (a case of death after manipulation of the cervical and thoracolumbar spine is reported). The level of evidence regarding the effectiveness of increase carrying, reduce stimulation of the child, and avoid lifting and patting the baby is low.

In summary, none of the currently available treatments for the management of IC appears to be effective, also because of a lack of uniformity in the definitions of IC, primary outcomes and instruments used in the different intervention trials. For this reason, we then decided to examine also the evidence available for three hypothetical mechanisms that could be involved in the etiology of IC: immaturity of GI motility, immaturity of bile acids absorption with subsequent alteration of

absorptive mechanisms, and alterations in the microbiome. The understanding of these potential mechanisms could allow the development of new therapeutic strategies for IC.

Immaturity of the Intestinal Motility

Considering the evidence of a transient dysregulation of small intestinal motility, that depends on both the extrinsic and enteric neural control, it is possible that immaturity of the enteric nervous system during development may cause intestinal hypermotility and contribute to the development of IC (16, 17).

Bile Acid Immaturity

Several elements of the enterohepatic circulation are altered in the neonate, such as:

a) levels and composition of the bile in the GI tract and in the serum, with serum concentrations of bile acids that increase gradually reaching a peak at 1 month of life, and slowly decrease starting from 5 months of age (18-20);

b) immaturity of the alternative pathway of bile acids synthesis, with a higher cholic acid (CA) to cheno-deoxycholic acid (CDCA) ratio and a higher glycine/taurine ratio (21). Interestingly, there is a decline in the ratios of CA/CDCA and of glycine/taurine conjugate in most infants within 4–5 months of age, which corresponds to the timing of resolution of IC;

c) immaturity in the intestinal absorption of bile salts, with an impairment of the enterohepatic circulation that allows the passive absorption of a fraction of bile salts with subsequent loss of part of the pool, that may contribute to the steatorrhea and "diarrhea" of the newborn (22, 23);

d) steatorrhea in the neonatal period, that often occurs during the first month of life (24).

The presence of steatorrhea and the alterations in bile acids can regulate the composition of the gut microbiome (25).

Alterations of the Gut Microbiome

It has been demonstrated that colicky infants are more frequently colonized with *Clostridium difficile* during the time of colic than age-matched controls; this difference disappears by the age of 3 months, even if stool fatty-acid profiles between the infants who had suffered from severe colic compared to

control infants are still different (26). Moreover, faecal samples of infants with IC have higher counts of coliform bacteria and lower counts of lactobacilli compared with children not suffering from colic (27, 28).

In conclusion, the immaturity in hepatic synthesis, intraluminal levels, and intestinal absorption of bile acids in the neonate could result in malabsorption of fat, with a potential secondary effect on the gut microbiome composition. The alterations in the colonic microbial flora may result in an increased nutrient fermentation and reduced levels of dehydroxylated bile acids with a subsequent effect on colonic contractile activity (29).

The results of this review on therapeutic options and new pathogenetic hypotheses for IC have been published in *Neurogastroenterolgy and Motility* in 2017.

Received: 17 June 2016 | Accepted: 19 August 2016

DOI: 10.1111/nmo.12943

REVIEW ARTICLE

WILEY Neurogastroenterology & Motility NGM

Exploring hypotheses and rationale for causes of infantile colic

M. Camilleri[1] | S.-Y. Park[1] | E. Scarpato[2] | A. Staiano[2]

[1]Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

[2]Department of Translational Medical Science, Section of Pediatrics, University "Federico II", Naples, Italy

Correspondence
Michael Camilleri, MD, Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA.
Email: camilleri.michael@mayo.edu

Abstract

Background: Infantile colic is a frequent problem in neonates and infants. This review addresses current management including the results for nutrient modifications; soy-based formulas; and prebiotics, probiotics, and synbiotics.

Purpose: Given the evidence that there is still an unmet clinical need, as current treatments are incompletely efficacious, we have examined the evidence around three hypothetical mechanisms that could potentially be involved in etiopathogenesis of infantile colic: immaturity of bile acid mechanisms that alter intraluminal and absorptive mechanisms, immaturity in motility and alterations in the microbiome. Understanding these potential mechanisms may lead to the introduction of diagnostic procedures that should enhance the selection or individualization of therapy for infantile colic.

KEYWORDS
formulas, nutrition, prebiotics, probiotics, synbiotics

1 | DEFINITION, CRITERIA, AND CAUSES OF INFANTILE COLIC

Infantile colic (IC) often results in excessive crying and accounts for 10–20% of pediatrician visits of infants aged 2 weeks to 3 months.[1] In 2001, it was reported to cost the United Kingdom National Health Service in excess of £65 million per year.[2] Infantile colic is a syndrome characterized by paroxysms of irritability and inconsolable crying and screaming, accompanied by clenched fists, drawn-up legs, and a red face. It presents typically in the second or third week after birth, and peaks at 5–8 weeks of age; it usually resolves spontaneously by 4 months of age. The prevalence is estimated to be between 5% and 28%.[1] The currently used diagnostic criteria for IC are the Rome IV criteria, which include all of the followings: (i) paroxysms of irritability with fussing or crying that start and stop without obvious causes; (ii) symptoms lasting ≥3 hours a day and occur ≥3 days a week for ≥1 week; (iii) absence of failure to thrive, in infants from birth to 5 months of age.[1] These criteria are adapted from the "Rule of Three" originally proposed by Wessel et al.[3]: 3 hours per day, ≥3 days per week, ≥3 weeks. An underlying organic cause for the colic is found in less than 5% of these infants. Thus, it is usually benign and self-limiting.[4] Pathogenesis of IC is still unclear, but it has been associated with different causes, such as alterations in intestinal microflora and gut hormones, gas production, allergy to cow's milk proteins, behavioral problems (e.g. family tension and parental anxiety), increasing maternal age, first born status and maternal smoking.[5] Moreover, it is also possible that IC represents the last stage of the physiological developmental "crying curve" of healthy infants, with no evidence that the crying is caused by pain in the abdomen or any other part of the body.[1] Given these diverse associations, it is not surprising that treatment is non-specific and not driven by data.

2 | CURRENT APPROACHES TO TREATMENT OF IC

In this section, we will summarize the findings of several systematic or narrative reviews that evaluated the different types of pharmacological, nutritional, and behavioral interventions available for the treatment of IC. The role of probiotics, prebiotics, and synbiotics is discussed in the section on the hypothesis of alterations in the microbiota.

3 | PHARMACOLOGICAL APPROACHES

Hall et al.[5] and Lucassen[6] systematically reviewed literature on treatments for IC. Considering pharmacological treatment, two different randomized controlled trials (RCTs) found no difference when simethicone, which prevents gas bubbles from forming in the gastrointestinal tract, was compared to placebo.[7, 8] On the contrary, one RCT found simethicone to be effective in the management of crying attacks.[9] Nonetheless, this study was of poor-quality and the definition of colics was not clear.[6] Regarding dicyclomine hydrochloride, an anticholinergic agent with a relaxing effect on smooth muscle, two different RCTs[10, 11] found favorable results on crying time. However, due to reported side effects, such as dyspnea, respiratory collapse, apnea, asphyxia, pulse rate fluctuations, and muscular hypotonia, this drug is not approved for use in infants younger than 6 months of age.[5] Finally, the last drug assessed for the management of IC is cimetropium bromide, a muscarinic antagonist with direct spasmolytic activity. There is only one RCT available, and the authors describe a significant decrease in the duration of colic episodes with cimetropium bromide compared to placebo.[12] However, an increase in sleepiness is reported, and the level of evidence is poor because of methodological fails.[6] Due to the uncertain efficacy for the management of IC and considering the possible adverse effects, this drug has never been approved for use in the U.S. and Canada. In conclusion, pharmacological treatment is not recommended for the management of infants with colics.

4 | NUTRITION MODIFICATION

Numerous studies have evaluated the efficacy of hydrolyzed formulas in bottle-fed infants or low-allergen maternal diets in breastfed infants. The effect of casein hydrolysate milk has been evaluated in several studies. In a recent review, Lucassen[13] identified two RCTs that demonstrated an effect of this intervention on infant distress and crying time. The first study from Hill et al.[14] compared the effects of maternal hypoallergenic diet/casein hydrolysate formula to standard care (breast milk or cow's milk formula), and found a significant reduction in infants' distress level in the active diet group compared to the standard care group. In the second study,[15] Arikan et al. found that an hydrolyzed formula administered for 7 days was effective in reducing the duration of crying in colicky infants, compared with baseline. Nevertheless, for both studies, the level of evidence is very low, due to weak methods or incomplete reporting of the data.[13] Moreover, a study by Jakobsson et al.[16] highlighted a reduction in crying duration using two types of casein hydrolyzed formulas vs cow's milk formula, while Forsyth[17] found no significant difference between casein hydrolysate and cow's milk formula. In addition, for these two last studies the level of evidence is poor due to unclear randomization and lack of calculation of patients needed to treat.[5]

Similarly, another RCT[18] compared whey hydrolysate milk to cow's milk formula, and showed a reduction in crying from baseline. Yet, the quality of evidence is low due to unmasked blinding. Another study[19] highlighted a reduction in the number of colic episodes using a partially hydrolyzed whey formula with oligosaccharides, B-palmitic acid, and low lactose. Nevertheless, the presence of several modified ingredients makes it difficult to evaluate the effects of whey hydrolysate alone.[5]

Considering all the aforementioned evidence, the recommendation is to avoid changes in the type of formula if the child is thriving. However, in a selected subset of formula-fed infants, such as children with atopy, a trial with a hypoallergenic formula may be an effective treatment for IC,[20, 21] though it is important to highlight that this suggestion is not based on evidence from RCTs, but on clinical reasoning.[13]

The benefits of soy-based formulas in treatment of IC are not supported by evidence of sufficient quality.[13] In addition, due to the high phyto-estrogen content that may affect long-term reproductive health, soy-based formulas are not recommended for use in healthy infants and should not be used during the first 6 months of life, as stated by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition.[22]

The use of low-lactose milk or high-fiber formula is ineffective and is not supported by evidence of sufficient quality.[5, 13]

4.1 | Summary of nutrition modification

Changes in infant formula are often tried based on assumption that there may be intolerance or allergy, but this is seldom present, and it is important to emphasize avoiding changes in the type of formula if the child is thriving and only consider a hypoallergenic formula if there is evidence of atopy.

5 | BEHAVIORAL APPROACHES

Chiropractic manipulation helps some patients, but may be no more effective than a nurse's cuddling for 10 minutes. In a meta-analysis, when combining only those trials with a low risk of such performance bias, the results of manipulation did not reach statistical significance.[23]

Key Points

- Infantile colic, typically manifested as excessive crying in infants, accounts for 10-20% of pediatrician visits of infants aged 2 weeks to 3 months
- The published literature (including systematic reviews) on therapy for infantile colic reveals significant unmet needs despite the use of specialty nutrition, milk formulas, prebiotics, probiotics, and synbiotics
- There is evidence in support of three mechanisms for infantile colic which are related to the transient immaturity of intestinal functions: the enterohepatic functions and bile acid homeostasis, gastrointestinal motility, and the colonic microbiome. Further integrated studies of these mechanisms are recommended to find novel approaches for diagnosis and therapy of this common and distressing condition.

Moreover, a case of death after manipulation of the cervical and thoracolumbar spine in a 3-months-old infant is reported. For this reason, considering the lack of evidence of safety and effectiveness, manipulation of the vertebral column is not recommended.[13]

The advice to increase carrying,[24] to reduce stimulation of the child by not lifting and patting the baby,[25] to use a car ride simulator or the counseling of the mother about specific management techniques[26] are not proven to be effective, and the level of quality of evidence is low.[13]

6 | SUMMARY OF THE EVIDENCE

It is important to highlight that a recent systematic review from Steutel et al.[27] showed a general lack of agreement about definitions, primary outcome measures, and instruments used in intervention trials on IC. Therefore, this lack of uniformity makes it difficult to evaluate and compare the results of the different trials. Even with the limitations associated with the lack of uniformity, the systematic analyses of the trials generally reach the same conclusion, that is, that none of the currently available treatments appears to be effective in the management of IC. For this reason, given the unmet clinical need, we explored alternative hypotheses that could lead to the identification of the mechanism(s) of IC, and may lead to opportunities for individualizing treatment of IC in the future.

7 | HYPOTHESES

Given the prevailing timing of IC, which presents typically in the second or third week after birth, peaks at 5–8 weeks of age, and usually resolves spontaneously by 4 months of age, we explored three hypotheses:

Firstly, immaturity of hepatic synthesis, reduced intraluminal levels of bile acids, and impaired ileal absorption of bile acids in the neonate result in malabsorption of fat and other nutrients, with potential for secondary effects on colonic microbial flora.

Secondly, the colonic microbial flora are abnormal and result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon.

Thirdly, immaturity of the enteric nervous system (ENS) leads to abnormal motor and sensory functions of the intestine and colon.

Overall, the literature provides evidence for interaction among these three mechanisms, and this review highlights the interplay among these mechanisms and the potential for their identification that may lead to novel approaches to the management of IC.

8 | LITERATURE SUPPORTING THE HYPOTHESIS OF BILE ACID IMMATURITY

There are several elements in the enterohepatic circulation that are immature in the neonate, based on animal and human studies. The evidence is summarized here:

8.1 | Abnormal levels and composition of bile in the alimentary tract and serum

Reductions in bile salt pool size, synthesis, and intestinal concentrations have been demonstrated in neonates[28,29]; maturity may be influenced by dexamethasone or phenobarbital administered to the mother prior to delivery. In addition, Kawasaki et al.[30] showed that serum concentrations of primary and total bile acids increased gradually in the neonatal period, with peak serum levels reached at 1 month of age, with predominance of primary serum bile acids by 3 months of age, with a significant increase in the primary total bile acid ratio by 5 months of age and declining to the ratios observed in adults by 4–6 years of age.

8.2 | Fasting duodenal aspirate bile acid

Measurements of fasting duodenal aspirate bile acid showed higher cholic acid (CA) to chenodeoxycholic acid (CDCA) ratio and higher glycine to taurine conjugates of the bile acids (both being 3-alpha-hydroxy bile acids) at younger postnatal age in human milk-fed preterm infants.[31] These data suggest immaturity in the alternative pathway of bile acid synthesis, which requires 27 alpha hydroxylase steps in the biosynthesis from cholesterol. In addition, the increased glycine conjugation suggests failure of peroxisomal function, as the normal ratio of conjugates is 3:1 (glycine to taurine). Interestingly, there is a decline in the ratio of CA to CDCA and glycine to taurine conjugate ratio in most infants within about 4–5 months, which corresponds to the timing of resolution of IC.

8.3 | Fetal gallbladder bile

Profiles (collected postmortem) of fetal gallbladder bile are similar to those in the intestine with the exception of sulfate conjugates[32] and the proportion of deoxycholic acid (DCA). Thus, one study noted that DCA was notably absent from the bile of infants and some children,[33] and this may suggest that the dehydroxylation of CA by colonic bacteria may have contributed to the absence of DCA in the gallbladder bile; however, this was based on bile from gallbladders obtained postmortem from 30 human subjects rather than from otherwise healthy subjects.

The significance of this finding relative to intestinal colic is unclear, although studies in infants and children with inborn errors of bile acid metabolism (such as defects in amidation) may present with fat-soluble vitamin deficiency[34] and illustrate the potential role of immaturities in bile acid synthesis in the neonate.

8.4 | Immaturity in hepatic synthesis of bile acids

Immaturity in hepatic synthesis of bile acids is supported by evidence of abnormal levels of nuclear receptors in developing rat hepatocytes.[35] Thus, bile acid transporters (FXR, PXR, LXR-alpha, PPAR-alpha, RAR-alpha, LRH1, and SHP) involved in bile acid formation are poorly developed in the fetal stage, but their expression gradually

matures postnatally and reaches adult levels by 4 weeks of age. This immaturity of hepatic synthesis might therefore be a factor in the IC observed in the first 4 weeks postnatally, but may be one of the factors that initiates the cascade of events leading to IC observed after 4 weeks of age.

8.5 | Immaturity in intestinal absorption of bile salts

In a series of landmark studies, Lester et al. investigated immaturity in intestinal absorption of bile salts. They showed that the ileal mechanism for active transport of taurocholate was undeveloped in the fetus and newborn infant, leading to the conjecture that enterohepatic circulation of bile salt during the perinatal period is limited to that fraction of bile salt absorbed passively, thus resulting in loss of bile salt from the immature intestine that may contribute to steatorrhea and to the "diarrhea" of newborn infants[36, 37]; similar findings were observed in dogs.[38] Lester[39] drew attention to the analogy between immaturity of bilirubin conjugation and excretion in neonatal jaundice that resolves itself in a few days, and immaturity in bile acid production and function, that resolves in a few weeks.

8.6 | Steatorrhea in neonatal period

Watkins et al.[40] reported that total fecal lipid excretion is normal in infants 3–11 days and 23–72 days of age (n=4 in each group, median 11.65 g [IQR 7.65, 17.2] in neonates, 6.6 [5.7, 15.9] in older infants, *P*=.49); however, they demonstrated that, the presence of increase in neutral fecal lipid (e.g. monoglycerides) in neonates may reflect either defective lipolysis in newborn infants (which may result in insufficient lipid micellization and/or mucosal transport for optimal lipid absorption) or colonic bacterial hydrolysis of triglycerides.[40]

In addition, steatorrhea often occurs during the first month, and decreases during the first postnatal month (as shown by the fall in the steatocrit curve from 7th to 28th day) and, by 45 days, few babies have steatorrhea.[41]

In the next section, we discuss the potential relationship between changes in bile acids and the microbiome, to which one can also add the potential that steatorrhea in the neonate could result in additional perturbation that may lead to IC, for example in the presence of high concentrations of fatty acids or bile acids in the infant's colon. Although such studies have not been conducted in infants or children, it has been demonstrated in adults that higher concentrations of long chain and short chain fatty acids, and even relatively low concentrations of the bile acid, CDCA (1 mM infused into the distal colon), can induce high amplitude propagated contractions[42, 43] that are frequently sensed or may be associated with pain.

9 | LITERATURE SUPPORTING MICROBIAL ALTERATIONS IN THE NEONATE

Immediately after birth, a diverse flora of staphylococci, streptococci, enterococci, and enterobacteriaceae colonizes the sterile gut. Anaerobic colonization occurs in the second day of life starting with bifidobacteria.[44] Infants receive their 'original inoculum' of bacteria prenatally with the transfer of bacteria through umbilical blood, by contact with vaginal and intestinal microbiota during birth and by skin contact and milk during breast-feeding. This colonization may be essential for the maturation of the gut-associated lymphoid tissue, and intestinal epithelial homeostasis.[44–46] In 14 healthy, full-term infants followed from birth to 12 months of age, the composition of the microbiota varied widely from baby to baby, but within an individual baby, there were recognizable features of the microbial community for months, and the intestinal microbiota began developing toward an adult profile 5 days after birth and had evolved toward the characteristics of the adult gastrointestinal microbial profile by 1 year of age.[47] Nevertheless, more recent studies showed that the adult GI microbial profile is not yet reached by 1 year of age.[48, 49] Two important principles regarding the gastrointestinal microbiota in infants are the transfer from mother to infant during the perinatal period[50] and adaptation to the specific environment of the child, as demonstrated by comparisons of the gut microbiota of 6-month-old infants who were breast-fed and received an age-appropriate diet typical for each area living in rural Malawi (higher proportions of *Bifidobacteria* and *Bacteroides/Prevotella* group bacteria) compared to urban Finland (*Clostridium perfringens* and *Staphylococcus aureus*).[51] While both the type of feed and the mode of delivery at the birth of the infant have major impact on gut microbiome, the literature does not provide strong evidence that infants that are breastfed compared to formula fed, or those born by vaginal delivery compared to Caesarian section have differences in the prevalence of infantile colic.

9.1 | Association of changes in microbiota and IC

In earlier studies, colicky infants were more frequently colonized with *Clostridium difficile* during the time of colic than were the age-matched controls; this difference disappeared by age 3 months, when it was noted that stool fatty-acid profiles were different between the infants who had suffered from severe colic and the control infants. The fatty-acid profiles were also influenced by the age of the infant, the mode of delivery, antimicrobial drugs taken by the mother during delivery, and breast-feeding and type of feeding.[52] Fecal samples were found to have higher counts of coliform bacteria and lower counts of lactobacilli in infants with colic symptoms compared with children not suffering from colic[53, 54]; moreover, different colonization patterns of lactobacilli were found among colicky and healthy infants: *Lactobacillus brevis* and *L. lactis* were found only in colicky infants, whereas *L.acidophilus* was found only in healthy infants.[55] Interestingly, *L. delbrueckii* subsp. delbrueckii DSM 20074 and *L. plantarum* MB 456 had antimicrobial effects against six species of gas-forming coliforms isolated from colicky infants.[56] These interesting studies on different *Lactobacillus* species need replication by other research groups.

In other studies, *Klebsiella* species were more prevalent in colic patients than in control patients, whereas *Enterobacter/Pantoea*

species were detected only in the control patients; in the same study, fecal calprotectin levels were twofold higher in infants with colic than in control infants.[57] The proportion of *Bifidobacterium* counts to total bacterial counts and to a lesser extent, the frequency of *Lactobacillus* spp. at the age of 3 weeks were inversely associated with the amount of crying and fussing during the first 3 months.[58] A probiotic *Bifidobacterium breve* B632 species inhibited growth of gas-forming Enterobacteriaceae in fecal microbiota cultures from a colicky infant.[59]

Using phylogenetic microarray for studying the human gastrointestinal microbiota (the human intestinal tract chip [HITChip] assay), infants with colic showed lower microbial diversity and stability than control infants in the first weeks of life; there were also differences in the abundance of certain bacteria at 2 weeks suggesting that microbial signatures may explain the colic phenotype.[60] The colic phenotype correlated positively with specific groups of proteobacteria, including bacteria related to *Escherichia*, *Klebsiella*, *Serratia*, *Vibrio*, *Yersinia*, and *Pseudomonas*, but negatively with bacteria belonging to the Bacteroidetes and Firmicutes phyla. The latter phyla include some lactobacilli and canonical groups known to produce butyrate and lactate.[61]

It has been postulated that early increased levels of pathogenic bacteria and reductions of lactobacilli, bifidobacteria or butyrate-producing bacteria produce intestinal pain and inflammation in the infant, and that this in turn causes excessive crying.[62]

9.2 | Trials of prebiotics, probiotics and synbiotics in IC

Given the potential effects of prebiotics, probiotics, and synbiotics on intestinal motility and sensory neurons, contractile activity of the intestine, anti-inflammatory effects and alterations of the microbiome, several studies have explored their potential clinical benefit (Tables 1 and 2)[63–71] and have also been evaluated in three recent systematic reviews.[72–74] Although *Lactobacillus reuteri* may be effective as a treatment strategy for crying in exclusively breastfed infants with colic, the evidence supporting probiotic use for the treatment of IC or crying in formula-fed infants remains unresolved. The administration of *L. reuteri DSM 17938* at a dose of 10^8 CFU once a day appears to reduce crying times in infants with IC, especially in exclusively or predominantly breastfed infants.[72–74] Nevertheless, these industry-sponsored trials require replication, particularly in formula-fed patients.

9.3 | Relationship of microbiome to bile acids

Perturbations of the microbiota shape the bile acid pool and modulate the activity of bile acid-activated receptors. Bile acids, in turn, can also regulate the composition of the gut microbiome at the highest taxonomic levels.[75] Several molecules made or modified by the microbiota including short-chain fatty acids, succinate, mucin O-glycans, secondary bile acids, and the AI-2 quorum sensing auto-inducer affect the growth and virulence of pathogens.[76]

10 | LITERATURE SUPPORTING IMMATURITY OF INTESTINAL MOTILITY IN NEONATE AND INFANCY

There is evidence of transient dysregulation of the repertoire of small intestinal motility that facilitates normal propulsion and depends on the function of the extrinsic and enteric neural control. Thus, it is postulated that immaturity of the ENS during development may cause intestinal hypermotility in infants with colic, particularly during the first few weeks of life. There are no formal motility studies to support abnormal gastrointestinal motility in patients with infant colic; the circumstantial evidence supporting this hypothesis is based on the evidence of immaturity of normal patterns of motility in prematurity and neonates, and evidence of postnatal, delayed maturation of interstitial cells of Cajal (pacemakers in the intestine) in cases of neonatal pseudo-obstruction.[77]

In the following sections, we review the normal development of the neural control of gut motor functions [reviewed in detail elsewhere[78]], abnormal motor repertoire associated with prematurity, and potential therapeutic approaches to normalize the dysfunction.

10.1 | Ontogeny of neural control of intestinal motility

The ENS develops in utero by migration of neural crest cells to the developing alimentary canal. The ENS cells are derived from precursor cells from three axial levels of the neural crest. Vagal neural crest cells from the developing hindbrain colonize the gut by migration in a rostro-caudal direction; whereas, enteric neurons arrive in the hindgut from the lumbosacral level via a caudo-rostral wave of colonization. Movement of the neural crest cells through the gut mesenchyme, survival in the gut, and differentiation into mature cells are influenced by the microenvironment within the developing gut. Thus, migration of neural crest cells and the sequence of innervation of different levels of the gut are regulated by specific signaling molecules that include transcription factors, neurotrophic factors (e.g., the glial-derived neurotrophic factor and its receptor subunits), and the neuregulin signaling system. These facilitate the growth, differentiation, and persistence of the migrating nerve cells once they arrive in the gut. Neuregulins are structurally related signaling proteins, which are likely to have important roles in the development, maintenance, and repair of the nervous system and other selected tissues.

10.2 | Evidence of immature small intestinal motility

The Berseth group conducted an extensive series of studies of antral and small intestinal motility in preterm and term infants.[79–82]

10.2.1 | Duodenal motility patterns

In preterm and term infants, dudodenal motility patterns differ. Intestinal motor characteristics are more immature in preterm than

TABLE 1 Trials with *L. reuteri* strains in infantile colic

Author, year (ref. no)	Type of study/study population/intervention	Outcomes	Results
Savino et al. 2007 (69)	• Prospective, open-label, randomized controlled trial • 83 breastfed infants • *L. reuteri* ATCC 55730 (10^8 CFU), once a day for 28 days vs simethicone (60 mg/day), twice a day for 28 days	• Reduction in daily average crying time	• Significant reduction in daily median crying times in probiotic group vs simethicone group at day 28 ($P<.001$)
Savino et al. 2010 (96)	• Randomized, double-blind, placebo-controlled trial • 46 exclusively breastfed infants • *L. reuteri* DSM 17938 vs placebo, once a day for 21 days	• Primary outcome: reduction in average crying time on day 21 • Secondary outcomes: number of "responders" (those who experienced a decrease in the daily average crying time of 50% from baseline) in each group on days 7, 14, and 21; effects on the intestinal microbiota	• Significant reduction in daily median crying time in the probiotic group vs placebo group ($P=.22$), at day 21 • Significantly higher number of responders in the probiotic group compared with placebo group, at times 7, 14, and 21 ($P=.006$, $P=.007$, and $P=.36$, respectively) • Significant increase in fecal *Lactobacilli* ($P=.002$), and reduction in fecal *Escherichia coli* in the probiotic group ($P=.001$). No differences in *Bifidobacteria* and *C. butyricum*
Szajewska et al. 2013 (71)	• Randomized, double-blind, placebo-controlled trial • 80 exclusively or predominantly (>50%) breastfed infants • *L. reuteri* DSM 17938 (10^8 CFU) vs placebo, once a day for 21 days	• Primary outcomes: "treatment success" (reduction in the daily average crying time ≥50%) at days 7, 14, 21, and 28; duration of crying (minutes/day) • Secondary outcomes: reduction in daily average crying time; persistence of IC after the intervention; parental perception of colic severity; parental/family quality of life	• Treatment success significantly higher in the probiotic group vs the placebo group, at all time points ($P<.05$) • Significant reduction in median daily crying time in the probiotic group at days 14, 21, and 28 ($P<.0001$) • Significant reduction in parental perception of colic severity, and improved parental/family quality of life in the probiotic group compared with the placebo group ($P<.0001$).
Sung et al. 2014 (70)	• Randomized, double-blind, placebo-controlled trial • 167 breastfed or formula-fed infants • *L. reuteri* DSM 17938 (10^8 CFU) vs placebo (maltodextrin), once a day for 28 days	• Primary outcome: daily duration of cry or fuss at 1 month • Secondary outcomes: duration of cry or fuss episodes; number of cry or fuss episodes; sleep duration of infants; maternal mental health; family functioning; parents quality of life; infants functioning; infant fecal microbiota; calprotectin levels	• At 1 month, the probiotics group cried or fussed 49 minutes/day more than the placebo group ($P=.02$). Difference mainly due to more fussing in the probiotic group ($P=.002$) • No significant difference in all secondary outcomes
Chau et al. 2015 (63)	• Randomized, double-blind, placebo-controlled trial • 52 exclusively breastfed infants • *L. reuteri* DSM 17938 (10^8 CFU) vs placebo, once a day for 21 days	• Primary outcome: reduction in the duration of average crying and fussing times, from baseline to day 21, to <3 hours/day • Secondary outcomes: number of "responders" to treatment (those who experienced a decrease in the daily average crying and/or fussing time ≥50% from baseline) on days 7, 14 and 21	• Total average crying and fussing times shorter in the *L. reuteri* group vs the placebo group ($P=.028$) • Significantly greater reduction in daily crying and fussing times in the probiotic group vs placebo group ($P=.045$), at the end of the treatment
Mi et al. 2015 (67)	• Randomized, single-blind, placebo-controlled trial • 39 exclusively or predominantly breastfed infants • *L. reuteri* DSM 17938 (10^8 CFU) vs placebo, once a day for 28 days	• Primary outcome: "treatment success" (reduction in the daily average crying time ≥50%) • Secondary outcomes: mean reduction in daily average crying time, parental satisfaction, and reduction in maternal depression	• Treatment success in 100% of the probiotic group vs 15.7% of placebo group ($P<.01$), at the end of the treatment period • Significant reduction in daily crying time in the probiotic group ($P<.01$) • Significant improvement of parental satisfaction and maternal depression ($P<.01$)

CFU, colony forming unit.

TABLE 2 Trials with *L. rhamnosus GG*, prebiotics and synbiotics in infantile colic

Authors, year (ref. no)	Type of study/study population/ intervention	Outcomes	Results
Dupont et al. 2010 (64)	• Randomized, multi-center, double-blind, placebo-controlled trial • 66 formula-fed infants • Experimental formula (enriched with alpha-lactalbumin, *L. rhamnosus*, *Bifidobacterium infantis*, reduced in protein and lactose contents, and thickened with corn starch) vs control formula	• Effects on crying, irritability, and agitation without crying duration • Effects on regurgitation, flatulence/gas, and vomiting	• No differences between the two groups for crying duration • Feeding-related GI side effects were significantly lower with the experimental formula (P=.01)
Partty et al. 2013 (68)	• Randomized, double-blind, placebo-controlled trial • 94 preterm infants • Prebiotic mixture of galacto-oligosaccharides and polydextrose 1:1 (600 mg/day) vs *L. rhamnosus* GG ATCC 53103 (10^9 CFU) vs placebo (microcrystalline, cellulose, and dextrose anydrate), once a day from days 1 to 30 and twice a day from days 31 to 60	• Effects on infant crying, fussing, and irritability, and on microbiota development	• Significantly less frequent excessive criers in the prebiotic and probiotic groups vs the placebo group (P=.02) • Higher proportion of *Lactobacillus-Lactococcus-Enterococcus* group relative to total bacterial count in stools of excessive criers vs contented infants (P=.005) • Lower proportion of *Clostridium histolyticum*-type bacteria to total bacterial count in the fecal samples of probiotic group compared to the prebiotic and placebo groups (P=.047)
Giovannini et al. 2014 (65)	• Randomized, double-blind, parallel group trial • 199 breastfed infants and 163 formula-fed • Formula-fed infants randomized to either control formula or a GOS-supplemented formula (0.4 g/100 mL)	• Effects on GI symptoms (colic, stool consistency and frequency, regurgitation) • Effects on the intestinal microbiota	• Supplemented group normal and soft stools in 89% of the episodes; significantly lower incidence of colic • Supplemented group had lower count of *Clostridium* and higher count of *Bifidobacterium* compared to the control group
Kianifar et al. 2014 (66)	• Randomized, double-blind, placebo-controlled trial • 50 breastfed infants • Synbiotic mixture (1 billion CFU of seven probiotics: *L. casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *B. infantis*, *L. Bulgaricus*; and fructo-oligo-saccharides) vs placebo, once a day for 30 days	• Primary outcome: "treatment success" (reduction in the daily average crying time >50%) • Secondary outcomes: symptom resolution (reduction in daily crying time >90%); duration of colic (minutes/day); weight	• Treatment success higher in the synbiotic group compared with placebo group, at days 7 (P<.005) and 30 (P<.01) • Symptom resolution higher in the synbiotic group vs the placebo group at day 7 (P<.03) but not at day 30

CFU, colony forming unit.

term infants; clustered phasic contractions occur more frequently and are of shorter duration and lower amplitude. Duodenal clusters are significantly less common, but their amplitudes increase with increasing gestational age.[81]

10.2.2 | Antral motility

Antral motility consists of isolated single contractions and clustered phasic contractions in term and preterm infants, with no differences in the occurrence or amplitude of antral activity between the two groups of infants and with no change in antral motor activity with advancing gestational age.[79] The proportion of antral clusters that was temporally associated with duodenal activity was significantly lower in preterm infants than in term infants (P<.001). Moreover, the degree of association of antral and duodenal activity increased significantly with gestational age.

These data show that fasting antral motor activity is comparable in preterm and term infants, and the temporal coordination of antral and duodenal activity develops in association with progressive changes in duodenal motor activity in the preterm infant. One way to enhance the functional maturation of these motor functions is enteral feeding. Thus, early-fed infants were able to tolerate full oral nutrition sooner, had fewer days of feeding intolerance, and had shorter hospital stays in preterm infants.[81] This is also achieved with intragastric feeding,[79] and the effect is specific for motor, rather than mucosal, maturation.[82] In part, this maturation is also enhanced by the postnatal development of gut neuroendocrine signals.[80] Thus, fasting plasma gastrin and peptide YY levels were low in the preterm human (n=19) and canine neonate during the first postnatal week, but the plasma levels of both increased with postnatal age. Motor quiescence during fasting (in contrast to the excessive incoordinated contractile activity manifested as clustered phasic contractions) becomes a more prominent

feature of newborn intestinal motor functions postnatally.[75] The inhibition of this contractile activity appears to coincide with the level of peptide YY, which generally reduces contractile activity and is a major factor in mediating the ileal brake in the mature gut.[83,84] Conversely, the motilin receptor agonist, erythromycin, is able to induce phase III migrating motor complexes after 32 weeks' gestation, suggesting that early use of erythromycin as a prokinetic agent may not be useful in early preterm infants, may be partially useful in older preterm infants, and may be most useful in full-term infants.[85] Finally, the relevance of the maturation of the motor repertoire is confirmed by experience showing that assessment of intestinal motility serves as a useful clinical guide in the feeding management of the newborn.[86] These observations provide the basis for the hypothesis that enteric motor immaturity may conceivably result in infantile colic.

