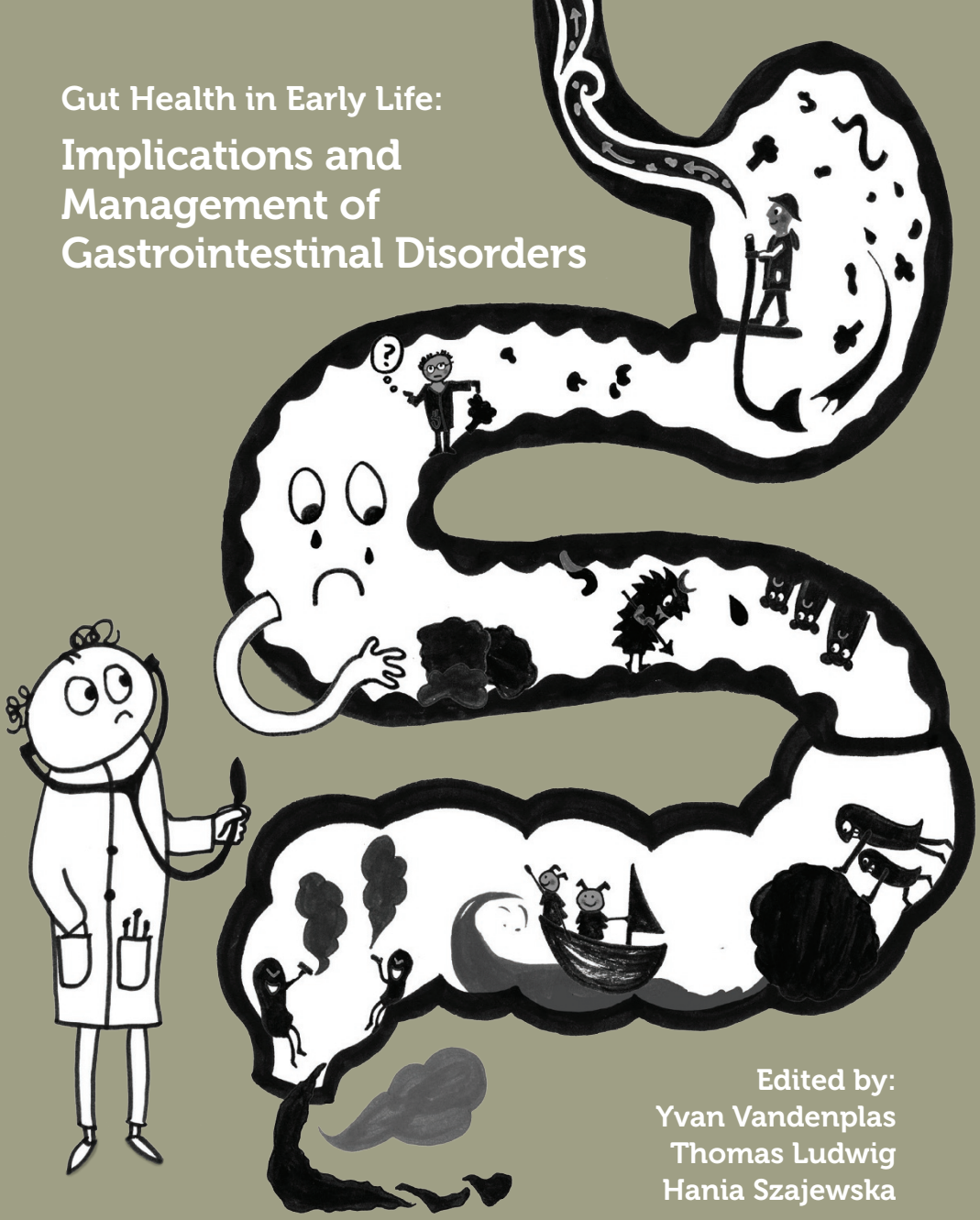
Gut Health in Early Life:

Implications and Management of Gastrointestinal Disorders



Edited by:
Yvan Vandenplas
Thomas Ludwig
Hania Szajewska

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Editors:

Professor Yvan Vandenplas
Head of Department of Paediatrics
Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel
Brussels, Belgium

Dr. med. Thomas Ludwig
Principal Scientist Pediatric Gastroenterology
Department of Developmental Physiology and Nutrition
Danone Nutricia Research
Utrecht, The Netherlands

Professor Hania Szajewska
Professor and Chair
Department of Paediatrics, The Medical University of Warsaw
Warsaw, Poland

Contributors:

Professor Michael Turner
Professor of Obstetrics and Gynaecology
UCD Centre for Human Reproduction
Coombe Women and Infants University Hospital
Dublin, Ireland

Professor Léonardo Gucciardo
Head of Department
Department of Obstetrics and Prenatal Medicine
Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel
Brussels, Belgium

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Disclaimer

Any information provided herein with regard to diagnosis and therapeutic management of gastrointestinal disorders is intended to serve as a guide only, and should not take the place of careful diagnostic work-up and appropriate clinical judgment. Therapy dosages and recommendations may vary between countries.

