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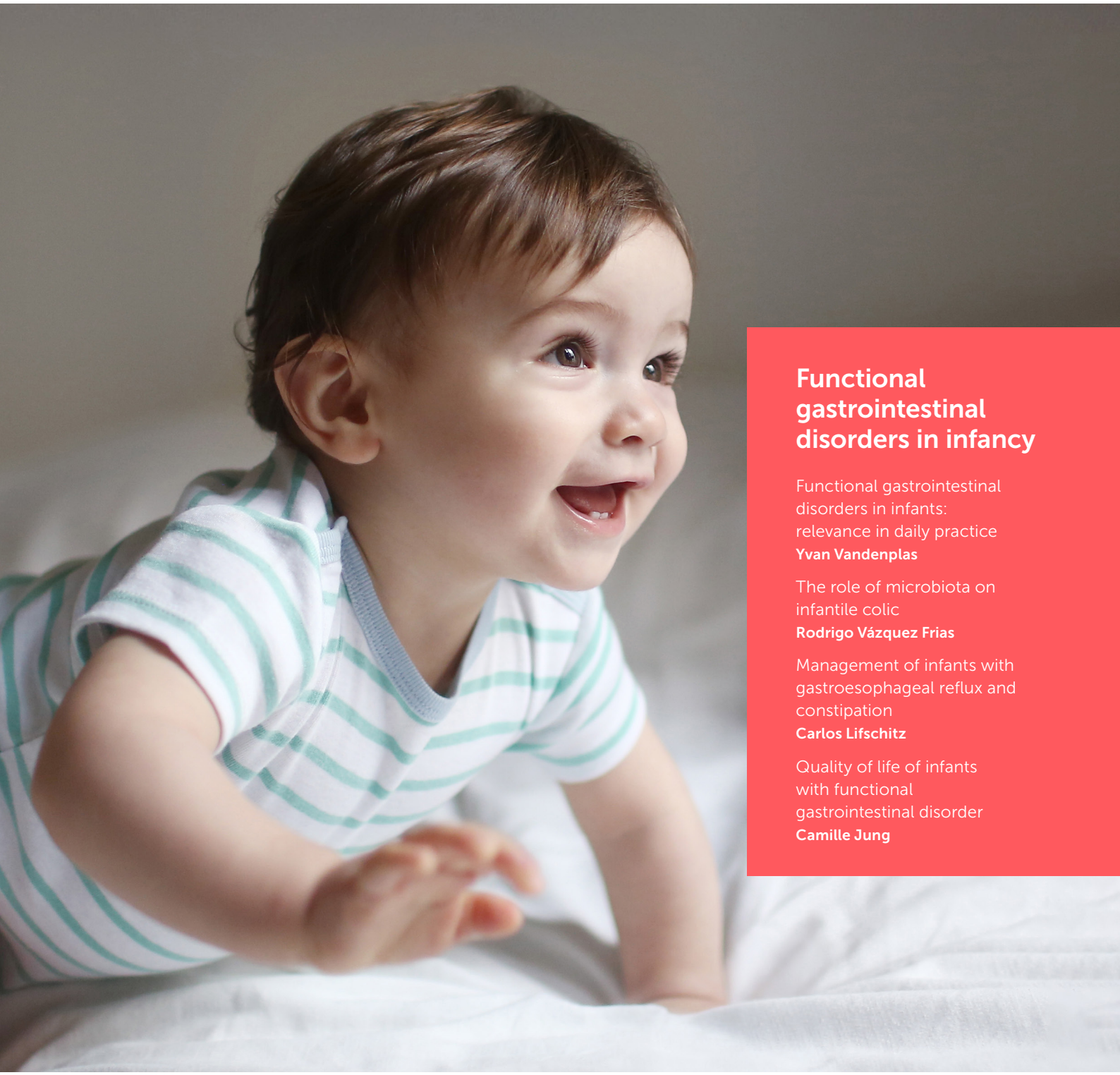
the nest



Functional gastrointestinal disorders in infancy

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Functional gastrointestinal disorders in infants: relevance in daily practice

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Key messages:

- Functional gastrointestinal disorders (FGIDs) in infancy are frequent, worldwide.
- The majority of infants present with a combination of FGIDs.
- The management of FGIDs in infants consists of parental reassurance and guidance and nutritional intervention.
- Nutritional interventions are effective and safe.