11 | THERAPEUTIC OPPORTUNITIES FOR IMMATURITY OF MOTOR FUNCTION

The extrinsic parasympathetic and sympathetic nerves serve to modulate the preprogrammed functions controlled by the ENS. The peristaltic reflex involves an afferent component that is mediated by intrinsic primary afferent neurons, ascending contractions (e.g., cholinergic and tachykininergic neurons), and descending relaxation (nitrergic or vasoactive intestinal peptidergic neurons). The observation of normal variability in heart rate in children with colic suggests that extrinsic parasympathetic control of viscera is normal.[87] Overall, the hypothesis that IC may be a disorder of gastrointestinal motor function requires further support through measurements of motility in infants with IC. Meanwhile, the studies of the ontogeny of the enteric neural control and maturation of the repertoire in small intestinal motility provide support for the concept that dysregulation and immaturity of intestinal motility contribute to the development of infantile colic.[88, 89]

Irrespective of the precise mechanism, there appears to be incoordination or spasm of intestinal motility, and this has led to the use of antispasmodic drugs, such as dicyclomine[11] or cimetropium bromide,[12] which are generally muscarinic cholinergic antagonists. In addition, development of interdigestive migrating motor complexes appears to be associated with relief of colic. Such complexes are associated with high motilin levels.[90, 91] Beneficial effects are reported with some herbal teas, such as fennel, lemon balm and chamomile, or with phytotherapeutic agents,[92, 93] though the mechanisms and potential effects of all of these therapies on motor incoordination are unclear.

12 | POTENTIAL INTERACTIONS BETWEEN THREE HYPOTHETICAL MECHANISMS IN INFANTILE COLIC AND CONCLUSION

Overall, the literature provides evidence for interaction among these three mechanisms, and this review highlights the interplay among these mechanisms and the potential for their identification that may lead to novel approaches to the management of infantile colic.

The immaturity of hepatic bile acid synthesis, intraluminal levels, and ileal absorption of bile acids in the neonate result in malabsorption of fat, with potential for secondary effects on colonic microbial flora. The latter changes may result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon, where the contractile activities may be significantly altered, based on studies of the effects of primary (dehydroxylated) bile acids in the human adult colon exposed to estimated loads of ~1 mM chenodeoxycholate.[43] These levels are likely to be achieved in the neonatal colon. However, no such studies are available to assess whether the immaturity of the ENS and the increase in intracolonic bile acid and fat content increases the propensity to abnormal motor and sensory functions of the intestine and colon in the neonate or infant with IC. Further research on these three, potentially interacting mechanisms may lead to novel approaches to more specific diagnosis and management of infantile colic. Thus, with the availability of noninvasive tests that assess hepatic synthesis of bile acids (serum 7αC4),[94] gastric emptying in neonates using breath test measurements,[95] and stool microbiome studies (including phylogenetic microarray by HITChip assay), it is conceivable that there may be opportunities for individualizing therapy based on objective biomarker(s) in infants whose colic does not respond to the customary first line therapies.

ACKNOWLEDGMENT

The authors thank Mrs. Cindy Stanislav for excellent secretarial help.

FUNDING

Dr. Camilleri is funded by grant R01-DK92179 from National Institutes of Health for studies on bile acid diarrhea.

DISCLOSURE

The authors have no relevant conflicts of interest.

AUTHOR CONTRIBUTION

MC concept of study, authorship; S-YP literature review, authorship; ES literature review, authorship; AS discussions on pediatric practice, clinical relevance, mechanisms and authorship.

REFERENCES

1. Benninga MA, Nurko S, Faure C, Hyman PE, St. James Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150:1443–1455.
2. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child*. 2001;84:15–19.
3. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics*. 1954;14:421–435.
4. Akhnikh S, Engelberts AC, van Sleuwen BE, L'Hoir MP, Benninga MA. The excessively crying infant: etiology and treatment. *Pediatr Ann*. 2014;43:e69–e75.

5. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *J Paediatr Child Health*. 2012;48:128–137.
6. Lucassen P. Colic in infants. *BMJ Clin Evid*. 2010;2010. pii: 0309.
7. Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (simethicone). *Acta Paediatr Scand*. 1985;74:446–450.
8. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics*. 1994;94:29–34.
9. Sethi KS, Sethi JK. Simethicone in the management of infant colic. *Practitioner*. 1988;232:508.
10. Hwang CP, Danielsson B. Dicyclomine hydrochloride in infantile colic. *Br Med J (Clin Res Ed)*. 1985;291:1014.
11. Weissbluth M, Christoffel KK, Davis AT. Treatment of infantile colic with dicyclomine hydrochloride. *J Pediatr*. 1984;104:951–955.
12. Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr*. 2002;34:417–419.
13. Lucassen P. Colic in infants. *BMJ Clin Evid*. 2015;2015. pii: 0309.
14. Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol*. 1995;96:886–892.
15. Arikan D, Alp H, Gözüm S, Orbak Z, Cifçi EK. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. *J Clin Nurs*. 2008;17:1754–1761.
16. Jakobsson I, Lothe L, Ley D, Boerschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr*. 2000;89:18–21.
17. Forsyth BWC. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J Pediatr*. 1989;115:521–526.
18. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. *Pediatrics*. 2000;106:1349–1354.
19. Savino F, Palumeri E, Castagno E, 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;60:1304–1310.
20. Shergill-Bonner R. Infantile colic: practicalities of management, including dietary aspects. *J Fam Health Care*. 2010;20:206–209.
21. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. *Nutrition*. 2013;29:184–194.
22. Agostoni C, Axelsson I, Goulet O, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006;42:352–361.
23. Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. *Cochrane Database Syst Rev*. 2012;12:CD004796. doi:10.1002/14651858.CD004796.pub2.
24. Barr RG, McMullan SJ, Spiess H, et al. Carrying as colic "therapy": a randomized controlled trial. *Pediatrics*. 1991;87:623–630.
25. McKenzie S. Troublesome crying in infants: effect of advice to reduce stimulation. *Arch Dis Child*. 1991;66:1416–1420.
26. Parkin PC, Schwartz CJ, Manuel BA. Randomized controlled trial of three interventions in the management of persistent crying of infancy. *Pediatrics*. 1993;92:197–201.
27. Steutel NF, Benninga MA, Langendam MW, de Kruijff I, Tabbers MM. Reporting outcome measures in trials of infant colic. *J Pediatr Gastroenterol Nutr*. 2014;59:341–346.
28. Watkins JB, Ingall D, Szczepanik P, Klein PD, Lester R. Bile-salt metabolism in the newborn - measurement of pool size and synthesis by stable isotope technic. *N Engl J Med*. 1973;288:431–434.
29. Watkins JB, Szczepanik P, Gould JB, Klein P, Lester R. Bile salt metabolism in the human premature infant. Preliminary observations of pool size and synthesis rate following prenatal administration of dexamethasone and phenobarbital. *Gastroenterology*. 1975;69:706–713.
30. Kawasaki H, Yamanishi Y, Miyake M, Mura T, Ikawa S. Age- and sex-related profiles of serum primary and total bile acids in infants, children and adults. *Tohoku J Exp Med*. 1986;150:353–357.
31. Boehm G, Braun W, Moro G, Minoli I. Bile acid concentrations in serum and duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. *Biol Neonate*. 1997;71:207–214.
32. Naritaka N, Suzuki M, Sato H, et al. Profile of bile acids in fetal gallbladder and meconium using liquid chromatography-tandem mass spectrometry. *Clin Chim Acta*. 2015;446:76–81.
33. Bongiovanni AM. Bile acid content of gallbladder of infants, children and adults. *J Clin Endocrinol Metab*. 1965;25:678–685.
34. Heubi JE, Setchell KD, Jha P, et al. Treatment of bile acid amidation defects with glycocholic acid. *Hepatology*. 2015;61:268–274.
35. Balasubramaniyan N, Shahid M, Suchy FJ, Ananthanarayanan M. Multiple mechanisms of ontogenic regulation of nuclear receptors during rat liver development. *Am J Physiol*. 2005;288:G251–G260.
36. de Belle RC, Vaupshas V, Vitullo BB, et al. Intestinal absorption of bile salts: immature development in the neonate. *J Pediatr*. 1979;94:472–476.
37. Lester R. Diarrhea and malabsorption in the newborn. *N Engl J Med*. 1977;297:505–507.
38. Lester R, Smallwood RA, Little JM, Brown AS, Piasecki GJ, Jackson BT. Fetal bile salt metabolism. The intestinal absorption of bile salt. *J Clin Invest*. 1977;59:1009–1016.
39. Lester R. Introduction. Bile acid metabolism in the newborn. *J Pediatr Gastroenterol Nutr*. 1983;2:335–336.
40. Watkins JB, Bliss CM, Donaldson RM Jr, Lester R. Characterization of newborn fecal lipid. *Pediatrics*. 1974;53:511–515.
41. Iacono G, Carroccio A, Cavataio F, et al. Steatocrit test: normal range and physiological variations in infants. *J Pediatr Gastroenterol Nutr*. 1990;11:53–57.
42. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G443–G449.
43. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. *Gastroenterology*. 1986;91:100–107.
44. Gueimonde M, Laitinen K, Salminen S, Isolauri E. Breast milk: a source of bifidobacteria for infant gut development and maturation? *Neonatology*. 2007;92:64–66.
45. Jiménez E, Fernández L, Marín ML, et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. *Curr Microbiol*. 2005;51:270–274.
46. Jiménez E, Marín ML, Martín R, et al. Is meconium from healthy newborns actually sterile? *Res Microbiol*. 2008;159:187–193.
47. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS Biol*. 2007;5:e177.
48. Hollister EB, Riehle K, Luna RA, et al. Structure and function of the healthy pre-adolescent pediatric gut microbiome. *Microbiome*. 2015;3:36.
49. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486:222–227.
50. Rautava S, Luoto R, Salminen S, Isolauri E. Microbial contact during pregnancy, intestinal colonization and human disease. *Nat Rev Gastroenterol Hepatol*. 2012;9:565–576.
51. Grzeskowiak L, Collado MC, Mangani C, et al. Distinct gut microbiota in southeastern African and northern European infants. *J Pediatr Gastroenterol Nutr*. 2012;54:812–816.
52. Lehtonen L, Korvenranta H, Eerola E. Intestinal microflora in colicky and noncolicky infants: bacterial cultures and gas-liquid chromatography. *J Pediatr Gastroenterol Nutr*. 1994;19:310–314.
53. Savino F, Cresi F, Pautasso S, et al. Intestinal microflora in breastfed colicky and non-colicky infants. *Acta Paediatr*. 2004;93:825–829.

54. Savino F, Cordisco L, Tarasco V, Calabrese R, Palumeri E, Matteuzzi D. Molecular identification of coliform bacteria from colicky breastfed infants. *Acta Paediatr*. 2009;98:1582–1588.
55. Savino F, Bailo E, Oggero R, et al. Bacterial counts of intestinal Lactobacillus species in infants with colic. *Pediatr Allergy Immunol*. 2005;16:72–75.
56. Savino F, Cordisco L, Tarasco V, et al. Antagonistic effect of Lactobacillus strains against gas-producing coliforms isolated from colicky infants. *BMC Microbiol*. 2011;11:157.
57. Rhoads JM, Fatheree NY, Norori J, et al. Altered fecal microflora and increased fecal calprotectin in infants with colic. *J Pediatr*. 2009;155:823–828.e1.
58. Partty A, Kalliomaki M, Endo A, Salminen S, Isolauri E. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. *PLoS ONE*. 2012;7:e32495.
59. Simone M, Gozzoli C, Quartieri A, et al. The probiotic *Bifidobacterium breve* B632 inhibited the growth of Enterobacteriaceae within colicky infant microbiota cultures. *Biomed Res Int*. 2014;2014:301053.
60. Rajilić-Stojanović M, Heilig HG, Molenaar D, et al. Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. *Environ Microbiol*. 2009;11:1736–1751.
61. de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. *Pediatrics*. 2013;131:e550–e558.
62. de Weerth C, Fuentes S, de Vos WM. Crying in infants: on the possible role of intestinal microbiota in the development of colic. *Gut Microbes*. 2013;4:416–421.
63. Chau K, Lau E, Greenberg S, et al. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating *Lactobacillus reuteri* DSM 17938. *J Pediatr*. 2015;166:74–78.
64. Dupont C, Rivero M, Grillon C, Belaroussi N, Kalindjian A, Marin V. Alpha-lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance. *Eur J Clin Nutr*. 2010;64:765–767.
65. Giovannini M, Verduci E, Gregori D, et al. ; PLAGOS Trial Study Group. Prebiotic effect of an infant formula supplemented with galacto-oligosaccharides: randomized multicenter trial. *J Am Coll Nutr*. 2014;33:385–393.
66. Kianifar H, Ahanchian H, Grover Z, et al. Synbiotic in the management of infantile colic: a randomised controlled trial. *J Paediatr Child Health*. 2014;50:801–805.
67. Mi GL, Zhao L, Qiao DD, Kang WQ, Tang MQ, Xu JK. Effectiveness of *Lactobacillus reuteri* in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. *Antonie Van Leeuwenhoek*. 2015;107:1547–1553.
68. Partty A, Luoto R, Kalliomaki M, Salminen S, Isolauri E. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: randomized, double-blind, placebo-controlled trial. *J Pediatr*. 2013;163:1272–1277, e1–2.
69. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics*. 2007;119:e124–e130.
70. Sung V, Hiscock H, Tang M, et al. Treating infant colic with the probiotic *Lactobacillus reuteri*: a randomised double-blind placebo-controlled trial. *BMJ*. 2014;348:g2107.
71. Szajewska H, Gyrczuk E, Horvath A. *Lactobacillus reuteri* DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo controlled trial. *J Pediatr*. 2013;162:257–262.
72. Anabrees J, Indrio F, Paes B, Al Faleh K. Probiotics for infantile colic: a systematic review. *BMC Pediatr*. 2013;13:186.
73. Harb T, Matsuyama M, David M, Hill R. Infant colic - what works: a systematic review of interventions for breastfed infants. *J Pediatr Gastroenterol Nutr*. 2016;62:668–686.
74. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the treatment of infantile colic: a systematic review [published online 2 May 2016]. *J Pharm Pract*. 2016. pii: 0897190016634516.
75. Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. *Trends Mol Med*. 2015;21:702–714.
76. Vogt SL, Peña-Díaz J, Finlay BB. Chemical communication in the gut: effects of microbiota-generated metabolites on gastrointestinal bacterial pathogens. *Anaerobe*. 2015;34:106–115.
77. Kenny SE, Vanderwinden JM, Rintala RJ, et al. Delayed maturation of the interstitial cells of Cajal: a new diagnosis for transient neonatal pseudoobstruction. Report of two cases. *J Pediatr Surg*. 1998;33:94–98.
78. Camilleri M. Enteric nervous system disorders: genetic and molecular insights for the neurogastroenterologist. *Neurogastroenterol Motil*. 2001;13:277–295.
79. al Tawil Y, Berseth CL. Gestational and postnatal maturation of duodenal motor responses to intragastric feeding. *J Pediatr*. 1996;129:374–381.
80. Baker J, Berseth CL. Postnatal change in inhibitory regulation of intestinal motor activity in human and canine neonates. *Pediatr Res*. 1995;38:133–139.
81. Berseth CL. Effect of early feeding on maturation of the preterm infant's small intestine. *J Pediatr*. 1992;120:947–953.
82. Owens L, Burrin DG, Berseth CL. Minimal enteral feeding induces maturation of intestinal motor function but not mucosal growth in neonatal dogs. *J Nutr*. 2002;132:2717–2722.
83. Spiller RC, Trotman IF, Higgins BE, et al. The ileal brake-inhibition of jejunal motility after ileal fat perfusion in man. *Gut*. 1984;25:365–374.
84. Spiller RC, Trotman IF, Adrian TE, Bloom SR, Misiewicz JJ, Silk DB. Further characterisation of the 'ileal brake' reflex in man-effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptide YY. *Gut*. 1988;29:1042–1051.
85. Jadcherla SR, Berseth CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr*. 2002;34:16–22.
86. Berseth CL. Assessment in intestinal motility as a guide in the feeding management of the newborn. *Clin Perinatol*. 1999;26:1007–1015.
87. Kirjavainen J, Jahnukainen T, Huhtala V, et al. The balance of the autonomic nervous system is normal in colicky infants. *Acta Paediatr*. 2001;90:250–254.
88. Shamir R, St. James-Roberts I, Di Lorenzo C. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. *J Pediatr Gastroenterol Nutr*. 2013;57(suppl 1):S1–S45.
89. Vanderhoof JA, Murray ND, Young RJ. Infantile colic—a functional bowel disorder? *Pract Gastroenterol*. 1999;23:39–41.
90. Lothe L, Ivarsson A, Lindberg T. Motilin, vasoactive intestinal peptide and gastrin in infantile colic. *Acta Paediatr Scand*. 1987;76:316–320.
91. Savino F, Grassino EC, Guidi C, Oggero R, Silvestro L, Miniero R. Ghrelin and motilin concentration in colicky infants. *Acta Paediatr*. 2006;95:738–741.
92. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (FoeniculumVulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *AlternTher Health Med*. 2003;9:58–61.
93. Savino F, Cresi F, Castagno E, Silvestro L, Oggero R. A randomized double-blind placebo controlled trial of a standardized extract

of Matricariaerecutita, Foeniculumvulgare and Melissa officinalis (ColiMil) in the treatment of breastfed colicky infants. *Phytother Res*. 2005;19:335–340.

94. Freudenberg F, Gothe F, Beigel F, Rust C, Koletzko S. Serum 7-alpha-hydroxy-4-cholesten-3-one as a marker for bile acid loss in children. *J Pediatr*. 2013;163:1367–1371.e1.
95. Staelens S, Van den Driessche M, Barclay D, et al. Gastric emptying in healthy newborns fed an intact protein formula, a partially and an extensively hydrolysed formula. *Clin Nutr*. 2008;27:264–268.
96. Savino F, Cordisco L, Tarasco V, et al. *Lactobacillus reuteri* DSM 17938 in infantile colic: a randomized, double blind, placebo-controlled trial. *Pediatrics*. 2010;126:e526–e533.

Chapter 3

Definition and Diagnosis of Functional Gastrointestinal Disorders: the Rome Criteria and the Optimization of Clinical Trials

3.1 The Mediterranean-European Area Project on Functional Gastrointestinal Disorders

3.1.1 *Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area*

The Mediterranean-European Area project (MEAP) on FGIDs is a multi-stage project that aims to implement international collaboration in the field of FGIDs, to allow a better understanding of the epidemiology and of the diagnostic-therapeutic approach to these disorders. In 2012, preliminary data obtained through an informal network, including adult and paediatric gastroenterological centers from the Mediterranean area, revealed the following information regarding the epidemiology, diagnosis, and treatment of FGIDs: insufficient knowledge of epidemiological data on FGIDs; inadequate application of the Rome criteria; and lack of standardization in the therapeutic approach to FGIDs, particularly for paediatric patients (30). Taking into account these findings, we decided to launch the first stage of the MEAP: an international multicentre prospective survey with the aim of precisely define the diagnostic and therapeutic approach to children with suspected FGIDs by general paediatricians from different Mediterranean countries. The coordinator for each country randomly identified, from a national database, a sample of general paediatricians fairly distributed across the national territory. Selected paediatricians were contacted by email and were asked to complete 3 questionnaires investigating their approach to patients with symptoms suggestive for a FGIDs. Given the large number of existing FGIDs, we decided to focus on 3 of the most prevalent disorders: functional constipation (FC), functional regurgitation (FR), and irritable bowel syndrome (IBS). The questionnaires consisted of 2 different sections: the first investigating the use of diagnostic tools (including the Rome criteria), and the second evaluating the most used treatment options for FC, FR, and IBS.

We collected a total of 278 questionnaires (mean response rate of 25%) from 9 different countries: Croatia, Greece, Israel, Italy, Lebanon, Montenegro, Serbia, Slovenia, and Spain.

Functional Constipation

Regarding the diagnosis of FC, only 29% of the surveyed paediatricians used the Rome III criteria, with 42% of the sample still considering FC as an exclusion diagnosis. Moreover, 40% of the sample declared to perform a rectal examination in each patient with constipation. In addition, our data show a lack of uniformity in the definition of FC, with some paediatricians relying mainly on stool consistency, some basing it on bowel frequency, and others on retentive postures or faecal incontinence. A systematic review by Kuizenga-Wessel et al. reported that, in 45 clinical trials, 22 different definitions of FC were used (31). This lack of uniformity in the definition of FC jeopardizes the results of clinical trials and is reflected in the heterogeneity of definitions reported in clinical practice in our study. Treatment of FC varies between the different countries, with 98% of the paediatricians suggesting dietary interventions, mainly increasing fibre and water intake. However, paediatricians should not assume a diet poor in fibre to be the cause of constipation and should be aware that the evidence of beneficial increase in dietary fibre or fluids for treating childhood constipation is lacking. In addition, we found that 94% of paediatricians also prescribed medications, mainly laxatives. The most used osmotic laxative was polyethyleneglycole, while the most used irritative laxative was senna.

Functional Regurgitation

Eight percent of the responders based the diagnosis of FR on personal experience, and 31% considered FR as an exclusion diagnosis, with only 22% of the sample using Rome III diagnostic criteria. Moreover, it is good to note that 97% based the treatment of FR on parental reassurance, 77% prescribed thickened feeds, and 70% smaller volume of feeds, in accordance with the North American Society for Pediatric Gastroenterology Hepatology and Nutrition-European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for infants with uncomplicated recurrent regurgitation that recommend only reassurance, parental education, and modification of

feeding composition (32). However, 21% of the surveyed paediatricians prescribed proton pump inhibitors (PPIs) or H2-blockers, and 13% prokinetic agents. These data is discouraging, since it is well known that PPIs are not effective on gastroesophageal reflux disease symptoms in infants (33) and that evidence of efficacy and safety of H2-blockers in infants and children is limited and of poor quality (34). Moreover, the prescription of unnecessary therapies in infants with a functional disorder is a serious cause of concern, especially considering that PPIs can increase the susceptibility to infections (35).

Irritable Bowel Syndrome

Considering IBS, 88% of the subjects declared to make a "positive" diagnosis, even if only 26% strictly applied the Rome III criteria. Treatment was mainly focused on the predominant symptom (pain, diarrhea or constipation), with analgetics representing the most prescribed treatment for pain, and dietary advice the most used suggestion for constipation and diarrhea.

In conclusion, our data show a wide variability in the diagnostic approach to FGIDs with paediatricians frequently relying on personal experience. The note that <30% of the sample refers to the Rome III criteria is disappointing. Moreover, a large number of paediatricians insists on the exclusion of other diagnoses when managing subjects with a suspected FGIDs. This approach is counterproductive since, as abovementioned, one of the advantages of using symptom-based diagnostic criteria is to reduce anxiety that drives the families to seek multiple consultations (36). Educational efforts are required to ensure a ''positive'', symptom-based approach to functional disorders, avoiding inappropriate use of healthcare resources and excessive treatment of overall benign conditions. In addition, although the Rome criteria and, in general, clinical practice guidelines are endorsed by scientific societies and are generally available online, a consistent effort is required to increase knowledge and to improve the outcome in patients.

The results of this survey study on the diagnostic-therapeutic approach to suspected FGIDs have been published in *Journal of Pediatric Gastroenterology and Nutrition* in 2017.

Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area

*Elena Scarpato, *Paolo Quitadamo, †Enriqueta Roman, ‡Danijela Jojkic-Pavkov, §Sanja Kolacek, ||Alexandra Papadopoulou, ||Eleftheria Roma, ¶Raanan Shamir, ¶Michal R.B. Lev, #Branko Lutovac, #Veselinka Djurisic, **Rok Orel, ††Aziz Koleilat, ††Sirin Mneimneh, *Vincenzo Coppola, ‡‡Enrico Corazziari, and *Annamaria Staiano

ABSTRACT

Objectives: Childhood functional gastrointestinal disorders (FGIDs) are common conditions associated with significant morbidity and high healthcare costs. This multicenter study aimed at assessing the clinical approach to infants (0–6 months) and children/adolescents (4–18 years) with suspected FGIDs by pediatricians from the Mediterranean Area.

Methods: A survey evaluating the diagnostic approach, including the use of Rome II and III criteria, and the therapeutic management of some of the most prevalent FGIDs, such as irritable bowel syndrome (IBS), functional constipation (FC), and functional regurgitation (FR), was distributed to a sample of pediatricians.

Results: We collected 278 questionnaires from 9 countries (Croatia, Greece, Israel, Italy, Lebanon, Montenegro, Serbia, Slovenia, and Spain). Rome III criteria are used to diagnose FC by 28.8%. Treatment of FC is based on dietary modifications (97.5%) and osmotic laxatives (93.5%). Rome III criteria are used to diagnose FR by 22.3% of the responders, in contrast to 79.5% who rely on personal experience for diagnosis. Reported treatments mainly consist of reassurance (96.8%) and thickened feedings (77.3%). Nevertheless, 21.2% prescribe proton pump inhibitors or H2-blockers to infants with FR. Rome III criteria are used to diagnose IBS by only 25.9%. Moreover, 86% of the pediatricians base IBS therapy on the predominant symptom. The most prescribed treatments are analgesics (36.6%) for pain control, dietary advice (41.5%) for diarrhea-predominant IBS, and dietary advice (47.8%) for constipation-predominant IBS.

Conclusions: Our data show that the use of Rome III diagnostic criteria is not sufficiently widespread among pediatricians, and that large variability remains in the management of FGIDs within the different Mediterranean countries surveyed.

Key Words: functional constipation, functional regurgitation, irritable bowel syndrome, Rome criteria, survey, therapeutic approach

(*JPGN* 2017;64: e142–e146)

What Is Known

- Childhood functional gastrointestinal disorders are associated with significant morbidity and high healthcare costs.
- The Rome criteria allow a "positive" approach to these disorders to avoid unnecessary and invasive tests to rule out an organic cause.
- Knowledge of clinical guidelines among pediatricians from the Mediterranean Area is poorly documented.

What Is New

- Despite the development of the Rome criteria, wide variability in the diagnostic approach to functional gastrointestinal disorders persists.
- Although the Rome diagnostic criteria and the clinical practice guidelines are endorsed by scientific societies and are generally available online, a consistent effort is required to increase knowledge among pediatricians and to improve the outcome in patients.

Functional gastrointestinal disorders (FGIDs) include a combination of chronic or recurrent gastrointestinal age-dependent symptoms not explained by known biochemical or structural abnormalities (1). FGIDs represent a challenging group of conditions frequently misdiagnosed in children and associated with

Received June 7, 2016; accepted February 15, 2017.

From the *Department of Translational Medical Sciences, Section of Pediatrics, University Federico II, Naples, Italy, the †Department of Pediatrics, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, the ‡Department of Pediatrics, Institute for Child and Youth Health Care of Vojvodina, Medical Faculty Novi Sad, Novi Sad, Serbia, the §Referral Centre for Pediatric Gastroenterology and Nutrition, University Children's Hospital, Zagreb, Croatia, the ||First Department of Pediatrics, University of Athens, Athens Children's Hospital "Agia Sophia", Athens, Greece, the ¶Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, the #Clinical Centre of Montenegro, Institute for Children's Disease, Podgorica, Montenegro, the **Children's Hospital, University Medical Centre, Ljubljana, Slovenia, the ††Makassed University General Hospital, Beirut, Lebanon, and the ‡‡Department of Internal Medicine and Medical Specialties, University Sapienza, Rome, Italy.

Address correspondence and reprint requests to Annamaria Staiano, Department of Translational Medical Sciences, Section of Pediatrics, University of Naples "Federico II", Via S. Pansini 5, 80131 Naples, Italy (e-mail: staiano@unina.it).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

The project is funded by a network grant from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000001550

significant morbidity and high healthcare costs. In the United States, from 1997 to 2009, the number of discharges with a primary diagnosis of FGIDs has increased slightly, and the total mean cost per discharge significantly increased from $6.115 to $18.058 (2).

Given the lack of biological markers and of criterion standard tests, FGIDs are currently diagnosed based on a set of symptoms defined by the Rome diagnostic criteria. The recently released Rome IV criteria allow a "positive" approach to these disorders by encouraging clinical diagnosis without the need to rule out organic disease in an attempt to avoid unnecessary and invasive tests (3). Despite the existence of the Rome criteria, diagnostic approaches still appear to vary widely between countries, probably due to several factors, including cultural customs. Currently, in many countries the diagnosis of FGIDs is still mainly inferred after several inappropriate investigations with high burden related to healthcare costs and patient anxiety surrounding diagnostic testing. Preliminary data obtained through an informal network, including adult and pediatric gastroenterological centers from the European Mediterranean area, revealed the following information regarding the epidemiology, diagnosis, and treatment of FGIDs: evidence of insufficient epidemiologic knowledge of FGIDs; improved but still inadequate application of Rome III diagnostic criteria; and lack of standardization in the therapeutic approach to FGIDs, particularly for pediatric patients (Scarpato E, Corazziari E, Irastorza I, et al., unpublished data, 2012: Cross-cultural knowledge, diagnosis and treatment of functional gastrointestinal disorders in children: the Mediterranean Pediatric FGID Project. ESPGHAN Update, Stockholm, Sweden). Therefore, considering the results of this preliminary survey that involved healthcare workers from specialized centers, we hypothesized that the same lack of standardization in the clinical management of FGIDs might have been found, to a greater extent, in general pediatricians. The present study was aimed to assess the diagnostic and therapeutic approaches to children with suspected FGIDs by general pediatricians from different Mediterranean countries. The data obtained provided an estimate of the adherence to the clinical guidelines and of the use of the Rome criteria, and may allow us to program interventions aimed at their implementation in the clinical practice.

METHODS

This was a prospective multicenter survey performed in 9 countries of the Mediterranean area: Croatia, Greece, Israel, Italy, Lebanon, Montenegro, Serbia, Slovenia, and Spain. The coordinator for each country used a national database to randomly identify a sample of general pediatricians, fairly distributed across the entire national territory. Selected pediatricians were contacted by email and were asked to complete 3 questionnaires investigating their approach to patients with symptoms suggestive of FGIDs. To simplify completion of the questionnaires and given the large number of existing FGIDs, we focused on functional constipation (FC), functional regurgitation (FR), and irritable bowel syndrome (IBS), 3 of the most prevalent disorders (4–6). Specifically, the involved pediatricians were asked to refer to infants (0–6 months) when answering the questionnaire on FR, and to children/adolescents (4–18 years) when answering the questionnaires on FC and IBS. The questionnaires, developed by members of the Department of Translational Medical Sciences, Section of Pediatrics, at the University of Naples and of the Department of Internal Medicine at the University of Rome, consisted of 2 different sections: one evaluating the use of diagnostic tools (including the Rome criteria), and the other investigating the most used treatment options for these disorders (Supplemental Digital Content 1–3, *http://links.lww.com/MPG/A918*). The study coordinator for each participating country translated the original English version of the questionnaires into the native language of their country. To validate the translation, a different person for each country translated the questionnaires back to English. The original questionnaires and the back-translated questionnaires (both in English) were compared to ensure that the meaning was not modified during the translation process. The national data obtained from the questionnaires were collected and analyzed by the principal coordinator. Results were collected from October 2014 to March 2015. The study was approved by the Ethic Committees of the coordinating center (University of Naples) and of all participating centers, and was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. Data were entered into Excel (Microsoft, Redmond, WA) and analyzed with GraphPad software version 5.01 (GraphPad Software, La Jolla, CA). Statistical analyses included Student *t* test and Mann-Whitney test, when appropriate, with significance accepted at the $P \leq 0.05$ level. Results are expressed as mean ± standard deviation and percentages. These comparative data are not shown, because the study did not claim to detect statistically relevant differences in the management of FGIDs among pediatricians from the 9 participating countries. No data were available to accurately assess the sample size. The power evaluation for both univariate and multivariate tests has been computed with the SPSS (SPSS 20.0, Chicago, IL) Multivariate Anova, considering an overall number of 167,444 European pediatricians (first type error, 0.05; second type error, 0.05; power, 85%) (7).

RESULTS

We sent 1107 questionnaires to pediatricians within 9 European countries. The number of responders was 278 (25% response rate); the number of questionnaires sent out and returned, and the response rate for each country are shown in Table 1.

Functional Constipation

According to the answers given by the involved pediatricians about the diagnosis of FC, Rome diagnostic criteria are used by 110 of 278 (40%) of the pediatricians. Of note, 30 of 278 (11%) still rely on Rome II criteria, whereas only 80 of 278 (29%) use the updated Rome III criteria. To formulate a diagnosis of FC, 245 of 278 (88%) declared they rely mainly on stool consistency, 249 of 278 (90%) on reduced bowel frequency, 225 of 278 (81%) on retentive postures, and 215 of 278 (77%) on the presence of fecal incontinence. In addition, 118 of 278 (42%) still consider FC a diagnosis of exclusion after completing a thorough diagnostic evaluation for other etiologies. Furthermore, 85 of 278 (31%) consider fecal retention as a different clinical entity from FC, and declare to differentiate these

TABLE 1. Number of questionnaires sent out/returned and response rate for each participating country

Country	No questionnaires sent out	No questionnaires returned	Response rate, %
Spain	532	80	15
Italy	245	64	26
Greece	61	32	52.5
Serbia	50	32	64
Croatia	25	20	80
Israel	50	20	40
Montenegro	24	15	62.5
Slovenia	100	10	10
Lebanon	20	5	25
Total	1107	278	25.1

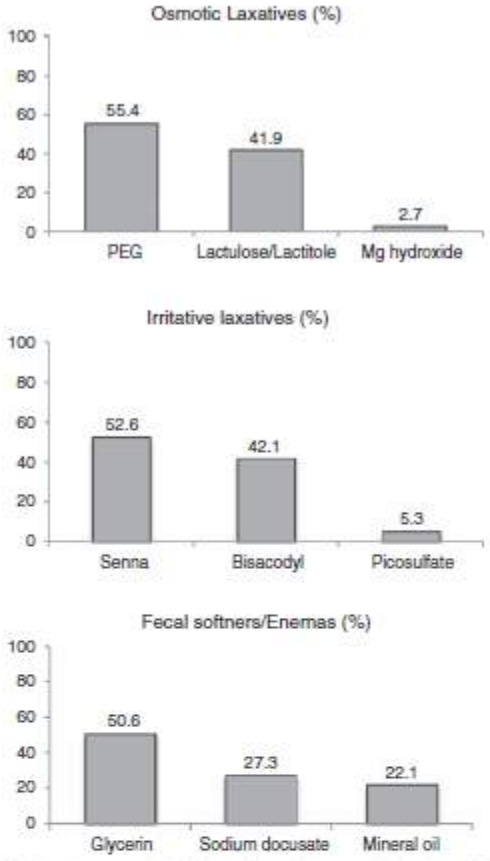

FIGURE 1. Most prescribed drugs for each group of laxatives. PEG = polyethyleneglycol.

2 disorders based on medical history and physical examination of the child. In addition, 111 of 278 (40%) perform a digital rectal examination in every patient with constipation. FC is considered in the differential diagnosis of acute abdominal pain in 235 of 278 (85%).

Treatment varies; 271 of 278 (98%) suggest dietary intervention, mainly increasing both fiber and water intake (226/271 [83%]); a small minority (7/271 [3%]) recommend reducing milk consumption. The most commonly used medications are laxatives (260/278 [94%]) (Fig. 1), whereas the use of fecal softeners administered orally or rectally is advised by 154 of 278 (55%) and stimulant laxatives by 38 of 278 (14%). Moreover, only 16 of 278 (6%) give parents behavioral advice (eg, toilet training).

Functional Regurgitation

Most of the responders (178/278 [80%]) rely on personal experience to diagnose FR. Moreover, 87 of 278 (31%) consider FR a diagnosis of exclusion, whereas 89 of 278 (32%) claim to use the Rome diagnostic criteria; 62 of 278 (22%) use Rome III criteria, whereas 27 of 278 (12%) use Rome II criteria.