Glossary

CMPA	cow's milk protein allergy
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FGID	functional gastrointestinal disorder
FOS	fructo-oligosaccharides
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GOS	galacto-oligosaccharides
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IgE	immunoglobulin E
lcFOS	long chain fructo-oligosaccharides
PEG	polyethylene glycol
PPIs	proton pump inhibitors
NEC	necrotizing enterocolitis
scGOS	short chain galacto-oligosaccharides

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CHAPTER 1

Introduction

Implications and Management of Gastrointestinal Disorders is the second Essential Knowledge Briefing under the Gut Health in Early Life series, which examines general and digestive health in early life. This series is intended as a practical guide for healthcare professionals (HCPs) working with infants and their families. While the first Essential Knowledge Briefing focused on gut microbiota and its influence on gut health, this book focuses on the prevalence, causes, diagnosis, and management of common functional gastrointestinal disorders (FGIDs) and digestive problems in pregnant women and most particularly, in infants.

Functional gastrointestinal disorders

FGIDs include a variable combination of symptoms in otherwise healthy individuals, which cannot be explained by obvious structural or biochemical abnormalities.[1] Despite an abundance of isolated findings and hypotheses, the etiology of most FGIDs remains to be elucidated.[2,3]

In infants, FGID symptoms are frequent and often age-dependent. The literature suggests that more than half of infants display at least one FGID symptom during the first year after birth, including regurgitation/gastro-esophageal reflux (GER), constipation, dyschezia, diarrhea or excessive gas.[2-6] In addition, about 20% of infants display symptoms of infantile colic (excessive crying and fussing without an obvious underlying cause).[2,7-10] These symptoms may cause parents to worry, and drive them to seek medical advice.[11]

Pregnant women also frequently experience FGIDs, which are likely to be caused by hormonal, physiological, and structural

changes in the body during pregnancy.[12] Up to 90% of women experience nausea, the most frequent gestational FGID.[13-15]

In infants, the nervous and digestive systems continue to develop after birth, and it has been hypothesized that FGIDs could be a result of physiological maturation processes.[2,3] Very little is known about the complex physiological development of the digestive system in term, healthy newborns, but it is clear that postnatal exposure to various nutrients influences this development process in some measure.[16] In the months following birth, levels of various digestive enzymes begin to transition to adult levels, reflecting the complex nature of gastrointestinal development in early life (**Figure 1**).

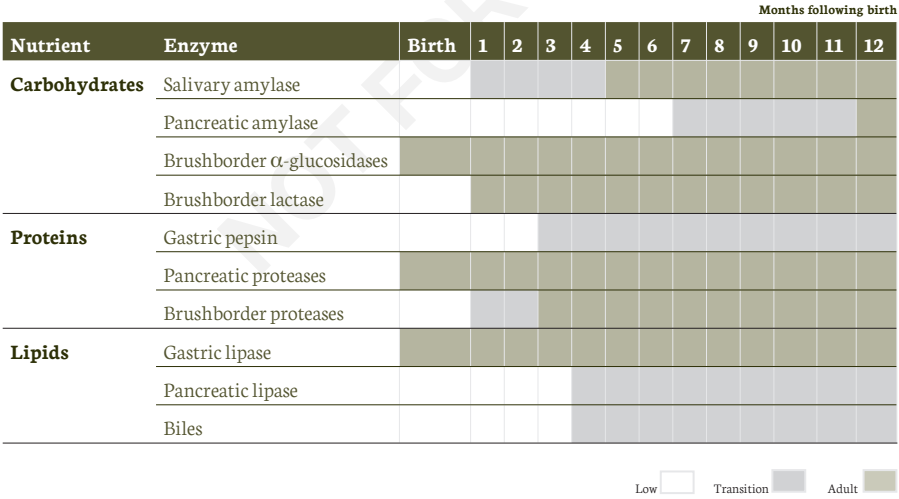


Figure 1. Maturation of enzymatic digestive functions in the first year after birth

After birth, the digestive system and its enzymatic functions are still developing. In brief, gut development is a complex, interdependent process. It includes also the development of various neurological, and biochemical processes. Gastric acid secretion, for example, develops over the first year after birth, and is necessary for the maturation of gastric pepsin activity. [5,17-21]

Figure courtesy of Evan Abrahamse, Danone Nutricia Research, The Netherlands

A healthy gastrointestinal tract

The gastrointestinal tract, with its large, convoluted surface structure, is our largest interface with the outside world, and is a key driver of health and wellbeing.[16]

As discussed in the first Essential Knowledge Briefing in this series, gut health can be defined as a "state of physical and mental wellbeing in the absence of gastrointestinal complaints that require the consultation of a doctor, in the absence of indications or risks of bowel disease, and in the absence of confirmed bowel disease".[22]

The gut barrier which lines the gastrointestinal tract, performs a range of complex metabolic functions (for example, mucus production, protein synthesis, and regulation of absorption), prevents harmful bacteria from colonizing the gastrointestinal tract, and promotes interactions between commensal bacteria and the immune system that are essential for proper development of the gastrointestinal tract and the immune system.[22] A healthy gastrointestinal tract also mediates signaling to the brain to regulate energy homeostasis, and appears to modulate mood and mental wellbeing.[22]

Breastfeeding and physiological gastrointestinal development

Birth constitutes a dramatic transition in nutrient supply from the placenta to the gastrointestinal tract. Initial exposure to human milk requires the gastrointestinal tract to begin to digest and metabolize nutrients to generate energy.[16] While human milk has been shown to have a direct impact on the development of the

infant's digestive system, very little is known about the complex postnatal development of the gastrointestinal tract in healthy, term infants, as to study this would require invasive investigations.[16]

