Insert for Paediatricians

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Content

Introduction

The first year of an infant's life is characterized by rapid developmental changes. Sometimes these changes can be accompanied by functional gastrointestinal symptoms such as crying, infant regurgitation or constipation, which are not explainable by structural or biochemical abnormalities. Functional gastrointestinal symptoms in otherwise healthy infants do not usually pose a health risk, provided parents are informed and symptoms are adequately addressed so as not to result in ongoing emotional distress or unnecessary treatment. However, scientific research into the human gut microbiome contributes to an optimized understanding of healthy early childhood development: Findings from this area are therefore aimed at developing approaches to be able to modulate the early life microbiome in a more targeted manner in the future. Meanwhile, the understanding of these functional disorders – including the long- and short-term consequences on the development of infants affected, but also of possible influencing factors such as dietary interventions during the first months of life and the role of the gut-brain axis, is increasing.

Scientific Group on Human Milk Research

The Gut – Challenges in the First Year of Life

The term "functional gastrointestinal disorders" (FGIDs) summarizes chronic or recurrent gastrointestinal disorders that cannot be explained by structural or biochemical abnormalities [1]. FGIDs represent the most common diagnosis in gastroenterology and are also frequently observed in children of all ages and have a significant impact on the infant's quality of life or the daily life of their families [2]. FGIDs are diagnosed according to the symptom-based Rome criteria developed by the working committees of the Rome foundation. After the original introduction of the Rome criteria for adults, the FGIDs criteria became available for children in 1999 with the Rome II criteria. While the research literature for infants and toddlers in the field of FGIDs was initially limited, the understanding of the various functional gastrointestinal disorders in these age groups has improved and expanded significantly in the decades that followed. After several revisions of the criteria, the definition of FGIDs has evolved from the mere absence of organic explanations to a stress-related or psychiatric disorder to a motility disorder and finally – with the revised Rome III criteria – to a disorder of gastrointestinal functioning [3]. One of the most important recent developments concerned the improved understanding of the role of the gut-brain axis in FGIDs [4]. The concept of the gut-brain axis, which is based in particular on findings in adults with irritable bowel syndrome, can be also better communicated to parents than the difficult-to-understand non-specific "functional" terminology [3].

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Table 1 Most common functional gastrointestinal disorders in neonates and toddlers as defined in the Rome IV criteria: Age at which these occur (modified after [1, 4])

Disorder	Age	Prevalence
Infant regurgitation (G1)	Week 3 to month 12	41–67 %
Infant colic (G4)	Early infancy to month 5	5–19 %
Functional constipation (G7)	Birth to adulthood	3–27 %

For the first time as part of the Rome III criteria, FGIDs in younger children (neonates and toddlers) were differentiated from FGIDs in older children (children and adolescents). In the Rome IV criteria, the diagnostic criteria of seven functional gastrointestinal disorders (G1–G7) are defined for the age group of neonates and toddlers. Prof. Dr. Marc Benninga, Amsterdam, Netherlands, provided an overview of the most common disorders – namely infant regurgitation, infant colic and functional constipation – and how best to classify them according to the current Rome criteria (**Tab. 1**).

Behavioral and somatic long-term consequences

FGIDs in the first months of life not only represent a challenge for the affected children and parents, but can also have long-term effects: It has been shown that the prevalence of FGIDs is higher in children with a history of infantile distress such as colic, regurgitation or functional constipation and is still higher years later than in children without such a history [5]. According to a study of European infants and toddlers (n=2.751), infant regurgitation is associated with the highest prevalence at ages 0–12 months, while constipation is most common in toddlers. In addition, multivariate regression analyses revealed that the prevalence of any FGIDs correlated with younger age, formula feeding in infants, and domestic violence in toddlers aged 13–48 months [6]. These data also point to the importance of increased sensitivity to signs of domestic violence. Interestingly, in a study with 197 infants (<24 months), no different FGID prevalence rates could be demonstrated between preterm and term infants. An exception was infant regurgitation, which was observed more frequently in term infants (35.1 % and 15.6 %; p <0.001) [7].

Infant regurgitation

While physiological gastroesophageal reflux (GER) is characterized by the retrograde involuntary backflow of gastric contents into the esophagus (with or without regurgitation and vomiting) and has no pathological value, in a gastroesophageal reflux disease (GERD), the regurgitation of gastric contents is associated with complications or contributes to tissue damage. The distinction is important because recognizing infant regurgitation helps to avoid unnecessary doctor visits, extended diagnostic testing or therapy (especially with hastily prescribed proton pump inhibitors) for suspected GERD during the first year of life. In this regard, the Rome IV criteria are helpful, which states that for the diagnosis of an infant regurgitation syndrome, the following two criteria must be met in otherwise healthy infants aged three weeks to 12 months [1]:

- regurgitation two or more times per day for three or more weeks,
- no retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing.