Parental reassurance is noted by 269 of 278 (97%) to have a major role for treatment of FR. Thickened feeds are usually

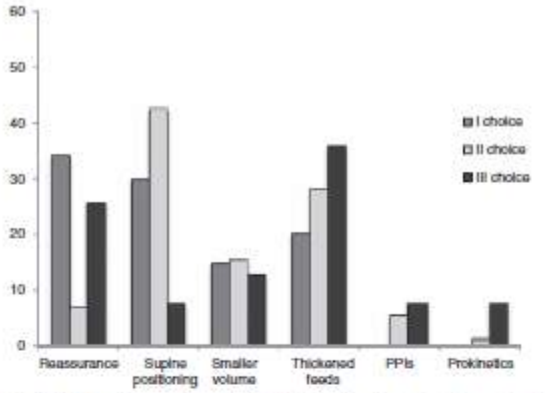

FIGURE 2. First, second, and third choice treatments for functional regurgitation (%). PPIs = proton pump inhibitors.

prescribed by 215 of 278 (77%), smaller volume feedings by 194 of 278 (70%), and supine positioning by 187 of 278 (67%). Notably, 59 of 278 (21%) prescribe proton pump inhibitors (PPIs) or H2-blockers, and 28 of 278 (13%) prescribe prokinetic agents. (Fig. 2)

Irritable Bowel Syndrome

Most (245/278 [88%]) are comfortable making a ''positive'' IBS diagnosis. Nevertheless, only 123 of 278 (44%) claim to follow Rome criteria. More specifically, 51 of 278 (18%) still rely on Rome II criteria, whereas 72 of 278 (26%) apply Rome III criteria. A minority (125/278 [45%]) conduct diagnostic testing for other etiologies before arriving at a diagnosis of IBS.

Treatment of IBS is mainly focused on the predominant symptoms (pain, diarrhea, or constipation) by 224 of 278 (81%) of the respondents. The most frequently prescribed treatments for control of pain, diarrhea, and/or constipation are summarized in Figure 3.

DISCUSSION

This multicenter study aimed to investigate the diagnostic and therapeutic approach of general pediatricians to children with symptoms suggestive of FGIDs. We have performed a survey including a sample of pediatricians from 9 Mediterranean countries, evaluating their clinical management of some of the most frequent FGIDs: FC, FR, and IBS. Our data show persistent wide variability in the diagnostic approach to FGIDs. This variability may be due to the large number of pediatricians who insist on exclusion of other diagnoses before diagnosing these disorders. They frequently rely on personal experience, irrespective of the availability of standardized diagnostic criteria. General application of Rome criteria by less than half of the surveyed pediatricians (with <30% referring to the updated Rome III diagnostic criteria) is still disappointing. A report of the Rome Foundation Working Team on cross-cultural multinational research, which evaluated implementation of diagnostic criteria and treatment availability for FGIDs, found that knowledge and use of Rome criteria were deficient, especially among general practitioners (8). Similarly, Schurman et al (9) surveyed American primary care pediatricians to evaluate their approach to children with chronic abdominal pain and documented the same lack of familiarity with the Rome criteria.

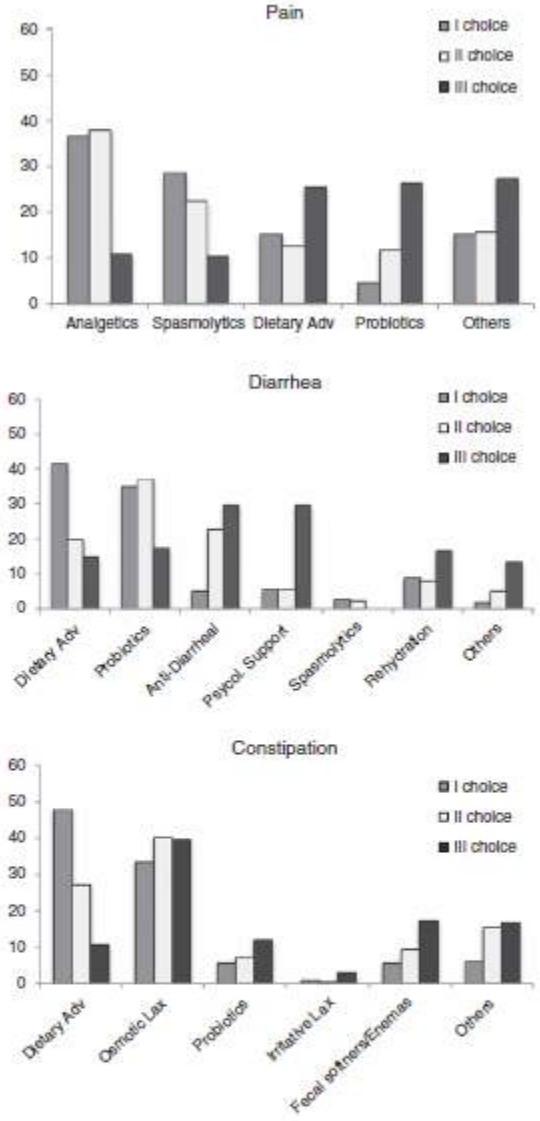

FIGURE 3. Most widely used treatments for patients with irritable bowel syndrome, based on the predominant symptom (%). Adv = advice.

This approach is counterproductive since one of the advantages of symptom-based diagnostic criteria is to reduce anxiety that drives a family to seek multiple consultations (11). Nonadherence to the Rome Criteria is also shown by our finding that 31% of the pediatricians consider fecal retention as a different clinical entity from FC. This may be due to the fact that the former classification of the Rome II committee divided the nonorganic forms of constipation into infant dyschezia, FC, and functional fecal retention. Because this division was, however, not evidence based, the Rome III committee decided to combine these 2 entities into a single category named "FC" (12).

In addition, our data show lack of uniformity in the definition of FC; some pediatricians rely mainly on stool consistency for their diagnosis of FC, some base it on bowel frequency, and others diagnose FC in patients with retentive postures or fecal incontinence. Considering the answers to our questions, it is clear that there is a portion of pediatricians for whom the diagnosis is based on more than 1 parameter at the same time. This means that they "unknowingly" use the Rome criteria in the clinical practice, even if they do not declare it when specifically required. For this reason, it is possible that the percentage of pediatricians that uses the Rome criteria in the daily practice is slightly higher than the value reported by the questionnaires.

A recent systematic review by Kuizenga-Wessel et al (13) reported that in 45 clinical trials, 22 different definitions of FC were used. Lack of uniformity in the definition of FC jeopardizes the results of clinical trials and is reflected in the heterogeneity of definitions used in clinical practice in our study.

Our data demonstrate that the majority of pediatricians treat FC with dietary intervention, mainly represented by an increase of both fiber and water intake. Borowitz et al (14) already found that half of the physicians involved in their study recommended a dietary intervention for FC. Another survey performed in 2011 (15) showed that dietary recommendations were given by 97% of the interviewed physicians. Similarly, in a recent study from Yang and Punati (16), the most common initial interventions for constipation were represented by an increase in fluids (92%) and in dietary fiber (90%). Nevertheless, pediatricians should not assume a diet poor in fiber to be the cause of constipation and should be aware that the evidence of beneficial increase in dietary fiber or fluids for treating childhood constipation is lacking (15,17).

To treat FR, our data suggest that most pediatricians rely on parental reassurance, thickened feedings, and smaller volumes of feedings. This therapeutic approach is consistent with the North American Society for Pediatric Gastroenterology Hepatology and Nutrition-European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for infants with uncomplicated recurrent regurgitation (pediatric gastroesophageal reflux) that recommend only reassurance, parental education, and modification of feeding composition (18). We also, however, identified use of PPIs/H2-blockers (21%) and prokinetics (13%) in children with a diagnosis of FR. These data are discouraging, considering that it has been well demonstrated that PPIs are not effective in reducing gastroesophageal reflux disease symptoms in infants (19,20) and that evidence of efficacy and safety of H2-blockers in infants and children is limited and of poor quality (21). The prescription of unnecessary medications in infants with a functional disorder is a serious cause of concern, especially because PPIs can be associated with an increase in susceptibility to respiratory infections (22), acute gastroenteritis, and community-acquired pneumonia (23,24). Despite the fact that overuse of PPIs in the first year of life has already been documented in several studies (25–27), our data suggest that the clinical management of these patients still requires modification.

The authors are aware of the methodological shortcomings of the present study. The survey nature of the study represents a significant limitation. Survey studies are frequently characterized by a relatively low return rate (10,28,29). We are, however, confident that even though only 25% of the targeted pediatricians answered the questionnaires, this value represents a sensible sample to provide an overview on the clinical approach to FGIDs. Nevertheless, as in all the survey-based studies, it is unknown if the answers of the responders are comparable to those of nonresponders. Moreover, considering that participation in the present study was voluntary, it is conceivable that the majority of the responders represent pediatricians with increased interest in FGIDs and who

therefore are better informed on these types of disorders. In addition, this survey study may be influenced by an unavoidable potential bias related to the Hawthorne effect (30). The Hawthorne effect refers to a phenomenon in which a study subject's behavior is altered as a result of the subject's awareness of being under observation. According to this effect, pediatricians could have over-reported their use of Rome criteria and perhaps under-reported not-standardized medical management. For this reason, it is possible that our data even overestimate the rate of adherence to standardized diagnostic criteria and recommendations and that, in reality, the clinical approach may even be less evidence based. So, this consideration further strengthens our findings.

Finally, we were not able to perform a survey including all the Mediterranean countries due to a lack of response of some countries originally involved.

The results of our survey demonstrate the persistent gap between what is defined by guidelines/recommendations and daily practice. Implementing recommendations in clinical practice is a complex process. Nevertheless, several studies evaluated the efficacy of different methods to perform implementation. Quitadamo et al (31) demonstrated that simple, inexpensive training methods, such as podcasts or synopsis, are effective in increasing adherence to recommendations by European pediatricians. Similarly, Nicastro et al (32) showed the efficacy of E-learning in increasing knowledge of guidelines and improving clinical practice in physicians managing children with acute gastroenteritis. Thus, the methods described to put in place educational interventions are multiple, require a limited economic effort, and are easy to perform.

Educational efforts are required to ensure a ''positive,'' symptom-based approach to functional disorders, avoiding inappropriate use of healthcare resources and excessive treatment of overall benign conditions. Moreover, although the Rome diagnostic criteria and the clinical practice guidelines are endorsed by scientific societies and are generally available online, a consistent effort is required to increase knowledge among pediatricians and to improve the outcome in patients.

Acknowledgments: The Mediterranean-European Area Project on FGIDs is a project launched and supported by ANEMGI-Onlus.

REFERENCES

1. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut* 1999;45(suppl II):II60–8.
2. Park R, Mikami S, LeClair J, et al. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. *Neurogastroenterol Motil* 2015;27:684–92.
3. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology* 2016;150:1456–68.
4. Lewis ML, Palsson OS, Whitehead WE, et al. Prevalence of functional gastrointestinal disorders in children and adolescents. *J Pediatr* 2016;177:39–43.
5. Játiva E, Velasco-Benítez CA, Koppen IJ, et al. Prevalence of functional gastrointestinal disorders in schoolchildren in Ecuador. *J Pediatr Gastroenterol Nutr* 2016;63:25–8.
6. Van Tilburg MA, Hyman PE, Walker L, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J Pediatr* 2015;166:684–9.
7. Katz M, Rubino A, Collier J, et al. Demography of pediatric primary care in Europe: delivery of care and training. *Pediatrics* 2002;109:788–96.
8. Schmulson M, Corazziari E, Ghoshal UC, et al. A four-country comparison of healthcare systems, implementation of diagnostic criteria, and treatment availability for functional gastrointestinal disorders: a report of the Rome Foundation Working Team on cross-cultural, multinational research. *Neurogastroenterol Motil* 2014;26:1368–85.
9. Schurman JV, Kessler ED, Friesen CA. Understanding and treatment of chronic abdominal pain in pediatric primary care. *Clin Pediatr (Phila)* 2014;53:1032–40.
10. Dhroove G, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? *J Pediatr Gastroenterol Nutr* 2010;51:579–83.
11. Rouster AS, Karpinski AC, Silver D, et al. Functional gastrointestinal disorders dominate pediatric gastroenterology outpatient practice. *J Pediatr Gastroenterol Nutr* 2016;62:847–51.
12. Drossman DA, Corazziari E, Delvaux M, et al. Rome III: The Functional Gastrointestinal Disorders—. 3rd ed. McLean, VA: Degnon Associates; 2006.
13. Kuizenga-Wessel S, Heckert SL, Tros W, et al. Reporting on outcome measures of functional constipation in children—a systematic review. *J Pediatr Gastroenterol Nutr* 2016;62:840–6.
14. Borowitz SM, Cox DJ, Kovatchev B, et al. Treatment of childhood constipation by primary care physicians: efficacy and predictors of outcome. *Pediatrics* 2005;115:873–7.
15. Burgers R, Bonanno E, Madarena E, et al. The care of constipated children in primary care in different countries. *Acta Paediatr* 2012;101:677–80.
16. Yang CH, Punati J. Practice patterns of pediatricians and trainees for the management of functional constipation compared with 2006 NASPGHAN guidelines. *J Pediatr Gastroenterol Nutr* 2015;60:308–11.
17. Tabbers MM, Di Lorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014;58:258–74.
18. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
19. Van der Pol RJ, Smits MJ, Van Wijk MP, et al. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics* 2011;127:925–35.
20. Chen IL, Gao WY, Johnson AP, et al. Proton pump inhibitor use in infants: FDA reviewer experience. *J Pediatr Gastroenterol Nutr* 2012;54:8–14.
21. Van der Pol R, Langendam M, Benninga M, et al. Efficacy and safety of histamine-2 receptor antagonists. *JAMA Pediatr* 2014;168:947–54.
22. Tighe MP, Afzal NA, Bevan A, et al. Current pharmacological management of gastroesophageal reflux in children: an evidence-based systematic review. *Paediatr Drug* 2009;11:185–202.
23. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955–60.
24. Canani RB, Cirillo P, Roggero P, et al. Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006;117:e817–20.
25. Barron JJ, Tan H, Spalding J, et al. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr* 2007;45:421–7.
26. Khoshoo V, Edell D, Thompson A, et al. Are we overprescribing antireflux medications for infants with regurgitation? *Pediatrics* 2007;120:946–9.
27. Orenstein SR, Hassall E. Infants and proton pump inhibitors: tribulations, no trials. *J Pediatr Gastroenterol Nutr* 2007;45:395–8.
28. Diaz DM, Winter HS, Colletti RB, et al. Knowledge, attitudes and practice styles of North American pediatricians regarding gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007;45:56–64.
29. Szajewska H, Hoekstra JH, Sandhu B. Management of acute gastroenteritis in Europe and the impact of the new recommendations: a multicenter study. *J Pediatr Gastroenterol Nutr* 2000;30:522–7.
30. Mangione-Smith R, Elliott MN, McDonald L, et al. An observational study of antibiotic prescribing behavior and the Hawthorne effect. *Health Serv Res* 2002;37:1603–23.
31. Quitadamo P, Urbonas V, Papadopoulou A, et al. Do pediatricians apply the 2009 NASPGHAN-ESPGHAN guidelines for the diagnosis and management of gastroesophageal reflux after being trained? *J Pediatr Gastroenterol Nutr* 2014;59:356–9.
32. Nicastro E, Lo Vecchio A, Liguoro I, et al. The impact of E-learning on adherence to guidelines for acute gastroenteritis: a single-arm intervention study. *PLoS One* 2015;10:e0132213.

3.1.2 *Functional Gastrointestinal Disorders: Prevalence study in Children and Adolescents in the Mediterranean part of Europe*

The MEAP is a multi-stage study funded by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), that aims to promote international collaboration in the field of FGIDs. The first stage of the MEAP study has been described in the first section of this chapter (Section 3.1.1), and consisted in a survey on the diagnostic and therapeutic approach to children with suspected FGIDs by general paediatricians from Mediterranean countries; the second stage's aim was the translation of the standardized Questionnaires on Paediatric Gastrointestinal Symptoms based on Rome III Criteria (QPGS-RIII), for non-English speaking patients, in order to assess the prevalence of FGIDs in the European Mediterranean Area.

The prevalence of FGIDs based on Rome III criteria ranges between 12% and 29%. A study from Lewis et al., who recruited 949 mothers of children and adolescents in the US, found an overall prevalence of 23.1% based on parental report (37). Numerous other studies evaluated the epidemiology of FGIDs, even if most of them considered only small community samples (38, 39), single countries (e.g. Greece, or Norway) (40, 41), or selected age ranges (e.g. adolescents) (42). Nevertheless, prevalence of FGIDs in the Mediterranean-European area is poorly defined; for this reason, we decided to take advantage of the existing international research network established during the first stage of the MEAP to assess the prevalence of FGIDs in a community sample of children and adolescents of the Mediterranean-European area. This school-based, prospective, multicenter study represented the third stage of the MEAP, and involved 13,750 children aged 4-18 years from 9 different countries: Croatia, Greece, Israel, Italy, Jordan, Lebanon, Macedonia, Serbia, and Spain. Subjects were enrolled in randomly selected schools distributed throughout the national territory of the involved countries, including both large cities and small centers. The prevalence of FGIDs was assessed using the QPGS-RIII, a validated questionnaire specifically designed to diagnose FGIDs in children and adolescents (43), translated for non-English speaking countries during the second stage of the MEAP.

In our study, we have included 6,602 children aged 4-10 years (group A: mean age, 7.7±1.9 years; girls (F) 50.8%), and 7,148 adolescents aged 11-18 years (group B: mean age, 13.8±2.1 years; F, 50.6%). The mean response rate was 69%. In children from group A, overall prevalence of FGIDs was 20.7% (F 46.5%), with one FGID identified in 17.4% of the subjects, and a combination of two FGIDs identified in 2.8%, of three FGIDs in 0.4%, and of four FGIDs in 0.1%. The most frequent disorders were FC (11.7%), IBS (4%), aerophagia (3.5%), and abdominal migraine (AM) (3.1%). Focusing on adolescents, we found that overall prevalence of FGIDs was 26.6% (F 55%), with a single FGID recorded in 19.5% of the subjects, two FGIDs in 6%, three FGIDs in 1%, and four FGIDs in 0.1%. The most frequent disorders were FC (13.1%), AM (7.8%), aerophagia (6.3%), and IBS (5.6%). Our data are comparable to other studies evaluating the prevalence of all FGIDs according to Rome III criteria (37, 38, 40). However, unlike most of the previous studies, we separated the analysis of children (4-10 years) from that of adolescents (11-18 years) to identify age dependent differences in the prevalence of FGIDs and, in particular, to obtain information on FGIDs prevalence in younger children in whom data is scarce worldwide. According to our data, prevalence of most FGIDs is higher in adolescents compared to children. In addition, we found that, in subjects aged 11-18 years, FGIDs were significantly more frequent in girls (M 23.4% vs F 29.1%, P<.001). Increased prevalence of FGIDs in girls is well known, and has been previously described in studies conducted in single countries (38, 40, 42). Finally, we also identified significant differences in the prevalence of specific FGIDs among some of the involved countries. For example, we reported a significantly lower prevalence of FC in Croatia and Serbia, a higher prevalence of aerophagia in Croatia, a higher prevalence of AM in Israel and Spain (especially in younger children), and a higher prevalence of IBS in Israel. The reasons behind these differences are not completely clear. Nevertheless, since FGIDs are considered multifactorial disorders, it can be speculated that they represent the result of a variability in the environment, diet, microbiome, and genetic background among the involved countries and suggest that the results of single country studies may not be generalized.

Our study was the first study evaluating the prevalence of FGIDs in a large sample of children and adolescents from Mediterranean countries, confirming that FGIDs are common disorders and that their frequency increases with age. The differences in the prevalence among the involved countries suggest a role of environmental and genetic factors in the pathogenesis of FGIDs. Further studies are needed to evaluate the impact of these factors in the onset of FGIDs.

The results of this international epidemiologic study on the prevalence of FGIDs in the Mediterranean-European Area have been accepted for publication in *Clinical Gastroenterology and Hepatology* in 2017.

Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents in the Mediterranean Region of Europe

Elena Scarpato,[*] Sanja Kolacek,[‡] Danijela Jojkic-Pavkov,[§] Vlatka Konjik,[||] Nataša Živković,[§] Enriqueta Roman,[¶] Aco Kostovski,[#] Nikolina Zdraveska,[#] Eyad Altamimi,[**] Alexandra Papadopoulou,[‡‡] Thomai Karagiozoglou-Lampoudi,[§§] Raanan Shamir,[||||] Michal Rozenfeld Bar Lev,[||||] Aziz Koleilat,[¶¶] Sirin Mneimneh,[¶¶] Dario Bruzzese,[##] Rosaura Leis,[***] and Annamaria Staiano[*]; MEAP Group

[*]Section of Paediatrics, Department of Translational Medical Sciences, [##]Department of Public Health, University "Federico II," Naples, Italy; [‡]Referral Centre for Paediatric Gastroenterology and Nutrition, "University Children's Hospital," Zagreb, Croatia; [§]Department of Paediatrics, Institute for Child and Youth Health Care of Vojvodina, Medical Faculty Novi Sad, Novi Sad, Serbia; [||]Department of Paediatric Gastroenterology, University Hospital Osijek, Osijek, Croatia; [¶]Department of Paediatrics, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [#]University Children Hospital, Faculty of Medicine, Skopje, Macedonia; [**]Pediatric Department, Jordan University of Science and Technology, Irbid, Jordan; [‡‡]First Department of Paediatrics, University of Athens, Athens Children's Hospital "Agia Sophia," Athens, Greece; [§§]Nutrition and Dietetics Department, School of Food Technology and Nutrition, Technological Education Institute, Thessaloniki, Greece; [||||]Institute of Gastroenterology, Nutrition and Liver Diseases, Sackler Faculty of Medicine, Tel Aviv University, "Schneider Children's Medical Center of Israel," Petach Tikva, Israel; [¶¶]Makassed University General Hospital, Beirut, Lebanon; [***]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain

BACKGROUND & AIMS: Little is known about the prevalence of functional gastrointestinal disorders (FGIDs) in children from the Mediterranean area of Europe. We aimed to assess the prevalence of FGIDs in children and adolescents in this region.

METHODS: We collected data on 13,750 children (4–18 years old) enrolled in the Mediterranean–European Area Project, a school-based health study performed in Croatia, Greece, Israel, Italy, Jordan, Lebanon, Macedonia, Serbia, and Spain. Data were collected from March to June and in September of 2016. We analyzed data from 6602 students 4 to 10 years old (group A; mean age, 7.7 ± 1.9 y), and 7148 subjects 11 to 18 years old (group B; mean age, 13.8 ± 2.1 y). Children with FGIDs were identified based on answers to questionnaires on pediatric gastrointestinal symptoms, selected based on Rome III criteria.

RESULTS: In group A, the prevalence of FGIDs was 20.7%. The most frequent disorders were functional constipation (11.7%), irritable bowel syndrome (IBS, 4%), aerophagia (3.5%), and abdominal migraine (3.1%). The prevalence of abdominal migraine was significantly higher in girls than in boys ($P = .007$). In group B, the overall prevalence of FGIDs was 26.6%. The most frequent disorders were functional constipation (13.1%), abdominal migraine (7.8%), aerophagia (6.3%), and IBS (5.6%). In group B, FGIDs had a higher prevalence among girls than boys ($P < .001$). In both groups, we found significant differences in the prevalence of specific disorders among specific countries.

CONCLUSIONS: In an analysis of data on children 4 to 18 years old from the Mediterranean–European Area Project, we found FGIDs to be more frequent in girls. Functional constipation, aerophagia, abdominal migraine, and IBS are the most common disorders. However, the prevalence of FGIDs varies significantly among countries.

Keywords: MEAP; Epidemiology; Survey; Abdominal Pain.

Abbreviations used in this paper: AM, abdominal migraine; F, female; FAP, functional abdominal pain; FC, functional constipation; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; M, male; MEAP, Mediterranean–European area project; QPGS-RIII, questionnaires on pediatric gastrointestinal symptoms based on Rome III criteria.

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2017.11.005

The Mediterranean–European Area project (MEAP) on functional gastrointestinal disorders (FGIDs) is a multistage project funded by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Its aim is to promote international collaboration in the field of FGIDs to evaluate the diagnostic–therapeutic approach to children with suspected FGIDs, to estimate the prevalence of these disorders, and to improve the dissemination of standardized diagnostic criteria.

FGIDs are common disorders characterized by chronic or recurrent gastrointestinal (GI) symptoms, not related to structural or biochemical abnormalities. Because of the lack of specific biological markers, FGIDs currently are defined according to the criteria established by the Rome Foundation, which are updated regularly.[1–3] The advantage of using the Rome criteria in clinical practice is that they permit a positive approach, avoiding unnecessary tests to rule out an organic cause, with a consequent beneficial effect on both patient's health and health care costs.

The prevalence of FGIDs based on Rome III criteria ranges between 12% and 29%. A recent study from Lewis et al,[4] who recruited a US sample of 949 mothers of children and adolescents aged 4 to 18 years, found an overall prevalence of 23.1% based on parental report. Several studies attempted to evaluate the epidemiology of FGIDs according to Rome III criteria. However, most of them assessed the prevalence only in small community samples,[5,6] in single countries (eg, Greece or Norway),[7,8] in selected age ranges (eg, adolescents),[9] or focused mainly on abdominal pain–related disorders.[10–12] In the Mediterranean–European area the prevalence of FGIDs is poorly defined. Therefore, as part of the MEAP, we launched an international multicenter study to assess the prevalence of FGIDs in a large community sample of children and adolescents from the Mediterranean–European area. The first stage of the MEAP study consisted of a survey on the diagnostic and therapeutic approaches to children with suspected FGIDs by general pediatricians from European–Mediterranean countries, and showed inadequate knowledge and use of the Rome III diagnostic criteria and a lack of standardization in the therapeutic approach to FGIDs.[13] The second stage translated the standardized Questionnaires on Paediatric Gastrointestinal Symptoms based on Rome III Criteria (QPGS-RIII), for non–English-speaking countries, to assess the prevalence of FGIDs. The present study represented the third stage of the MEAP and was conducted through the existing international research network established during the first stage of the project, with the aim of assessing the prevalence of FGIDs in children and adolescents from the Mediterranean–European area.

Methods

This school-based, prospective, multicenter study was performed in 9 countries in the Mediterranean–European area: Croatia, Greece, Israel, Italy, Jordan, Lebanon, Macedonia, Serbia, and Spain. To obtain a nationwide sample, we surveyed subjects aged 4 to 18 years enrolled in schools (nursery schools, primary schools, and secondary schools) distributed throughout the national territory of the involved countries, including both large cities and small centers. For each city, the schools were selected randomly from a list of all the schools available in the territory. The criteria for the selection of the schools were the same in all involved countries. In most of the countries only public schools were included, with the exception of Jordan, Spain, and Lebanon, which also included private schools. The National coordinator for each country contacted the directors of the selected schools to obtain permission to conduct the study. From each school, randomly selected classes were surveyed. The parents/legal guardians and their children then were invited to a meeting for an explanation of the study procedures and the collection of consent to participate. Children were included if consent was provided and in the absence of alarm symptoms suggestive of an organic disease. Informed consent was obtained by parents/legal guardians of the involved children, and by subjects older than 10 years of age. To ensure complete understanding, the printed versions of the study questionnaires were completed in the presence of the study staff, who were available for clarifications.

The study was approved by the Ethic Committees of the coordinating center (University of Naples) and of all the participating centers, and was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. All data were collected anonymously.

Rome Questionnaires

The prevalence of FGIDs was assessed using the QPGS-RIII translated for non–English-speaking countries during the second stage of the MEAP. The ~~QPGS-III~~ is a validated questionnaire, specifically designed to diagnose FGIDs in children and adolescents.[14] For each participating country, the principal investigators translated the original English version of the questionnaires into the native language of their countries. Then, a different person from each country translated the questionnaires back to English; finally, the original questionnaires and the back-translated questionnaires (both in English) were compared to ensure that the meaning was not modified during the translation process. In Israel, the questionnaire also was fully validated by the Rome Foundation; in Greece, the pre-existing official translation of the Rome III questionnaires was used.[7]

The parent-report form was used for subjects between ages 4 and 10 years, and the self-report form was used for subjects between ages 11 and 18 years.

Data Collection and Statistical Analyses

Data were collected from March to June, and in September 2016, during school time. The national data from each country were entered into a Microsoft Excel database (Microsoft, Redmond, WA) specifically designed for the study. All data were sent to the coordinating center (University of Naples) for data analysis. For each FGID an algorithm was created to diagnose the disorder according to the QPGS-RIII scoring system. In case of lack of answers necessary to diagnose a specific disorder, the subject was considered missing for that disorder and was excluded from the prevalence analysis. Likewise, in the case of lack of data on sex, the subject was considered as missing and was excluded from the analysis. These data are available from the authors upon request.

Quantitative variables were synthetized using means ± SD whereas categoric variables were described using absolute frequencies and percentages. The prevalence of each disorder was estimated by calculating the ratio between the affected subjects and the total number of valid cases for each disorder. The corresponding 95% CIs were computed using the Clopper–Pearson exact method. Comparisons between ages, sex, and countries were assessed using the chi-square test or the Fisher exact test when appropriate. The issue of multiplicity in country comparison was addressed using the Bonferroni procedure; for each comparison, statistical significance was determined as $P < .001$. All the statistical analyses were performed using the statistical platform R. The R code for the assignment of diagnosis is available from the authors upon request.

Results

We surveyed a total of 13,750 subjects between 4 and 18 years of age from 9 countries in the Mediterranean–European area. The mean response rate was 69%. The number of subjects surveyed and the response rate in each participating country are shown in Table 1. Specifically, we included 6602 subjects between ages 4 and 10 years (group A: mean age, 7.7 ± 1.9 y; girls [females (F)], 50.8%), and 7148 subjects between ages 11 and 18 years (group B: mean age, 13.8 ± 2.1 y; F, 50.6%). The prevalence values of all FGIDs defined according to Rome III criteria in both study groups are summarized in Table 2.

In subjects ages 4 to 10 years, the overall prevalence of FGIDs was 20.7% (F, 46.5%). One FGID was identified in 17.4% of the subjects, a combination of 2 FGIDs was identified in 2.8%, 3 FGIDs were identified in 0.4%, and of 4 FGIDs were identified in 0.1%. The most frequent disorders were functional constipation (FC) (11.7%), irritable bowel syndrome (IBS) (4%), aerophagia (3.5%), and abdominal migraine (AM) (3.1%). In this age group we did not find differences in the overall prevalence of FGIDs between sexes. However, focusing on single disorders, we found that the prevalence of AM (boys [males (M)] of 2.5% vs F 3.8%; $P = .007$) was significantly higher in girls than in boys. In contrast, nonretentive fecal incontinence was more prevalent in boys (M, 0.8% vs F, 0.3%; $P = .036$). The prevalence of all FGIDs in children ages 4 to 10 years in the different countries is shown in Table 3.

In subjects ages 11 to 17 years, the overall prevalence of FGIDs was 26.6% (F, 55%), with a single FGID recorded in 19.5% of the subjects, 2 FGIDs in 6%, 3 FGIDs in 1%, and 4 FGIDs in 0.1%. The most frequent disorders were FC (13.1%), AM (7.8%), aerophagia (6.3%), and IBS (5.6%). In this age group we found that FGIDs were significantly more frequent in girls (M, 23.4% vs F, 29.1%; $P < .001$). Looking at the different countries separately, we found that the prevalence of FGIDs was significantly higher in girls in Croatia (M, 21.8% vs F, 37.1%; $P < .001$), Serbia (M, 4.4% vs F, 10.2%; $P = .005$), and Spain (M, 22.1% vs F, 28.5%; $P = .045$), and showed a trend toward significance in Italy (M, 17.8% vs F, 24.8%; $P = .007$).

A higher prevalence in girls compared with boys also was found with regard to single FGIDs, such as aerophagia (7.5% vs 5.1%, respectively; $P < .001$), functional

Table 1. Number of Subjects, Mean Age, Sex, and Response Rate in Each Participating Country

	Group A: 4–10 y				Group B: 11–18 y					
Country	N	M, %	F, %	Age, *y*, means ± SD	N	M, %	F, %	Age, *y*, means ± SD	Total	Response rate, %
Croatia	809	48.9	51.1	6.6 ± 2	907	30.7	69.3	14.8 ± 1.9	1716	80
Greece	727	58.3	41.7	9.9 ± 0.5	589	54.9	45.1	16.8 ± 0.7	1316	58
Israel	399	50.6	49.4	7.1 ± 1.9	823	42.4	57.6	13.8 ± 2.2	1222	52
Italy	1070	50.2	49.8	8.1 ± 1.8	1048	50.2	49.8	13.3 ± 1.9	2118	79
Jordan	822	50.7	49.3	8.1 ± 1.4	772	56	44	14 ± 1.8	1594	80
Lebanon	537	46.6	53.4	7.3 ± 1.9	470	50.6	49.4	14.1 ± 1.8	1007	83
Macedonia	711	48.8	51.2	8 ± 1.8	844	50.3	49.7	14.7 ± 2.2	1555	74
Serbia	828	37.4	62.6	7.2 ± 1.6	829	46.6	53.4	12.6 ± 1.4	1657	65
Spain	699	48.6	51.4	7.2 ± 1.9	866	49.2	50.8	14.1 ± 2.2	1565	52
Total	6602				7148				13,750	69

Table 2. FGID Prevalence in Children and Adolescents

Disorder	Group A: 4–10 y, n = 6602			Group B: 11–18 y, n = 7148		
	Valid cases	N (prevalence)	95% CI	Valid cases	N (prevalence)	95% CI
Vomiting and aerophagia						
Adolescent rumination syndrome	6269	2 (0.03%)	0.0–0.1	6865	8 (0.1%)	0.0–0.2
Cyclic vomiting syndrome	6184	19 (0.3%)	0.2–0.5	6797	37 (0.5%)	0.4–0.7
Aerophagia	5956	209 (3.5%)	3.0–4.0	6509	413 (6.3%)	5.8–7.0
Abdominal pain–related FGIDs						
Functional dyspepsia	6453	23 (0.3%)	0.2–0.5	7039	38 (0.5%)	0.4–0.7
Irritable bowel syndrome	6117	243 (4%)	3.5–4.5	6862	383 (5.6%)	5.0–6.1
Abdominal migraine	6061	189 (3.1%)	2.7–3.6	6858	535 (7.8%)	7.1–8.5
Functional abdominal pain	6101	31 (0.5%)	0.3–0.7	6908	26 (0.4%)	0.2–0.6
Functional abdominal pain syndrome	6156	15 (0.2%)	0.1–0.4	6944	40 (0.6%)	0.4–0.8
Constipation and incontinence						
Functional constipation	5899	688 (11.7%)	10.8–12.5	6325	832 (13.1%)	12.3–14.0
Nonretentive fecal incontinence	6269	34 (0.5%)	0.4–0.7	6680	26 (0.4%)	0.2–0.6

dyspepsia (0.8% vs 0.3%, respectively; $P = .008$), IBS (6.4% vs 4.5%, respectively; $P = .001$), and AM (9.7% vs 5.5%, respectively; $P < .001$). Interestingly, in this age group we also found statistically significant differences in the prevalence of specific FGIDs among some of the involved countries. The prevalence of FGIDs in subjects ages 11 to 18 years in the different countries is shown in Table 4.

Finally, we detected statistically significant differences ($P < .001$) in the prevalence of specific disorders among some of the participating countries. These comparisons are summarized in Table 5.