According to the WHO, during the first 6 months after birth, infant feeding should ideally consist exclusively of human milk.[23] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) agrees that exclusive breastfeeding for around 6 months is a desirable goal, but notes that partial breastfeeding as well as breastfeeding for shorter periods of time are also valuable.[24] ESPGHAN further takes the position that complementary feeding should not be introduced before 17 weeks and not later than 26 weeks.[25]

Breastfeeding is the normative standard in infant feeding and nutrition.[26] Infants who are breast-fed experience a measure of protection against various disorders, the best documented of which are infectious diarrhea and acute otitis media.[24,27,28] In addition, a systematic review and meta-analysis by the WHO on the long-term effects of breastfeeding on infants concluded that breastfeeding also reduces the risk of:[29]

- High blood pressure
- Elevated cholesterol
- Type II diabetes
- Overweight and obesity
- Academic/learning difficulties

Human milk provides the infant with lipids that have specific functionality aside from energy, including the production of essential fatty acids, phospholipids, and cholesterol. Research shows that healthy development of both the digestive and nervous systems depends upon the presence of such lipids in the diet.[16]

In addition, non-absorbable human milk oligosaccharides found in human milk are fermented by commensal gut bacteria to produce short chain fatty acids, which can then be absorbed and used as a source of energy by the infant. Short chain fatty acids can also be metabolized by other bacteria and promote their growth, bind pathogenic bacteria and viruses, and block sites of potential pathogen adhesion in the gastrointestinal tract.[30-34]

Human milk is thought to be an important source of bacteria that may help to colonize the infant gastrointestinal tract and contribute to the composition of the gut microbiota.[16,31,32] As discussed in the first Essential Knowledge Briefing, microbial colonization of the gastrointestinal tract primarily occurs after birth, and development of the gut microbiota has been strongly associated with health and disease. The gut microbiota is involved in multiple physiological processes, including nutrient harvest from food, micronutrient (vitamin) production, defense against pathogens, development of the immune system, metabolic health, and mood and behavior[22,30,31,33,35,36] (**Figure 2**).

Gastrointestinal disorders in early life therefore appear to have great significance with regard to health and development in infancy and beyond. These infant gastrointestinal disorders are discussed in detail in **Chapters 3 and 4**.

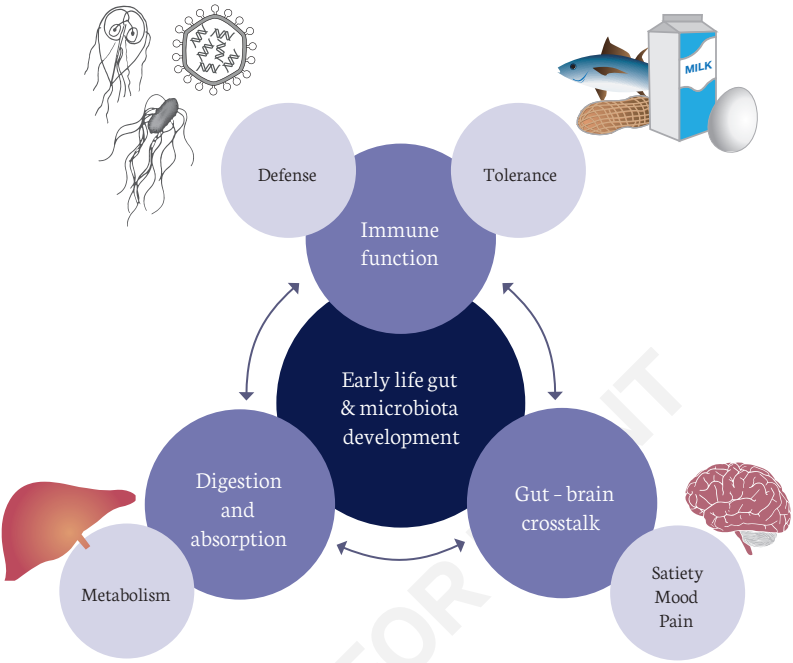
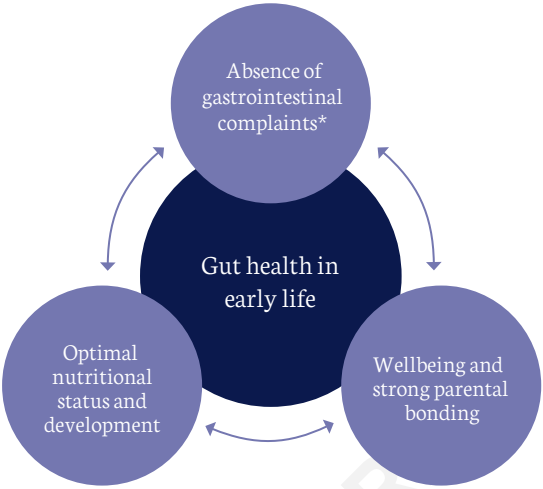


Figure 2. Significance of early life gut and microbiota development

The development of the digestive system and gut microbiota has a fundamental impact on the development of the immune, metabolic, and nervous system. The digestive tract with its large surface constitutes the largest interface to the outside world, and hosts unsurprisingly about 70% of the human body's immune cells. These serve not only to protect the organism against viral and bacterial pathogens, but also to adapt and confer tolerance to a multitude of food-derived antigens. Digestion and absorption of nutrients has a significant impact on the metabolism, energy homeostasis, mood, and overall wellbeing. Thus by definition, gut health goes beyond the absence of disease.