The peak of uncomplicated infant regurgitation is around three months of age, and in the natural course, infant regurgitation usually resolves by the age of 12–15 months [8]. The cause of infant regurgitation is often multifactorial, including, e. g., relative overfeeding, the position of the child (supine position), or a relatively short esophagus [1].

Potential signs suggestive of GERD may vary and are extremely difficult to recognize, especially since infants and small children are unable to verbalize their symptoms [9]. However, further diagnostic evaluation in children aged <2 years should be initiated if "red flag" symptoms such as hematemesis, hematochezia, consistently forceful vomiting, failure to thrive, food refusal, diarrhea, are also present. Anatomical abnormalities should also be ruled out if regurgitation persists beyond the first year of life, started early in the neonatal period, or is associated with bilious vomiting, dehydration and/or other complications [1, 9].

Functional constipation

Functional constipation is often the result of withholding behavior: The bowel absorbs more water and produces harder stools [1]. However, it is also important to keep in mind the age-related development of the defecation rate

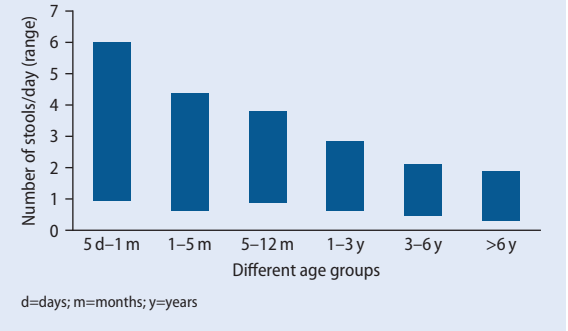


Figure 1 ◀ Bowel frequency in different age groups (n=662) (modified after [10])

in healthy children showing a wide interindividual variability and a decrease with age, as Benninga emphasized, citing an Italian study (**Fig. 1**) [10].

For practical reasons, children with and without toilet training have been differentiated since the Rome IV criteria: The majority of toddlers are younger than 2.5 years and are not toilet trained. In children up to 4 years of age, at least two of the following criteria must be met in order to diagnose functional constipation:

- two or fewer defecations per week,
- history of excessive stool retention,
- history of painful or hard bowel movements,
- history of large-diameter stools, or presence of a large fecal mass in the rectum [1].

According to Benninga, in over 90 % of cases, the constipation is not due to organic diseases. Common symptoms in infants ≤2 years include hard stools, rectal discomfort, painful bowel movements and stool withholding [11]. However, child abuse should always be considered as a potential cause of functional constipation. The chances of a clinical outcome in adulthood improve if a treatment-requiring constipation is treated without any major delay: As shown by a study, infants with constipation symptoms (median age: 3.5 months) for less than three months before presentation achieved higher cumulative success rates than infants with longer symptom duration [12].

Infant colic

Another commonly reported phenomenon is infant colic, which is defined in the Rome IV diagnostic criteria as a syndrome [1] that

- affects infants <5 months,
- and involves recurrent or prolonged periods of crying, fussing or irritability and, according to the caregivers, occurs for no apparent reason and cannot be prevented or resolved by the caregivers,
- without any evidence of infant failure to thrive, fever, or illness.

With the establishment of the Rome IV criteria, assessment of the duration of crying in infants suspected of having colic has become less relevant. Despite the usually self-limiting nature of infantile colic with crying peaks at the time of about 4–6 weeks, with a steady decline within 12 weeks, it may be associated with considerable stress for the infant and parents/family. In the short term, the risk of maternal depression occurring after several months may increase, and a possible link between excessive crying and shaking baby syndrome should also be considered. Behavioral problems, an increased risk of migraine, abdominal pain or a disturbed family functioning were described as possible long-term effects for children and adolescents with infant colic in the case history [13]. A prospective study reported a higher prevalence of allergic rhinitis, atopic eczema and food allergies in 10-year-old children with a history of infant colic [14].

To exclude other, more serious underlying medical causes, a careful history examination should be taken during diagnostic work-up, including recording of sleep, nutrition, pre- and perinatal problems, psychosocial circumstances, and physical examination. In the case of "red flag" symptoms, further assessments are also indicated here (**Box**) [13].