Discussion

This school-based cross-sectional study recruited a large number of children and adolescents nationwide for each of the 9 included countries from the Mediterranean–European area, with the aim of evaluating the prevalence of FGIDs according to Rome III criteria by using an already established international network.

Our main finding was that 20.7% of children ~~ages~~ 4 to 10 years and 26.6% of adolescents ~~ages~~ 11 to 18 years fulfilled the Rome III criteria for at least 1 FGID. Although the data for the Mediterranean area are scarce, our findings are comparable with other studies evaluating the prevalence of all FGIDs according to Rome III criteria. Our results were similar to those of the study from Bouzios et al[7] that included 1658 Greek children between ages 4 and 18 years that found a prevalence of 23.5%, the study from Saps et al[5] including 373 Colombian children that reported a prevalence of 29%, or the earlier-mentioned study from Lewis et al[4] in which the prevalence of FGIDs was 23.1%. In the present study, unlike most of the previous studies conducted in single countries, we separated the analysis of children ~~ages~~ 4 to 10 years from that of adolescents ~~ages~~ 11 to 18 years to identify age-dependent differences in the prevalence of FGIDs and in particular information on ~~FGID~~ prevalence in younger children in whom data are scarce worldwide.

Table 3. FGID Prevalence (%) in Children Between Ages 4 and 10 Years, in All Involved Countries

	Croatia	Greece	Israel	Italy	Jordan	Lebanon	Macedonia	Serbia	Spain
Vomiting and aerophagia									
Adolescent rumination syndrome	0	0	0.2	0	0	0.2	0	0	0
Cyclic vomiting syndrome	0.5	0.3	0.3	0.1	0.6	0.7	0	0	0.4
Aerophagia	10.4	1.1	1.6	1.9	5.3	4	1.9	0.7	3.6
Abdominal pain–related FGIDs									
Functional dyspepsia	0.1	0.1	0.5	0.6	0.1	0.7	0.1	0.5	0.4
Irritable bowel syndrome	4.3	2.2	6.7	4.6	3.4	4.1	2.2	1.3	7.3
Abdominal migraine	1.9	2.7	5.4	2.0	3.0	3.8	3.0	0.7	6.9
Functional abdominal pain	0	0.3	0.8	0.5	0.1	0.6	0.3	0	2.1
Functional abdominal pain syndrome	0.2	0.1	0.8	0.2	0.1	0.4	0	0	0.6
Constipation and incontinence									
Functional constipation	4.6	13.4	9.8	18.6	14.4	11.4	7.6	4.4	17.9
Nonretentive fecal incontinence	0.7	0.4	0.8	0.1	0.8	0.4	0.1	0	1.7

Table 4. FGIDs Prevalence (%) in Children Between Ages 11 and 18 Years, in All Involved Countries

	Croatia	Greece	Israel	Italy	Jordan	Lebanon	Macedonia	Serbia	Spain
Vomiting and aerophagia									
Adolescent rumination syndrome	0.1	0.3	0.2	0	0.1	0	0.1	0	0.1
Cyclic vomiting syndrome	0.4	0	0.9	0	2.3	0.4	0.4	0.1	0.6
Aerophagia	18.3	6.3	6.0	2.6	7.3	4.4	6.0	2.9	3.0
Abdominal pain–related FGIDs									
Functional dyspepsia	0.1	0.2	1.1	0.6	0.6	1.1	0.1	0.2	0.9
Irritable bowel syndrome	8.4	5.8	10.6	3.8	4.4	6.2	3.5	2.0	6.2
Abdominal migraine	10.7	5.2	16.2	5.1	5.8	4.7	6.6	1.9	11.9
Functional abdominal pain	0	0.7	0.4	0.8	0.3	0.6	0.1	0	0.6
Functional abdominal pain syndrome	0.6	0.5	0.7	1.1	0.3	0.2	0.4	0.7	0.2
Constipation and incontinence									
Functional constipation	6.9	15.8	16.6	14	20	14.6	22.3	2.5	8.8
Nonretentive fecal incontinence	0	0	0.6	0.1	0.1	0.2	0.9	0.8	0.6

Our data show that the prevalence of most FGIDs is higher in adolescents compared with children, and in girls compared with boys, even if the difference in the prevalence related to sex becomes statistically significant only in older children. Increased prevalence in girls is well known, and has been described in previous studies in single countries.[5,7,9,15] The same is true for age-related differences between sexes, which have been described previously by others, such as in the study from Sagawa et al,[9] which included 3976 Japanese adolescents ages 10 to 17 years.

Regarding the age-related differences in the prevalence, it has to be stated that because of the lack of correlation between children's and parents' answers on the QPGS-RIII, a comparison between the 2 groups is not possible because the differences could be owing either to age or to the reporter.

Evaluating the various FGIDs we found that, in accordance to single-country studies,[4,7,5,15] the most frequent FGID in both age groups was FC, with a prevalence ranging between 11.7% and 13.1%. Furthermore, the prevalence of IBS in our study was similar to previous reports from single countries,[5,9,12,15–17] and the same was true for aerophagia.[4,7,15] In contrast to previous studies,[5,9,11,15–17] we found a higher prevalence of AM, representing one of the most frequent disorders in our population, and a lower prevalence of functional abdominal pain (FAP) and FAP syndrome, in accordance with the studies by Lewis et al[4] and Bouzios et al.[7] It can be argued that AM rarely is diagnosed in clinical practice, whereas FAP and FAP syndrome are encountered much more commonly. The reason for these differences is unknown, and can be justified only partially by the diagnostic criteria used. In fact, it is known that the prevalence of AM estimated with Rome III criteria tends to be 4-fold higher than with Rome II criteria, probably because of the Rome III criteria's low negative predictive value, which can lead to the incorrect diagnosis of other FAP disorders such as AM, as stated by the Rome IV Committee.[3] However, all the other studies considered used the Rome III criteria, but not all of them found such a high prevalence of AM. Possible variations among the countries in the microbiome, diet, and genetic background could be a plausible hypothesis for the differences obtained in different studies.

Finally, we found significant variations in the prevalence of some FGIDs among different European countries. For example, we reported a significantly lower prevalence of FC in Croatia and Serbia, a higher prevalence of aerophagia in Croatia, a higher prevalence of AM in Israel and Spain (especially in younger children), and a higher prevalence of IBS in Israel. The reasons for these differences are not clear. However, considering the multifactorial pathogenesis of FGIDs, it can be speculated that they represent the result of the earlier-mentioned variability in the environment, diet, microbiome, and genetic background among the involved countries and suggest that the results of single-country studies may not be generalized. In addition, because the translations of the QPGS-RIII have not been validated in most of the countries, it also is possible that variations in understanding of the terminology among children of different countries could explain some of the differences found. Moreover, we found that Serbian prevalence values tended to be lower than in other countries for the majority of the disorders. This could be owing to the higher number of missing data from Serbian questionnaires compared with other countries.

There were some limitations to our study. This was a parent and patient report, which suffered from the potential biases inherent to this type of reporting. Also, our study did not collect data on demographic characteristics, socioeconomic status, or diet. The lack of demographic data do not ensure that the sample is representative of the country prevalence. Moreover, knowledge of these data could have allowed a better understanding of the reported intercountry differences. However, our study was not originally launched to evaluate the impact of these factors on the prevalence of FGIDs. In addition, most of the QPGS-RIII translations

Table 5. Country Comparison of FGID Prevalence in All Involved Countries

	Croatia (A)	Greece (B)	Israel (C)	Italy (D)	Jordan (E)	Lebanon (F)	Macedonia (G)	Serbia (H)	Spain (I)
4–10 years									
Aerophagia	B, C, D, E, F, G, H, I				B, C, D, H	B, H			H
Irritable bowel syndrome			B, G, H	H					B, E, G, H
Abdominal migraine			A, D, H			H			A, B, D, E, G, H
Functional abdominal pain									A, B, D, E, G
Functional constipation		A, G, H	A, H	A, C, F, G, H	A, G, H	A, H			A, C, G, H
Nonretentive fecal incontinence									D, G, H
11–18 years									
Cyclic vomiting syndrome					A, B, D, F, G, H				
Aerophagia	B, C, D, E, F, G, H, I		D		D, H, I		D		
Irritable bowel syndrome	D, G, H	H	D, E, G, H			H			H
Abdominal migraine	B, D, E, F, H	H	A, B, D, E, F, G, H	H	H		H		B, D, E, F, G, H
Functional constipation	H	A, H, I	A, H, I	A, H, I	A, H, I	A, H	A, D, F, H, I		H

NOTE. Each country is identified by a letter (eg, Croatia = A; Greece = B; and so forth). Each column refers to a single country; the letters in the rows identify the countries in which the prevalence is significantly lower compared with the country of the column. The prevalence of each disorder in all the countries is shown in Tables 3 and 4.

have not been validated. Nevertheless, the forward/backward translation, and the availability of the study staff to ensure understanding of the QPGS-RIII, should have ensured the reliability of the questionnaires. Finally, because methodologies in the different study sites have not been checked, it is possible that subtle differences in the sampling procedures or translation issues have contributed to the country differences.

The major strength of this study was the large number of participants. Also among the strengths was the central analysis of the data, securing the uniformity in both symptom-based diagnosis of FGIDs and in the processing of the missing data.

This study evaluated the prevalence of FGIDs in a very large sample of children and adolescents from the Mediterranean–European area. Our findings confirm that FGIDs are found commonly in children and adolescents, especially girls, and that their frequency increases with age. Most interestingly, the prevalence of FGIDs varied significantly among different Mediterranean countries, suggesting that in fact there may be differences in genetic background, diet, environment both physical and socioeconomic, and microbiome. Further multinational studies are needed to evaluate the impact of demographic characteristics, socioeconomic status, and diet on the occurrence of FGIDs, allowing a better understanding of the reported intercountry differences in the prevalence of the various FGIDs.

References

1. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. Gut 1999;45(Suppl I):I60–I68.
2. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527–1537.
3. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. Gastroenterology 2016. Epub ahead of print.
4. Lewis ML, Palsson OS, Whitehead WE, et al. Prevalence of functional gastrointestinal disorders in children and adolescents. J Pediatr 2016;177:39–43.
5. Saps M, Nichols-Vinueza DX, Rosen JM, et al. Prevalence of functional gastrointestinal disorders in colombian school children. J Pediatr 2014;164:542–545.
6. Zablah R, Velasco-Benitez CA, Merlos I, et al. Prevalence of functional gastrointestinal disorders in school-aged children in El Salvador. Rev Gastroenterol Mex 2015; 80:186–191.
7. Bouzios I, Chouliaras G, Chrousos GP, et al. Functional gastrointestinal disorders in Greek children based on ROME III criteria: identifying the child at risk. Neurogastroenterol Motil 2017;29:3.
8. Helgeland H, Flagstad G, Grøtta J, et al. Diagnosing pediatric functional abdominal pain in children (4–15 years old) according to the Rome III criteria: results from a Norwegian Prospective Study. J Pediatr Gastroenterol Nutr 2009; 49:309–315.

9. Sagawa T, Okamura S, Kakizaki S, et al. Functional gastrointestinal disorders in adolescents and quality of school life. J Gastroenterol Hepatol 2013;28:285–290.
10. Altamimi EM, Al-Safadi MH. Abdominal pain-predominant functional gastrointestinal disorders in Jordanian school children. Gastroenterology Res 2014;7:137–142.
11. Korterink JJ, Diederen K, Benninga MA, et al. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS One 2015;10:e0126982.
12. Udoh E, Devanarayana NM, Rajindrajith S, et al. Abdominal pain-predominant functional gastrointestinal disorders in adolescent Nigerians. J Pediatr Gastroenterol Nutr 2016; 62:588–593.
13. Scarpato E, Quitadamo P, Roman E, et al. Functional gastrointestinal disorders in children: a survey on clinical approach in the Mediterranean area. J Pediatr Gastroenterol Nutr 2017; 64:e142–e146.
14. Walker L, Caplan A, Rasquin-Weber A. Manual for the Questionnaire on Pediatric Gastrointestinal Symptoms. Nashville, TN: Vanderbilt University Medical Center, 2000.
15. Játiva E, Velasco-Benitez CA, Koppen IJ, et al. Prevalence of functional gastrointestinal disorders in schoolchildren in Ecuador. J Pediatr Gastroenterol Nutr 2016;63:25–28.
16. Lu PL, Saps M, Chanis RA, et al. The prevalence of functional gastrointestinal disorders in children in Panama: a school-based study. Acta Paediatr 2016;105:e232–e236.
17. Devanarayana NM, Mettananda S, Liyanarachchi C, et al. Abdominal pain-predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology, and association with emotional stress. J Pediatr Gastroenterol Nutr 2011;53:659–665.

Reprint requests
Address requests for reprints to: Annamaria Staiano, MD, Section of Paediatrics, Department of Translational Medical Sciences, University of Naples Federico II, Via S. Pansini, 5, 80131 Naples, Italy. e-mail: staiano@unina.it; fax: (39) 081-7463116.

Conflicts of interest
The authors disclose no conflicts.

Funding
This project was funded in part by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Appendix. Mediterranean–European Area Project Collaborating Group

Panayota Kafritsa (First Department of Paediatrics, University of Athens, Athens Children's Hospital "Agia Sophia," Athens, Greece), Sandra Brusa (Department of Maternal and Child Health, Paediatrics and Neonatology Unit, S. Maria della Scaletta Hospital, Imola (BO), Italy), Angelo Campanozzi (Institute of Paediatrics, University of Foggia, Foggia, Italy), Claudio Romano (Unit of Paediatrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi," University of Messina, Messina, Italy), Silvia Salvatore (Department of Experimental and Clinical Medicine, Paediatrics, University of Insubria, Varese, Italy), Evelina Kotzakioulafi (Nutrition and Dietetics Department, School of Food Technology and Nutrition, Technological Education Institute, Thessaloniki, Greece), Josefa Barrio (Department of Paediatrics, Hospital Universitario de Fuenlabrada, Madrid, Spain), Maria Luz Cilleruelo (Department of Paediatrics, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain), Mercedes Juste (Department of Paediatrics, Hospital Universitario San Juan, Alicante, Spain), Carolina Gutiérrez-Junquera (Department of Paediatrics, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain), Tena Trbojević and Lana Ivković (Referral Centre for Paediatric Gastroenterology and Nutrition, "University Children's Hospital," Zagreb, Croatia).

3.2 *Functional Chronic Constipation: Rome III Criteria versus Rome IV Criteria*

Functional constipation is one of the most common FGIDs in children and adolescents, as confirmed by data from the MEAP project presented in the previous section of this chapter (Section 3.1.2). It is characterized by difficult, painful, and infrequent evacuation of hard stools, with symptoms that frequently occur early in life, around 2.3 years (44), and that may have a negative impact on quality of life, school performance, and social interactions (45).

Diagnostic approach to FC is of paramount importance, since a correct diagnosis allows an early therapeutic intervention. Currently, the diagnosis of FC is based on the Rome IV criteria (3), which represent the update of the Rome III criteria (2). In Rome IV criteria minor changes have been made: a) in the neonate/toddler group, the age limit for the diagnosis of functional dyschezia has been brought up to 9 months, and typical symptoms of infant dyschezia (e.g. straining and crying) have been associated also with unsuccessful passage of stools, and not only with successful defecations; b) in the child/adolescent group, the duration of symptoms needed to fulfill the criteria for diagnosis has been decreased from 2 to 1 month; c) a differentiation between children who are/are not toilet trained has been introduced, to help the recognition of faecal incontinence even in toddlers.

Taking account of these modifications, we decided to perform a prospective study to evaluate the diagnostic agreement between the Rome III and Rome IV criteria, and to estimate the effect on prevalence established using the related two questionnaires. We enrolled 215 children, divided in 2 age groups: 81 neonates/toddlers aged <4 years (mean age 14.6±7.2 months), and 134 children/adolescents aged 4-17 years (mean age 111.5±46.3 months). Our data show that, despite the reduction in the symptoms duration, the Rome IV criteria have the same applicability of the Rome III criteria for the diagnosis of functional defecation disorders (19% vs 17.6%, respectively; Cohen's κ test agreement κ 0.72). The prevalence of FC was assessed through the questions on defecation frequency (<2 times/week), stool consistency, painful defecation, stool withholding behavior, large diameter stools and faecal incontinence. Prevalence of FC was 17.6% with Rome IV criteria, and

19% with Rome III (*P*=.47). So, despite the reduction in the symptom duration, we did not miss a significant number of diagnoses of FC.

Considering the neonate/toddler group, we found that 28% reported hard stools, 8% painful defecations, 5% large diameter stools, 4% faecal incontinence, and 1% a bowel frequency ≤2 times /week, according to both questionnaires. In the child/adolescent group, 29.8% reported painful defecation, 28% faecal incontinence, 8% large diameter stools, and 7% a bowel frequency ≤2 times /week, according to both questionnaires. On the contrary, we found that prevalence of hard stools was 19.4% with Rome IV, and 23.1% according to Rome III criteria (*P*=.1). Finally, in Rome IV criteria a differentiation has been made between children who are toilet trained and children who are not. In accordance with previous literature (46), we found that 30% of children aged 0-4 years had acquired toilet training skills (median age 27.6 months).

In conclusion, our study highlighted that the new Rome IV criteria have the same applicability of the Rome III criteria. Moreover, we demonstrated that, despite the reduction in the symptom duration, the new Rome IV criteria do not fail to diagnose children with FC and that they may improve the treatment outcomes because of an earlier diagnosis.

The results of this study have been submitted to *The Journal of Paediatrics* in 2017.

Elsevier Editorial System(tm) for The Journal of Pediatrics

Manuscript Draft

Manuscript Number:

Title: FUNCTIONAL CHRONIC CONSTIPATION: ROME III CRITERIA VERSUS ROME IV CRITERIA

Article Type: Original Article

Keywords: constipation; diagnosis; questionnaires; Rome III criteria; Rome IV criteria

Corresponding Author: Dr. Annamaria staiano, M.D.

Corresponding Author's Institution: University of Naples Federico II

First Author: Caterina Strisciuglio, MD

Order of Authors: Caterina Strisciuglio, MD; Marina Russo, MD; Elena Scarpato, MD; Dario Bruzzese, Dr; Casertano Marianna; Annamaria staiano, M.D.

Abstract: Background and Aims: Functional constipation (FC) is one of the most common functional gastrointestinal disorders, diagnosed according to the Rome criteria. In 2016, the revised pediatric Rome IV criteria were published. In this study, we aimed to evaluate the agreement between Rome III and Rome IV criteria for the diagnosis and the prevalence of FC.
Material and Methods: Children from infancy to 17 years otherwise healthy seen for a well-child visit, were recruited for the study. A prospective longitudinal design was used. The Questionnaires on Pediatric Gastrointestinal Symptoms (QPGS) for parents of infants and toddlers up to 4 years age (Form A), for parents of children and adolescents from 4 up to 10 years (Form B) and for children and adolescents aged 10 to 17 years (Form C) were used for diagnosis of FC. Cohen kappa coefficient (k) was used to measure agreement between the two questionnaires. The prevalence of FC was assessed based on the questionnaires according to the Rome III and Rome IV criteria.
Results: 215 children (mean age, 47.6 months; 104 males) were screened. There was no statistically significant difference in the diagnosis of FC prevalence between Rome IV and Rome III criteria (38/215 [17.6%] vs 41/215 [19.0%]; P .034) in any of the groups. The agreement Cohen's kappa test showed k= 0 .72.
Conclusion: Our study demonstrates that the new Rome IV have the same applicability of Rome III criteria for the diagnosis of FC, despite the reduction in the symptoms duration. This is of key importance in the management of childhood FC, since a delay in diagnosis is negatively related to recovery.

FUNCTIONAL CHRONIC CONSTIPATION: ROME III CRITERIA VERSUS ROME IV CRITERIA

Marina Russo[1*], Caterina Strisciuglio[2*], Elena Scarpato[1], Dario Bruzzese[3], Marianna Casertano[2] and Annamaria Staiano[1]

[1] Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Naples [2] Department of Women, Child and Specialist Surgery, University of Campania "Luigi Vanvitelli", Naples[3] Department of Public Health, University of Naples "Federico II", Naples.

*Marina Russo and Caterina Strisciuglio participated equally in this study.

Abbreviations: FC Functional Constipation – BSS Bristol stool form – QPGS Questionnaire on Pediatric Gastrointestinal Symptoms

Key words: constipation, diagnosis, questionnaires, Rome III criteria, Rome IV criteria

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to declare.

Word count: 3063

Address all correspondence to:
Annamaria Staiano, MD
Department of Translational Medical Sciences
Section of Pediatrics
University of Naples, Federico II
Via S. Pansini, 5
80131 Naples, Italy
Tel: +39(0)817462679
E-mail: staiano@unina.it

Introduction

Functional constipation (FC) is a common defecation disorder in children, characterized by difficult, painful, and infrequent evacuation of hard stools. The prevalence of FC in the pediatric population ranges between 0.7%-29.6% and it has been reported to have a high impact on health system costs (1,2). Symptoms often occur early in life; a recent study from the US has shown that the median age of onset of FC is 2.3 years (3). Constipation symptoms may lead to reduction in health related quality of life, poor school performances and difficult social interactions at a time that the child is known to lay social and educational foundations for its future (4-5). Because FC is such a major pediatric health care problem occurring at a young age, it is of great importance to diagnose it accurately and promptly. A correct diagnosis allows early therapeutic intervention, which is fundamental in the management of childhood FC; indeed a delay in the diagnosis and in the subsequent treatment is negatively related to recovery (4). Currently, the diagnosis of FC is based on the new Rome IV criteria (5), which are the updated version of the Rome III criteria (6) (Table I). Only minor changes have been made in the Rome IV diagnostic criteria compared to the previous Rome III criteria. In the group of neonate/toddlers based on the study by Kramer et al. (7), the age limit for the diagnosis of functional dyschezia now has been brought up to 9 months (6). Moreover, also symptoms typical of infant dyschezia such as straining and crying have been associated with unsuccessful passage of stools and not only with successful defecation. In the group of child/adolescent the only modification is the decrease from 2 months to 1 month in the duration of symptoms needed to fulfill the criteria for the diagnosis. In accordance with the latest European and the North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) constipation guidelines (8), a shorter duration of symptoms is needed for the definition of FC in the child/adolescent group. Finally, in Rome IV criteria, currently there is a differentiation between children who are toilet trained and children who are not. This might help to better recognize, even in toddlers, fecal incontinence and the presence of large stools.

We aimed to evaluate the agreement between Rome III and Rome IV criteria for the diagnosis of FC and the effect of the related two questionnaires on establishing the prevalence of FC.

Methods

Subjects

Study subjects were consecutively recruited among otherwise healthy children between infancy and under age 18 years, referred to general practitioners, school physicians, and pediatricians for routine well-child visits.

Ethical considerations

Written informed consent was obtained from participants' parents, and the assent was obtained for all patients older than 10 years. The study was approved by the Institutional Review Board of the University of Naples "Federico II".

Measures and Procedures

The Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS) is a validated and scored research instrument designed to classify gastrointestinal symptoms associated with FGIDs according to the Rome III and IV criteria (5,6). Because diagnostic criteria are distinct for infants and toddlers (from 0 to under 4 years) and for children and adolescents (from 4 to under 18 years), each questionnaire is presented in 3 forms: Form A, for parents of infants and toddlers up to age 4 years; Form B, for parents of children and adolescents age 4 up to 10 years; and Form C, for children and adolescents age 10 to 17 years. All 3 forms include sociodemographic and medical/developmental information.

Parents of all children younger than 10 years and adolescents aged 10 to 17 years completed the age related QPGS of both Rome III and Rome IV criteria in the waiting room. A

research assistant introduced the questionnaires and was present to assist if needed. Compilation of both questionnaires took about 10 minutes.

Questions were posed concerning the main characteristics of children's bowel habits: frequency of bowel movements, consistency of stools, onset of constipation symptoms, family history of constipation, hard or painful bowel movements, urgency or feeling of an unfinished bowel movement, mucus in stool, history of large-diameter stools that may block up the toilet, withholding stools for fear of pain, squeezing the legs or buttocks together (retentive posturing), fecal incontinence (staining or soiling) during the day and/or night, a large fecal mass in the rectum, and the presence of associated symptoms.

All data were analyzed to establish how many patients met the Rome III, the Rome IV or both criteria.

Statistical Analysis

Continuous data are expressed as mean standard deviation (SD). Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY). For categorical variables the $\chi 2$ test,, with or without exact correction, or the Fisher's exact test were used where appropriate. To test the agreement of the Rome III and Rome IV criteria with regard to constipation the Cohen's measure was applied. A 2-sided P value <0.05 was considered statistically significant.

Results

In a 6-month period, 220 children (mean age, 47 months; 104 males) were consecutively screened. Five of these patients were excluded because their parents were not able to answer the QPGS questionnaires. Clinical and demographic characteristics of the 215 children enrolled, are shown in Table 3. Functional defecation disorders were not diagnosed significantly more often by Rome III (41 [19%]) than by Rome IV criteria (38 [17.6%]) and the agreement Cohen's κ test showed a good agreement between fulfillment of the criteria for FC according to the Rome III and Rome IV definitions (κ 0.72).

In the 4-17 years group, 28 patients (20%) were positive under Rome IV criteria and the same number (20%) was positive under Rome III criteria. In the 0 months to 4 years group, 10/81 (12.3%) were positive under Rome IV criteria and 13/81 (16%) were positive under Rome III criteria (Table II). In particular, in the sub-group 0-6 months 2/35 children (5%) were positive under Rome IV criteria and just 1/35 patient under Rome III criteria (2%). No statistically significant difference was reported in the diagnosis of FC between the Rome IV and the Rome III criteria in each of the three groups (P=0.18, P=0.34,P=1;respectively).

The prevalence of FC was assessed based on the questions regarding defecation frequency (<2 times per week), stool consistency, painful defecation, stool withholding behavior, large diameter stools and fecal incontinence.

Applying the Rome IV questionnaire the global prevalence of FC was 17.6% (38/215). Using the Rome III questionnaire it was 19% (41/215); this difference was not statistically significant (P =0.47). Thirty-eight patients/215 (17.6%) fulfilled both the Rome III and the Rome IV criteria for constipation. Three patients /215 (1.3%) fulfilling the Rome III criteria for FC did not satisfy the Rome IV criteria. These three patients were all from the group aged 0 to 4 years (Table II). All these patients were considered constipated according to Rome III questionnaire, but not using the Bristol Stool Scale, present in the Rome IV questionnaire, which defines bowel consistency. Fecal incontinence was present in 42/215 (19.5%) subjects, all from the children and adolescents group.

Subgroup analysis

Neonate and Toddler group

Looking at the clinical characteristics of the neonate and toddler group (0-4 years old) we found that 1/81 (1%) patient showed a bowel frequency ≤2 times /week, 4/81 had large diameter stools and 10/81 (28%) reported hard stool according to both questionnaires. Regarding painful defecations 7/81 (8%) patients were identified according to both Rome III and Rome IV, all were

from 7 month to 4 years of age. Fecal incontinence was present in 4/81 (4%) according to Rome III and Rome IV questionnaires (Table III).

Child and Adolescent group

In the child–adolescent group (4-17 years old) 10/134 (7%) patients showed a bowel frequency ≤2 times /week according to both Rome III and Rome IV criteria. Moreover 26/134 (19.4%) reported hard stool according to Rome IV questionnaire, while 31/134 (23.1%) according to Rome III questionnaire (p 0.1). Regarding painful defecation 40 children /134 (29.8%) were identified. 11/134 (8%) had large diameter stools. Fecal incontinence was present in 38/134 patients (28%) according to both Rome III and Rome IV criteria (Table III).

DISCUSSION

Our study shows that the new Rome IV criteria have the same applicability of the Rome III criteria for the definition of FC, despite the reduction in the symptoms duration. This is very important because it is well know that an earlier diagnosis improves the outcome of childhood with FC. In a study of Bongers et al, they demonstrated that one of the factors of constipation's recurrence in adulthood was a longer delay between onset of symptoms and first visit, together with an older age at onset and lower defecation frequency at study entry (9). We showed that even reducing the time of symptoms presentation, we did not miss any diagnosis. Indeed, we found that the overall prevalence of constipation was 19% according to Rome III criteria and 17.6% according to Rome IV criteria.

A systematic review of the available literature reported that the global prevalence of childhood FC ranges from 0.7% to 30% (6,7). According to this review (1) Asian countries seem to have a lower prevalence of constipation (median 10.8%), compared to North America (16%),

Europe (19.2%) and Oceania (19.7%). The authors suggested that the reason for this discrepancy is maybe due to diverse cultural, dietary, genetic, environmental and socioeconomic conditions and different health care systems. Although, there is also a lack of uniformity in the criteria used for the diagnosis, since not all of these studies adopted Rome III criteria. In our study, we found a fair agreement between Rome IV and Rome III criteria in establishing the prevalence of FC.

Concerning the prevalence of functional gastrointestinal disorders in infants and toddlers, only limited studies using the Rome III criteria have been published. [8,9]. In these studies the prevalence in toddlers was reported to be higher than in infants (8,9), which is in line with recent findings from a retrospective chart review study, which described that the median age of onset of functional constipation in children was 2.3 years (11). In accordance with these previous study, we found that the prevalence of FC was lower in the neonate group according to both Rome III and Rome IV criteria, whereas it was higher in the toddler's group.

In the Rome IV questionnaires, another change has been the introduction of the Bristol stool form scale for the assessment of stool consistency in the group of children and adolescent. Indeed, we found a different percentage of patients reporting hard stools according to Rome III and Rome IV questionnaires; however, this difference did not reach statistical significance regarding the FC prevalence. Therefore, our results are in accordance with the study from Koppen et al., which demonstrated that the agreement between the Bristol stool form scale and the parental report for assessing the prevalence of FC is excellent (12). As the previous authors reported, we also demonstrated that the introduction of the Bristol stool form did not affect the assessment of the prevalence of FC. This is most likely because the Rome criteria encompass more criteria than stool consistency alone. Indeed the Rome III criteria for hard and painful stools are a combined criterion and children fulfill these criteria, if they have either hard stools or painful defecation. This decreases the impact of stool consistency alone in diagnosing FC.

Finally, in Rome IV criteria a last differentiation has been made between children who are toilet trained and children who are not, expecting this could be relevant for the criterion of fecal incontinence and for the description of large stools. In our study, 30% of children with an age between 0-4 years had acquired toilet training skills with a median age of 27,6 months in

accordance with previous literature (13). However, in our population fecal incontinence was reported only in four children from 0 to 4 years. We had a global prevalence of 19.5% for fecal incontinence (FI), this is in line with the observation that FI is only present in 20% of children with FC treated in primary care (14,15).

The strength of our study is that we have drawn these children from a large general outpatient clinic based sample and had an adequate number of cases to have a good statistical power and draw conclusions. Furthermore, we "diagnosed" FC not only on the basis of a questionnaire, but we also included a physical examination. Indeed, it is still important to recognize that a questionnaire is only a screening tool, and an evaluation by a physician is always necessary to actually diagnose functional defecation disorders.

In summary, this study highlights that the new Rome IV criteria have the same applicability of the Rome III criteria. We conclude that the new Rome IV criteria do not fail the diagnosis of constipation, despite the reduction in the symptoms duration. However, they may improve the outcome in the treatment of FC due to an earlier diagnosis.

Bibliography

1) Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Prac Res Clin Gastroenterol 2011;25:3-18.
2) van den Berg MM, Benninga MA, DiLorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006;101:2401–9.
3) Bongers MEJ, van Dijk M, Benninga MA, Grootenhuis MA. Health related quality of life in children with constipation-associated fecal incontinence. J Pediatr 2009;154:749-53.
4) Chogle A and Saps M. Yield and cost of performing screening tests for constipation in children. Can J Gastroenterol. 2013 Dec;27(12):e35-8. Epub 2013 Nov 13.

5) Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527-37.

6) Hyams J.S., Di Lorenzo C., Saps M, Shulman RJ, Staiano A, van Tilburg M.Childhood Functional Gastrointestinal Disorders: Child/Adolescent. Gastroenterology 2016;150:1456–1468

7) Kramer EA, den Hertog-Kuijl JH, van den Broek LM, van Leengoed E, Bulk AM, Kneepkens CM, et al. Defecation patterns in infants: a prospective cohort study.Arch Dis Child. 2015 Jun;100(6):533-6.

8) Evaluation and treatment of constipation in children: summary of updated recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2006;43:405–7

9) Bongers MEJ, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics 2010;126:e156-62

10) Devanarayana NM, Rajindrajith S. Association between constipation and stressful life events in a cohort of Sri Lankan children and adolescents. J Trop Pediatr 2010;56:144–8.

11) Devanarayana NM, Adhikari C, Pannala W, et al. Prevalence of functional gastrointestinal diseases in a cohort of Sri Lankan adolescents: comparison between Rome II and Rome III criteria. J Trop Pediatr, in press.

12) Koppen I.J, Velasco-Benitez C.A, Benninga MA, Di Lorenzo C, Saps M.Using the Bristol Stool Scale and Parental Report of Stool Consistency as Part of the Rome III Criteria for Functional Constipation in Infants and Toddlers

13) Schum TR, Kolb TM, McAuliffe TL, Simms MD, Underhill RL, Lewis M. Sequential acquisition of toilet-training skills: a descriptive study of gender and age differences in normal children. Pediatrics,2002;109:E48.

14) Loening baucke V. Prevalence rates for constipation and faecal and urinary incontinence Arch. Dis Child 2007;92 :486-9

15) Simeone D, Miele E, Boccia G, Marino A, Troncone R, Staiano A.Prevalence of athopy in children with chronic constipation. Arch Dis Child 2008;93:1044-7

Table I

Diagnostic criteria according to Rome III and Rome IV for child and adolescent

---

Rome III Criteria

Functional constipation: Must include 2 or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of irritable bowel syndrome:

- Two or fewer defecations in the toilet per week
- At least 1 episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet
- Criteria must be fulfilled at least once per week for at least 2 months before diagnosis.
- Non retentive fecal incontinence: Must include all of the following in a child with a developmental age of at least 4 years:
- Defecation into places inappropriate to the social context at least once per month
- No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms
- No evidence of fecal retention

Rome IV

Diagnostic Criteria for Functional Constipation Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

- 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
- At least 1 episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that can obstruct the toilet
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Table II. Distribution of the 215 patients according to the Rome III and Rome IV criteria, stratified for the 2 age classes

Age group	Roma III -/Rome IV-	Rome III -/ Rome IV+	Rome III+/ Rome IV-	Rome III+/ Rome IV+	p
Under 4 y (n81)	68 (83.9)	0	3 (3)	10(12.3)	0.18
4 to17 y (n134)	106(79.1)	0	0	28(20.8)	0.34
Total (n215)	174(80.9)	3(1.3)	0	38(17.6)	0.21

Data are number (%).

+, positive; -, negative.

Table III. Clinical characteristics of all study patients and according to age

Patient characteristics	All patients	4 to 17 years	<4 years	P
Number of patients	215	134	81	--
Mean age (months) (DS)	46,8	111.5 ± 46.3	14.6± 7.2	--
Females, n (%)	111(51.6)	75 (55.9)	36 (44)	0.590
Symptoms, n (%)				
Defecation frequency ≤2/week	11 (5)	10 (7)	1 (1)	0.41
Painful defecation	47 (21)	40(29.8)	7(8)	0.515
History of large-diameter stools	15(6)	11 (8)	4(4)	
Fecal incontinence (%)	42 (19.5)	38 (17)	4(4)	–

SD, standard deviation.