Figure courtesy of Thomas Ludwig, Danone Nutricia Research, The Netherlands



* not managable by parents or healthcare professionals

Figure 3. The impact of gut health in early life

Gut health impacts several fundamental aspects of psychosocial, physical, and mental wellbeing. Physiological gut function is vital for the digestion and absorption of micro- and macronutrients, and thus, has utmost relevance for the overall nutritional status that determines growth and development e.g. of the nervous system. Gastrointestinal disturbances have been identified as stressors in early life that can have a long lasting negative impact on the quality of life of families.

Figure courtesy of Thomas Ludwig, Danone Nutricia Research, The Netherlands

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CHAPTER 2

Maternal gastrointestinal health during and after pregnancy

Disclaimer

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Frequent functional gastrointestinal disorders during pregnancy

Women are susceptible to several gastrointestinal disturbances and digestive disorders during pregnancy.[1-3] Although such complaints are not unique to pregnancy, in pregnant women they are believed to be caused by specific physiological, hormonal, and structural body changes that occur during pregnancy and as a result of delivery.[1,2] Many women present with multiple conditions and require a combination of management approaches. Despite the high prevalence of digestive problems in pregnancy,[1] our current understanding of their etiology is limited. Pregnancy has a major physiological effect on gastrointestinal motility, but appears to have little effect on gastrointestinal secretion or absorption.[3]

Disorders related to physiological modifications in pregnancy may include nausea, mild reflux/heartburn, and constipation. More severe pregnancy-related gastrointestinal complications may include ***hyperemesis gravidarum*** ("hyperemesis"), severe reflux with esophagitis or ulceration, functional diarrhea and irritable bowel syndrome (IBS). These more severe gastrointestinal disturbances can, in severe cases, be associated with maternal nutritional deficiencies that may adversely affect fetal growth and development.[4]

It is imperative that healthcare professionals have a good understanding of the pathophysiology of gastrointestinal disturbances during pregnancy, and are aware of appropriate interventions or therapies that are known to be safe to both the

woman and the infant, particularly during the first trimester.[1,5] Women should be offered reassurance and psychological support wherever necessary.

Nausea and vomiting

Prevalence

Nausea affects 50% to 90% of all pregnant women.[4,6] In 25% to 55% of cases, the feeling of nausea is accompanied by vomiting.[3] Nausea and vomiting are more frequent during the first trimester, peak around weeks 10 to 15, and subside by approximately week 20.[3,6] In most women, symptoms occur in the mornings and tend to improve later in the day.[3]

While most women suffer from relatively mild symptoms, 0.5% to 3% of pregnancies are characterized by hyperemesis, a more severe condition involving frequent vomiting.[6]

Causes

The cause of nausea and vomiting during pregnancy remains unknown, although changes in hormones such as estrogen, human chorionic gonadotropin (hCG), and thyroid hormones have been implicated.[7-9] hCG is structurally similar to thyroid stimulating hormone (TSH),[10] and may act to stimulate excess production of thyroxine (T4) during early pregnancy, which may trigger or aggravate nausea in pregnancy.[11]

Other possible contributing factors include alterations in

gastric tone and motility, gastrointestinal transit time, gastrointestinal sensitivity, vestibular physiology, serum osmolarity, and psychological factors.[3,4,12] There is also growing evidence that prenatally acquired, latent *Helicobacter pylori* infections may be activated by the hormonal and immunological changes of pregnancy, and contribute to the development of hyperemesis.[13]

Impact and risks

Nausea and vomiting impose an appreciable burden on the mother in terms of quality of life. Family and social functioning, ability to perform daily activities, stress levels, and psychological health may be significantly impacted.[6] However, with the exception of hyperemesis, the prognosis for both mother and infant is excellent; no association has been shown between nausea/vomiting during pregnancy and maternal complications such as diabetes, hypertension, proteinuria, pre-eclampsia, or anemia, or infant complications such as low birth weight, fetal death, or congenital malformations.[3]

Hyperemesis is the most frequent cause for hospitalization during the first trimester of pregnancy.[6] Excessive vomiting may place both mother and fetus at risk of dehydration, malnutrition, metabolic ketosis, acid/base disturbances, vitamin deficiencies, and electrolyte disturbances including hypokalemia.[12,14-16]

Management[3,15,16]

Non-pharmacologic approaches	Pharmacologic approaches
• Reassurance • Small, frequent meals • Restricting quantities of indigestible material and encouraging intake of digestible carbohydrates • Decreasing fat content in food (fat may delay gastric emptying) • Nutritional support in severe cases Note: the evidence to support natural supplements, e.g. ginger, raspberry leaf, peppermint, or spearmint, or approaches such as transcutaneous nerve stimulation, acupressure, and psychotherapy is limited	• Pyridoxine (vitamin B6) • Intravenous vitamin B1 supplementation in cases of prolonged hyperemesis (to prevent Wernicke's encephalopathy) • Anti-emetics in cases of intractable vomiting Note: to be used with caution; phenothiazines should be avoided • Metoclopramide Note: limited safety data in pregnancy
Hospitalized patients	
• Nil-by-mouth, IV hydration, and correction of electrolytes • Parenteral nutrition may be initiated if intractable vomiting does not stop within 24-48 hours • When enteral feeding is re-introduced, start with water, slowly advancing through clear liquids to a bland diet (high-starch, low-fat)	