Historically, functional gastrointestinal disorders (FGIDs) got limited attention from health care providers because i) symptoms were considered to improve and finally disappear over time, ii) there was no disease, and iii) families had other health care priorities such as infant mortality and morbidity which was much higher than today. Typically, the impact of FGIDs in health care goes hand in hand with the living standard. However, this does not mean that the incidence of FGIDs in infants in developing countries differs from that in the western world. The incidence of troublesome regurgitation in Indonesia is exactly the same as reported in the literature, but Indonesian mothers seek less frequently medical help.[1] The same applies for crying: presumably, healthy Polish infants cry significantly more than infants in Belgium and Spain.[2] The most frequent FGIDs are troublesome regurgitation (~25%), infantile colic (~20%) and constipation (~10%).

Worldwide, at least 25% of infants suffer from at least one FGID. While most guidelines discuss FGIDs as separate manifestations, more than 75% of the infants present with more than one FGID; 15% even present with three.[3] Conclusion: i) FGIDs in infancy are frequent, worldwide; ii) the majority of infants present with a combination of FGIDs.

The next question that needs to be addressed is: So what? Does it matter? FGIDs in infants are traditionally considered to disappear spontaneously over time. However, that statement is not valid for constipation as 25% of children with functional constipation continue to experience symptoms at adult age. Infantile colic improves after the age of 3–4 months; regurgitation decreases at 6 months, and certainly between 12 and 15 months. However, there is evidence that FGIDs do have a long-term impact on the quality of life of the infant and the family. FGIDs are a cause of feeding difficulties causing also discontinuation of breastfeeding.[4] FGIDs are a well-known cause of parental stress, depression and insecurity.[5] FGIDs are also a cause of behavioral disorders of the infant. Quality of life of a family with an infant with a FGID is still challenged three years later.[6] An infant presenting with frequent regurgitation early in life has a 2 to 5 times higher risk to have gastroesophageal reflux (GER) symptoms when 9 years old. Also the opposite has been shown: children with abdominal pain-related FGIDs at 7.9 years of age had higher prevalence of GI distress during the first three months of life. Ex-colicky children displayed more negative emotions according to the temperament scale. Four year old children with a history of infantile colic still present more negative moods during meals, and report more stomach-ache.[6] Although relationships regarding crying and mother-infant interaction remain extremely complex, the findings point toward a possible temperamental contribution to the pathogenesis of infantile colic.