In most cases, however, neither laboratory tests nor radiological examination procedures are necessary. In very few cases is an infant colic due to a serious organic cause – most commonly infections of the urinary tract – with a prevalence of less than 5 % [13]. Even if the pathophysiological mechanisms that cause infant colic have not yet been fully elucidated, there are a number of explanatory approaches that are currently being discussed, such as the mode of feeding (breast-fed/formula-fed), gastrointestinal factors (e. g., cow's milk protein intolerance), family stress, neurodevelopmental factors, or microbial pattern (dysbiosis) (**Fig. 2**).

From gut microbiota to human milk

The human gut microbiota plays a central role in the infant development and health, and the adult intestine can accommodate up to 10^{14} bacterial cells, which are mainly dominated by the phyla *Bacillota* and *Bacteroidota* [15]. Early gut microbial colonization patterns have been shown to influence immune development and host metabolism, and differences in composition driven by environmental factors may affect susceptibility to metabolic (e. g., obesity phenotype, type 1 and type 2 diabetes mellitus), immunologic (e. g., allergies) and even behavioral/psychiatric disorders (e. g., autism, depression) into adulthood [16]. Consequently, a better understanding of the early interaction between the infants' microbiota and the maturation of the immune system, metabolism and behavior including adequate brain development, as well as the possible impact factors on the early infant gut microbiome, is needed. The gold standard as a nutritional source, human milk (HM),

Red Flags

Diagnostic work-up of infant colic:
Red flag symptoms that may help to identify more serious organic causes:

- Extreme or high-pitched cry
- Lack of diurnal rhythm
- Symptoms persisting beyond 5 months of age
- Presence of frequent regurgitation, vomiting, diarrhea, weight loss
- Failure to thrive
- Family history of migraine
- Family history of atopy
- Abnormal physical examination
- Maternal drug ingestion
- Fever or illness
- Severe anxiety in the parents
- Parental depression

modified after [13]

provides the optimum active ingredients for the necessary microbial species to thrive in the infant gut.

Contrary to the earlier view that HM is a sterile liquid, HM's own microbiota are now known to exist which are optimally adapted for the infant health and immune development. For example, HM includes commensal bacteria that may further improve infant health by preventing adhesion of pathogens and promoting gut colonization with beneficial microbes [17].

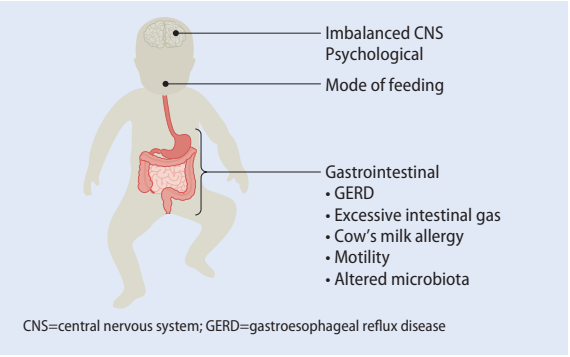


Figure 2 ◀ Infant colic: possible mechanisms contributing to infant colic (modified after [13])

Early dynamic changes in the human milk microbiome

The microbial colonization of the host begins with the birth, and is subject – as Prof. Dr. Catherine Stanton, Cork, Ireland, explained – to a dynamic development, especially during the first months of life. As shown in the INFAMILK cohort study, the HM microbiome changes its pattern over the course of lactation from birth to six months. In a cohort of 80 lactating women, a decrease in HM microbiota diversity was observed throughout this time, with the greatest difference seen between week 8 and 24. According to Stanton, during the first six months of lactation nine genera predominated, including *Staphylococcus, Streptococcus, Pseudomonas, Acinetobacter, Bifidobacterium, Erysipelatoclostridium, Brevundimonas, Flavobacterium*, and *Rhodococcus*. *Streptococcus* had the highest mean relative abundance at week 1 and 24, whereas *Pseudomonas* predominated at week 4 and week 8; *Bifidobacterium* and *Lactobacillus* reached their relative peak at the time of week 4 [18]. The lactation stage was shown to be of crucial importance for changing composition of the HM microbiome, while factors such as birth mode, maternal weight or infant sex had no significant influence, Stanton reported. With the increase of C-section-delivered infants, the question also arises to which extent the mode of delivery (among other possible environmental factors) affects the infant gut microbiome composition if vertical transmission of the vaginal bacterial community to the newborn is absent. Indeed, the mode of delivery has an impact on the infant gut microbiome, as demonstrated in clinical trials [19, 20].