Heartburn

Prevalence and symptoms

Between 30% and 80% of pregnant women present with heartburn. Classic symptoms include burning in the sternum region, which is typically worse after meals, and acid regurgitation. Heartburn may arise during any trimester, but often occurs at around 5 months and is most troublesome during the final trimester.[3]

Causes

Heartburn usually arises during pregnancy, persists throughout, and resolves with delivery. Heartburn may also arise from pre-existing gastroesophageal reflux disease (GERD).[3]

Studies have shown that lower esophageal sphincter pressure progressively decreases during pregnancy, particularly after approximately 20 weeks.[3] Nearly all women have low sphincter pressure by the last month of pregnancy, which returns to normal in the post-partum period. It is thought that these changes in sphincter pressure may be primarily related to elevated levels of progesterone, along with the possible influence of estrogen. Increased abdominal pressure as a result of an enlarging uterus in the later stages of pregnancy may also compromise an already weakened esophageal sphincter.[3]

Impact and risks

Symptoms are usually mild, and, while quality of life is impacted by gestational reflux symptoms, complications such as erosive esophagitis, strictures, or esophageal bleeding are rare.[3]

Management[3]

Non-pharmacologic approaches	Pharmacologic approaches
• Avoiding eating late at night or before bed • Raising the bed head • Avoiding trigger foods and medications	*Non-systemic therapies* • Antacids are safe during pregnancy and lactation Note: avoid sodium bicarbonate-containing antacids as these may lead to metabolic alkalosis and fluid overload in mother and fetus; antacids may also interfere with iron absorption • Sucralfate (only if needed, FDA category B drug) *Systemic therapies* • H2RAs e.g. ranitidine, cimetidine may be administered in more severe cases, after an evening meal Note: FDA category B drugs*; these cross the placental barrier and are excreted in human milk • Proton pump inhibitors (PPIs) e.g. lansoprazole, omeprazole Note: only to be used in women with severe symptoms confirmed on endoscopy, who do not respond to H2RAs (FDA category C drug† for pregnancy use). Not recommended during breastfeeding • Meperidine or midazolam may be administered after the first trimester, although these are not FDA-approved for use in pregnancy

H2RA, histamine type II receptor antagonist

* *FDA category B drugs are defined as those for which animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women*

† *FDA category C drugs are defined as those for which animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.*

Constipation

Prevalence and symptoms

Constipation is defined by the Rome III diagnostic criteria as a history of the patterns described below occurring over the past 3 months, with symptom onset at least 6 months prior to diagnosis. In one large survey, self-reporting showed high sensitivity using these Rome III criteria as the gold standard.[1,17,18]

1. Symptoms must include at least two of the following:
    a) Straining at defecation during ≥ 25% of bowel movements
    b) Lumpy or hard stool in ≥ 25% of bowel movements
    c) Sensation of incomplete evacuation after ≥ 25% of bowel movements
    d) Sensation of anorectal obstruction/blockage in ≥ 25% of bowel movements
    e) Manual facilitation of ≥ 25% of defecations
    f) Fewer than three bowel movements per week
2. Loose stools are rarely present without the use of laxative
3. Insufficient criteria for IBS

Constipation is a frequent disorder in the general population with regional prevalence in adults of 20% and above.[19-21] New-onset constipation or worsening of pre-existing constipation

during pregnancy is thought to occur in approximately one-third of women during the third trimester of pregnancy,[1,14,22] and generally resolves quickly during the post-partum period.[3]

Causes

The etiology of constipation during pregnancy appears to be multi-factorial.[1,3] Possible factors include slower gastrointestinal motility, poor nutritional and fluid intake related to nausea, psychological stress, decreased physical activity, mechanical compression from the enlarged uterus, and iron or calcium supplementation.[4,14] Slower GI motility is most likely to be a result of elevated progesterone levels during the later stages of pregnancy.[3,14] Consideration should be given to the exclusion of medical conditions such as hypercalcemia, hypothyroidism, diabetes mellitus, and ulcerative lesions associated with inflammatory bowel disease (IBD).[4]

Impact and risks

Discomfort and pain frequently accompany constipation, and affect maternal quality of life to varying degrees.[23] Prolonged straining in cases of constipation has been associated with the development of anal fissure and hemorrhoids.[22,24] In addition, some experts have expressed concern that chronic constipation increases intra-abdominal pressure and may therefore be associated with pelvic organ prolapse.

Interestingly, an association between constipation in mothers and constipation in their children has been reported.[25] The impact of this finding and potential strategies for prevention remain to be elucidated.