3.3 *Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique.*

The perception of the symptoms of FC is different between the patients, their parents and the healthcare professionals (HCPs). This causes a lack of agreement on the definitions and outcomes in therapeutic trials which makes it difficult to pool the results of different studies. In 2016, Kuizenga-Wessel et al. assessed the definitions and outcomes in randomized controlled trials conducted in children with FC, and confirmed the existence of a heterogeneity in these parameters (31). In order to address this issue, we decided to develop a core outcome set (COS), which is an agreed, standardized set of outcomes that guides on the measures that should be reported in a clinical trial. In the last few years, several COS were developed for various paediatric conditions, like acute diarrhoea, asthma, and infantile colic (47-49); all these studies used the Delphi technique to identify important outcomes.

The use of a COS improves healthcare and increases the capability to evaluate the efficacy of an intervention. However, it is mandatory to include items that matter to the stakeholders. For this reason, in the definition of the COS for FC, we decided to involve not only the HCPs, but also the parents and the patients. In fact, a study from Farrell et al. demonstrated that, when evaluating children with FC, the symptoms of concern differ between parents and HCPs (50).

The study was commissioned by the ESPGHAN, via the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT), and was structured in different steps. First, we conducted a survey among HCPs attending two international paediatric gastroenterology conferences, asking them to list up to five harmful/beneficial treatment outcomes which guided their clinical decision in the management of children with FC, in an inpatient and outpatient setting. The survey was completed by 109 HCPs from 28 different countries. For infants aged 0–1 years, the HCPs reported 89 outcomes for the outpatient setting, and 74 for the inpatient setting, while for children aged 1–18 years, they reported 76 outcomes for the outpatient, and 72 outcomes for the inpatient setting. Moreover, we collected data from 165 parents of children with

FC from 4 different countries (Belgium, Italy, Poland, and The Netherlands), who were asked to list up to five treatment outcomes that made them feel their child was managed adequately (comfortable), and five treatment outcomes that made them feel their child was managed inadequately (uncomfortable). Concerning children aged 0–1 years, 28 outcomes for the adequate, and 26 for the inadequate management were reported, while for subjects aged 1–18 years, 52 outcomes for the adequate and 45 for the inadequate management were reported. Finally, we also included 50 patients aged ≥12 years (mean age 14.8 years) who were asked the same questions as their parents, and reported 21 outcomes for the adequate and 22 for the inadequate management.

In the subsequent step, all the reported outcomes were classified in predefined domains, which are subcategories used to group similar outcomes. All the outcomes mentioned by ≥10% of the participants were included in a shortlist. The shortlists were sent to 80 HCPs who participated in the first survey, who were asked to rate the outcomes considering the clinical relevance, and to prioritise outcomes by selecting five outcomes they thought to be most important in guiding their clinical decision-making; 50/80 (63%) completed the questionnaire. The top 5 outcomes obtained for outpatient and inpatient settings were similar, so we combined them into one preliminary outcome set per age group. In addition, a new group of 80 parents and 50 (mean age 13.8 years) patients received the shortlists to rank the outcomes, and to prioritise them by selecting the five outcomes that made them feel most (un)comfortable. The outcomes that made the parents and the patients feel comfortable and uncomfortable were similar, so we created for each group a single preliminary outcome set. Finally, the five outcomes with the highest rank were selected for each group. In general, stakeholders agreed on the identification of the most important outcomes, even if some discrepancies were present. For example, parents and patients, but not HCPs found “abdominal pain” as an important outcome. In fact, although it is not a characteristic feature of FC, 10%–70% of children with FC refer abdominal pain, which can have an impact on quality of life, reducing social activities and leading to school absenteeism (51). Also for “defecation frequency” we found some discrepancy, with HCPs considering it one of the most important treatment outcomes, in contrast to

parents and patients. Those preliminary outcome sets for HCPs, parents and patients, were combined to create a draft COS that was presented to an expert panel during the COMMENT meeting at the ESPGHAN meeting in Athens, Greece (2016), to reach consensus regarding the final COS.

The final COS for children aged 0-18 years included: defecation frequency; stool consistency; painful defecation; quality of life of parents and patients; side effects of treatment; faecal incontinence, if age appropriate; abdominal pain, if age appropriate; school attendance, if age appropriate. We recommend researchers to use this COS to decrease outcome heterogeneity and improve comparability of study results.

The results of this study have been published in *BMJ Open* in 2017.

BMJ Paediatrics Open

Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique

Sophie Kuizenga-Wessel,[1] Nina Francesca Steutel,[1] Marc Alexander Benninga,[1] Thierry Devreker,[2] Elena Scarpato,[3] Annamaria Staiano,[3] Hania Szajewska,[4] Yvan Vandenplas,[2] Merit Monique Tabbers[1]

To cite: Kuizenga-Wessel S, Steutel NF, Benninga MA, *et al*. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. *BMJ Paediatrics Open* 2017;**1**:e000017. doi:10.1136/bmjpo-2017-000017

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2017-000017).

SK-W and NFS contributed equally.

Received 30 March 2017
Revised 14 June 2017
Accepted 14 June 2017

[1]Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands
[2]Department of Paediatrics, Free University of Brussels, Brussels, Belgium
[3]Department of Translational Medical Sciences - Section of Paediatrics, University of Naples Federico II, Naples, Italy
[4]Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland

Correspondence to
Ms Nina Francesca Steutel; n.f.steutel@amc.uva.nl

ABSTRACT

Objective Patients, their parents and healthcare professionals (HCPs) have a different perception regarding the symptoms of functional constipation (FC). Consequently, a lack of agreement exists on definitions and outcomes used in therapeutic trials of FC. Therefore, our aim was to develop a core outcome set (COS) for FC for children aged 0–1 year and 1–18 years.

Design and setting Prospective study design: primary, secondary and tertiary care settings.

Methods This COS was developed using a Delphi technique. First, HCPs, parents of children with FC and patients aged ≥12–18 years were asked to list up to five outcomes they considered relevant in the treatment of FC. Outcomes mentioned by >10% of participants were included in a shortlist. In the next phase, outcomes on this shortlist were rated and prioritised by HCPs, parents and patients. Outcomes with the highest scores were included in a draft COS. In a face-to-face expert meeting, the final COS was determined.

Results The first phase was completed by 109 HCPs, 165 parents and 50 children. Fifty HCPs, 80 parents and 50 children completed the subsequent phase. The response rate was between 63% and 100% in both steps. The final COS for all ages consisted of: defecation frequency, stool consistency, painful defecation, quality of life, side effects of treatment, faecal incontinence, abdominal pain and school attendance.

Conclusion The use of this COS for FC will decrease study heterogeneity and improve comparability of studies. Therefore, researchers are recommended to use this COS in future therapeutic trials on childhood FC.

What is already known about this subject?

- Heterogeneity in defining and measuring outcomes hampers comparison of efficacy trial results.
- A core outcome set (COS) for functional constipation (FC) can solve this issue.

What this study hopes to add?

- Involvement of healthcare professionals, parents and patients in the development of this COS for FC ensured that appropriate outcomes are measured.
- Final COS: defecation frequency, stool consistency, painful defecation, quality of life, side effects of treatment, faecal incontinence (if age appropriate), abdominal pain (if age appropriate) and school attendance (if age appropriate).

INTRODUCTION

Functional constipation (FC) is a common problem with a worldwide prevalence of 0.7%–29.6%.[1] Approximately 95% of children with constipation has FC, meaning that no organic or anatomic cause can be identified.

Standard definitions and criteria for FC exist but are rarely used in research and clinical practice.[2] In 1999, the first diagnostic criteria for paediatric functional gastrointestinal disorders were published: the Rome II criteria. Several studies showed, however, that these were too restrictive and were therefore modified into the Rome III criteria (2006) and recently into the Rome IV criteria.[3–8]

Differences in outcome definitions, measurement and reporting across clinical trials make it difficult to pool study results. Moreover, negative results are less likely to be reported, which can cause bias.[9] These problems can be tackled by developing agreed standardised sets of outcomes: core outcome sets (COS). COS serve as a guide for what should be measured and reported, but measured outcomes do not need to be restricted to the COS. Researchers can examine additional outcomes that might be of interest to them.[10–12]

COS increase consensus about the efficacy of an intervention and can improve healthcare, but it needs to contain outcomes that really matter to stakeholders. It is important to involve healthcare professionals (HCPs), parents and patients with FC when developing a COS. Especially since the literature

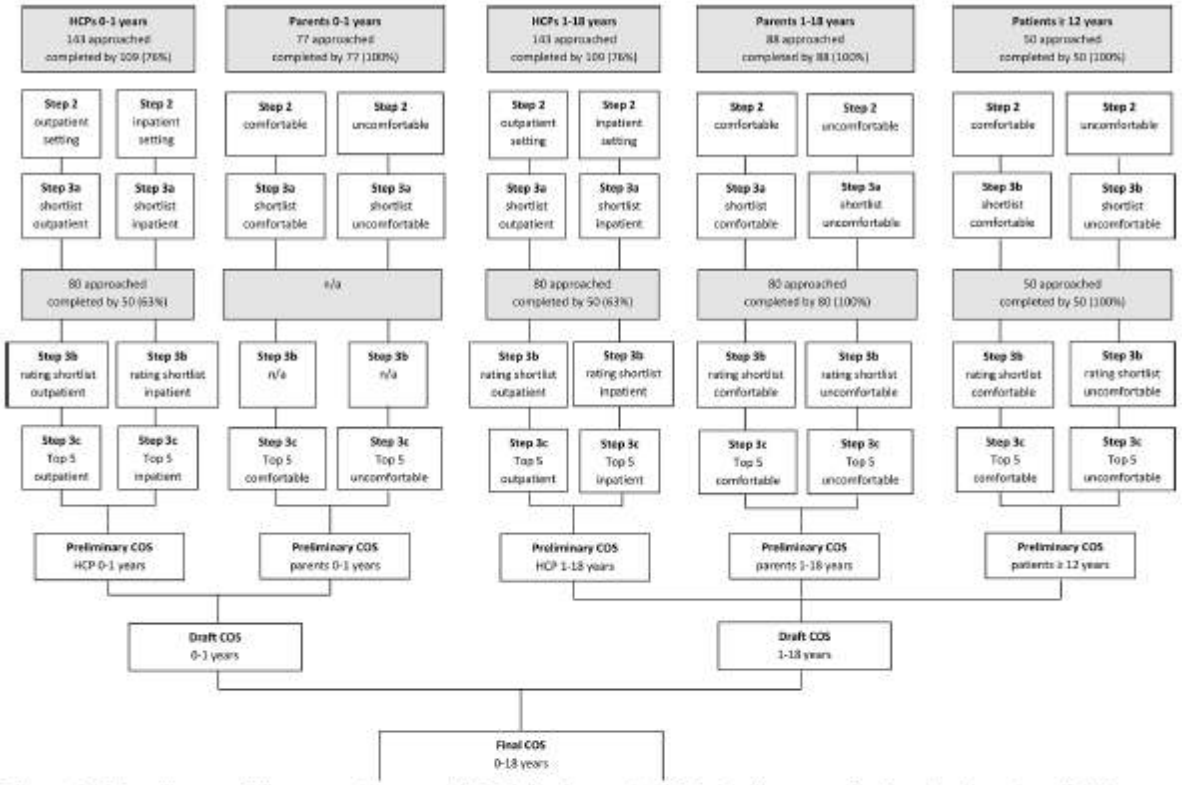

Figure 1 Flow diagram of the core outcome set (COS) development. HCPs, healthcare professionals; n/a, not applicable.

has shown that parents of children with FC have different concerns regarding their child's symptoms than HCPs.[15]

In recent years, several COS were developed for paediatric topics such as acute diarrhoea, infant colic and asthma.[14–16] These studies used the Delphi technique to identify clinically important outcomes for HCPs and parents. Sinha *et al* also involved patients ≥12 years in this process.[16]

This work was commissioned by the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT), an initiative of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). COMMENT agreed that consensus was needed on core outcomes for FC. Therefore, we aim to develop a COS for therapeutic trials in children with FC, in primary to tertiary care settings.

METHODS

The method for the COS development was based on previous publications.[14–16]

The Medical Ethics Review Committee confirmed that the Medical Research Involving Human Subjects Act did not apply to this study and therefore official approval by the committee was not required.

Descriptive statistics were used to summarise results.

In step 1, we systematically assessed how definitions and outcomes were defined in therapeutic randomised controlled trials of children with FC. Results were published in two manuscripts; one concerning children ≤4 years and another concerning children aged 1–18 years.[2 17]

Table 1 Country of practice of participating HCPs

Country of practice	No of HCPs
Italy	18
Israel	14
UK	10
Poland	9
The Netherlands	7
Mexico/Turkey	4
Belgium/Ecuador/Germany/Greece	3
Brazil/Czech Republic/New Zealand/ Norway/Romania/Sweden/Thailand/USA	2
Australia/Canada/Croatia/France/Japan/ Jordan/Spain/Philippines/Russia	1
Not reported	6
Total	109

HCPs, healthcare professionals.

Participants

In step 2, we collected important treatment outcomes among stakeholders.

A survey was conducted among HCPs visiting two international paediatric gastroenterology conferences. Participants were randomly approached and asked to list up to five harmful/beneficial treatment outcomes, which they considered important and guided their clinical decision-making in outpatient and inpatient settings, as outcomes could differ in these settings. Data regarding profession and country of practice were collected. We aimed to include ≥100 HCPs.[14]

We aimed to include 160 parents in four countries (Belgium, Italy, Poland and the Netherlands). Parents of children with FC (according to the Rome III criteria) were randomly approached by their child's treating physician to participate in this anonymous survey.[5 6] Parents were asked to list up to five treatment outcomes that made them feel comfortable or made them feel that their child was being treated adequately. The same question was asked for treatment outcomes that made parents feel uncomfortable or made them feel their child was being treated inadequately. Questions were translated into the native language of parents and answers were carefully translated back to English by their HCP.

As an anonymous pilot study, we assessed which treatment outcomes were relevant to patients ≥12 years, diagnosed with FC according to the Rome III criteria.[5 16]

We aimed to include 50 patients at the gastroenterology outpatient clinic of the Emma Children's Hospital/Academic Medical Centre, Amsterdam, the Netherlands. Children were randomly invited by their doctor and questions from the parental survey were adjusted for this population.

Outcomes

In step 3, reported outcomes were classified in predefined domains based on our findings in step 1 (defecation, associated symptoms, use of medication, treatment success, quality of life (QoL) and hospital).[2 17] Domains functioned as subcategories to group outcomes with similar characteristics. When necessary, we added new domains based on survey results. Similar outcomes were combined and outcomes mentioned by ≥10% of participants were included in a shortlist. The 10% threshold was chosen by COMMENT to keep shortlists manageable. Ten separate shortlists were created.

Next, shortlists for HCPs were sent to those that participated in the first survey and agreed to participate in the second survey as well. They were asked to rate outcomes on clinical relevance on a scale of 0–4 (0=not relevant, 4=very relevant) and to prioritise outcomes by selecting five outcomes they thought to be most important in guiding their clinical decision-making.

A new group of parents and patients with FC, from the same four countries, was invited to participate in this phase. They received shortlists for parental and patient outcomes, respectively, and were asked to rank outcomes on a scale of 0–4 (0=does not make me feel (un)comfortable, 4=makes me feel very (un)comfortable) and to prioritise them by selecting the five outcomes that made them feel most (un)comfortable. Surveys were returned anonymously. We aimed to include 80 parents and 50 patients.[14 16]

Subsequently, the five outcomes with the highest rank were selected for each group. This resulted in preliminary outcome sets for HCPs, parents and patients, for both age groups.

After combining the preliminary outcome sets for each age group, a draft COS was presented to an expert panel during the COMMENT Working Group (WG) meeting at the ESPGHAN meeting in Athens, Greece (2016). Here consensus (a unanimous decision) regarding the final COS was reached by discussion.

RESULTS

Flow diagram of COS development is shown in figure 1. One hundred and nine out of 143 (76%) HCPs completed the first questionnaire. They originated from 28 countries (table 1) and included 52 paediatric gastroenterologists, 24 general paediatricians, 17 fellows, 4 residents in paediatrics, 4 paediatric nutritionists, 3 researchers, 3 not specified, 1 intern and 1 general doctor. In some originating countries, healthcare is organised in such a way that paediatricians represent primary and secondary care as well.

For infants aged 0–1 years, 89 and 74 different outcomes were reported for outpatient and inpatient settings, respectively. For children aged 1–18 years, 76 and 72 different outcomes were reported for outpatient and inpatient settings, respectively. Table 2 shows an example of reported outcomes.

One hundred and sixty-five parents (100%) of children with FC completed the first questionnaire. Parents of infants aged 0–1 years reported 28 treatment outcomes that made them feel comfortable and 26 outcomes that made them feel uncomfortable. Parents of children aged 1–18 years reported 52 treatment outcomes that made them feel comfortable and 45 that made them feel uncomfortable.

Fifty patients ≥12 years (mean age 14.8 years; response rate 100%) completed the first questionnaire. Patients reported 21 outcomes that made them feel comfortable and 22 that made them feel uncomfortable.

Table 3 shows outcomes that were reported most frequently.

Creating a shortlist and final COS

Fifty out of 80 HCPs (63%) completed the second questionnaire regarding the rating and prioritising of outcomes on the shortlist. Since the top 5 of outcomes for outpatient and inpatient settings were rather similar (tables 4 and 5), we combined these into one preliminary outcome set per age group.

Table 2 Outcome measures as reported by healthcare professionals (HCPs) for the outpatient setting in children 1–18 years; step 2 (n=109)

Subdomain	Outcome	n
Domain: defecation		
Constipation	Duration of constipation	3
	Constipation	2
	Disappearance of constipation	2
Defecation frequency	Defecation frequency	60
	Regular soft bowel movements	1
Stool consistency	Stool consistency	34
	Quality of stools	3
Painful defecation	Pain with defecation	21
Domain: associated symptoms		
Abdominal pain/discomfort	Abdominal pain	42
	Discomfort	14
	No bowel distention	1
	Abdominal bloating	1
Faecal incontinence	Faecal incontinence	28
Bowel habits—other	Blood in stool	9
	Less anxious to defecate	3
	Normal bowel movement	2
	Less stool withholding	2
	Clarity of bowel movement	1
	Amount of stool	1
	Sensation of emptying	1
	Number of days without stool	1
	Emergency defecation on the way to school	1
Crying	Crying	4
Straining	Straining	3
Other gastrointestinal complaints	Less gas	1
Domain: quality of life		
Quality of life	Quality of life of child/parents	18
	Reduce stress in family	4
	Reduce parental anxiety	3
	Behaviour/energy/mood of child	3
	Normal social life	1
	Parent's discomfort	1
Domain: treatment success		
Faecal impaction	Rectal impaction	3
	Faecal impaction resolves	1
	Efficiency of disimpaction	1
	No effect of clean out	1
Satisfaction	Satisfaction of child/parent	4
	Patient satisfaction	1
	Parental satisfaction	1
Treatment compliance	Treatment compliance	5

Continued

Table 2 Continued

Subdomain	Outcome	n
Diet	Diet	3
	Improve appetite/normalisation of food intake	3
	Eating problems	2
	Less milk	1
	More fibre	1
	Nutritional status	1
Education	Parental reassurance	1
	Explanation of normal stool pattern	1
	Explanation of long duration of therapy	1
	Re-education	1
	Explanation about the disease	1
Improvement	Time to improvement of symptoms	2
	Improvement of clinical status	1
Adequate relief	Adequate relief rated by patients and parents	1
Lack of success	Lack of success	1
Domain: use of medication		
Medication	Use of laxatives	8
	Characteristics of medication (like taste and side effects)	8
	Re-education of pharmacological treatment	2
	No medication required	2
	Efficacy of medication	2
	Decrease of harmful medication	1
	Already used medication	1
Domain: hospital		
Hospital visits	Fewer consultations with HCPs	3
	Number of visits to outpatient department	1
Domain: other		
Growth	Thriving/growth	5
	Weight loss	1
Other	School attendance	4
	Manage anal fissure	3
	Sleep	2
	Frequency of voiding	1
	Costs of treatment	1
	Presence of alarm symptoms	1
	Adequate nursing by family	1
	Physical examination	1
	Colonic transit time	1
	Decrease of diameter of the rectum	1
	Control of sphincter	1

Three unclear outcomes such as 'familiar environment' and 'organisation' were not displayed.

In step 2, only five outcomes were mentioned by >10% of the parents of infants 0–1 years. It was unnecessary to approach new parents for step 3, as the rating and prioritising would not affect the top 5 outcomes.

All 80 parents of children 1–18 years (100%) completed step 3 . Tables 4 and 5 show the shortlists that were rated and prioritised by parents. Since outcomes that made parents feel comfortable and uncomfortable were rather

Table 3 Outcomes most often reported in step 2

Infants 0–1 years		
HCP	**Outpatient setting**	**Inpatient setting**
	Defecation frequency (51%)	Defecation frequency (46%)
	Abdominal pain (32%)	Stool consistency (28%)
	Stool consistency (30%)	Abdominal pain (20%)
Parents	**Comfortable**	**Uncomfortable**
	Stool consistency (39%)	Stool consistency (56%)
	Defecation frequency (38%)	Straining (38%)
	Crying (17%)	Defecation frequency (34%)
Children 1–18 years		
HCP	**Outpatient**	**Inpatient**
	Defecation frequency (55%)	Defecation frequency (46%)
	Abdominal pain (39%)	Abdominal pain (27%)
	Stool consistency (30%)	Stool consistency (26%)
Parents	**Comfortable**	**Uncomfortable**
	Defecation frequency (41%)	Abdominal pain (40%)
	Abdominal pain (39%)	Faecal incontinence (25%)
	Stool consistency (25%)	Defecation frequency (25%)
Patients	**Comfortable**	**Uncomfortable**
	Abdominal pain (66%)	Abdominal pain (58%)
	Defecation frequency (40%)	Defecation frequency (35%)
	Faecal incontinence (32%)	Faecal incontinence (28%)

HCP, healthcare professional.

similar for this age group, we combined these into one preliminary outcome set.

Fifty patients (mean age 13.8 years; response rate 100%) completed the rating and prioritising of outcomes (table 6). Outcomes that made patients feel comfortable and uncomfortable were rather similar and we combined these into one preliminary outcome set.

The preliminary COS of HCPs and parents of infants 0–1 years old were comparable. Therefore, these were combined into the following draft COS: defecation frequency, stool consistency, painful defecation, discomfort, crying, abdominal pain, treatment success, straining and QoL of parents.

We repeated this process for children 1–18 years but added the outcomes mentioned by patients aged ≥12 years. The preliminary COS of HCPs, parents and patients appeared to be comparable as well, except for the following outcomes: 'abdominal pain' (mentioned by parents and patients), 'treatment success' (parents) and 'school attendance' (patients). We combined outcomes into the following draft COS: defecation frequency, stool consistency, painful defecation, QoL (child and parents), faecal incontinence, abdominal pain, school attendance and treatment success.

The draft COS for both age groups was presented in a COMMENT WG meeting. Regarding the COS for 0–1 years, it was unanimously decided to exclude 'discomfort', 'abdominal pain' and 'crying' in the final COS, since these outcomes are non-specific and cannot with certainty be attributed to FC or the treatment effect. Additionally, it was decided to exclude 'straining', since 'painful defecation' was already included in the COS. 'Treatment success' was excluded as it is assumed to be a combination of the included outcomes.

Regarding the COS for 1–18 years, it was unanimously decided to add two outcomes mentioned by parents/patients: 'abdominal pain' and 'school attendance'. 'Treatment success' was excluded for the same reason as above.

Since the applicability of a treatment depends on a balance between benefits and side effects of that treatment, it is recommended to assess 'side effects' as part of the COS.[18] Although 'side effects of treatment' were mentioned by <10% of respondents, we added this outcome to the COS. The COS for infants 0–1 years therefore includes: defecation frequency, stool consistency, painful defecation, QoL of the parents and side effects of treatment. The COS for children 1–18 years includes: defecation frequency, stool consistency, painful defecation, QoL of patients and parents, faecal incontinence, abdominal pain, school attendance and side effects of treatment.

For practical reasons, we combined these into one final COS for all children aged 0–18 years (box 1).

DISCUSSION

HCPs, parents and patients ≥12 years were involved in a Delphi technique to develop a COS for children with FC aged 0–18 years. Stakeholders largely agreed on which outcomes were most important, but some discrepancies existed. Parents and patients found 'abdominal pain' more important than HCPs. Although it is not a characteristic feature of FC, 10%–70% of children with FC are suffering from abdominal pain which can have a large impact on their well-being.[19] Abdominal pain can lead to school absenteeism and reduce participation in social activities. Another discrepancy regarded 'defecation frequency': depending on the age group, 46%–55% of HCPs found this the most important treatment outcome, whereas parents and patients mentioned this less often as an important outcome.

Interestingly, most Rome IV criteria are represented in our COS, except for 'presence of a large faecal mass

Table 4 Shortlist outcome measures (rated and prioritised) for infants 0–1 years old

Rank	Outcome measures	Domain	Percentage	Average rating
Healthcare professionals				
Outpatient setting				
1	Defecation frequency	Defecation	96	3.14
2	Painful defecation	Defecation	94	2.98
3	Stool consistency	Defecation	82	3.20
4	Discomfort	Associated symptoms	74	2.28
5	Quality of life (parents)	Quality of life	64	1.76
6	Abdominal pain	Associated symptoms	36	1.44
7	Crying	Associated symptoms	36	0.18
8	Faecal incontinence	Associated symptoms	18	0.76
Inpatient setting				
1	Defecation frequency	Defecation	92	3.18
2	Stool consistency	Defecation	88	3.24
3	Painful defecation	Defecation	84	2.94
4	Discomfort	Associated symptoms	72	2.30
5	Quality of life (parents)	Quality of life	62	2.31
6	Time of hospitalisation	Hospital	52	1.82
7	Abdominal pain	Associated symptoms	28	1.50
8	Faecal incontinence	Associated symptoms	22	0.80
Parents				
Comfortable				
1	Stool consistency	Defecation	N/A	N/A
2	Defecation frequency	Defecation		
3	Crying	Associated symptoms		
4	Abdominal pain	Associated symptoms		
5	Treatment success	Treatment success		
Uncomfortable				
1	Stool consistency	Defecation	N/A	N/A
2	Straining	Associated symptoms		
3	Defecation frequency	Defecation		
4	Crying	Associated symptoms		
5	Painful defecation	Defecation		

N/A, not applicable.
Outcomes ranked 1 to 5 no background colour and outcomes ranked 6 to 8 (if applicable a darker colour to visualise they were excluded from the top 5.

in the rectum', 'retentive posturing' and 'large diameter stools' which were mentioned by 3%, 2% and 0% of HCPs, respectively. Furthermore, 'faecal incontinence' was mentioned as an important outcome for infants aged 0–1 years. A potential explanation for this could be that this was a Rome III criterion for children aged 0–4 years. Since this is very difficult to assess in children wearing diapers, the Rome IV criterion 'faecal incontinence' is only used as an additional criterion to diagnose FC in toilet-trained children.[8]

One of the strengths of this study is the high response rate. Furthermore, participation of physicians around the globe, involvement of parents from four European countries and inclusion of patients increase the generalisability of our COS. This study has some limitations. First, our study focused on children whose FC is managed by hospital paediatricians. In some participating countries, however, healthcare is organised in such a manner that paediatricians represent primary and secondary care as well. Although we included participants from around the globe, developing countries were under-represented which may limit the external validity of this COS in a developing country setting. Data collection from HCPs occurred at international paediatric gastroenterology

Table 5 Shortlist outcome measures (rated and prioritised) for children 1–18 years old

Rank	Outcome measures	Domain	Percentage	Average rating
Healthcare professionals				
Outpatient setting				
1	Faecal incontinence	Associated symptoms	94	3.63
2	Defecation frequency	Defecation	84	3.50
3	Painful defecation	Defecation	78	3.24
4	Stool consistency	Defecation	78	3.16
5	Quality of life (child/parents)	Quality of life	76	3.31
6	Abdominal pain	Associated symptoms	66	2.60
7	Discomfort	Associated symptoms	24	1.76
Inpatient setting				
1	Faecal incontinence	Associated symptoms	88	3.59
2	Defecation frequency	Defecation	86	3.48
3	Stool consistency	Defecation	78	3.24
4	Painful defecation	Defecation	74	3.18
5	Quality of life (child/parents)	Quality of life	70	2.98
6	Abdominal pain	Associated symptoms	52	2.54
7	Time of hospitalisation	Hospital	40	2.28
8	Discomfort	Associated symptoms	12	1.72
Parents				
Comfortable				
1	Quality of life (child and parents)	Quality of life	83	3.41
2	Abdominal pain	Associated symptoms	77	3.30
3	Faecal incontinence	Associated symptoms	76	3.24
4	Painful defecation	Defecation	66	2.96
5	Stool consistency	Defecation	65	3.16
6	Treatment success	Treatment success	64	3.08
7	Defecation frequency	Defecation	47	2.67
8	Complete information given by doctor	Other	36	2.81
Uncomfortable				
1	Lack of treatment success	Treatment success	88	2.40
2	Abdominal pain	Associated symptoms	84	2.95
3	Stool consistency	Defecation	78	2.57
4	Defecation frequency	Defecation	68	2.40
5	Faecal incontinence	Associated symptoms	62	2.28
6	Lack of information given by doctor	Other	44	1.92

Outcomes ranked 1 to 5 no background colour and outcomes ranked 6 to 8 (if applicable a darker colour to visualise they were excluded from the top 5.

conferences. This may have caused bias since these HCPs often treat patients with severe and long-lasting FC, and they could therefore have chosen different outcomes compared with primary care physicians. Also, patients ≥12 years were recruited in a tertiary care setting as a pilot study. Only recruiting patients in such a specialised setting might have led to biased results.

Furthermore, since answers were collected anonymously in both Delphi rounds, we were unable to assess any potential differences between respondents and non-respondents. The Delphi technique is well suited as a method for consensus building, but it is a time-consuming process, that requires active participation throughout the Delphi process, which can result in high dropout rates.[20] However, our response rates were 63%–100% in both steps.

Another potential limitation is the use of questionnaires that were developed in English and thereafter translated into

Table 6 Shortlist outcome measures of patients ≥12 years old

Rank	Outcome measures	Domain	Percentage	Average rating
Comfortable				
1	Abdominal pain	Associated symptoms	86	3.52
2	School absence	Treatment success	74	3.14
3	Faecal incontinence	Associated symptoms	66	2.86
4	Quality of life (child)	Quality of life	54	2.94
5	Defecation frequency	Defecation	52	2.58
6	Stool consistency	Defecation	42	2.46
7	Use of medication	Use of medication	16	1.92
Uncomfortable				
1	Abdominal pain	Associated symptoms	86	3.38
2	School absence	Treatment success	70	3.08
3	Faecal incontinence	Associated symptoms	68	3.06
4	Quality of life (child)	Quality of life	50	2.74
5	Defecation frequency	Defecation	48	2.48
6	Stool consistency	Defecation	40	2.42
7	Use of medication	Use of medication	22	2.18

Outcomes ranked 1 to 5 no background colour and outcomes ranked 6 to 8 (if applicable a darker colour to visualise they were excluded from the top 5.

Box 1 Final core outcome set for functional constipation in children 0–18 years

- Defecation frequency
- Stool consistency
- Painful defecation
- Quality of life of parents and patients
- Side effects of treatment
- Faecal incontinence, if age appropriate
- Abdominal pain, if age appropriate
- School attendance, if age appropriate

four different languages. Although this was done carefully, it is possible that this resulted in subtle changes in questions or answers. Some responses in step 2 were somewhat open to interpretation; therefore, we may have misinterpreted and incorrectly combined outcomes. Furthermore, not all outcomes mentioned by parents or patients were included in the final COS. The WG unanimously decided that these outcomes were non-specific for FC (crying, discomfort) or already included in the COS (straining, treatment success).

As mentioned before, a COS is the basis for what should be measured and reported in clinical trials, but researchers can add more outcomes if needed.[21] Selective reporting should be avoided by presenting results for both core outcomes and additional outcomes.

To enable comparison of trial results, there is not only a need for consensus regarding outcomes, we also need homogeneity in used definitions of FC. We recommend to use the recently published and internationally accepted Rome IV criteria for FC in future trials.[7]

COS have the potential to improve evidence-based healthcare, but their creation does not automatically lead to its implementation and it would therefore be valuable to assess how widely this COS is being implemented.

In conclusion, the COS for childhood FC (0–18 years) consists of defecation frequency, stool consistency, painful defecation, QoL and side effects. Faecal incontinence, abdominal pain and school attendance should be measured if age appropriate. We recommend researchers to use this COS to decrease outcome heterogeneity and improve comparability of study results.

Acknowledgements We thank all HCPs, parents and patients who completed the questionnaires, and JJ Korterink, MH Vriesman and K Wojtyniak for their help with the recruitment.

Contributors SK-W: participated in the design of the study, collected data, performed data analyses, drafted the initial manuscript and approved the final manuscript as submitted. NFS: participated in the design of the study, collected data, performed data analyses, drafted the initial manuscript and approved the final manuscript as submitted. MAB: participated in the design of the study, supervised drafting of the manuscript and approved the final manuscript as submitted. TD: collected data, participated in writing the manuscript and approved the final manuscript as submitted. ES: collected data, participated in writing the manuscript and approved the final manuscript as submitted. AS: participated in the design of the study, collected data and approved the final manuscript as submitted. YV: participated in the design of the study, collected data and approved the final manuscript as submitted. HS: participated in the design of the study, collected data and approved the final manuscript as submitted. MMT: participated in the design of the study, supervised drafting of the manuscript and approved the final manuscript as submitted.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Commissioned; externally peer reviewed.

Data sharing statement Tables with reported outcome measures of step 2 are available from the authors.

REFERENCES

1 Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol* 2011;25:3–18.
2 Kuizenga-Wessel S, Benninga MA, Tabbers MM. Reporting outcome measures of functional constipation in children from 0 to 4 years of age. *J Pediatr Gastroenterol Nutr* 2015;60:446–56.
3 Baker SS, Liptak GS, Colletti RB, *et al*. Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999;29:612–26.
4 Boccia G, Manguso F, Coccorullo P, *et al*. Functional defecation disorders in children: PACCT criteria versus Rome II criteria. *J Pediatr* 2007;151:e1:394–98.
5 Rasquin A, Di Lorenzo C, Forbes D, *et al*. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;130:1527–37.
6 Hyman PE, Milla PJ, Benninga MA, *et al*. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
7 Hyams JS, Di Lorenzo C, Saps M, *et al*. Functional disorders: children and adolescents. *Gastroenterology* 2016:S0016-5085(16)00181-5.
8 Benninga MA, Faure C, Hyman PE, *et al*. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2016:1443–55.
9 Benstoem C, Moza A, Autschbach R, *et al*. Evaluating outcomes used in cardiothoracic surgery interventional research: a systematic review of reviews to develop a core outcome set. *PLoS One* 2015;10:e0122204.
10 Wuytack F, Smith V, Clarke M, *et al*. Towards core outcome set (COS) development: a follow-up descriptive survey of outcomes in Cochrane reviews. *Syst Rev* 2015;4:73.
11 Gargon E, Williamson PR, Clarke M. Collating the knowledge base for core outcome set development: developing and appraising the search strategy for a systematic review. *BMC Med Res Methodol* 2015;15:26.
12 Clarke M, Williamson PR. Core outcome sets and systematic reviews. *Syst Rev* 2016;5:11.
13 Farrell M, Holmes G, Coldicutt P, *et al*. Management of childhood constipation: parents' experiences. *J Adv Nurs* 2003;44:479–89.
14 Karas J, Ashkenazi S, Guarino A, *et al*. . A core outcome set for clinical trials in acute diarrhoea. *Arch Dis Child* 2015;100:359–63.
15 Steutel NF, Benninga MA, Langendam MW, *et al*. Reporting outcome measures in trials of infant colic. *J Pediatr Gastroenterol Nutr* 2014;59:341–6.
16 Sinha IP, Gallagher R, Williamson PR, *et al*. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials* 2012;13:103.
17 Kuizenga-Wessel S, Heckert SL, Tros W, *et al*. Reporting on outcome measures of functional constipation in children: a systematic review. *J Pediatr Gastroenterol Nutr* 2016;62:840–6.
18 Boers M, Kirwan JR, Wells G, *et al*. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745–53.
19 Bharucha AE, Wald A, Enck P, *et al*. Functional anorectal disorders. *Gastroenterology* 2006;130:1510–8.
20 Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. *Int J Nurs Stud* 2001;38:195–200.
21 Kilic L, Erden A, Bingham CO, *et al*. The reporting of patient-reported outcomes in studies of
patients with rheumatoid arthritis: a systematic review of 250 articles. *J Rheumatol* 2016;43:1300–5.