How the microbiota and brain are linked

Crying behavior as a result of an intestinal dysbiosis could also be explained by the already mentioned gut-brain axis: The gut and the brain are linked bidirectionally, and communication occurs via different mechanisms, including through gut microbiota and its metabolites [13].

The analysis of the neuro-biological circuits that enable bidirectional communication between the gut microbiome and the brain is one of the topics addressed by Prof. Dr. Karl-Herbert Schäfer, Zweibrücken, Germany. Schäfer reminded that the gut compromises the largest and most complex nervous system beyond the CNS, acting autonomously and in close interaction with the microbiota: The enteric nervous system (ENS) is organized into interconnected neural networks that are embedded within different layers of the gut wall [21]. According to recent findings, changes in the microbiota not only have the potential to trigger metabolic changes, but also to influence individual well-being via the ENS and gut-brain axis, and beyond that to influence the course of neurodegenerative diseases [22]. Conversely, as indicated above, breast milk is an important factor influencing postnatal development of the ENS. In a rodent model, for example, it could be shown for isolated human milk proteins that these support the amount of surviving neurons and neurite outgrowth [23].

Parental reassurance and education

FGIDs are among the most common reasons for pediatric consultations in infants younger than four months. Gastrointestinal symptoms often occur in combination: According to data from France, 78 % of infants up to six months with FGIDs had multiple digestive symptoms, 63 % of them with two disorders. Infants with multiple FGIDs are at greater risk of weight gain, poor quality of life, shorter breastfeeding times, and overuse of prescription drugs [24].

For children and caregivers, FGID symptoms cause tremendous distress, which can set off a chain reaction of infant discomfort and crying, triggering parental anxiety, and leading to repeated consultations of healthcare professionals and higher healthcare costs. If FGIDs are involved and organic underlying diseases are therefore excluded, according to Prof. Dr. Hugues Piloquet, Nantes, France, the parental reassurance and education, as well as nutritional advice, are of paramount importance (**Fig. 3**) [25]. As part of the nutritional advice, the benefit of breastfeeding should be emphasized and supported where possible. Parents should

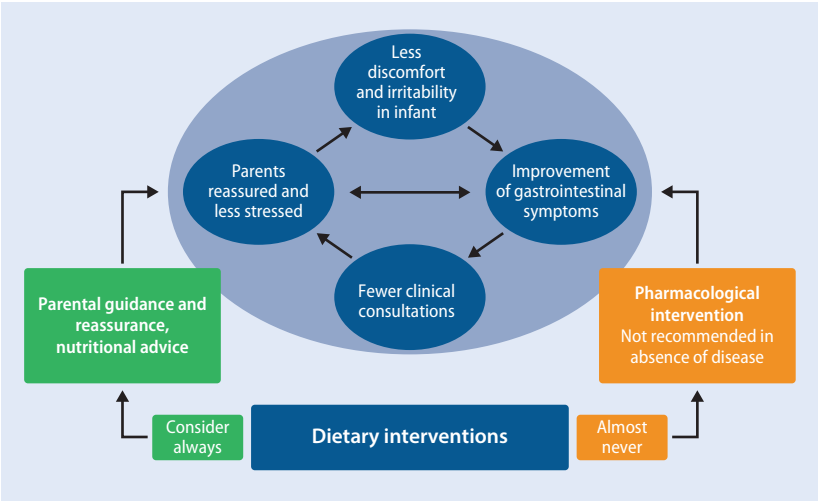


Figure 3 ▲ Infants' functional gastrointestinal symptoms – a frequent reason for healthcare consultations (modified after [25])

also be made aware that overfeeding can aggravate symptoms and should be avoided. Also, the parents should be informed that regurgitation and colic are temporary problems in the first few months of life and mostly resolve spontaneously. Information should also be provided on special formulas to be considered in the case of persistent symptoms with proven effects on formula-fed infants. Parents should be made aware that pharmacological approaches are rarely required (with the exception of laxatives for functional constipation), and are mostly ineffective in FGIDs that occur in infants. In particular, the use of medically unindicated proton pump inhibitors, pain relieving agents, or over-the-counter remedies should be avoided before the first birthday [18].

Potential effects of infant formula

The current data on dietary modifications in infant colic is still limited. A Cochrane review concluded that the evidence for individual dietary modifications is too low to be able to make specific recommendations [26].