Management

Primary prevention of constipation is important, and involves a healthy diet with regular increased intake of dietary fiber (fruit, vegetables, nuts, seeds, and wholegrains), particularly as pregnancy advances. Other suggestions include reducing intake of caffeine and fatty foods and increasing fluid intake.[14,22]

Management approaches include:[1,4,14,22]

Non-pharmacologic approaches	Pharmacologic approaches
• Reassurance and education on expected bowel function during pregnancy • Increasing physical activity levels • Increasing fluid and fiber intake up to recommended levels • Using bulk-forming agents	• Osmotic laxatives, e.g. polyethylene glycol (PEG) stimulate fluid accumulation in the gastrointestinal tract Note: 1%-4% of PEG is absorbed, but PEG is not metabolized and unlikely to have a teratogenic effect. Not FDA-approved for use in pregnancy: category C* • Bulk-forming laxatives (fiber supplements), e.g. psyllium, polycarbophil • Stimulant laxatives, e.g. bisacodyl or casanthranol, may be more effective than bulking laxatives Note: to be used intermittently only, and only as a second-line option. Adverse effects such as abdominal pain and diarrhea may limit their use • Stool softeners e.g. docusate sodium Note: mineral and castor oils and saline hyperosmotics should be avoided during pregnancy

* *FDA category C drugs are defined as those for which animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.*

Only 1%-2% of women who suffer from constipation during pregnancy use laxatives,[1] possibly because there is substantial lack of evidence supporting their safety during pregnancy.[14]

Diarrhea

Prevalence

Pregnancy-associated functional diarrhea may occur, although there are no recent data on its prevalence.[1] Functional diarrhea is defined by the Rome III criteria as loose or watery stools without pain occurring in at least 75% of stools, with onset at least 6 months prior to the diagnosis.[17,26]

Causes

Functional diarrhea during pregnancy is hypothesized to arise from changes in prostaglandins, which may affect the propulsion of gastrointestinal contents.[1,27] Diarrhea may be acute, or become chronic.

Frequent causes of acute functional diarrhea are similar to the non-pregnant population. Causes of acute diarrhea not classified as "functional" may include viral agents, bacterial infections, or medications.[1,4]

Causes of chronic, non-infectious diarrhea may include medications, food intolerances (e.g. to sugars or sugar substitutes), malabsorption, IBD, or IBS.[1,4]

Impact and risks

Maternal dehydration and electrolyte imbalance, weight loss, and malnutrition may develop in severe cases.[1] Evidence suggests that severe dehydration in pregnancy may adversely affect the development of the renin-angiotensin system in the infant, affecting blood pressure and fluid balance.[28]

Management[1]

In the first instance, it is important to prevent gastroinstestinal upset in pregnant women through proper food safety and hygiene. When acute diarrhea occurs, treatment involves a conservative approach first, followed by pharmacologic intervention if necessary.

Non-pharmacologic approaches	Pharmacologic approaches
• Oral rehydration • Salted and potassium-rich foods	• Electrolytes (oral or intravenous) • Anti-diarrheal agents, e.g. loperamide • Note: diphenoxylate with atropine is not recommended due to teratogenicity; bismuth subsalicylate is not recommended due to an association with low birth weight and increased risk of perinatal mortality

Irritable bowel syndrome

Prevalence and symptoms

As previously mentioned, either pre-existing or new-onset IBS is a frequent cause of diarrhea and constipation during pregnancy.[1,4] The estimated prevalence of IBS is approximately 10%-15% in the

general North American population.[4] Studies in different Asian populations indicate varying prevalence, depending upon diagnostic criteria, although the overall prevalence appears to be similar to the West.[28] IBS is more frequent in women than men, and onset often occurs during childbearing years.[4,29]

IBS is characterized by chronic abdominal pain with diarrhea and/or constipation; other frequent symptoms include reflux, bloating, flatulence, and nausea.[4,30,31]

Causes

In cases of new-onset IBS arising during pregnancy, it is thought that IBS may be attributable to several inter-related factors, including altered GI motility, altered intestinal secretion, dysregulation of the gut-brain axis, and the increased stress of pregnancy.[4,5] Changes in gut microbiota compositions of IBS patients have also been demonstrated.[32]

Impact and risks

While IBS is associated with discomfort for the pregnant woman, there does not appear to be any evidence of maternal IBS adversely impacting the infant.[5]

Management

Systematic reviews on the management of IBS in the general population indicate conflicting evidence, with a trend towards the efficiency of dietary interventions, especially with specific fermentable fibers and probiotics.[33-39]

Management approaches include:[4]

Non-pharmacologic approaches	Pharmacologic approaches
• Education • Dietary intervention (increasing fiber in constipation-dominant patients; kaolin/pectin in diarrhea-dominant patients) • Psychological intervention	• Osmotic laxatives for constipation (when response to dietary fiber is inadequate) • Loperamide for diarrhea (to be used judiciously and infrequently in pregnant patients) • Antispasmodic medications (to be used with caution in pregnancy) • Tricyclic antidepressants in cases of chronic pain (pregnancy category C*)

* *FDA category C drugs are defined as those for which animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.*

Inflammatory bowel disease

IBD is an autoimmune disease. Pre-existing IBD, including Crohn's disease and ulcerative colitis, may cause bowel function changes due to pregnancy-induced alterations in immune function.[1,40]

Prevalence and triggers

The prevalence of IBD is approximately 0.4% in the general adult Western population,[41] but appears to be considerably lower in Asian populations.[42]

In women with dormant IBD at the time of conception, the rate of relapse is approximately the same as in non-pregnant women,[2]

with approximately one-third relapsing during pregnancy.[14,40] However, among women with active disease at the time of conception, it may be expected that approximately one third of women will improve, one third will stay the same, and one third will experience continued or worsening symptoms.[2,4,14,40]