Chapter 4
- Treating Functional Gastrointestinal Disorders -

4.1 *Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants*

Gastroesophageal reflux (GER) is a condition that occurs frequently in healthy infants, due to numerous physiological factors, and tends to resolve spontaneously in 95% of infants within 12 to 14 months of life (52). However, in some infants, it can cause a wide spectrum of distressing symptoms, such as cough, food refusal, irritability, regurgitation, and vomiting (53). In case of an uncomplicated recurrent regurgitation, it is important to recognize physiological GER, which is painless and does not affect growth.

The therapeutic management of GER is mainly based on non-pharmacological interventions (e.g. thickened feeds, smaller feeds, and body positioning), while drugs should be prescribed only to infants who do not benefit from conservative measures (32). However, even if most anti-reflux medications are associated with severe adverse effects (54), widespread use of empirical therapies in infants is still reported (55), as it has been demonstrated in our survey conducted in general practitioners from the Mediterranean-European area (56) and in a study conducted by Barron et al. which described that, between 1999 and 2004, the prescriptions of PPIs increased by approximately 800% (57). This approach reveals a need for harmless, efficacious symptomatic therapies in the management of infant GER in the daily practice, to reduce the dramatic increase in PPI prescriptions.

Previous studies conducted in infants demonstrated that sodium alginate is more effective than placebo in reducing the mean frequency and severity of vomiting (58, 59), and that, when associated with bicarbonates, it reduces the frequency, height, and acidity of reflux, with the same efficacy as acid suppressors, but no systemic effects (60). Since a new formulation containing magnesium alginate was developed (Gastrotuss Baby, DMG Italia SRL, Pomezia, Italy), we decided to perform a randomized, open-label, controlled trial to evaluate the efficacy on a GER symptom score of 3 different treatments: 1) reassurance with lifestyle changes combined and a magnesium (Mg) alginate

formulation plus simethicone; 2) reassurance with lifestyle changes and rice-starch thickened formula; 3) reassurance with lifestyle changes alone.

We enrolled 75 consecutive full-term, formula-fed infants (41 boys; median age 5 months; range 1-10), affected by infant regurgitation, according to the Rome III criteria (61), and no evidence of other chronic disease. Symptoms related to GER were evaluated using the Infant Gastroesophageal Reflux Questionnaire (I-GERQ, revised) (62), a validated questionnaire based on the characteristics of feeding, regurgitation, crying, bowel habits, stool alteration, weight gain, hiccups, respiratory symptoms, family history of GER and allergy, and parental suspicion of GERD. In case of a score >7, the subject was considered as affected by GER (63). Patients were then randomized to one of the 3 study groups: group A – consisting of 25 infants treated with reassurance and lifestyle changes + Mg alginate plus simethicone; group B – consisting of 25 infants treated with reassurance and lifestyle changes + rice-starch thickened non-hydrolysed formula; group C – consisting of 25 infants treated with reassurance and lifestyle changes. Eighty-nine percent of the subjects completed 1 month of treatment: patients treated with Mg alginate plus simethicone, and those treated with the thickened formula showed a significant reduction of symptoms ($P<.005$ and $P<.02$, respectively), with 48% of those treated with Mg alginate plus simethicone that were free of symptoms compared to 16% of those treated with the thickened formula ($P<.03$). Moreover, treatment with Mg alginate plus simethicone was more effective on GER symptoms than reassurance alone ($P<.0001$), while no statistical difference was found comparing thickened formula with reassurance alone ($P<.1$). Eighty-five percent of the subjects completed 2 months of treatment: all the 3 groups of patients, irrespective of the management, showed a reduction in the symptom score. However, Mg alginate resulted more effective in reducing the symptom scores, with a higher rate of symptom-free patients at both 4 and 8 weeks.

Our study demonstrated that Mg alginate plus simethicone was more rapid and effective, compared to thickened formula, on all the symptoms of GER evaluated, including irritability,

respiratory symptoms, vomiting and feeding compliance. Even if it is well known that GER is a benign condition that resolves spontaneously within 12 to 14 months of life, a non-systemic treatment can be prescribed to improve symptoms and reduce the distress for infants and their family.

The results of this study on the effect of magnesium alginate plus simethicone in the management of GER in infants have been published in *Journal of Pediatric Gastroenterology and Nutrition* in 2016.

Effect of Magnesium Alginate Plus Simethicone on Gastroesophageal Reflux in Infants

Dario Ummarino, Erasmo Miele, Massimo Martinelli, Elena Scarpato, Felice Crocetto, Elisa Sciorio, and Annamaria Staiano

ABSTRACT

Objectives: Gastroesophageal reflux (GER) is a frequently occurring condition in infants capable of causing distressing symptoms. The aim of our study is to evaluate the efficacy of Mg alginate plus simethicone (Gastrotuss Baby, DMG Italia SRL, Pomezia, Italy), compared with rice-starch–thickened formula or with reassurance alone, in the treatment of GER in infants.

Methods: The present randomized controlled trial was conducted in full-term infants affected by symptoms suggestive of GER, evaluated through a validated questionnaire (Infant Gastroesophageal Reflux Questionnaire Revised). The patients were randomized into 3 groups according to treatment (group A: Mg alginate plus simethicone; group B: thickened formula; group C: reassurance with lifestyle changes). Evaluation of symptom scores was performed after 1 month (T1) and 2 months (T2).

Results: A total of 64 (85.3%) of 75 enrolled infants (median age 5 months; range 1–10) concluded the study. After 1 month of treatment (T1), infants treated with Mg alginate plus simethicone showed a statistically significant improvement in symptoms compared with the thickened formula and reassurance ($P < 0.03$, < 0.0001, respectively). At the end of the study, all 3 groups of patients showed a significant reduction in symptom scores ($P < 0.002$, < 0.038, < 0.03, respectively). Median symptom score values were more significantly reduced in group A than in group B and in group C (group A vs group B $P < 0.002$; group A vs group C $P < 0.0001$; group B vs group C $P < 0.001$).

Conclusions: Mg alginate plus simethicone seems to be more efficacious on GER symptom scores than thickened formula and reassurance with lifestyle changes alone.

Key Words: alginate, gastroesophageal reflux, infants, reassurance, simethicone, thickened formula

(*JPGN* 2015;60: 230–235)

Received March 24, 2014; accepted July 23, 2014.

From the Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II," Naples, Italy.

Address correspondence and reprint requests to Annamaria Staiano, MD, Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II," Via S. Pansini, 5, 80131 Naples, Italy (e-mail: staiano@unina.it).

Supplemental digital content is available for the present article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of the present article on the journal's Web site (*www.jpgn.org*).

www.clinicaltrials.gov registration no.: NCT01858584

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000000521

Gastroesophageal reflux (GER) is a physiological condition that occurs several times per day in healthy infants, because it can be promoted by a number of physiological factors. GER in healthy infants, children, and adults can cause few or no symptoms (1,2). In infants, the most common symptoms associated with GER are irritability, cough, anorexia/food refusal, regurgitation, and vomiting (3–6). This condition tends to resolve spontaneously in 95% of infants within 12 to 14 months of life (7,8). Parents are more likely to be worried when vomiting is frequent, or when the infant cries constantly, and often seek medical help because of regular regurgitation.

According to the guidelines of the North American and the European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN), the therapeutic management of GER can be achieved by using nonpharmacological interventions such as body positioning, modification of feeding methods, or milk thickening, limiting drug administration to those infants who do not benefit from conservative measures or those with clinical complications of GER (1,2,9); however, widespread use of empirical antireflux medications in infants, both during hospital recovery and after discharge, has been reported (10). Most of these drugs have been reported to cause adverse effects (11,12).

The American management guidance for pediatricians suggests the use of alginate in physiological GER but does not recommend the use of surface agents where there are serious symptoms or with gastroesophageal reflux disease (GERD) complications (2); however, in the literature, there are conflicting results regarding the effect of alginate on GER symptoms in infants (1,2). Clinical studies showed that sodium alginate significantly decreases the mean frequency and severity of vomiting in infants compared with placebo (13,14). Moreover, it has been reported that sodium alginate, associated with bicarbonates, reduces the frequency, height, and acidity of reflux, showing the same efficacy as acid suppressors, with no systemic effects (15). The addition of sodium bicarbonate to the formulation contributes to the formation of a gel, converting it into carbon dioxide, which is entrapped within the forming foam. It then floats on the gastric content and preferentially enters the esophagus during reflux episodes (16). Recently, a new formulation containing magnesium alginate has been developed (Gastrotuss Baby, DMG Italia SRL, Pomezia, Italy). Magnesium alginate should offer the advantages of a 3-fold higher viscosity compared with sodium alginate (1000–1800 mPa vs 300–700 mPa) and reduce the sodium uptake for the patients. Nevertheless, the formulation has not yet been evaluated in clinical trials, either in adults or in children.

On the contrary, a placebo-controlled study with alginate in infants showed that although symptoms improved with therapy, the only objective change on combined multichannel intraluminal impedance/pH metry (pH/MII) evaluation was a minimal decrease in reflux height in the esophagus (17).

The aim of the present randomized, open-label, controlled trial was to evaluate the efficacy of 3 different treatments (reassurance with lifestyle changes and a magnesium alginate aluminum-free formulation plus simethicone, reassurance with lifestyle changes and thickened formula, and reassurance with lifestyle changes alone) on GER symptom score. Our secondary aim was to evaluate the safety and tolerability of magnesium alginate plus simethicone.

METHODS

The present prospective randomized, open-label, controlled trial was conducted from September 2012 to September 2013, in consecutive full-term, formula-fed infants, ages 1 to 12 months, affected by symptoms suggestive of GER. Infants were enrolled by 6 general pediatricians from the Italian National Health System. Each pediatrician enrolled consecutive patients with infant regurgitation defined according to the Rome III criteria (18). Evidence of chronic diseases, hepatic, renal, or cardiac diseases, metabolic or central nervous system diseases, or use of acid suppressor treatment (H_2-receptor antagonists or proton pump inhibitors [PPIs]), thickened formula, or a history of prematurity or atopy was considered an exclusion criterion.

A validated questionnaire (19) (Infant Gastroesophageal Reflux Questionnaire [I-GERQ], modified) was completed at enrollment and during the follow-up visits. The I-GERQ Revised is a 35-item questionnaire based on the characteristics of regurgitation (quantity and frequency), feeding, bowel habits, crying, hiccups, respiratory symptoms, weight gain, stool alteration, family history of GER and allergy, and parental suspicion of GERD. Each question gives a score of 0 to 1 to give a maximum score of 35. Patients with a symptomatic score $\geq$7 were considered affected by GER (19). The parents were asked to complete the questionnaire.

Patients with infant regurgitation defined according to the Rome III criteria and with a positive symptom score were randomly assigned to 3 groups. The parents of all of the enrolled infants were reassured on the benign nature of the condition and were advised to apply lifestyle changes, provided by means of oral and written instructions. In particular, parents were explained that GER is a functional disorder in the absence of any organic cause and were invited to follow modifications in feeding practices (20), with a reduction in the quantity and an increase in the frequency of the feedings, and to keep the infant in a supine position during sleep (21) (see Appendix, *http://links.lww.com/MPG/A359*). In addition to reassurance and lifestyle changes, the first group (group A) was treated with magnesium alginate aluminum-free formulation plus simethicone, at a dose of 2.5 mL 3 times per day for infants weighing <5 kg or 5 mL 3 times per day for those weighing >5 kg, to be given 10 minutes after feeding. In addition to reassurance and lifestyle changes, the second group (group B) was treated with a formula thickened with rice starch. The amount of rice starch in the formula was 14.3 g per 100 mL of milk (14.3%) for infants younger than 6 months and 14.2 g per 100 mL of milk (14.2%) for older infants. The formula was milk-based and nonhydrolyzed. The third group (control group—group C) was instructed to continue with lifestyle changes, and parents were reassured on the benign nature of the condition. All of the patients were treated for 8 weeks. Parents of the patients were counseled by one of the authors (F.C.) before starting, during, and at the end of the study period regarding any adverse effects of the treatments. In addition, all of the parents were asked to report any possible adverse effects in a daily diary. Compliance was assessed by counting returned bottles for group A and questioning the parents for group B and for group C.

Each pediatrician reevaluated the enrolled infants after 4 weeks (T1) and after 8 weeks (T2) of treatment. Patients with a symptom score <7 points in the questionnaire were considered clinically free of symptoms. The clinician who evaluated the questionnaire results at enrollment and at the follow-up visits was blind to the infants' treatments. Excellent compliance was defined as no violation of the protocol with respect to the study treatments. None of the patients underwent invasive evaluations such as MII and upper endoscopy. The manufacturer had no role in the conception, design, or conduct of the study, or in the analysis or interpretation of the data. The study proposal was approved by the ethics committee of the University of Naples "Federico II." Informed consent was obtained at enrollment from the parents of all of the enrolled infants.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS 21.0, IBM SPSS Statistics, Armonk, NY). The required sample size (75 infants) was calculated at a 2-tailed significance level of 5% and with a power of 80% to detect a 30% decrease in symptom score. A randomization list was generated using Microsoft Excel 11.0. The randomization list was based on the random extraction of numbers (1–75) in the 3 groups. Variables were screened for their distribution, and appropriate parametric or nonparametric tests were adopted as required. The Student *t* test, Mann-Whitney *U* test, and analysis of variance were used for non-normally distributed variables, whereas χ^2 and Fisher exact test were used for categorical variables where appropriate. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 75 consecutive infants (boys/girls 41/34; median age 5 months; range 1–10) with symptoms suggestive of GER were enrolled in the study. According to the randomization list, 25 patients were treated with Mg alginate plus simethicone (group A), 25 infants were treated with thickened formula (group B), and 25 patients were enrolled in reassurance with lifestyle changes (group C).

Demographic data at enrollment are shown in Table 1. Symptom score was not statistically different between the 3 groups at enrollment ($P < 0.2$) (Table 1). In our population, we found that all of the patients (100%) showed regurgitation and vomiting with different grades (Table 1), whereas 25 of 75 patients (33.3%) showed mild respiratory symptoms, such as coughing, hoarseness, hiccups, and stridor (Table 1).

During the treatment, 11 of 75 infants (14.6%) dropped out of the study. A flow diagram showing the progress of infants through the study with the corresponding reason for dropping out is presented in Figure 1.

A total of 67 of 75 patients (89.3%) completed 1 month of treatment. Patients treated with Mg alginate plus simethicone (group A) and those treated with the thickened formula (group B) showed a significant reduction of symptoms ($P < 0.005$, < 0.02, respectively), whereas the median symptom score in group C decreased with a trend toward statistical significance ($P < 0.07$) (Fig. 2). A total of 12 of 25 patients (48%) treated with Mg alginate plus simethicone were free of symptoms compared with 4 of 25 patients (16%) treated with the thickened formula ($P < 0.03$). None of the patients in group C showed a negative symptom score after 4 weeks of treatment. At T1 (after 4 weeks), Mg alginate plus simethicone was more effective on GER symptoms than reassurance ($P < 0.0001$), whereas no statistical difference was found when we compared the thickened formula with the reassurance alone ($P < 0.1$). After 4 weeks, patients treated with Mg alginate plus simethicone showed a median symptom score not significantly

TABLE 1. Demographic data, symptom scores, and frequencies of specific symptoms in the 3 groups of infants with GER, according to the treatment (group A: Mg alginate; group B: thickened formula; group C: reassurance alone), at the enrollment and at the follow-up

	T0				T1				T2*			
Group	A, N = 25	B, N = 25	C, N = 25	P	A, N = 25	B, N = 25	C*, N = 17	P	A, N = 24	B, N = 23	C, N = 17	P
Boys, %	14 (56)	14 (56)	13 (54)	1	14 (56)	14 (56)	8 (47)	0.8	14 (58.3)	13 (56.5)	8 (47)	0.7
Age, mo (range)	5 (1–10)	5 (2–10)	5 (2–10)	0.3	6 (2–11)	6 (3–11)	6 (2–10)	0.5	7 (3–12)	8 (4–12)	7 (4–11)	0.4
Symptom score, median (range)	15 (8–24)	13 (8–19)	13 (7–19)	0.2	7 (1–20)	10 (5–16)	12 (7–14)	0.2	1 (0–19)	5 (0–15)	8 (2–14)	.01
Esophageal symptoms												
Regurgitation and vomiting, %	25 (100)	25 (100)	25 (100)	1	21 (84)	25 (100)	17 (100)	0.03	6 (25)	13 (56.5)	15 (88.2)	0.00
Projectile vomiting, %	14 (56)	14 (56)	10 (40)	0.3	10 (40)	10 (40)	3 (17.6)	0.2	2 (8.3)	6 (26.1)	2 (11.7)	0.2
Vomiting with pain, %	10 (40)	12 (48)	11 (44)	0.8	2 (8)	7 (28)	3 (17.6)	0.2	0	4 (17.4)	1 (5.9)	0.1
Extraesophageal symptoms												
Cough, %	7 (28)	6 (24)	7 (28)	0.9	4 (16)	4 (16)	2 (11.7)	0.9	0	2 (8.7)	2 (11.7)	0.3
Hoarseness, %	3 (12)	3 (12)	3 (12)	1	1 (4)	1 (4)	2 (11.7)	0.5	1 (4.2)	1 (4.3)	2 (11.7)	0.5
Stridor, %	5 (20)	4 (16)	3 (12)	0.8	3 (12)	3 (12)	3 (17.6)	0.8	1 (4.2)	1 (4.3)	3 (17.6)	0.2
Hiccups, %	17 (68)	17 (68)	15 (60)	0.8	13 (52)	14 (56)	6 (35.3)	0.4	5 (20.8)	7 (30.4)	6 (35.3)	0.5

* The percentages were evaluated according to the dropout of the patients.

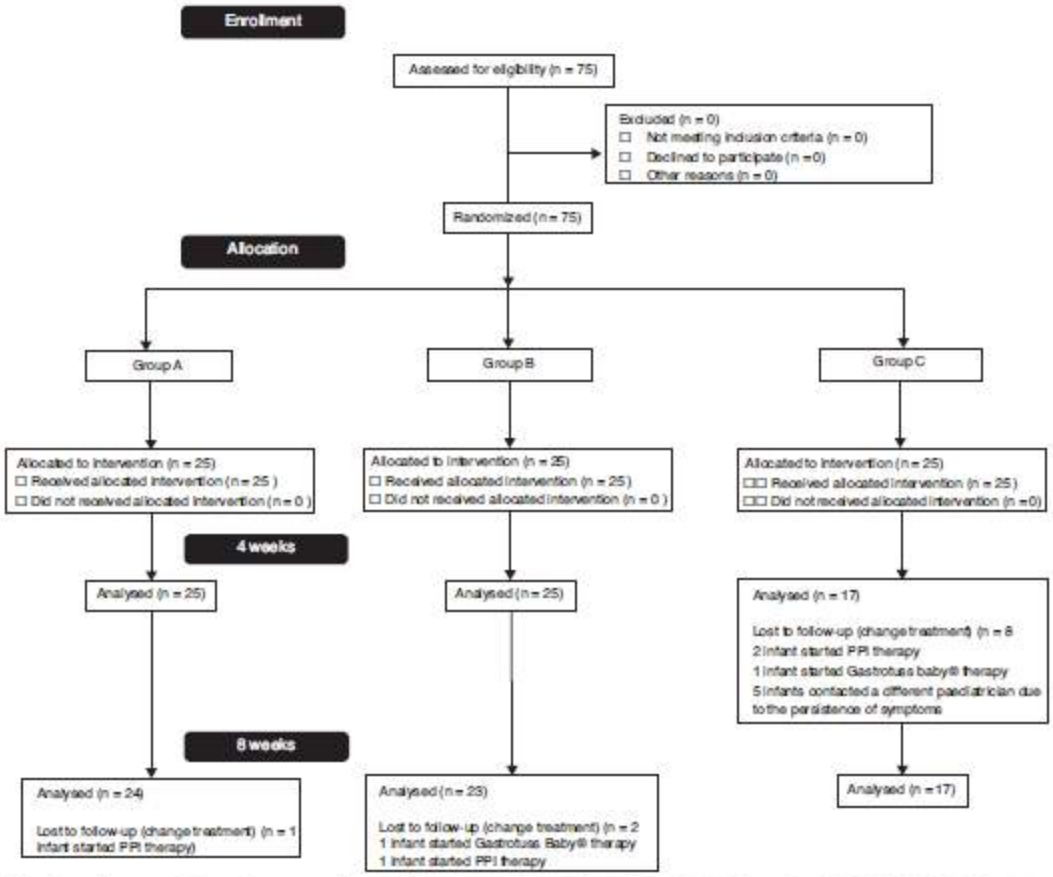

FIGURE 1. Flow diagram of the patients according to the treatment (Consolidated Standards of Reporting Trials [CONSORT] flow diagram).

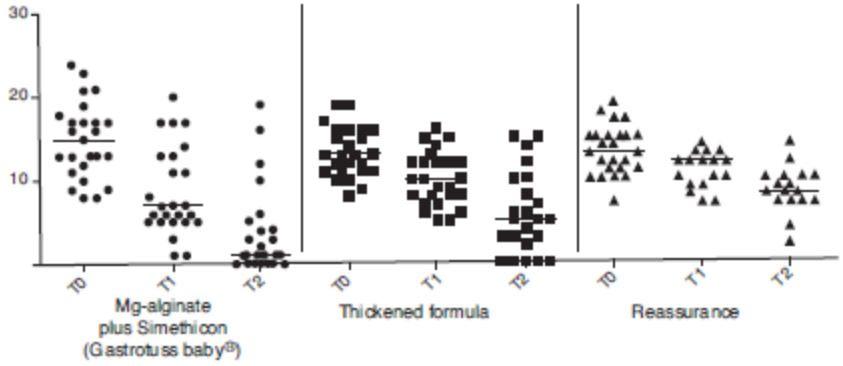

FIGURE 2. Median and distribution of the symptom scores according to the treatment at enrollment and the follow-ups. Symptom score was not statistically different between the 3 groups at enrollment ($P < 0.2$). At the end of the study, all of the 3 groups of patients showed a significant reduction in symptom scores ($P < 0.002$, <0.038, <0.03, respectively). Median symptom score values were more significantly reduced in group A than in group B and in group C (group A vs group B $P < 0.002$; group A vs group C $P < 0.0001$; group B vs group C $P < 0.001$).

different from that shown by patients treated with the thickened formula (7, 1–20 vs 10, 5–16 [median, range, respectively]; $P < 0.1$) (Table 1; Fig. 2).

A total of 64 of 75 patients (85.3%) completed 2 months of treatment. At the end of the treatment period, 3 groups of patients, irrespective of the management, showed a reduction of symptom score ($P < 0.002$, <0.038, <0.03, respectively) (Fig. 2). A total of 20 of 24 infants (83.3%) treated with Mg alginate were free of symptoms compared with 15 of 23 patients (65.2%) treated with the thickened formula ($P < 0.2$). Two of 17 patients (11.76%) treated with parents' reassurance and lifestyle changes were free of symptoms. Both Mg alginate plus simethicone and thickened formula–treated infants showed a significant reduction in symptom score if compared with patients treated with reassurance ($P < 0.0001$, <0.001, respectively). In addition, patients treated with Mg alginate plus simethicone showed a median symptomatic score lower than that of patients treated with the thickened formula (1, 0–19 vs 5, 0–15 [median, range, respectively]; $P < 0.02$) (Table 1; Fig. 2).

No severe adverse effects were recorded for any of the 3 different treatments. One patient treated with Mg alginate plus simethicone presented with constipation. Compliance with the study treatments and control was 96% in group A, 92% in group B, and 68% in group C. None of the patients enrolled in group B changed the prescribed milk-based formula.

DISCUSSION

Our study shows that Mg alginate plus simethicone significantly improved symptom score after 8 weeks of treatment in infants with GER. The efficacy of the treatment was evident on all of the evaluated symptoms, including respiratory symptoms, hiccups, irritability, projective vomiting, and feeding compliance.

In some patients, GER can cause a wide spectrum of symptoms, which can stress the infants and their parents. In an infant with uncomplicated recurrent regurgitation, it may be important to recognize physiological GER, which is effortless, painless, and not affecting growth. In some patients, this condition can result in an inappropriate use of acid suppressive therapy (2–22). Barron et al reported a significant increase in PPI prescription in infancy, without any increase in GERD diagnosis. Between 1999 and 2004, the number of prescriptions increased by approximately 800% (23). In this situation, pediatricians should focus on minimal testing and conservative management. The last published NASPGHAN/ESPGHAN report recommends that GER should be treated with nonpharmacological interventions such as body positioning, modification of feeding methods, or milk thickening (1); however, recently Quitadamo et al clearly showed that the NASPGHAN/ESPGHAN guidelines are poorly adhered to by European general pediatricians (24). In detail, only 1.8% of them showed complete compliance with the guidelines, with 39% of general pediatricians prescribing PPIs in infants with unexplained crying and/or distressed behavior and 36% of them prescribing PPIs in infants with uncomplicated recurrent regurgitation and vomiting. These findings confirm the difficulties with operating solely within the above guidelines in day-to-day practice, highlighting the need for harmless, efficacious symptomatic therapies in the management of infant GER. Indeed, an additional aim of our study was to suggest an efficacious treatment for symptoms suggestive of GER in infants, without a systemic effect, to reduce the dramatic increase in PPI prescriptions. Our data suggest that Mg alginate plus simethicone could be a valuable and harmless option to be used in those patients in whom conservative therapies have failed. In addition, despite little difference in terms of cost, Mg alginate plus simethicone certainly has a significantly lower incidence of adverse effects when compared with PPIs.

Regarding lifestyle changes, mild symptoms of reflux without complications are often well managed with modification in nutrition, feeding practices, and positioning. Large-volume feeds can promote regurgitation in infants because of gastric distention and increased transient lower esophageal sphincter relaxation (21); however, restricting volume can result in an insufficient energy intake. Thus, increasing the caloric content of feeds while decreasing the total volume of feeds can relieve GER (1,25). Alternatively, adding rice cereal, starch, or carob bean gum, or other thickening agents, to the formula can decrease the amount of regurgitation. At present, thickened feeds are increasingly being used to treat infants with GER/GERD driven to a large extent by the baby food industry (21,25). On the contrary, in the literature, it has been demonstrated that thickened formulas increase the caloric intake and may predispose infants for later obesity (26).

Alginate-based raft-forming formulations have been marketed worldwide for >30 years under various brand names. Several studies evaluated the role and the importance of alginate in the treatment of GER; however, the efficacy of alginate has not been adequately studied in pediatric populations, and the use of alginate in the treatment of severe symptoms of GERD or esophagitis is not

recommended (2). This consideration is because of the controversial results of the effect of alginate in various pediatric studies.

Several studies evaluated the effects of alginate on the characteristics of reflux in infants through objective instrumental evaluation, such as pH metry or pH/MII, and the effect on symptoms reported by the parents. It has been reported that alginate is superior to placebo in reducing the frequency and quantity of reflux and symptoms (13–15).

In contrast, Del Buono et al did not find any difference in acid GER indices between an alginate formula and placebo, except for the lower esophageal peaks reached by the refluxate. This result could be influenced with the use of powder formulations not containing bicarbonate (17). In another study, Corvaglia et al evaluated the effect of alginate in preterm infants. They concluded that the effect of alginate was most evident on acid reflux and on total acid exposure, whereas alginate had no effect on nonacid reflux (27). In the literature, it is clear that the addition of sodium bicarbonate improves the capacity of the formulation to precipitate in gel form and reduce gastric content flow.

In our study, Mg alginate plus simethicone, thickened formula, and reassurance with lifestyle changes demonstrated efficacy on GER symptoms; however, Mg alginate was shown to be more efficacious in reducing symptom scores with a higher number of patients free of symptoms at both 4 and 8 weeks. The formulation of magnesium alginate used in the present study also contains simethicone. We speculate that, as previously reported (28), this component may contribute toward improving gastric distension with a synergistic reduction of transient lower esophageal sphincter relaxation.

In the present study, we also studied the adverse effects and patient acceptance of the different treatments. Both Mg alginate and thickened formula were not associated with significant clinical adverse effects. Adult studies demonstrated that sodium alginate can cause electrolyte disorders (29), whereas in pediatric populations it has been demonstrated that precipitation of alginate in the stomach can form a bezoar, responsible for a possible increase in reflux frequency (30–32).

The limitations of our study include a relatively high dropout rate, because of refusal of medication and loss to follow-up monitoring. Although the dropout rate may have partially influenced the significance of our results, these data once more underline the poor compliance with conservative treatments, such as reassurance and lifestyle changes. Another limitation is that we did not evaluate the characteristics of the reflux with an objective diagnostic test, such as pH/MII.

In conclusion, magnesium alginate was shown to be more rapid and more effective on all of the GER symptom scores compared with thickened formula. It is well defined that physiological GER has a tendency to resolve spontaneously in 95% of patients within 12 to 14 months of life (7,8). Nevertheless, a nonsystemic treatment can be used to improve symptoms that are distressing for infants and their family, to minimize the impact of spontaneous evolution. Mg alginate has been demonstrated to be more effective on symptoms with no systemic mode of action and to have a favorable safety profile. Further well-designed studies on the effect of magnesium alginate on the characteristics of reflux are needed.

REFERENCES

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
2. Lightdale JR, Gremse DA. Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics* 2013;131:e1684–95.
3. Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol* 2009;104:1278–95.
4. Rudolph CD, Mazur LJ, Liptak GS, et al., North American Society for Pediatric Gastroenterology and Nutrition. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32 (suppl 2): S1–31.
5. Martin AJ, Pratt N, Kennedy JD, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002;109:1061–7.
6. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. *Pediatrics* 2008; 122:e1268–77.
7. Campanozzi A, Boccia G, Pensabene L, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. *Pediatrics* 2009;123:779–83.
8. Hassall E. Talk is cheap, often effective: symptoms in infants often respond to non-pharmacologic measures. *J Pediatr* 2008;152:301–3.
9. Orenstein SR, Hassall E. Infants and proton pump inhibitors: tribulations, no trials. *J Pediatr Gastroenterol Nutr* 2007;45:395–8.
10. Malcolm WF, Gantz M, Martin RJ, et al. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics* 2008;121:22–7.
11. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing efficacy & safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr* 2009;154:514–20.
12. Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *J Pediatr* 2003;143:219–23.
13. Buts JP, Barudi C, Otte JB. Double-blind controller study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. *Eur J Pediatr* 1986;146:156–8.
14. Miller S. Comparison of the efficacy and safety of a new aluminum-free pediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. *Curr Med Res Opin* 1999;15:160–8.
15. Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for treatment of gastroesophageal reflux in preterm infants. *Aliment Pharmacol Ther* 2011;33:466–70.
16. Mandel KG, Daggy BP, Brodie DA, et al. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. *Aliment Pharmacol Ther* 2000;14:669–90.
17. Del Buono R, Wenzl TG, Ball G, et al. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. *Arch Dis Child* 2005;90:460–3.
18. Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
19. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? *J Pediatr Gastroenterol Nutr* 2005;40:210–5.
20. Khoshoo V, Ross G, Brown S, et al. Smaller volume, thickened formulas in the management of gastroesophageal reflux in thriving infants. *J Pediatr Gastroenterol Nutr* 2000;31:554–6.
21. Meyers WF, Herbst JJ. Effectiveness of positioning therapy for gastroesophageal reflux. *Pediatrics* 1982;69:768–72.
22. Putnam PE. Stop PPI express: they don't keep babies quiet. *J Pediatr* 2009;154:475–6.
23. Barron JJ, Tan H, Spalding J, et al. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr* 2007;45:421–7.
24. Quitadamo P, Papadopoulou A, Wenzl T, et al. European pediatricians' approach to children with GER symptoms: survey of the implementation of 2009 NASPGHAN-ESPGHAN guidelines. *J Pediatr Gastroenterol Nutr* 2014;58:505–9.
25. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. *J Pediatr* 1987;110:181–6.

26. Chao HC, Vandenplas Y. Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation. *Nutrition* 2007;23:23–8.
27. Corvaglia L, Spizzichino M, Zama D, et al. Sodium alginate (Gaviscon®) does not reduce apneas related to gastro-oesophageal reflux in preterm infants. *Early Hum Dev* 2011;87:775–8.
28. Holtmann G, Gschossmann J, Mayr P, et al. A randomized placebo-controlled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia. *Aliment Pharmacol Ther* 2002;16:1641–8.
29. Gawarammana IB, Coburn J, Greene S, et al. Severe hypokalemic metabolic alkalosis following ingestion of Gaviscon. *Clin Toxicol (Phila)* 2007;45:176–8.
30. Hewitt GJ, Benham ES. A complication of Gaviscon in a neonate—"the Gavisconoma." *Aust Paediatr J* 1976;12:47–8.
31. Sorbie AL, Symon DN, Stockdale EJ. Gaviscon bezoars. *Arch Dis Child* 1984;59:905–6.
32. Portuguez-Malavasi A, Aranda JV. Antacid bezoar in a newborn. *Pediatrics* 1979;63:679–80.

Chapter 5

- Conclusive Remarks –

Our studies have confirmed that FGIDs are extremely frequent conditions and that their frequency increases with age. The most frequent disorders in children and adolescents are functional constipation, irritable bowel syndrome, abdominal migraine, and aerophagia. In addition, we have found differences in the prevalence of various FGIDs among different countries of the Mediterranean-European area. These findings suggest a role of environmental, genetic, and dietetic factors in the pathogenesis of FGIDs. Further studies are needed to evaluate the impact of these factors on the onset of FGIDs, in order to allow the development of new therapeutic strategies.

Moreover, we have demonstrated that, in spite of the availability of the Rome criteria and of clinical practice guidelines endorsed by scientific societies, there is still a wide variability in the diagnostic approach to FGIDs, with most of the paediatricians still insisting on the exclusion of other conditions when managing subjects with FGIDs, with significant impact on healthcare costs and patients' well-being.

Educational efforts are required to ensure a ''positive'', symptom-based approach to functional disorders, avoiding inappropriate use of healthcare resources and excessive treatment of overall benign conditions

Chapter 6

- References –

1. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. Gut 1999; 45(Suppl II):II60-68.

2. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006 Apr; 130(5):1527-37.

3. Hyams JS, Di Lorenzo C, Saps M, et al. Functional Disorders: Children and Adolescents. Gastroenterology 2016 Feb 15. pii: S0016-5085(16)00181-5.

4. Park R, Mikami S, LeClair J, et al. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. Neurogastroenterol Motil 2015; 27(5):684-92.