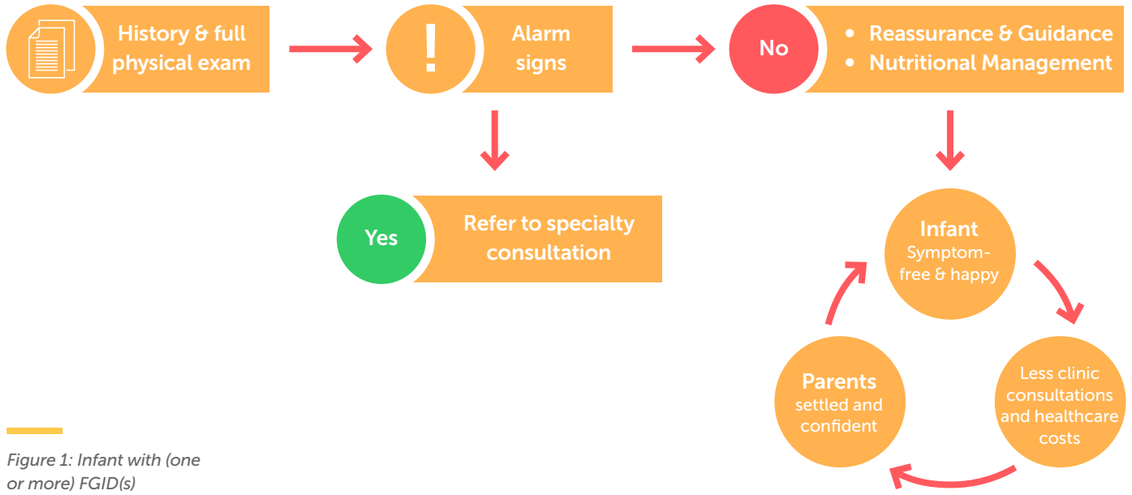

Figure 1: Infant with (one or more) FGID(s)

The development of the gastro-intestinal microbiome is recognized as important in promoting health in infants. An altered gut microbiome, referred to as dysbiosis, has an etiologic role in the development of FGIDs, such as distress and alterations is stool composition. Randomized controlled trials reported efficacy of probiotics in the management of FGIDs. Different probiotics, prebiotics, synbiotics and postbiotics have resulted in the effective prevention and management of constipation, distress and regurgitation in infants.

> There is quiet some evidence that FGIDs do have a long-term impact on the quality of life of the infant and the family

Conclusion:

The cornerstone of the management of FGIDs in infants consist of parental reassurance and guidance. Nutritional treatment, focusing on the development and preservation of a healthy balanced gastrointestinal microbiome, has been shown to be effective and safe.

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The role of microbiota on infantile colic

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Key messages:

- Growing scientific evidence suggests a link between the alterations in microbiota and infant colic.
- *Limosilactobacillus (L) reuteri* (previously known as *Lactobacillus reuteri**) DSM17938 is the probiotic strain with the highest evidence of efficacy and can be recommended for breastfed infants with infant colic.
- Partially hydrolyzed formula may offer some useful alternative to intact protein in the dietary management of infant colic, but more randomized controlled trials are needed to support its efficacy.

The amount and pattern of infant crying are age-dependent and change during the first months of life. There is an increased duration of crying in the first weeks of life, reaching a maximum between 6 and 8 weeks of age and then declining to more stable levels around 12 weeks of age.[1] The Rome IV criteria has drastically reviewed the clinical definition of infant colic (IC). According to it, infant colic occurs if 1) an infant is less than 5 months of age when the symptoms start and stop; 2) recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers; and 3) has no evidence of failure to thrive, fever, or illness.[2] All of the above should be present to diagnose infant colic. IC occurs in both breast-fed and formula-fed infants.[3] The etiology of IC is suggested to be multifactorial such as gastrointestinal, psychosocial, and neurodevelopmental, with increasing importance of the role of intestinal microbiome. Several studies have reported an association between IC and characteristics in intestinal microbiota such as lower bacterial diversity, higher abundance of Proteobacteria and lower abundance of Bifidobacterium and Lactobacillus.[4] The clinical management of infant colic includes: parental education, reassurance and empathy provided by the physician; modification of infant care and environmental routines. The treatment with pharmacological agents, like simethicone or lactase, is not supported by clinical evidence; while the use of certain probiotic strains may be helpful.[1]