Disease flare may also be related to deliberate discontinuation of medical therapy after conception.[40]

Impact and risks

IBD does not appear to be associated with pregnancy risks such as hypertension or proteinuria, nor with risks to the infant such as miscarriage or congenital abnormalities. However, some evidence suggests an association between IBD and adverse infant outcomes such as preterm birth, stillbirth, and growth restriction/low birth weight, particularly in women who experience active disease during pregnancy.[2,4,14,43]

Management

Active disease appears to impose a greater risk to pregnancy than active therapy.[2,14] Medications used to maintain remission should therefore generally be continued during pregnancy, with counseling to ensure compliance.[4]

Limited safety data are available on the safety of active therapy during pregnancy. The focus should be on establishing remission before conception and maintaining remission throughout.[2]

Pharmacological approaches:

- Sulfasalazine readily crosses the placenta but has not been associated with any fetal abnormalities. It is considered to be safe during breastfeeding. Folic acid supplementation should be given before conceiving and throughout pregnancy in all women, but is particularly important in women taking sulfasalazine[2,4,14]
- Topical 5-aminosalicylic acid (5-ASA) agents are considered safe[2,14]
- Immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine) have not been proven in clinical trials to be safe, although they have been used. *Methotrexate however, is contraindicated*[2]
- Corticosteroids have limited safety data but have not been associated with teratogenicity[2]
- Short-course antibiotics (metronidazole and ciprofloxacin) are considered to be safe during pregnancy[14]

After birth: Maternal benefits of breastfeeding

Human milk is the ideal nutrition for infants, and with its well-established benefits, breastfeeding is the gold standard in infant feeding. Human milk provides optimal nutrition and protective antibodies for the growing infant,[44]

while acting as a source of important commensal bacteria, and human milk oligosaccharides that help establish the infant's gut microbiota. As discussed in the first Essential Knowledge Briefing, a healthy gut microbiota appears to be closely associated with both the immediate and long-term health of the infant.[45]

Breastfeeding is also known to offer several health benefits to lactating mothers.[45] Among other benefits, women who have breast-fed for at least 6 to 8 months have been reported to have a lower incidence of breast cancer, ovarian cancer, and endometrial cancer later in life compared with those who have not.[45-48]

As well as encouraging maternal bonding, some evidence also suggests breastfeeding reduces a woman's risk for disorders such as hypertension, diabetes, and rheumatoid arthritis.[45,49,50]

Chapter highlights

- Women are more susceptible to several functional gastrointestinal disorders during pregnancy, including nausea, vomiting, heartburn, constipation, and diarrhea.
- Changes in gastrointestinal motility during pregnancy are believed to be caused by increased levels of circulating female sex hormones, particularly progesterone, hCG, and estrogens.
- Gastrointestinal problems during pregnancy, particularly nausea and vomiting, may become an additional source of stress, hindering a mother's ability to take part in normal daily activities.
- Gastrointestinal problems during pregnancy do not appear to have long-term adverse implications for either the woman or the infant. However, persistent hyperemesis may place the pregnant woman and her fetus at risk of dehydration, malnutrition, and electrolyte disturbances.
- For most gastrointestinal problems during pregnancy, dietary and lifestyle interventions are the first-line approach. Pharmacological approaches may be required in some cases, but both prescription and over-the-counter medications should be limited to those known to be safe during pregnancy, particularly during the first trimester of pregnancy.
- As well as benefits for the infant, breastfeeding has been associated with several health benefits for the mother, including a reduction in the risk of breast, ovarian, and endometrial cancers, diabetes, hypertension, and rheumatoid arthritis.

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CHAPTER 3

Functional gastrointestinal disorders in infants and young children

Functional gastrointestinal disorders

Many infants develop digestive problems during the first few months after birth. While some gastrointestinal disorders have underlying pathologies, the vast majority are "functional disorders", characterized by chronic or recurrent symptoms that are not readily explained by physiological abnormalities, and which tend to resolve as the infant grows and develops.[1]

The most frequent FGIDs include regurgitation/vomiting/GER, infantile colic, constipation, dyschezia, diarrhea, and excessive gas production.[2,3] In a large study following nearly 3000 infants, 55% experienced at least one FGID between birth and 6 months of age.[4] Among the different studies, the prevalence of infant FGIDs varies, which may be attributable to differences in definitions, study design, data collection methods, ethnicity, and diet.[5] Preterm infants and those with a low birth weight for gestational age are more likely to be affected by functional digestive disorders.[4] Information on the prevalence, causes, and diagnosis of several frequently observed infant digestive conditions, along with practical algorithms for their clinical management, are provided in **Chapter 4**.

Impact of maternal diet on gastrointestinal health in breast-fed infants

The composition of human milk shows dynamic changes over the lactation period according to an infant's nutritional needs at various stages,[6] and varies according to maternal diet, highlighting the importance of good maternal nutrition.[7] Dietary modulation of human milk is possible in some cases; for example, in breast-fed

infants in whom cow's milk allergy is suspected, removal of cow's milk protein from the maternal diet is recommended.[8] Other known or suspected allergens such as nuts, seafood, and egg may also be deliberately excluded from the maternal diet in cases of suspected allergy or intolerance.