5. Hoekman DR, Rutten JM, Vlieger AM, et al. Annual Costs of Care for Pediatric Irritable Bowel Syndrome, Functional Abdominal Pain, and Functional Abdominal Pain Syndrome. J Pediatr 2015; 167(5):1103-8.

6. Lindley KJ, Glaser D, Milla P. Consumerism in healthcare can be detrimental to child health: lessons from children with functional abdominal pain. Arch Dis Child 2005; 90:335–337.

7. Benninga MA, Nurko S, Faure C, et all. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016; 150:1443–1455.

8. Akhnikh S, Engelberts AC, van Sleuwen BE, et al. The excessively crying infant: etiology and treatment. Pediatr Ann 2014; 43:e69–e75.

9. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J Paediatr Child Health 2012; 48:128–137.

10. Hill DJ, Hudson IL, Sheffield LJ, et al. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. J Allergy Clin Immunol 1995; 96:886–892.

11. Arikan D, Alp H, Gözüm S, et al. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. J Clin Nurs 2008; 17:1754–1761.

12. Jakobsson I, Lothe L, Ley D, et al. Effectiveness of casein hydrolysate feedings in infants with colic. Acta Paediatr. 2000; 89:18–21.

13. Shergill-Bonner R. Infantile colic: practicalities of management, including dietary aspects. J Fam Health Care 2010; 20:206–209.

14. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. Nutrition 2013; 29:184–194.

15. Agostoni C, Axelsson I, Goulet O, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2006; 42:352–361.

16. Shamir R, St. James-Roberts I, Di Lorenzo C. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. J Pediatr Gastroenterol Nutr 2013; 57:S1–S45.

17. Vanderhoof JA, Murray ND, Young RJ. Infantile colic—a functional bowel disorder? Pract Gastroenterol 1999; 23:39–41.

18. Watkins JB, Ingall D, Szczepanik P, et al. Bile-salt metabolism in the newborn – measurement of pool size and synthesis by stable isotope technic. N Engl J Med 1973; 288:431–434.

19. Watkins JB, Szczepanik P, Gould JB, et al. Bile salt metabolism in the human premature infant. Preliminary observations of pool size and synthesis rate following prenatal administration of dexamethasone and phenobarbital. Gastroenterology 1975; 69:706–713.

20. Kawasaki H, Yamanishi Y, Miyake M, et al. Age-and sex-related profiles of serum primary and total bile acids in infants, children and adults. Tohoku J Exp Med 1986; 150:353–357.

21. Boehm G, Braun W, Moro G, et al. Bile acid concentrations in serum and duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. Biol Neonate 1997; 71:207–214.

22. de Belle RC, Vaupshas V, Vitullo BB, et al. Intestinal absorption of bile salts: immature development in the neonate. J Pediatr 1979; 94:472–476.

23. Lester R. Diarrhea and malabsorption in the newborn. N Engl J Med 1977; 297:505–507.

24. Iacono G, Carroccio A, Cavataio F, et al. Steatocrit test: normal range and physiological variations in infants. J Pediatr Gastroenterol Nutr 1990; 11:53–57.

25. Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. Trends Mol Med 2015; 21:702–714.

26. Lehtonen L, Korvenranta H, Eerola E. Intestinal microflora in colicky and noncolicky infants: bacterial cultures and gas-liquid chromatography. J Pediatr Gastroenterol Nutr 1994; 19:310–314.

27. Savino F, Cresi F, Pautasso S, et al. Intestinal microflora in breastfed colicky and non-colicky infants. Acta Paediatr 2004; 93:825–829.

28. Savino F, Cordisco L, Tarasco V, et al. Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatr 2009; 98:1582–1588.

29. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. Gastroenterology 1986; 91:100–107.

30. Scarpato E, Corazziari E, Irastorza I, et al., unpublished data, 2012: Cross-cultural knowledge, diagnosis and treatment of functional gastrointestinal disorders in children: the Mediterranean Pediatric FGID Project. ESPGHAN Update, Stockholm, Sweden.

31. Kuizenga-Wessel S, Heckert SL, Tros W, et al. Reporting on outcome measures of functional constipation in children—a systematic review. J Pediatr Gastroenterol Nutr 2016; 62:840–6.

32. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009; 49:498–547.

33. Van der Pol RJ, Smits MJ, VanWijk MP, et al. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics 2011; 127:925–35.

34. Van der Pol R, Langendam M, Benninga M, et al. Efficacy and safety of histamine-2 receptor antagonists. JAMA Pediatr 2014; 168:947–54.

35. Canani RB, Cirillo P, Roggero P, et al. Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics 2006; 117:e817–20.

36. Rouster AS, Karpinski AC, Silver D, et al. Functional gastrointestinal disorders dominate pediatric gastroenterology outpatient practice. J Pediatr Gastroenterol Nutr 2016; 62:847–51.

37. Lewis ML, Palsson OS, Whitehead WE, et al. Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents. J Pediatr 2016; 177:39-43.

38. Saps M, Nichols-Vinueza DX, Rosen JM, et al. Prevalence of Functional Gastrointestinal Disorders in Colombian School Children. J Pediatr 2014; 164:542-5.

39. Zablah R, Velasco-Benítez CA, Merlos I, et al. Prevalence of functional gastrointestinal disorders in school-aged children in El Salvador. Rev Gastroenterol Mex 2015 Jul-Sep; 80(3):186-91.

40. Bouzios I, Chouliaras G, Chrousos GP, et al. Functional gastrointestinal disorders in Greek Children based on ROME III criteria: identifying the child at risk. Neurogastroenterol Motil 2017 Mar; 29(3).

41. Helgeland H, Flagstad G, Grøtta J, et al. Diagnosing Pediatric Functional Abdominal Pain in Children (4–15 Years Old) According to the Rome III Criteria: Results from a Norwegian Prospective Study. J Pediatr Gastroenterol Nutr 2009; 49:309-315.

42. Sagawa T, Okamura S, Kakizaki S, et al. Functional gastrointestinal disorders in adolescents and quality of school life. J Gastroenterol Hepatol 2013; 28:285-90.

43. Walker L, Caplan A, Rasquin-Weber A. Manual for the Questionnaire on Pediatric Gastrointestinal Symptoms. Nashville, TN: Vanderbilt University Medical Center; 2000.

44. Bongers MEJ, van Dijk M, Benninga MA, et al. Health related quality of life in children with constipation-associated fecal incontinence. J Pediatr 2009; 154:749-53.

45. Chogle A and Saps M. Yield and cost of performing screening tests for constipation in children. Can J Gastroenterol 2013; 27(12):e35-8.

46. Schum TR, Kolb TM, McAuliffe TL, et al. Sequential acquisition of toilet-training skills: a descriptive study of gender and age differences in normal children. Pediatrics 2002; 109:E48.

47. Karas J, Ashkenazi S, Guarino A, et al. A core outcome set for clinical trials in acute diarrhoea. Arch Dis Child 2015; 100:359–63.

48. Steutel NF, Benninga MA, Langendam MW, et al. Reporting outcome measures in trials of infant colic. J Pediatr Gastroenterol Nutr 2014; 59:341–6.

49. Sinha IP, Gallagher R, Williamson PR, et al. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials 2012; 13:103.

50. Farrell M, Holmes G, Coldicutt P, et al. Management of childhood constipation: parents' experiences. J Adv Nurs 2003; 44:479–89.

51. Bharucha AE, Wald A, Enck P, et al. Functional anorectal disorders. Gastroenterology 2006; 130:1510–8.

52. Campanozzi A, Boccia G, Pensabene L, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. Pediatrics 2009; 123:779–83.

53. Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidencebased consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol 2009; 104:1278–95.

54. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing efficacy & safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr 2009; 154:514–20.

55. Malcolm WF, Gantz M, Martin RJ, et al. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. Pediatrics 2008; 121:22–7.

56. Scarpato E, Quitadamo P, Roman E, et al. Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area. J Pediatr Gastroenterol Nutr 2017; 64(6):e142-e146.

57. Barron JJ, Tan H, Spalding J, et al. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr 2007; 45:421–7.

58. Buts JP, Barudi C, Otte JB. Double-blind controller study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. Eur J Pediatr 1986; 146:156–8.

59. Miller S. Comparison of the efficacy and safety of a new aluminum-free pediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. Curr Med Res Opin 1999; 15:160–8.

60. Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for treatment of gastroesophageal reflux in preterm infants. Aliment Pharmacol Ther 2011; 33:466–70.

61. Hyman PE, Milla PJ, BenningaMA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006; 130:1519–26.

62. Orenstein SR, Hassall E. Infants and proton pump inhibitors: tribulations, no trials. J Pediatr Gastroenterol Nutr 2007; 45:395–8.

63. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: howmuch is predictable with questionnaires,pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr 2005; 40:210–5.

.

Chapter 7

- Other Publications –

INTERNATIONAL JOURNAL OF FOOD SCIENCES AND NUTRITION, 2017
http://dx.doi.org/10.1080/09637486.2017.1289502

Taylor & Francis
Taylor & Francis Group

COMPREHENSIVE REVIEW

Nutritional assessment and intervention in children with cerebral palsy: a practical approach

Elena Scarpato[a], Annamaria Staiano[a], Massimo Molteni[b], Gaetano Terrone[a], Alessandra Mazzocchi[c] and Carlo Agostoni[c]

[a]Department of Translational Medical Sciences – Section of Paediatrics, University of Naples "Federico II", Naples, Italy; [b]Child Psychopathology Unit, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) "Eugenio Medea", Lecco, Italy; [c]Department of Clinical Sciences and Community Health, University of Milan, Fondazione IRCCS "Cà Granda Ospedale Maggiore Policlinico", Milan, Italy

ABSTRACT

Cerebral palsy (CP) is associated with the presence of feeding disorders in almost 60% of the affected children with subsequent undernutrition reported in up to 46% of the subjects. Since undernutrition may have a detrimental impact on physical and cognitive development, the introduction of an adequate nutritional support should always be considered in children with neurological impairment. The aim of the present review is to provide a practical guide to the assessment of nutritional status in children with CP, in order to identify individuals at risk for malnutrition that need the introduction of an adequate and personalized nutritional support. This review summarizes the methods for the evaluation of oral-motor function, anthropometric parameters, body composition and energy balance in children with CP. Moreover, we reviewed the indications for the introduction of nutritional support, and the suggested modalities of intervention.

ARTICLE HISTORY
Received 12 October 2016
Revised 27 January 2017
Accepted 29 January 2017

KEYWORDS
Neurologically impaired children; enteral nutrition; nutritional support; anthropometry

Introduction

Cerebral palsy (CP) is the most common disability during childhood, with a prevalence of approximately 2–3.5 cases per 1000 live births, and a peak up to 65 per 1000 live births particularly in prematures weighing <1500 g at birth (Winter et al. 2002). The availability of neonatal intensive care units and high-technology diagnostic and therapeutic procedures led to an increased survival rate of premature and term infants with neurological impairment and to an improvement of the life expectancy of these children. According to data from the "North American Growth in Cerebral Palsy Project" 58% of the children with moderate to severe CP had feeding problems, that in 23% of the cases were of severe grade (Fung et al. 2002). Feeding disorders play a key role in the onset of undernutrition, documented in 29–46% of CP children with a prevalence that increases among children with older age, lower intelligence quotients and more severe neurological impairment (Marchand et al. 2006). A relevant part of the abnormal growth and body composition in children with CP is directly related to poor nutritional status, independent of potential confounders such as age, gender, disease severity, pubertal status and mid-parental height (Stallings et al. 1995). Considering the detrimental effect of undernutrition on physical and cognitive development, monitoring of nutritional status in children with neurological impairment is mandatory. An adequate nutritional support promotes weight gain and improves linear growth, globally enhances quality of life of the child and of the caregivers, and reduces the frequency of hospitalization. This review aims to provide a practical guide to the nutritional approach to children with CP, focusing on the assessment of oral-motor function, anthropometric parameters, body composition and energy balance, and on the indications for the introduction of nutritional support.

Clinical and feeding history

As in children without neurological impairment, the evaluation of patients with CP should start with a careful review of the clinical history. Special attention should be paid to the activity level, to the presence of comorbidities (e.g. gastrointestinal (GI) disorders, respiratory issues, contractures, scoliosis), and to the use of medications that can affect the nutritional

CONTACT Elena Scarpato elenascarpato@hotmail.it Department of Translational Medical Sciences – Section of Paediatrics, University of Naples "Federico II", via Pansini 5, Naples, Italy

status (e.g. antiepileptic drugs). Then the clinician should focus on the review of feeding history taking into account that the families broadly consider feeding as a time of nurture. In this phase, it is important to identify: (a) the caregivers involved in the feeding of the child, in all the different settings (e.g. at home or at school); (b) the timing and duration of the meals, and the technique and positioning during feeds (e.g. in a wheelchair); (c) the preferred foods and textures of the child; (d) the parental concerns regarding the safety of the feeding and the evidence of an unsafe swallowing (e.g. choking and coughing); (e) if any therapeutic intervention has already been tried, the evaluation of its impact on the child's nutritional status and growth (Samson-Fang & Bell 2013; Rempel 2015).

Oral-motor dysfunction

Due to the presence of feeding difficulties, the total food consumption in children with CP may be reduced. It has been demonstrated that poorer gross motor function is associated with increased difficulty with food/fluid textures, and that energy intake (EI) and texture of feeds differ markedly between different levels of functional abilities (Benfer et al. 2015). In fact, children with more severe oropharyngeal dysphagia (OPD) tend to consume a lower proportion of chewable foods and more fluids. The presence of OPD can be associated with problems in any or all the phases of swallowing. It is important to collect specific information from the parents to identify the "red flags" suggesting the presence of feeding/swallowing disorders, such as: (a) feeding time longer than 30 minutes, on a regular basis; (b) stressful mealtimes to the child or the caregiver; (c) lack of weight gain for 2–3 months, especially in the first 2 years of life; (d) history of respiratory illnesses, aspiration pneumonia, increased congestion at meal times, pharyngeal or laryngeal problems; and/or (e) gurgly voice quality (Arvedson 2013). Moreover, important additional information can be obtained performing a clinical observation during mealtime, to directly evaluate the presence of aspiration, the oral-motor skills, and the interaction between the child and the caregiver. In addition, in order to perform a complete oral sensorimotor and mealtime assessment, the clinician may benefit from the use of standardized scales to evaluate the presence of OPD. Unfortunately, according to a recent systematic review on objective measures of OPD in children with CP, a single instrument that allows a global evaluation of OPD in the clinical setting is currently unavailable. To date, the Schedule for Oral Motor Assessment (SOMA) and the Dysphagia Disorders Survey (DDS) are the tools with the strongest utility to support clinical decision-making, allowing to differentiate children with significant OPD from those with normal skills. Specifically, the SOMA is mainly a test of oral phase dysfunction and is intended for use in children with non-organic failure to thrive and CP aged between 10 and 42 months, while the DDS evaluates oral, pharyngeal and esophageal phase and is designed for children with developmental disabilities between 3 and 13 years of age. However, the need of a specific training certificate to use the DDS may limit its use in some settings (Benfer et al. 2012).

If the presence of a swallowing disorder is suspected, the child should be subjected to further investigation, such as an instrumental evaluation of swallowing through videofluoroscopic swallow studies.

Assessment of growth

Anthropometric measurement

Assessing anthropometric parameters is a crucial procedure in pediatric clinical evaluation. Nevertheless, these measurements are not always easy to perform in children with disabilities. Whenever possible, weight measurement should be obtained on a digital scale. Infants must be weighed naked, while older children can wear thin clothes. If the child is unable to stand, the use of a wheel chair scale is advisable, and proceeding by weight subtraction (Samson-Fang & Bell 2013). Assessment of height in children with CP is more challenging. In children younger than 2 years of age or in older children unable to stand, recumbent length should be obtained. When a standing height cannot be obtained because of the presence of scoliosis, contracture or inability to stand, segmental measures can be used to estimate height. In fact, Stevenson demonstrated that knee height (KH) and tibia length (TL) provide reliable alternatives to recumbent length in non-ambulatory children with CP, and developed specific equations to estimate stature in children with CP (Stevenson 1995). Tibia length corresponds to the distance between the supero-medial edge of the tibia and the inferior edge of the medial-malleolus, measured using a flexible tape. Knee height should be measured using a sliding caliper, with the knee and ankle of the child each bent to a 90° angle; KH corresponds to the distance between the heel and the anterior surface of the thigh, over the femoral condyles. The equations developed by Stevenson can only be applied to subjects aged less than 12 years, while in

Table 1. Equation for estimation of stature using segmental measures. Modified from Samson-Fang and Bell (2013).

Age 0–12 years – children with CP		
Segmental measure	Equation to estimate stature (S) (cm)	SE of estimate (cm)
Tibial length (TL)	$S = (3.26 \times TL) + 30.8$	1.7
Knee height (KH)	$S = (2.69 \times KH) + 24.2$	1.4
Age 12–18 years – typically developing children, validated in a small group of children with CP		
Race and gender	Equation to estimate stature (S) (cm)	SE of estimate (cm)
White males	$S = (2.22 \times KH) + 40.54$	4.21
Black males	$S = (2.18 \times KH) + 39.6$	4.58
White females	$S = (2.15 \times KH) + 43.21$	3.90
Black females	$S = (2.02 \times KH) + 46.59$	4.39

SE: standard error.

older children stature can be estimated using equations developed by Chumlea et al. (1994) derived in typically developing children and validated in a small group of patients with CP (Table 1).

Disease specific growth charts

Considering that growth patterns of CP children may be notably different from those of typically developing children, and that growth in this subset of patients is influenced by functional severity and feeding ability, it is advisable not to compare their anthropometric parameters to standard growth charts. For this reason, Brooks et al. (2011) developed CP-specific growth charts stratified by functional ability defined according to the Gross Motor Function Classification System (GMFCS). Since tube feeding may affect growth, GMFCS level V charts are different if the child is orally or tube-fed. In addition, Brooks et al. identified the low-weight threshold associated with increased morbidity and mortality, highlighting that this low-weight percentile is lower for GMFCS levels I to II (5th centile), compared to that of GMFCS levels III to V (20th centile). The complete set of CP-specific growth charts is available at www.lifeexpectancy.org/articles/newgrowthcharts.shtml.

Body composition

The evaluation of body composition is essential to objectively assess the nutritional status and the dynamics of fat and lean tissue mass in children with CP. However, the estimation of body composition in these children is not straightforward. As already discussed, anthropometric measurements, such as weight, height and body mass index (BMI) of children with CP should not be compared to conventional standards for typically developing children. Moreover, it has been widely demonstrated that BMI has only a moderate correlation with body fat percentage (BF%) in ambulatory individuals with CP (Kuperminc et al. 2010; Oeffinger et al. 2014). This is likely related to abnormalities in body composition frequently present in children with CP, such as increased total body water, severely depleted fat stores and decreased bone density (Stallings et al. 1995). The estimation of body composition in children can be obtained using a wide variety of techniques, with differences in feasibility, accuracy, and costs. The reference method for the evaluation of body composition in CP patients is dual-energy X-ray absorptiometry (DXA). Nevertheless, DXA assessments are not always easy to perform due to requirement of specialized equipment, and high costs. Simpler and less expensive methods to estimate body composition are skinfold thickness (SFT) measurements and bioelectric impedance analysis (BIA). As suggested by Samson-Fang and Stevenson (2000), triceps SFT measurement may represent a fairly sensitive and specific predictor of malnutrition. The routine measurement of triceps SFT is recommended in all subjects with CP, and in those with a value <10th centile for age as measured on standard charts (WHO 2016), it is advisable to perform a more accurate evaluation of nutritional status. The simplest and most reliable way to estimate BF% in these patients is through the use of two SFT measurements, in the modified Slaughter's equations developed by Gurka (Slaughter et al. 1988; Gurka et al. 2010) which are specific for CP-patients (Table 2). In fact, BMI and SFT alone do not provide a reliable calculation of BF%, while there is a good correlation between DXA-measured BF% and the estimations obtained using CP-specific Gurka's equations (Finbråten et al. 2015). It is important to highlight that compared to normally developing children those with severe CP (GMFCS IV–V) may have more intra-abdominal fat rather than subcutaneous fat. For this reason, BIA could perform better than SFT, in the estimation of BF% because it estimates body composition regardless of the fat localization (Rieken et al. 2011). In summary, in children with CP it may be advisable to routinely evaluate

Table 2. Prediction of body fat: original Slaughter equations and corrections for children with cerebral palsy. Modified from Gurka et al. (2010). Mac Keith Press 2009.

Population	Original Slaughter equation
Sum of skinfolds (triceps, subscapular) ≤ 35 mm	
Males	
Prepubescent (Tanner stage 1–2) white	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 1.7
Prepubescent (Tanner stage 1–2) black	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 3.2
Pubescent (Tanner stage 3) white	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 3.4
Pubescent (Tanner stage 3) black	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 5.2
Postpubescent (Tanner stage 4–5) white	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 5.5
Postpubescent (Tanner stage 4–5) black	% Body fat = 1.21 (tri + sub) − 0.008 (tri + sub)^2 − 6.8
Females (all)	% Body fat = 1.33 (tri + sub) − 0.013 (tri + sub)^2 − 2.5
Sum of skinfolds (triceps, subscapular) > 35 mm	
Males (all)	% Body fat = 0.783 (tri + sub) + 1.6
Females (all)	% Body fat = 0.546 (tri + sub) + 9.7
Cerebral-Palsy-specific corrections to Slaughter-estimated percentage body fat[a]	
Overall correction	+12.2
Additional correction for	
Males	−5.0
GMFCS levels II, IV, V	+5.1
Black race	−3.1
Pubescent	+2.0
Postpubescent	−4.6
Sum (triceps, subscapular) > 35 mm	−3.2

TRI + SUB: triceps skinfold + subscapular skinfold; GMFCS: Gross Motor Function Classification System.
[a]Instructions: always add 12.2 to the Slaughter-estimated % body fat. Then, if the individual falls into one or more of the additional categories, add that respective correction as well.

triceps SFT, and if possible, to perform a BIA evaluation in order to obtain a reliable estimation of BF to individualize the nutritional intervention.

Energy balance assessment

Energy expenditure

After assessing body composition, the specific caloric requirements and intakes of children with CP may be calculated, based on a reliable estimate of energy expenditure. Stallings et al. (1996) directly evaluated resting energy expenditure (REE) and total energy expenditure (TEE) in children with spastic quadriplegic cerebral palsy (SQCP) and healthy controls, showing that energy needs of children with SQCP are reduced in all the energy compartments (total, physical activity and resting). Several predicting equations have been developed to estimate REE and basal metabolic rate (BMR), in healthy infants and children. Nevertheless, as for the anthropometric parameters, these equations based on weight, height, age (sometimes) and sex, targeted to normally developing children (Table 3), tend to overestimate energy expenditure in children with CP (Rieken et al. 2011). Azcue et al. (1996) demonstrated that in children with SQCP, measured REE is lower than the REE predicted using the equations developed for healthy populations. For this reason, whenever possible and according to the availability of the required equipment in the pediatric service where the patient is evaluated, in CP children, individual energy expenditure should be directly measured (mainly through indirect calorimetry) to prevent errors in the estimation of energy expenditure and then requirements.

Energy intakes

Considering EIs, the available methods to estimate food intakes in children with CP are the 3-day or 7-day estimated food diary, and the 3-day weighed food diary. All the food records tend to be a burden on families, especially if the food needs to be weighed and reweighed, before and after the meal (e.g. in the 3-day weighed food diary) or if the number of recorded days is increased (e.g. in the 7-day estimated food record) (Walker et al. 2011), taking into account the practical difficulties arising with the basic disease of the child. Moreover, it has been described that the estimated food diaries can be inaccurate to evaluate the exact intakes in CP children, since the caregivers tend to overestimate the child's intakes and to underestimate the spillage of food, in agreement with observations even in healthy subjects. Walker et al. (2013) have recently validated in preschool aged children with CP a modified 3-day weighed food diary by comparing the reported EI to the measured TEE evaluated via doubly labeled water. In the modified version of the food diary, the parents are required to record all the foods and fluids offered reporting also the leftovers and spills (including vomiting and regurgitation), to include the brand names of foods, and to provide details on cooking method. An alternative to the 3-day weighed diary is represented by the 24-hour

Table 3. Equations for calculating REE and BMR (kcal/die) in infants and children.

Source	Gender	Equation
Infants from 0 to 3 years		
Schofield (W)	Male	BMR =59.48 × Wt − 30.33
	Female	BMR =58.29 × Wt − 31.05
Schofield (WH)	Male	BMR =0.167 × Wt +1517.4 × Ht − 617.6
	Female	BMR =16.25 × Wt +1023.2 × Ht − 413.5
Children from 3 to 10 years		
Schofield (W)	Male	BMR =22.7 × Wt +505
	Female	BMR =20.3 × Wt +486
Schofield (WH)	Male	BMR =19.6 × Wt +130.3 × Ht +414.9
	Female	BMR =16.97 × Wt +161.8 × Ht +371.2
Children from 10 to 18 years		
Schofield (W)	Male	BMR =13.4 × Wt +693
	Female	BMR =17.7 × Wt +659
Schofield (WH)	Male	BMR =16.25 × Wt +137.2 × Ht +515.5
	Female	BMR =8.365 × Wt +465 × Ht +200
All ages		
Harris–Benedict	Male	REE =66.47 + 13.75 × Wt +5.0 × Ht −6.76 × age
	Female	REE =655.10 + 9.56 × Wt +1.85 × Ht −4.68 × age

REE: resting energy expenditure; BMR: basal metabolic rate; W: weight; WH: weight and height; Wt: body weight in kilograms; Ht: length in meters.

recall of dietary intakes. It has been demonstrated that the 24-hour record accurately reflects EI on a group basis, compared to the measurement of TEE using doubly-labeled water. Nevertheless, its reliability is reduced for individual measurements (Johnson et al. 1996), and it is not validated for use in children with CP. For this reason, the use of the 24-hour recall should be considered only if an assessment via a 3-d weighed diary is not possible. Alternatively, three 24-hour recalls can be performed on alternate days, inclusive of one week-end day, or a 3-day weighed diary should be performed together with a 24-hour recall, to decrease the unavoidable methodological imprecision.

In conclusion, if the caregivers are adequately trained, the 3-day weighed food diary seems to provide the most accurate measure of the EI in children with CP, thus representing a reliable tool for the use in clinical practice.

Nutritional intervention

A personalized nutritional intervention should take into account the child's global nutritional status, the feeding abilities, and the estimated energy requirements. The indications of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Marchand et al. 2006) to start a nutritional intervention in neurologically impaired children are summarized in Table 4.

According to Rempel (2015), the targets of the nutritional intervention should be aimed at obtaining: (a) a weight >20th centile on disease specific growth charts; (b) a weight gain velocity of 4–7 g per day in children older than 1 year; (c) a protein and micronutrient intake similar to the requirements of age-matched peers, with a calcium and vitamin D intake that meets the age-appropriate requirements; and (d) a triceps SFT between 10 and 25th centile for age.

Table 4. Indications to start a nutritional intervention in neurologically impaired children (according to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition).

Evidence of oral motor feeding difficulties
Undernutrition (W/H <80% expected, BMI <5th centile)
Growth failure (H/A <90% expected)
Overweight (BMI >95th centile)
Individual nutrient deficiencies

W/H: weight-for-height; BMI: body mass index; H/A: height-for-age.

Oral nutrition

Oral nutrition can be maintained in children without oral-motor impairment and with a low risk of aspiration. The oral nutrition rehabilitation program should always be established with the assistance of a speech therapist and aims to increase the caloric and nutrient intake of the child, and to improve the physiological digestive processes. The most widely used interventions are positioning therapy, to ensure a correct position and support of the head during the meals including the use of appropriate chairs and utensils, the increasing in the caloric density of meals, and the adjustment of the textures of foods/liquids by modifying consistency and viscosity to suit the child's needs. The adjustment of the textures of foods/fluids is a common experience in the treatment of children with CP. In a recent study conducted on 99 children with CP aged between 18 and 36 months, Benfer et al. (2015) found that 39% of the children assumed diets modified in texture, with percentages increasing with the decline of gross motor function, up to values of 78% in children with GMFCS IV–V. A positive effect of positioning therapy on feeding safety and efficiency has been demonstrated, but no randomized controlled trials are available. Moreover, only limited evidence is available regarding the effects of texture modification (Arvedson 2013), leading us to conclude that the current level of evidence regarding the real benefits of feeding and swallowing interventions is poor.

Enteral nutrition

According to the recommendations from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the introduction of enteral

nutrition should be considered if: (a) oral intake is insufficient to meet >60–80% of individual requirements; (b) total feeding time takes place >4 to 6 h/day; (c) there is evidence of inadequate growth or weight gain; (d) there is a fall or a decrease in height velocity; (e) triceps skinfold is consistently <5th percentile for age (Braegger et al. 2010). In addition, enteral nutrition should be considered in case of severe chewing and swallowing dysfunction, or in case of aspiration during feeding. The type of enteral access depends on the clinical status and on the estimated duration of enteral feedings. In fact, nasogastric tubes are less invasive but should be used only in case of short-term nutritional support, since they may be easily displaced, or may determine nasal congestion, sinusitis and otitis media. Therefore, a gastrostomy tube or "button" is advisable in case of long-term enteral nutrition because it is less easily displaced and is more comfortable for the child. As for the way of administration, bolus feedings should always be preferred in the absence of gastro-esophageal reflux or delayed gastric emptying (GE), since they are more physiological and consistent with a diffuse stimulation of the endocrine and secretive functions of the GI tract. On the contrary, continuous infusions may be required in children who do not tolerate bolus feeds. In case of the need to administer large volumes, bolus feeds can be associated with continuous infusions of formula during the night (Marchand et al. 2006).

The decision process that accompanies the placement of a gastrostomy tube is usually complex. A recent systematic review on family experience with feeding tubes highlighted that even if parents report positive effects of gastrostomy tubes (e.g. weight gain, child happiness), they also point out several downsides (e.g. increased care needs, increased stress for the parents). For this reason, discussion between the caregivers and the healthcare providers is crucial to understand the family setting, to develop adaptive strategies to support the family in case of any challenges, and to optimize the decision-making process (Nelson et al. 2015).

Diet composition

There are no evidence-based guidelines for nutritional requirements in CP children. According to few observations, already mentioned, the caloric requirements of children with CP can be estimated between 60% and 70% of their normally developing counterparts (Rempel 2015). In case of severe malnutrition, an intake of 2 g/kg/day of protein and an additional 15–20% increase of caloric intake should be sufficient to ensure "catch up growth" (Penagini et al. 2015). The decision on the type of formula to administer should be based on the child's age, energy requirements, comorbidities and type of enteral access. Constipation is one of the most common comorbidities in children with CP, with an estimated prevalence ranging from 26% to 74% (Del Giudice et al. 1999; Park et al. 2004). Dietary intakes of water and fibers of CP patients are usually below the recommended amounts, mainly due to an objective difficulty to orally manage whole, fiber rich vegetable foods. Even though in children with CP, no correlation between fluid/fiber intake and constipation has been found (Veugelers et al. 2010), the initial approach to orally fed subjects with CP and mild constipation should still be directed toward an increase in the dietary intake of fibers. In tube-fed children, a formula supplemented with fibers (mainly constituted by non-digestible carbohydrates, whose development is technically in progress) may be useful, even if associated with a worsening of the bloating. In case of no response to the dietary management, a stool softener such as lactulose may be considered, while the use of polyethylene glycol or mineral oil should be avoided in case of gastroesophageal reflux, due to the significantly increased risk of aspiration (Sullivan 2008). Indeed, CP children frequently have symptoms related to GI dysmotility, such as gastroesophageal reflux, delayed GE and vomiting. Since the rate of GE can be influenced by meal's volume, caloric content, fat content and viscosity, a change in the composition of the formula may have an impact on GI symptoms. In fact, Brun et al. (2012) demonstrated that a meal containing 40% casein and 60% whey proteins showed a rate of GE significantly faster than a meal with 100% casein, and that hydrolysed whey and amino acids showed a comparable effect on GE. A more rapid GE has demonstrated also an effect on postprandial GI symptoms in children with CP using gastrostomy. In addition, Savage et al. (2012) investigated the effects of a casein-based formula versus two whey-based enteral formulas (either 50% whole whey protein or 100% whey partially hydrolyzed protein) on gastroesophageal reflux, GE and GI symptoms in children with severe CP, and confirmed that whey formulas emptied significantly faster than casein. They did not demonstrate a reduction in GI symptoms with whey versus casein formula, but found a significant difference between the two whey formulas. In fact, children consuming the 50% whole whey proteins formula experienced less symptoms than those consuming the formula with 100% whey partially hydrolyzed proteins. The authors hypothesized that this effect could be

related with the higher content of medium-chain triglycerides in the 100% whey formula. In parallel, also the nature of supplied carbohydrates should be carefully balanced among rapidly ingested sugars, positive for energy supply, and resistant starch and fibers for their effects – slow absorption and promotion of peristaltic movements. As for fats, the interplay between medium chain fatty acids, comparable to simple sugars as for effects, saturated fats, good for energy storage, and unsaturated fats, with multiple potential effects from inflammation to membranes and brain structure, should be carefully evaluated.

Concerning micronutrients, the standard recommendations for vitamins, minerals and trace elements intake should be followed as well. The only exception is vitamin D, because of the increased risk of deficiency due to antiepileptic drugs (especially hepatic enzyme inducers as phenobarbital or phenytoin) and insufficient sunlight exposure. Based on expert opinion, the suggested dose for vitamin D supplementation in this population is around 800–1000 UI of vitamin D (Penagini et al. 2015). Nevertheless, considering the possible occurrence of hypercalciuria in case of supplementation of calcium and vitamin D, it is advisable to evaluate calcium/osmolality ratio on spot urine at baseline, and at 6–12 months after having started the supplementation (Fehlings et al. 2012).

Conclusions

The assessment of nutritional status and following related interventions should be considered one of the cornerstones in the clinical evaluation of children with CP, and should always be based on a careful measurement of anthropometric parameters, body composition and individual energy balance by means of specific tools. The multidisciplinary approach to CP children aims to define a personalized nutritional support, which may have an impact not only on physical and cognitive development, but also on overall health related quality of life of the child and of the caregivers. Future research should be targeted to find: (1) easy to perform methodologies to target individual dietary needs; (2) easy to perform interventions to facilitate the direct access to the GI tract (e.g. second generation stomies); (3) palatable food choices, even if highly elaborated, to improve the acceptance of nutritional supplements if the natural oral route is maintained.

Disclosure statement

The authors report no conflicts of interest.

References

Arvedson JC. 2013. Feeding children with cerebral palsy and swallowing difficulties. Eur J Clin Nutr. 67:S9–S12.

Azcue MP, Zello GA, Levy LD, Pencharz PB. 1996. Energy expenditure and body composition in children with spastic quadriplegic cerebral palsy. J Pediatr. 129:870–876.

Benfer KA, Weir KA, Bell KL, Ware RS, Davies PS, Boyd RN. 2015. Food and fluid texture consumption in a population-based cohort of preschool children with cerebral palsy: relationship to dietary intake. Dev Med Child Neurol. 57:1056–1063.

Benfer KA, Weir KA, Boyd RN. 2012. Clinimetrics of measures of oropharyngeal dysphagia for preschool children with cerebral palsy and neurodevelopmental disabilities: a systematic review. Dev Med Child Neurol. 54:784–795.

Braegger C, Decsi T, Dias JA, Hartman C, Kolacek S, Koletzko B, Koletzko S, Mihatsch W, Moreno L, Puntis J, et al. 2010. ESPGHAN Committee on Nutrition. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr. 51:110–122.

Brooks J, Day S, Shavelle R, Strauss D. 2011. Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts. Pediatrics. 128:e299–e307.