Amongst the few probiotic strains used in the treatment of infant colic, *Limosilactobacillus (L) reuteri* (previously known as *Lactobacillus reuteri**) DSM 17938 has been the most studied. It inhibits pathogen growth and affects the immune system in different ways: through a modulatory effect of the pro-inflammatory signalling via Toll-like receptor 4 (TLR4) and nuclear factor-B (NF-B), resulting in decreased mucosal pro-inflammatory cytokines such as tumour necrosis factor-α (TNF–α) and interleukin-1β (IL-1β). Also, it modulates the composition of intestinal immune cells in neonatal gut, including dendritic cells and regulatory T cells.[5] According to a meta-analysis, using data from 4 double-blind trials, including 345 infants with colic, *L. reuteri* DSM 17938 is effective and can be recommended for treatment of breastfed infants with colic.[6] In addition to that, a recent study, not included in the meta-analysis, has shown that infants with colic treated with *L. reuteri* DSM 17938 for 30 days not only significantly decreased crying time, but also had confirmed reduction in faecal calprotectin and RORg/FOXP3 ratio, supporting the hypothesis of probiotic induced local and systemic reduction in inflammation.[7] More studies are needed for better understanding of the efficacy mechanism of probiotics in infant colic.

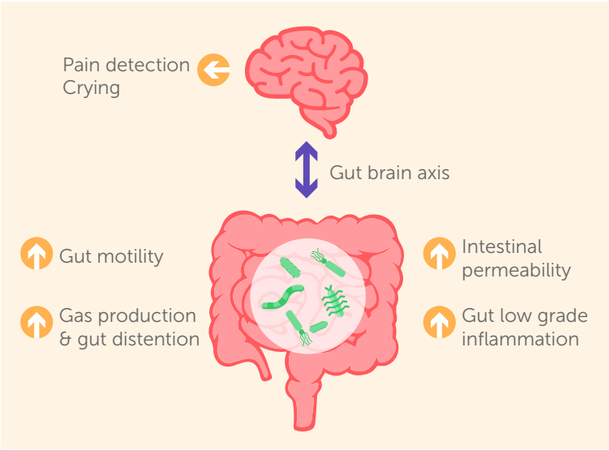

Figure 1: Possible mechanisms through which dysbiosis can contribute excessive crying/colic. Adapted from Zeevenhooven J et al, 2018

> Several studies among infants have reported an association between infant colic and characteristics in intestinal microbiota

There is evidence suggesting that partially hydrolyzed formula (pHF) use in non-exclusively breastfed infants maybe associated with decreased colic incidence compared with infants, fed intact protein infant formula.[1,8] pHF may offer some useful alternative to intact protein in the dietary management of common FGIDs, although well-designed, randomized trials are needed to allow to recommend the use of pHF for treatment in infants with FGIDs.[9]

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*Due to reclassification of *Lactobacillus genus* into groups of closely related species, *Lactobacillus reuteri* is renamed to *Limosilactobacillus reuteri* (see infographics at page 9)

Management of infants with gastroesophageal reflux and constipation

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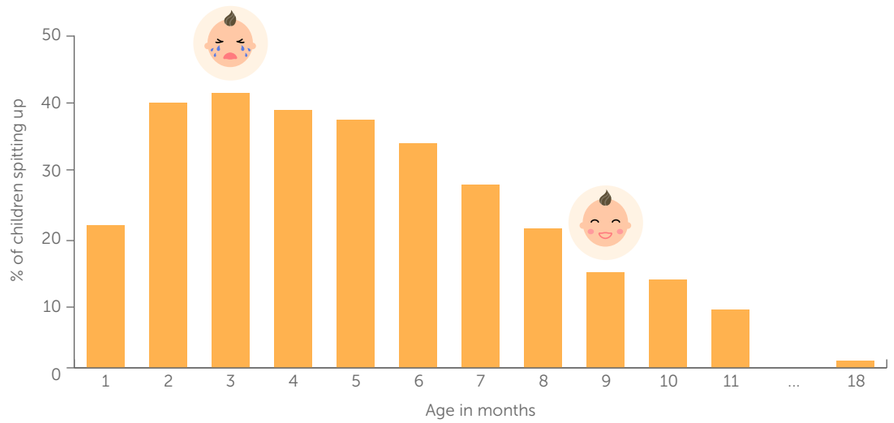
Key messages:

- Although we all know that functional gastrointestinal disorders (FGIDs) in infants are transient problems, parents sometimes want more than just words.
- Breastfeeding should never be discontinued as a form of treatment of a FGID.
- Dietary management if necessary, is the recommended treatment of regurgitation while medications can be used for treatment of constipation.