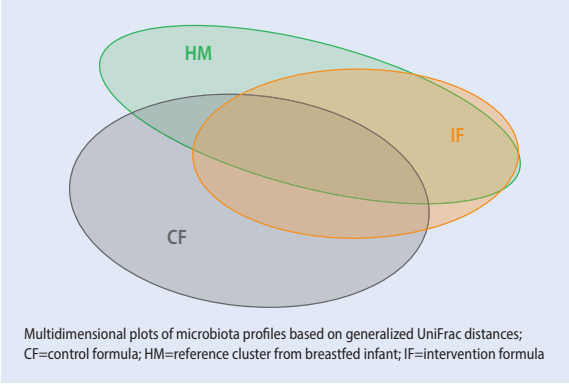
In a first high-quality randomized controlled study (RCT), however, it could be shown that a maternal low-allergen diet excluding cow's milk, eggs, peanuts, tree nuts, wheat, soy, and fish, was beneficial in reducing infant colic among breastfed infants [27]. For formula-fed infants, it could be shown that a hydrolyzed versus standard formula can, for example, lead to a reduction in the average crying time without side effects occurring [28]. Another RCT in healthy infants could show that a combination of fermented formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (scGOS-lcFOS) might reduce the incidence of infantile colic compared with scGOS-lcFOS or fermented formula alone [29].

Based on the knowledge that the intestinal microbiome is pathophysiologically relevant in infant colic, the supplemental use of probiotic microorganisms is considered a promising approach. According to a recent meta-analysis, there is high-level evidence available that probiotics are effective at reducing crying time in breast-fed infants [30].

Synbiotics may lead to less infections

Lacotobacilli comprise an important group of bacteria that are part of HM and are probably also significant for colonizing the intestines of infants. For children for whom breastfeeding is not possible, infant formula should ideally promote a similar development of their intestinal microbiota [31]. Furthermore, *Lactobacilli* are found comparatively rarely in the intestines of adults in industrialized countries – possibly as a result of an unbalanced diet or pharmacological interventions. For the HM-derived *Limosilactobacillus fermentum* CECT5716 in combination with galactooligosaccharides (GOS), a prebiotic, it could be shown in a RCT that healthy, bottle-fed children receiving synbiotic formula containing *L. fermentum* and GOS developed respiratory and gastro-intestinal infections less frequently than infants who received formula supplemented only with GOS [32].

Piloquet presented first results of a new clinical study examining the effects of a standard infant formula enriched with *L. fermentum* CECT5716 and GOS (synbiotic IF) on faecal microbiota and gut milieu parameters (e. g., pH value, immunoglobulin A [IgA]). The multicenter, double-blind RCT (registered in clinicaltrials.gov as NCT02221687 ["The Combiotic-Study (GOLF III)"]) included 540 French and Belgian children [31]. While both formulas were well tolerated, it could be shown how the fecal ecosystem changed during the first months of life with the addition of synbiotic IF compared to the control group (CF). Significant effects of the synbiotic IF compared with CF were visible at month 4, including higher occurrence of *Bifidobacterium* spp. and Lactobacillaceae and lower occurrence of *Blautia* spp., as well as *Ruminoccocus gnavus* and relatives. This was accompanied by lower fecal pH and concentrations of butyrate. After de novo clustering at four months of age, overall phylogenetic profiles of the infants receiving IF were closer to reference profiles of those fed with human milk than infants fed CF (**Fig. 4**) [31]. Further analyses of clinical outcomes including infections are ongoing.



Multidimensional plots of microbiota profiles based on generalized UniFrac distances; CF=control formula; HM=reference cluster from breastfed infant; IF=intervention formula

Figure 4 ◄ GOLF III: Microbiota profiles of the infants receiving IF were closer to reference profiles of those fed with human milk than infants fed CF (modified after [31])

Summary

- FGIDs are common in children of all ages and should be diagnosed according to the symptom-based Rome IV criteria.
- If FGIDs are diagnosed and therefore there are no organic medical causes with an indication for treatment, the first priority must be to reassure the parents.
- There is growing evidence that some prebiotics and probiotics can have a beneficial effect on some of the functional gastrointestinal symptoms.
- In formula-fed infants, synbiotic intervention formulas can offer a promising approach, as they have been shown to affect fecal and milieu-related parameters at an early age – with approximation to the microbiota profile of breast-fed infants.
- However, the HM with its natural pre- and probiotic components still remains gold standard of infant nutrition. Further controlled studies are desirable, e. g., using the microbiome analysis of C-section-delivered children to gain further insights into which components of the microbiome are missing and can possibly be supplied as nutritional intervention.

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