Brun AC, Størdal K, Johannesdottir GB, Bentsen BS, Medhus AW. 2012. The effect of protein composition in liquid meals on gastric emptying rate in children with cerebral palsy. Clin Nutr. 31:108–112.

Chumlea WC, Guo SS, Steinbaugh ML. 1994. Prediction of stature from knee height for black and white adults and children with application to mobility-impaired or handicapped persons. J Am Diet Assoc. 94:1385–1388.

Del Giudice E, Staiano A, Capano G, Romano A, Florimonte L, Miele E, Ciarla C, Campanozzi A, Crisanti AF. 1999. Gastrointestinal manifestations in children with cerebral palsy. Brain Dev. 21:307–311.

Fehlings D, Switzer L, Agarwal P, Wong C, Sochett E, Stevenson R, Sonnenberg L, Smile S, Young E, Huber J, et al. 2012. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: a systematic review. Dev Med Child Neurol. 54:106–116.

Finbråten AK, Martins C, Andersen GL, Skranes J, Brannsether B, Júlíusson PB, Syversen U, Stevenson RD, Vik T. 2015. Assessment of body composition in children with cerebral palsy: a cross-sectional study in Norway. Dev Med Child Neurol. 57:858–864.

Fung EB, Samson-Fang L, Stallings VA, Conaway M, Liptak G, Henderson RC, Worley G, O'Donnell M, Calvert R, Rosenbaum P, et al. 2002. Feeding dysfunction is associated with poor growth and health status in children with cerebral palsy. J Am Diet Assoc. 102:361–373.

Gurka MJ, Kuperminc MN, Bennis JA, Bennis JA, Grossberg RI, Houlihan CM, Stevenson RD, Henderson RC. 2010. Assessment and correction of skinfold thickness equations in estimating body fat in children with cerebral palsy. Dev Med Child Neurol. 52:e35–e41.

Johnson RK, Driscoll P, Goran MI. 1996. Comparison of multiple-pass 24-hour recall estimates of energy intake with total energy expenditure determined by the doubly

labeled water method in young children. J Am Diet Assoc. 96:1140–1144.
Kuperminc MN, Gurka MJ, Bennis JA, Busby MG, Grossberg RI, Henderson RC, Stevenson RD. 2010. Anthropometric measures: poor predictors of body fat in children with moderate to severe cerebral palsy. Dev Med Child Neurol. 52:824–830.
Marchand V, Motil K; NASPGHAN Committee on Nutrition. 2006. Nutrition support for neurologically impaired children: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 43:123–135.
Nelson KE, Lacombe-Duncan A, Cohen E, Nicholas DB, Rosella LC, Guttmann A, Mahant S. 2015. Family experiences with feeding tubes in neurologic impairment: a systematic review. Pediatrics. 136:e140–e151.
Oeffinger DJ, Gurka MJ, Kuperminc M, Hassani S, Buhr N, Tylkowski C. 2014. Accuracy of skinfold and bioelectrical impedance assessments of body fat percentage in ambulatory individuals with cerebral palsy. Dev Med Child Neurol. 56:475–481.
Park ES, Park CI, Cho SR, Na SI, Cho YS. 2004. Colonic transit time and constipation in children with spastic cerebral palsy. Arch Phys Med Rehabil. 85:453–456.
Penagini F, Mameli C, Fabiano V, Brunetti D, Dilillo D, Zuccotti GV. 2015. Dietary intakes and nutritional issues in neurologically impaired children. Nutrients. 7:9400–9415.
Rempel G. 2015. The importance of good nutrition in children with cerebral palsy. Phys Med Rehabil Clin N Am. 26:39–56.
Rieken R, van Goudoever JB, Schierbeek H, Willemsen SP, Calis EA, Tibboel D, Evenhuis HM, Penning C. 2011. Measuring body composition and energy expenditure in children with severe neurologic impairment and intellectual disability. Am J Clin Nutr. 94:759–766.
Samson-Fang LJ, Bell KL. 2013. Assessment of growth and nutrition in children with cerebral palsy. Eur J Clin Nutr. 67:S5–S8.
Samson-Fang LJ, Stevenson RD. 2000. Identification of malnutrition in children with cerebral palsy: poor performance of weight-for-height centiles. Dev Med Child Neurol. 42:162–168.
Savage K, Kritas S, Schwarzer A, Davidson G, Omari T. 2012. Whey- vs casein-based enteral formula and gastrointestinal function in children with cerebral palsy. JPEN J Parenter Enteral Nutr. 36:118S–123S.
Slaughter MH, Lohman TG, Boileau RA, Horswill CA, Stillman RJ, Van Loan MD, Bemben DA. 1988. Skinfold equations for estimation of body fatness in children and youth. Hum Biol. 60:709–723.
Stallings VA, Cronk CE, Zemel BS, Charney EB. 1995. Body composition in children with spastic quadriplegic cerebral palsy. J Pediatr. 126:833–839.
Stallings VA, Zemel BS, Davies JC, Cronk CE, Charney EB. 1996. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. Am J Clin Nutr. 64:627–634.
Stevenson RD. 1995. Use of segmental measure to estimate stature in children with cerebral palsy. Arch Pediatr Adolesc Med. 49:658–662.
Sullivan PB. 2008. Gastrointestinal disorders in children with neurodevelopmental disabilities. Dev Disabil Res Rev. 14:128–136.
Veugelers R, Benninga MA, Calis EA, Willemsen SP, Evenhuis H, Tibboel D, Penning C. 2010. Prevalence and clinical presentation of constipation in children with severe generalized cerebral palsy. Dev Med Child Neurol. 52:e216–e221.
Walker J, Bell KL, Boyd RN, Davies PS. 2013. Validation of a modified three-day weighed food record for measuring energy intake in preschool-aged children with cerebral palsy. Clin Nutr. 32:426–431.
Walker J, Bell KL, Caristo FM, Boyd RN, Davies PS. 2011. A review of energy intake measures used in young children with cerebral palsy. Dev Med Child Neurol. 53:569.
WHO (World Health Organization). 2016. Growth charts. Available from: http://www.who.int/childgrowth/standards/tsf_for_age/en/
Winter S, Autry A, Boyle C, Yeargin-Allsopp M. 2002. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics. 110:1220–1225.

Impact of Hiatal Hernia on Pediatric Dyspeptic Symptoms

*Elena Scarpato, †Maria D'Armiento, *Massimo Martinelli, *Valeria Mancusi, †Severo Campione, *Annalisa Alessandrella, *Annamaria Staiano, and *Erasmo Miele

ABSTRACT

Objectives: Hiatal hernia (HH) affects from 10% to 50% of adult population. The correlation between HH, gastroesophageal reflux disease, dyspeptic symptoms, and esophagitis has long been known in adults. The primary objective of our prospective observational study was to estimate the prevalence of HH in children undergoing esophagogastroduodenoscopy (EGD), irrespective of their symptoms.

Methods: We prospectively enrolled 111 consecutive children (48 boys and 63 girls; mean age 94.9 ± 52.3 months) referred for EGD. In all of the patients a symptomatic score assessment based on the Rome III criteria was used to measure frequency, severity, and duration of gastrointestinal symptoms. HH presence was endoscopically defined; esophagitis presence was evaluated either endoscopically and histologically. Children were divided in 2 age-range groups: <48 months (group 1) and >48 months (group 2).

Results: Twenty-three patients of 111 (20.7%) had evidence of a sliding HH at EGD. In children from group 2, we found a statistically significant association of HH with heartburn ($P = 0.03$, 95% confidence interval 1–9.3, $r^2 = 0.1$) and regurgitation ($P = 0.003$, 95% confidence interval 1.7–20.4, $r^2 = 0.3$). Regarding esophagitis presence, no association was found at any age either with defined esophagitis or with dilated intercellular spaces.

Conclusions: Prevalence of HH in our study population was 20.7%. According to our data, HH correlates with the presence of heartburn and regurgitation in children, but not in toddlers. No association was found with esophagitis at any age.

Key Words: epigastric pain, esophagogastroduodenoscopy, gastroesophageal reflux

(*JPGN* 2014;59: 795–798)

Hiatal hernia (HH) defines the herniation of elements of the abdominal cavity into the mediastinum, through a widening of the right crus of the diaphragm. It has been reported to affect from 10% to 50% of the adult population (1–3), but its real prevalence is still unknown because of different diagnostic criteria. The correlation between HH, gastroesophageal reflux disease (GERD), and dyspeptic symptoms has long been known in adults (4). The most common subtype is type I or sliding HH, which is strongly associated with GERD (5,6) and has been shown to be an independent risk factor for the disease (7). Patients with GERD associated with HH have increased exposure to acid reflux than subjects with GERD alone (8,9). In addition, adult patients with HH are significantly more likely to have dyspeptic symptoms compared with those without (10,11). Furthermore, reflux symptoms are more common in subjects with HH than in those without, even when reflux esophagitis is not present at upper endoscopy (2). The relation between HH and esophagitis has been clearly demonstrated in adults (12,13). Increases in HH size are significantly correlated with total esophageal acid exposure, acid-clearance time, and esophagitis severity (14); moreover, patients with HH have more severe esophagitis (1) and a worst response to treatment (15) than those without.

The prevalence of HH in children with gastroesophageal reflux (GER) varies between 6.3% and 41% (16–20), whereas few pediatric data are available on prevalence in children without GER. Ruigómez et al (21) retrospectively demonstrated that HH presence was associated with an increased risk of GERD diagnosis. Wu et al (22) have evaluated a cohort of 104 children with GERD symptoms, demonstrating that erosive esophagitis is more frequent in subjects with GERD and HH than in subjects with GERD without HH.

The primary aim of our study was to estimate the prevalence of HH in children undergoing esophagogastroduodenoscopy (EGD), irrespective of their symptomatology. The secondary aim was to evaluate the role of HH in esophagitis and in dyspeptic symptoms.

METHODS

We prospectively enrolled 111 consecutive children referred for EGD to the Department of Translational Medical Science, Section of Pediatrics of the University of Naples "Federico II" from December 2012 to June 2013. Patients who used drugs known to influence esophageal or gastric motility or affect gastric acid secretion or had any disease or underwent any surgical procedures that may affect gastric acid secretion or gastroesophageal motility or were unable/unwilling to give informed consent were excluded.

Evaluation of Gastrointestinal Symptoms

In all of the patients of the study population, a symptomatic score assessment based on the Rome III criteria (QPGS-RIII) was used to evaluate the presence of dyspeptic symptoms. The questionnaires use 5-point scales to measure frequency, severity, and duration of gastrointestinal (GI) symptoms. One parent-report version of the QPGS-RIII was used for the parents of children between 1 and 48 months of age; the other parent-report version was used for children between 48 months and 10 years of age; the self-report version was administered to children 10 years of age and older. According to the questionnaires, we considered dyspeptic symptoms to be the presence of regurgitation, vomiting, retching, and crying in children <48 months of age and the presence of

Received May 5, 2014; accepted August 10, 2014.
From the *Department of Translational Medical Sciences, Section of Pediatrics, and the †Department of Biomorphological and Functional Sciences, Section of Pathology, University of Naples "Federico II," Italy.
Address correspondence and reprint requests to Annamaria Staiano, Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II," Via S. Pansini, 5, 80131, Naples, Italy (e-mail: staiano@unina.it).
The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000000536

regurgitation, heartburn, bloating, belching, nausea, and early satiety in children between 48 months and 10 years of age.

Endoscopy

Endoscopic examination was carried out using a standard, forward-viewing pediatric endoscope (Fujinon EG530FP; Fujifilm Endoscopy, Wayne, NJ) by an experienced pediatric gastroenterologist (E.M.). The EGD was performed in an endoscopy room and children were sedated with midazolam administered intravenously (initial dose 0.05–0.1 mg/kg, total dose up to 0.6 mg/kg with a maximum of 6 mg in children <6 years of age and initial dose 0.025–0.05 mg/kg, total dose up to 0.4 mg/kg with a maximum of 10 mg in children >6 years of age). Multiple biopsies were taken from the duodenum, anthrum, corpus, and esophagus. The forceps biopsy specimens were obtained from macroscopically diseased areas, if present, or from the distal normal esophageal mucosa, at least 2 cm above the gastroesophageal junction (23).

Identification of the level of the diaphragmatic hiatus was done as described by Boyce (24). Cephalad displacement of the proximal margin of the gastric mucosal folds of >2 cm in relation to the hiatus, performed at the end of the EGD after deflation of the stomach, served as the endoscopic criterion for the diagnosis of an HH. In all of the patients, the presence of HH was also confirmed by retroflexing the scope into the stomach to assess gastroesophageal junction (GEJ) appearance (10).

HH was furthermore classified as type I or sliding HH, if the GEJ moved above the diaphragm together with some of the stomach; type II or paraesophageal HH, if part of the stomach herniated through the esophageal hiatus without movement of the GEJ; and type III, if elements of both types I and II hernias were present (25).

Esophagitis Assessment

Endoscopic grading was made according to the Hetzel-Dent classification: grade 1—erythema; grade 2—superficial ulceration or erosions involving 10% of the distal esophageal mucosa; grade 3—superficial confluent ulceration or erosions involving 10% to 50% of the distal esophageal mucosa; grade 4—deep ulceration or erosions involving 50% of the distal esophageal mucosa, and grade 5—stricture (26).

Histological severity was graded according to the Yierian-Fiocca classification. This classification evaluates the presence of basal cell layer hyperplasia, papillary elongation, dilated intercellular spaces, intraepithelial eosinophils, neutrophils and mononuclear cells, and erosions, to obtain a combined severity score: 0 to 0.25 normal mucosa (no lesions or one mild lesion); 0.5 to 0.75 mild esophagitis (2–3 mild lesions, or 1 mild lesion and one severe lesion); ≥1.0 severe esophagitis (4 mild lesions or >1 severe lesions) (27).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software package for Windows (version 13.0; SPSS, Chicago, IL.). The Student *t* test and the Mann-Whitney *U* test for normally distributed variables and the χ^2 and Fisher exact tests for categorical variables were used where appropriate. Statistical significance was predetermined as $P < 0.05$.

To evaluate the association between HH and the primary and secondary factors, we conducted 2 tests for matched-pair data along with linear and multivariate conditional logistic regression analysis.

Written, informed consent for participation in this study was obtained from parents of all of the patients and from all of the patients >6 years of age. The study was approved by the institutional review board of the University of Naples "Federico II."

RESULTS

Patients' Characteristics

During the study period, 111 consecutive children (48 boys and 63 girls, mean age 94.9 ± 52.3 months) referred for EGD were enrolled. Table 1 summarizes clinical characteristics of the enrolled patients. The patients' median age was 94.9 months (range 15 – 216). To simplify the evaluation of symptoms, the 111 children were divided in 2 age-range groups, according to the type of QPGS-RIII used: <48 months (group 1, n = 34, M/F: 15/19, age 15–48 months) and >48 months (group 2; n = 77; M/F: 33/44, age 49–216 months). Final diagnosis of the study population is reported in Table 2.

HH Prevalence in Children Undergoing EGD

Twenty-three patients of 111 (20.7%) had evidence of HH at EGD. Specifically, the prevalence of HH in our population varied between 5 of 34 (14.7%) children age <48 months and 18 of 77 patients (23.3%) age >48 months.

All 23 subjects showed a sliding HH and no significant correlation was found between the presence of HH and sex ($P = 1$, 95% confidence interval [CI] 0.1–5.6 in group 1; $P = 0.1$, 95% CI 0.9–8 in group 2), symptoms at diagnosis ($P = 0.7$ in group 1 and $P = 0.5$ in group 2), and final diagnosis ($P = 0.3$ and $P = 0.6$ in group 1 and group 2, respectively). Fourteen of 60 (23.3%) patients with a diagnosis of CD presented HH compared with 9 of 51 (17.6%) of the remaining patients ($P = 0.4$).

TABLE 1. Symptoms and signs at diagnosis

Symptoms	<48 mo (%) (n = 34)	>48 mo (%) (n = 77)
Heartburn	—	27 (35)
Recurrent abdominal pain	4 (11.7)	18 (23.3)
Constipation	13 (38.2)	34 (44.1)
Recurrent regurgitation	9 (26.4)	15 (19.4)
Bloating	—	14 (18.1)
Flatulence	—	21 (27.2)
Nausea	—	21 (27.2)
Early satiety	—	27 (35)
Belching	—	23 (29.8)
Dysphagia	5 (14.7)	2 (2.6)
Apnea	2 (5.8)	—
Crying	5 (14.7)	—
Retching	6 (17.6)	—
Vomiting	7 (20.5)	11 (14.1)
Chronic diarrhea	11 (32.3)	3 (3.8)
Irregular bowel movements	1 (2.9)	2 (2.6)
Iron deficiency anemia	1 (2.9)	2 (2.6)
Hematemesis	—	2 (2.6)
Failure to thrive	8 (23.5)	—
Hemoptysis	1 (2.9)	—
Weight loss	7 (20.5)	3 (3.8)
Positive CD serology	25 (73.5)	33 (42.8)

CD = celiac disease.

TABLE 2. Final diagnosis in children undergoing EGD

Diagnosis	<48 mo (%) (n = 34)	>48 mo (%) (n = 77)
CD	25 (73.5)	35 (45)
EE	—	4 (5.2)
Functional dyspepsia	4 (11.8)	19 (24.6)
GERD	1 (2.9)	6 (7.9)
Helicobacter *pylori* infection	1 (2.9)	3 (3.9)
Cyclic vomiting	—	3 (3.9)
IBD	—	3 (3.9)
FAP	—	1 (1.3)
Food allergy	1 (2.9)	1 (1.3)
Epistaxis	1 (2.9)	
Meckel diverticulum	—	1 (1.3)
Chronic gastritis	—	1 (1.3)
Functional abdominal pain	1 (2.9)	—

CD = celiac disease; EE = eosinophilic esophagitis; EGD = esophagogastroduodenoscopy; FAP = familial adenomatous polyposis; GERD = gastroesophageal reflux disease; IBD = inflammatory bowel disease.

Relation Between HH and GI Symptoms

Table 3 reports data regarding the association between GI symptoms (regurgitation, vomiting, retching, failure to thrive, weight loss, and crying) evaluated using QPGS-RIII questionnaires and the presence of HH in children <48 months of age. No statistically significant correlation was found in this subgroup of patients. Concerning children >48 months, there was no association between bloating, periumbilical pain, belching, nausea, and early satiety and HH. In contrast, we found a statistically significant association of HH with heartburn ($P = 0.03$, 95% CI 1–9.3, $r^2 = 0.1$) and regurgitation ($P = 0.003$, 95% CI 1.7–20.4, $r^2 = 0.3$) (Table 4). In fact, a clinical history of heartburn was found in 10 of 18 (55.5%) children with HH compared with only 17 of 59 (28.8%) children without HH. Similarly, regurgitation was present in 8 of 18 (44.4%) children with HH compared with 7 of 59 (11.8%) subjects without HH. Multivariate logistic regression analysis with HH as the dependent variable confirmed that regurgitation was the only independent variable significantly associated with the presence of HH (odds ratio = 6.057, 95% CI 1.3–19.5, $P = 0.003$) in children from group 2, whereas none of the variables resulted to be independently associated in children from group 1.

Relation Between HH and Esophagitis

Only 2 patients >48 months were found with an endoscopically defined grade II esophagitis. No association was, however, found at any age either with defined esophagitis ($P = 0.9$ in group 1 and $P = 0.7$ in group 2) or with dilated intercellular spaces ($P = 0.3$ and $P = 0.7$ in group 1 and group 2, respectively).

TABLE 3. GI symptoms in subjects with and without HH (<48 mo)

	HH (%)	no-HH (%)	Total	P	95% CI
Regurgitation	2 (40)	7 (24.1)	9	0.5	0.2–15
Vomiting	1 (20)	6 (20.7)	7	1	0.1–10
Retching	1 (20)	5 (17.2)	6	1	0.1–13
Failure to thrive	1 (2.9)	7 (20.6)	8	1	0.1–8.2
Weight loss	2 (20)	5 (24.1)	7	0.2	0.4–24
Crying	1 (20)	4 (20.7)	5	1	0.1–10

CI = confidence interval; GI = gastrointestinal; HH = hiatal hernia.

TABLE 4. GI symptoms in subjects with and without HH (>48 mo)

	HH (%)	No-HH (%)	Total	P	95% CI
Regurgitation	8 (44.4)	7 (11.7)	15	0.003	1.7–20.4
Heartburn	10 (55.6)	17 (28.3)	27	0.03	1–9.3
Bloating	4 (22.2)	10 (16.7)	14	0.7	0.3–5.2
Periumbilical pain	4 (22.2)	14 (23.3)	18	1	0.2–3
Belching	8 (44.4)	15 (25)	23	0.1	0.8–7
Nausea	5 (27.8)	16 (26.7)	21	1	0.3–3.4
Early satiety	8 (44.4)	19 (31.7)	27	0.3	0.5–5

CI = confidence interval; GI = gastrointestinal; HH = hiatal hernia.

DISCUSSION

This is the first pediatric prospective study evaluating the prevalence of HH in children regardless of the presence of GER-related symptoms. We found that HH was present in 20.7% of children undergoing EGD. Prevalence was higher in children >4 years of age (23.3%) compared with younger subjects (14.7%). According to our data, HH seems to be related to heartburn and regurgitation in children with >4 years of age, whereas the other typical symptoms of GER are not associated with HH at any age.

In adults, it is still controversial whether esophagitis is a predictable consequence of HH, but this construct became untenable with the observations that not all patients with HH had reflux disease, not all patients with esophagitis had concomitant hernias, and simple repair of an HH did not resolve GERD (4). So, apparently, in children as well as in adults, HH seems just a risk factor for the development of dyspeptic symptoms, rather than erosive esophagitis, without affecting the severity of the disease (4). Our data are in agreement with the data from Petersen et al (1), who endoscopically evaluated 930 adult patients referred for GI symptoms and highlighted that subjects with HH presented more frequently heartburn and regurgitation compared with those without. In addition, in a study of healthy subjects with GER symptoms, Stål et al (28) demonstrated that 62% had an HH compared with 14% of asymptomatic subjects; moreover, they showed that subjects with GERD had predominantly nonerosive esophagitis whereas only one-quarter of subjects had esophageal erythema or erosions. The prevalence of HH in children with GER varies between 6.3% (16) and 41% (17–20), whereas no data are available on the prevalence in children without GER/GERD. Different justifications may be proposed for wide range of results in diverse studies; different sample sizes and used methods for detecting HH may be the reasons. Hassal et al (18) characterized 166 pediatric patients who received long-term proton-pump inhibitors; an endoscopically defined HH was found in 39% of patients. Population-based studies have shown that approximately 50% of individuals with reflux symptoms without esophagitis and 75% of those with symptoms and esophagitis experience an HH (11,29). We did not find any relation between the presence of HH with severity of erosive esophagitis according to endoscopically or histologically defined esophagitis. Similar studies could not find any relation between HH and severity of erosive esophagitis (30,31). In adults, some reports demonstrated that both the presence and the size of HH are independent predictors of esophagitis presence and severity (1,8). Concerning pediatric patients, Gorenstein et al (16) compared the 24-hour pH-monitoring studies from children who had GER and HH to those from children who had GER without HH. The

prevalence of HH in their study population was 6.3%; furthermore, they found that the presence of HH in children with GER may predict increased failure of medical management. We could hypothesize that a shorter exposure of the distal esophagus to acid was not yet sufficient to determine the histological signs of esophageal damage or merely that HH does not predispose to erosive esophagitis in pediatric patients without comorbidities.

This study has some limitations. Sliding hiatus hernia is readily diagnosed by barium swallow radiography or endoscopy, when >2 cm in axial span (4). We, however, did not perform a barium swallow examination to confirm the endoscopic findings, for ethical reasons; therefore, it was not possible to perform a quantitative assessment of HH size. In addition, the prevalence of HH could have been overestimated owing to the lower esophageal sphincter relaxation consequent to the use of midazolam during the examination and to the presence of continuous crying during the majority of the examinations (32). False-positives, however, should have been strongly limited through the evaluation of GEJ by retroflexing the scope.

CONCLUSIONS

We assessed the prevalence of HH in a pediatric population undergoing EGD, irrespective of dyspeptic symptoms. According to our data, HH correlates with the presence of heartburn and regurgitation in children, but not in toddlers. Moreover, no association was found with either endoscopically or histologically defined esophagitis at any age.

REFERENCES

1. Petersen H, Johannessen T, Sandvik AK, et al. Relationship between endoscopic hiatus hernia and gastroesophageal reflux symptoms. *Scand J Gastroenterol* 1991;26:921–6.
2. Gordon C, Kang JY, Neild PJ, et al. The role of the hiatus hernia in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004; 20:719–32.
3. Mittal RK. Hiatal hernia: myth or reality? *Am J Med* 1997;103:33S–9S.
4. Kahrilas PJ. The role of hiatus hernia in GERD. *Yale J Biol Med* 1999;72:101–11.
5. El-Serag HB, Sonnenberg A. Associations between different forms of gastrooesophageal reflux disease. *Gut* 1997;41:594–9.
6. Xenos ES. The role of esophageal motility and hiatal hernia in esophageal exposure to acid. *Surg Endosc* 2002;16:914–20.
7. Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. *Eur J Gastroenterol Hepatol* 2004;16:495–501.
8. van Herwaarden MA, Samson M, Smout AJPM. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. *Gastroenterology* 2000;119:1439–46.
9. Jones MP, Sloan SS, Rabine JC, et al. Hiatal hernia size is the dominant determinant of esophagitis presence and severity in gastroesophageal reflux disease. *Am J Gastroenterol* 2001;96:1711–7.
10. Hyun JJ, Bak YT. Clinical significance of hiatal hernia. *Gut Liver* 2011;5:267–77.
11. Boeckxstaens GEE. Review article: the pathophysiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007;26:149–60.
12. Berstad A, Weberg R, Frøyshov Larsen I, et al. Relationship of hiatus hernia to reflux oesophagitis. A prospective study of coincidence, using endoscopy. *Scand J Gastroenterol* 1986;21:55–8.
13. Massey BT. Acid clearance, hiatal hernia size and oesophagitis: redress the egress regress. *Neurogastroenterol Motil* 2002;14:607–9.
14. Jones MP, Sloan SS, Jovanovic B, et al. Impaired egress rather than increased access: an important independent predictor of erosive oesophagitis. *Neurogastroenterol Motil* 2002;14:625–31.
15. Dickman R, Boaz M, Aizic S, et al. Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. *J Neurogastroenterol Motil* 2011;17:387–94.
16. Gorenstein A, Cohen AJ, Cordova Z, et al. Hiatal hernia in pediatric gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2001;33:554–7.
17. Thomas PS, Carré IJ. Findings on barium swallow in younger siblings of children with hiatal hernia (partial thoracic stomach). *J Pediatr Gastroenterol Nutr* 1991;12:174–7.
18. Hassal E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr* 2007;150:262–7.
19. Gilger MA, El-Serag HB, Gold BD, et al. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. *J Pediatr Gastroenterol Nutr* 2008;47:141–6.
20. El-Serag HB, Bailey NR, Gilger M, et al. Endoscopic manifestations of gastroesophageal reflux disease in patients between 18 months and 25 years without neurological deficits. *Am J Gastroenterol* 2002;97: 1635–9.
21. Ruigòmez A, Wallander MA, Lundborg P, et al. Gastroesophageal reflux disease in children and adolescents in primary care. *Scand J Gastroenterol* 2010;45:139–46.
22. Wu JF, Hsu WC, Tseng PH, et al. Combined multichannel intraluminal impedance and pH monitoring assists the diagnosis of sliding hiatal hernia in children with gastroesophageal reflux disease. *J Gastroenterol* 2013;48:1242–8.
23. Simeone D, Caria MC, Miele E, et al. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. *J Pediatr Gastroenterol Nutr* 1997;25:51–5.
24. Boyce WH. Endoscopic definitions of esophagogastric junction regional anatomy. *Gastrointest Endosc* 2000;51:586–92.
25. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the diagnosis and grading of hiatal hernia. *Best Pract Res Clin Gastroenterol* 2008;22: 601–16.
26. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe esophagitis after treatment with omeprazole. *Gastroenterology* 1988; 95:903–12.
27. Yerian L, Fiocca R, Mastracci L, et al. Refinement and reproducibility of histologic criteria for the assessment of microscopic lesions in patients with gastroesophageal reflux disease: the Esohisto project. *Dig Dis Sci* 2011;56:2656–65.
28. Stål P, Lindberg G, Ost A, et al. Gastroesophageal reflux in healthy subjects. Significance of endoscopic findings, histology, age, and sex. *Scand J Gastroenterol* 1999;34:121–8.
29. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005;40:275–85.
30. Yeom JS, Park HJ, Cho JS, et al. Reflux esophagitis and its relationship to hiatal hernia. *J Korean Med Sci* 1999;14:253–6.
31. Awad RA, Camacho S. *Helicobacter pylori* infection and hiatal hernia do not affect acid reflux and esophageal motility in patients with gastroesophageal reflux. *J Gastroenterol* 2002;37:247–54.
32. Pensabene L, Miele E, Del Giudice E, et al. Mechanisms of gastroesophageal reflux in children with sequelae of birth asphyxia. *Brain Dev* 2008;30:563–71.

Chapter 8

- Curriculum Vitae -

Main research fields:

- Paediatric nutrition (main fields: nutrition in inflammatory bowel disease, and children with neurological impairment)
- Paediatric gastroenterology (main fields: functional gastrointestinal disorders, inflammatory bowel diseases)
- Gastrointestinal Motility
- Effect of nutritional status on the immune function

List of publications in the years 2014-2017

1. Kuizenga-Wessel S, Steutel NF, Benninga MA, Devreker T, **Scarpato E**, Staiano A, Szajewska H, Vandenplas Y, Tabbers MM. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. BMJ Paediatrics Open 2017; 1:e000017. doi:10.1136/bmjpo-2017-000017.
2. **Scarpato E**, Quitadamo P, Roman E, Jojkic-Pavkov D, Kolacek S, Papadopoulou A, Roma E, Shamir R, Lev MRB, Lutovac B, Djurisic V, Orel R, Koleilat A, Mneimneh S, Coppola V, Corazziari E, Staiano A. Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area. J Pediatr Gastroenterol Nutr 2017; 64(6):e142-e146.
3. **Scarpato E**, Staiano A, Molteni M, Terrone G, Mazzocchi A, Agostoni C. Nutritional assessment and intervention in children with cerebral palsy: a practical approach. Int J Food Sci Nutr 2017; 68(6):763-770.
4. Camilleri M, Park SY, **Scarpato E**, Staiano A. Exploring hypotheses and rationale for causes of infantile colic. Neurogastroenterol Motil. 2017 Feb;29(2).

5. **Scarpato E**, D'Armiento M, Martinelli M, Mancusi V, Campione S, Alessandrella A, Staiano A, Miele E Impact of Hiatal Hernia on Pediatric Dyspeptic Symptoms. J Pediatr Gastroenterol Nutr 2014; 59(6):795-8.

6. Ummarino D, Miele E, Martinelli M, **Scarpato E**, Crocetto F, Sciorio E, Staiano A. Effect of Magnesium Alginate Plus Simethicone on Gastroesophageal Reflux in Infants. J Pediatr Gastroenterol Nutr 2015; 60(2):230-5.

Abstracts and Communications in the years 2014-2017

1. Altamimi E, **Scarpato E**, Alsaleh I, Ijam M, Tantawi K, AlKhdour M, Sarayreh Y, Younes AB, Aqtam B, Alassaf M, Bataineh M. Functional Gastrointestinal Disorders In Jordanian Children: Cross-Sectional Study. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition Montreal October 5-8, 2016.

2. Altamimi E, **Scarpato E**, Alsaleh I, Ijam M, Tantawi K, AlKhdour M, Sarayreh Y, Younes AB, Aqtam B, Alassaf M, Bataineh M. Functional Gastrointestinal Disorders In Jordanian School Children: An Epidemiological Study. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition Montreal October 5-8, 2016.

3. **E Scarpato**, E Altamimi, A Kostovski, S Kolacek, V Jurkovic, D Pavkov, R Shamir, M Barlev, and A Staiano. Prevalence Of Functional Gastrointestinal Disorders In The European-Mediterranean Area: Preliminary Data. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition Montreal October 5-8, 2016.

4. M Martinelli, **E Scarpato**, C Strisciuglio, MR Serra, E Miele, A Staiano. Survey On Dietary Habits Of A Pediatric Ibd Population In Southern Italy: Preliminary Results. 49th Annual Meeting of ESPGHAN Athens, May 25-28 2016.

5. **E Scarpato**, C Strisciuglio, M Martinelli, C Tortora, S Cenni, MR Serra, A Staiano, E Miele. Does Exclusive Enteral Nutrition Affect The Clinical Course In Paediatric Crohn's Disease Patients? 49th Annual Meeting of ESPGHAN Athens, May 25-28 2016

6. N Steutel, **E Scarpato**, R Turco, H Nijenhuis, Y Vandenplas, M Langendam, M Tabbers, M Benninga, A Staiano. Prevalence Of Functional Gastrointestinal Disorders In Young Belgian, Dutch And Italian Children, 49th Annual Meeting of ESPGHAN Athens, May 25-28 2016

7. **E. Scarpato**, P. Quitadamo, V. Coppola, A. Papadopoulou, E. Roma, M. Barlev, R. Shamir, D. Pavkov, E. Roman, B. Lutovac, A. Koleilat, A. Staiano. The European Mediterranean Area Project On Functional Gastrointestinal Disorders – First Phase. XXII CONGRESSO NAZIONALE SIGENP, Bari, 8-10 ottobre 2015.

8. **E Scarpato**, P Quitadamo, V Coppola, A Papadopoulou, E Roma, M Barlev, R Shamir, D Pavkov, E Roman, B Lutovac, V Djurisic, A Koleilat, and A Staiano. The European Mediterranean Area Project On Functional Gastrointestinal Disorders – First Phase: Preliminary Data. 48th Annual Meeting of ESPGHAN Amsterdam, May 6-9, 2015.

Awards

- Young Investigator Award at the Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition – ESPGHAN Prague 2017.
- Young Investigator Award at the World Congress of Paediatric Gastroenterology, Hepatology and Nutrition – WCPGHAN Montreàl 2016.

Invited as a Speaker years 2014-2017

- "Dalla ricerca al piacere della tavola. La Globalizzazione Alimentare: l'espressione del non-luogo."12-13 September 2017, Pozzuoli, Italy.
- "9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition and Human and Microbiota Health", 10-12 September 2017, Rome, Italy
- "La Pediatria Pratica III Edizione – Workshop di Nutrizione Pediatrica" 24-25 February 2017, Palermo, Italy.

- “Pediatria a Napoli. Il quesito del pediatra e la soluzione multidisciplinare.” 26-28 January 2017, Naples, Italy.
- “Dalla ricerca al piacere della tavola: quando la scelta è culturale.” 13-14 September 2016, Pozzuoli, Italy.
- “Percorsi In Pediatria: Oggi Parliamo Di… Paralisi Cerebrale Infantile.” 18 June 2016, Castellammare di Stabia, Italy.
- “Le PCI: definizione dei percorsi diagnostici, terapeutici e riabilitativi” 4-5 March 2016, Naples, Italy.
- “Il Decision Making in Nutrizione Pediatrica: rendere facili le scelte salutari.” 10-11 September 2015, Pozzuoli, Italy.

Teaching Activities

Professor of the Postgraduate Course in Paediatric Gastroenterology, Hepatology and Nutrition held at the Department of Paediatrics of the University of Naples “Federico II”, edition 2015, 2016, and 2017.