We will discuss here two of the three more frequent functional gastrointestinal disorders (FGIDs) in infants.

Gastroesophageal reflux

Although regurgitation can occur at any age, it peaks around 4 months of age, tapering from 6 months and declining in frequency until 12–15 months[1] (Figure 1).[2] When correctly identified, unnecessary doctor visits and investigations and therapy will be avoided. Treatment goals are to provide symptom relief, prevent complications and effective reassurance. In order to improve the caregiver-child interaction relieving the caregiver's fears about the condition may lead to reduction of parents' anxiety and consequently demand for medications, as management guidelines do not recommend their use. Multiple trials showed a lack of benefit of proton pump inhibitors in infants with regurgitation.[3] Discontinuation of breastfeeding is not recommended but alginates can be used to thicken breastmilk in the stomach. Early administration of *Limosilactobacillus (L) reuteri* (previously known as *Lactobacillus reuteri**) DSM17938 has been shown to control regurgitation episodes in full-term breastfed infants.[4] Thickened feedings and antiregurgitation formulas can decrease regurgitation in healthy formula fed infants and are part of the treatment guidelines, as well as an empirical trial of an extensively hydrolyzed protein formula. A study with a partially hydrolyzed whey formula (PHWF) supplemented with starch and *L. reuteri* DSM 17938 significantly reduced regurgitation compared to controls.[5] Overall, PHWF may offer a useful alternative to intact protein in the dietary management of common functional gastrointestinal symptoms.[6]



Natural History of regurgitation in infants and children constructed from data obtained from reference 2.

Constipation

Diagnosis of constipation in infants is relatively simple; it must include 1 month of at least 2 of the following: 1) two or fewer defecations per week 2) history of excessive stool retention, painful or hard bowel movements, 3) large-diameter stools and/or presence of a large fecal mass in the rectum.[7] This is the only infantile FGID for which treatment recommendations include medications: lactulose 1–2 g/kg, once or twice/day or polyethylenglycol 3350 0.2–0.8 g/kg/day.

However, parents usually don't like their infants to be on long term medication despite their lack of side effects, generally good results, palatability, ease of administration and cost. In the first year of life, dietary manipulation is almost impossible except for changing the formula type in non-breastfed infants. Prebiotics, small non digestible and nonabsorbable carbohydrates, have been shown to prevent or relief constipation in formula fed infants.[8] In addition, in a 2010 study,[9] the authors concluded that the administration of *L reuteri* (DSM 17938), a probiotic (live beneficial bacteria), administered to infants with chronic constipation had a positive effect on bowel frequency, even when there was no improvement in stool consistency. Because of their safety profile, probiotics may be an attractive option in the treatment of functional constipation.

> Because of their safety profile, probiotics may be an attractive option in the treatment of functional constipation

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*Due to reclassification of *Lactobacillus genus* into groups of closely related species, *Lactobacillus reuteri* is renamed to *Limosilactobacillus reuteri* (see infographics at page 9)

Quality of life of infants with functional gastrointestinal disorders

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Key messages:

- Although benign and with favorable outcome, functional gastrointestinal disorders (FGIDs) cause significant parental worry and anxiety.
- In FGIDs, improving quality of life is the major goal of treatment.
- Assessment of quality of life in these disorders should be a marker of effective management.

It is estimated that 20-30% of consultations during the first months of life are related to Functional gastrointestinal disorders (FGIDs).[1] Although FGIDs are benign and of favorable outcome, they cause significant parental worry and anxiety. FGIDs often occur in combination in the same infant, for example infant regurgitation associated with infant colic, which could complicate the message delivered to parents (Table 1). Physicians and more generally health caregivers may also have concerns about complications that are fortunately infrequent: maternal postpartum depression, shaken baby syndrome, early cessation of breastfeeding or behavior and sleep problems, etc.[2] These complications are partly related to the difficulties for parents to manage these FGIDs. Few studies have investigated the quality of life (QoL) of infants and their families in cases of FGID. This is partly related to the difficulty of having QoL scales, validated and specific to these disorders in infants. In a large French observational study on 815 infants, QoL was assessed with the Infant Quality of Life questionnaire (Qualin), which is a general QoL questionnaire validated in several languages.[3] Medical management was mainly based on dietary advices: prescription of an infant formula targeting the GI symptoms, lifestyle advice and reassurance. In this study, improved QoL was associated in multivariate analysis with younger age, lifestyle and dietary advices as well as partial breastfeeding (Table 2 and 3). More recently, Bellaiche et al have performed a study on 2757 infants under 6 months recruited by private French pediatricians in order to compare infant's QoL with a single FGID and to those with more than one FGIDs.[4] The used questionnaire was also the adapted-Infant Quality of Life questionnaire. In their study, multiple FGIDs were very frequent and represented almost 78% of their cohort, with the combination of gas/bloating and colic being the most frequent (in 28% of cases). Multiple FGIDs was associated with lower QoL compared to single FGID at inclusion and at follow-up visit, as well as a lower body weight and a shorter breastfeeding duration, reflecting the difficulty of caring for these infants. Using the PedsQL4.0 Generic Core Scale to measure QoL, Van Tilburg et al showed that the mean QoL score of infants suffering from FGID was 10 points lower on a scale of 100 than that of infants without FGID (p<0.001).[5] Another team found similar results in older children with FGID compared to healthy children.[6] Whereas FGIDs are not a life-threatening condition, QoL of infants and families is greatly impacted by these functional disorders. QoL is a marker of symptom severity that must be considered in the management of symptoms. It must therefore be the primary target of clinical management.

	Type of disorder	N°	%
Single FGID (n = 602)	Gas	40	1.5
	Constipation	55	2.0
	Colic	123	4.5
	Regurgitation	384	14.0
Two FGIDs (n = 1739)	Gas/Constipation	60	2.2
	Constipation/Colic	83	3.0
	Constipation/Regurgitation	130	4.7
	Gas/Regurgitation	209	7.6
	Colic/Regurgitation	481	17.4
	Gas/Colic	776	28.1
≥3 FGIDs (n = 406)	Gas/Constipation/Regurgitation	60	2.2
	Constipation/Colic/Regurgitation	81	2.9
	Gas/Constipation/Colic	117	4.3
	Gas/Constipation/Colic/Regurgitation	148	5.4
Total		2747	100

FGID = functional gastrointestinal disorder; n = number of infants.

Table 1: Prevalence of gastrointestinal (GI) disorders in all infants and distribution according to the type of GI[4]

	Mean change in score from inclusion to D15 (mean ± SD) by type of FGID[a]					
	Constipation (N=122)	Diarrhea (N=24)	Regurgitation (N=443)	Constant crying (N=35)	Regurgitation and diarrhea (N=57)	Regurgitation and constipation (N=134)
QUALIN Score	+11.46±30.17 (p<0.0001)	+6.77±16.44 (p=0.0438)	+11.02±53.84 (p<0.0001)	+10.60±18.48 (p=0.0007)	+7.21±22.01 (p=0.0136)	+9.99±31.37 (p=0.0002)

[a]FGID: functional gastrointestinal disorder; SD: standard deviation.

Table 2: Mean change in QUALIN scores between Inclusion and Day 15 according to the type of FGID[3]

Variable	Change in QoL[b]	Reference	p-value	Odds ratio	95%CI	
Age < 1 month vs >3 months	Increase	Stability	0.0470	1.71	1.01	2.89
Age [1;2] months vs >3 months	Increase	Stability	<0.0001	2.42	1.63	3.61
Age [2;3] months vs >3 months	Increase	Stability	0.0299	1.56	1.04	2.34
Partial breastfeeding Yes vs. No	Increase	Stability	0.0241	1.43	1.05	1.94
Dietary advice Yes vs. No	Increase	Stability	0.0016	1.63	1.20	2.19

[b]QoL: quality of life (assessed using the QUALIN questionnaire).

Table 3: Multivariate analysis of factors associated with an increase in quality of life[3]

> Quality of Life is a marker of symptom severity that must be considered in the management of symptoms

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THE BIG BREAKUP OF *Lactobacillus*

Scientists re-classify one genus into twenty-five genera

The *Lactobacillus* genus contained over 250 species. New DNA-based analytical tools enabled scientists to see that the species historically grouped under *Lactobacillus* were very genetically diverse and did not adhere to nomenclature conventions. Applying the most current methods, a global group of scientists collaborated to divide this genus into groups of closely related species—which share certain physiological and metabolic properties—under new genus names.

New names for some prominent *Lactobacillus* probiotic species

Current name	New name
Lactobacillus casei	*Lacticaseibacillus casei*
Lactobacillus paracasei	*Lacticaseibacillus paracasei*
Lactobacillus rhamnosus	*Lacticaseibacillus rhamnosus*
Lactobacillus plantarum	*Lactiplantibacillus plantarum*
Lactobacillus brevis	*Levilactobacillus brevis*
Lactobacillus salivarius	*Ligilactobacillus salivarius*
Lactobacillus fermentum	*Limosilactobacillus fermentum*
Lactobacillus reuteri	*Limosilactobacillus reuteri*

These probiotic *Lactobacillus* have not changed names:

- *Lactobacillus acidophilus*
- *Lactobacillus delbrueckii* subsp. *bulgaricus* (aka *Lactobacillus bulgaricus*)
- *Lactobacillus crispatus*
- *Lactobacillus gasseri*
- *Lactobacillus johnsonii*
- *Lactobacillus helveticus*

All new genera proposed for this group begin with the letter "L", so the abbreviated form of genus/species – such as *L. rhamnosus* – remain unchanged.

Species names and strain designations have not changed.

The new groupings may **facilitate our understanding of common mechanisms that could mediate probiotic health benefits**, because species that are more closely related (and therefore are more likely to share physiological traits) are grouped under the same genus.

Lactobacillus timeline

- **1901** *Lactobacillus* first described
- **1935** *Lactobacillus* casei Shirota – one of the earliest commercial probiotics – first sold
- **1975** 35 *Lactobacillus* species described to date
- **1982** DNA-based approach to taxonomy started with 16S rDNA sequencing
- **1983** *Lactobacillus rhamnosus* GG isolated by Goldin and Gorbach
- **1987** *Lactobacillus reuteri* species patented
- **1995** 67 *Lactobacillus* species described to date
- **2003** First *Lactobacillus* genome sequence – *L. plantarum* WCFS1
- **2005** 147 *Lactobacillus* species described to date
- **2015** Phylogenic analysis based on genomic DNA used to establish taxonomic groupings of microbes
- **2015** 265 *Lactobacillus* species described to date
- **2020** *Lactobacillus* genus taxonomy updated, now composed of 25 genera

You can find new *Lactobacillus* names easily here: http://lactobacillus.uantwerpen.be

What do the changes mean for scientists?

- New publications on *Lactobacillus* strains should use the new genus names. You may need to provide a brief explanation of the changes to editors or reviewers.
- When searching the scientific literature for a specific strain, it may be necessary to search under both the old genus name and the new genus name.

These *Lactobacillus* taxonomic changes are described in the following scientific paper: Zheng et al. 2020. A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerink 1901, and union of *Lactobacillaceae* and Leuconostocaceae. IJSEM. https://doi.org/10.1099/ijsem.0.004107

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