Effects of dysbiosis

As discussed in the first book of this series, growing evidence has linked dysbiosis – a disruption in healthy gut colonization and optimal microbiota composition – with the development of various infant disorders such as allergy, obesity, diabetes, infantile colic, IBS, IBD and autism.[9-17]

Impact of infantile colic as a hurdle for continuation of breastfeeding

During the first 3 months after birth, healthy infants generally cry for an average of 2 hours per day.[18] Persistent, inconsolable fussiness and crying in infants ("infantile colic") can be alarming and distressing to parents and caregivers, and anxious parents often seek the help of a healthcare professional.[18] International data indicates that between 9% and 26% of families seek help for excessive infant crying.[19] Thus, colic has a significant impact on family functioning and healthcare budgets.[20] Excessive crying may be due to physiological disturbance, disease, infant temperament, or parental factors such as level of maternal skill and responsiveness.[19]

Some studies have suggested an association between infantile colic and early discontinuation of breastfeeding.[21] One study showed that, in almost half of infants with infantile colic, exclusive breastfeeding was discontinued due to factors such as the mother's perceptions of infant hunger and colic behaviors.[22] Another study showed that, regardless of maternal education or infant pacifier use, the duration of full breastfeeding was significantly impacted by the presence of infantile colic symptoms in the infant.[23]

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CHAPTER 4

Diagnosing and managing digestive problems in infants and young children

Disclaimer
Any information provided herein with regard to diagnosis and therapeutic management of gastrointestinal disorders is intended to serve as a guide only, and should not take the place of careful diagnostic work-up and appropriate clinical judgment. Therapy dosages and recommendations may vary between countries.

When working with infants who present with gut-related problems, it can be challenging to distinguish between functional digestive problems, which should naturally resolve over time, and symptoms caused by underlying medical conditions that may sometimes require specialist referral for further clinical work-up.[1] In most cases, uncomplicated functional gastrointestinal disorders may be managed by evaluating feeding practices, reassuring parents, and, where necessary, offering infants adequate nutritional support.[1]

This chapter provides a brief overview of the diagnosis, prevalence, causes, and management of several frequent digestive disorders, including regurgitation, vomiting, infantile colic, defecation disorders (dyschezia, constipation, and diarrhea), and food allergy and hypersensitivities. Information on clinical management is intended to be used as a guide only, and should not be considered a substitute for appropriate clinical judgment or used as a protocol applicable to all infants. Further information may be found in the references listed at the conclusion of this chapter.

Regurgitation and vomiting

Definitions and diagnosis

Many healthy newborns and infants experience GER, which describes the passage of gastric contents upward into the esophagus. GER occurs mostly with clinically visible regurgitation, but may also occur without.[2,3] Other symptoms of GER associated

with regurgitation and/or vomiting are non-specific, and may include persistent crying, irritability, back arching, and sleeping problems.[3] When troublesome symptoms and/or complications continue, GERD may frequently be diagnosed.[2]

"Regurgitation" is defined as the passage of stomach contents into the pharynx or mouth. According to the Rome III criteria, a diagnosis of infant regurgitation happens when the infant experiences regurgitation episodes at least twice a day for at least 3 weeks in the absence of abnormal posture, apnea, aspiration, difficulty feeding or swallowing, failure to thrive, hematemesis, and nausea.[4,5] However, intervention may only be required if the infant presents with "more than four daily episodes of regurgitation during at least two weeks".[1]

Vomiting is not the same as regurgitation; vomiting is defined as a central nervous system reflex involving both involuntary and voluntary muscles.[2,4]

Prevalence

Regurgitation is the most frequent infant gastrointestinal disorder worldwide, and is often not a cause for concern. The overall prevalence of daily regurgitation in infants aged 3-4 months is estimated to be around 50%–60%.[2,6,7]

Reported prevalence data vary between studies, probably related to differing study designs and diagnostic criteria. One study showed that over half of infants experience daily spitting at 3-4 months of age.[8] A large study in Italian infants showed a prevalence of 23%

in the first 6 months,[9] while another study of infants in China showed a prevalence of 18% in the first 6 months.[10] However, in a study among infants in Thailand, the prevalence of daily regurgitation was 87% at 2 months of age, reducing to 46% at 6 months of age, and 8% at 12 months.[11]

Approximately 6% of infants experience vomiting.[9]

Causes

While some evidence suggests that the prevalence of regurgitation may be unrelated to the type of feeding,[11] there are also data that suggest that breast-fed infants regurgitate less.[8]

Factors contributing to the high incidence of GER in infants include a large amount of time spent in the prone (lying down) position, a relatively large fluid intake, a short esophagus, and an immature lower esophageal sphincter.[3] Overfeeding of infants can increase the intragastric pressure and cause spontaneous relaxations of the sphincter, exacerbating reflux.[6]

Impact

Most regurgitation occurs after ingestion of milk, and causes few or no symptoms.[2,12] According to epidemiological data, regurgitation occurring more than four times a day (which occurs in about 20% of infants) is considered by parents to be "troublesome", and they are more likely to seek medical help.[8,13,14]

GERD may have several consequences in infancy, including irritability, anemia, negative impact on growth, and possibly

respiratory events such as aspiration pneumonia.[2] However, regurgitation alone tends to cause few, if any, long-term effects.[2]

Management

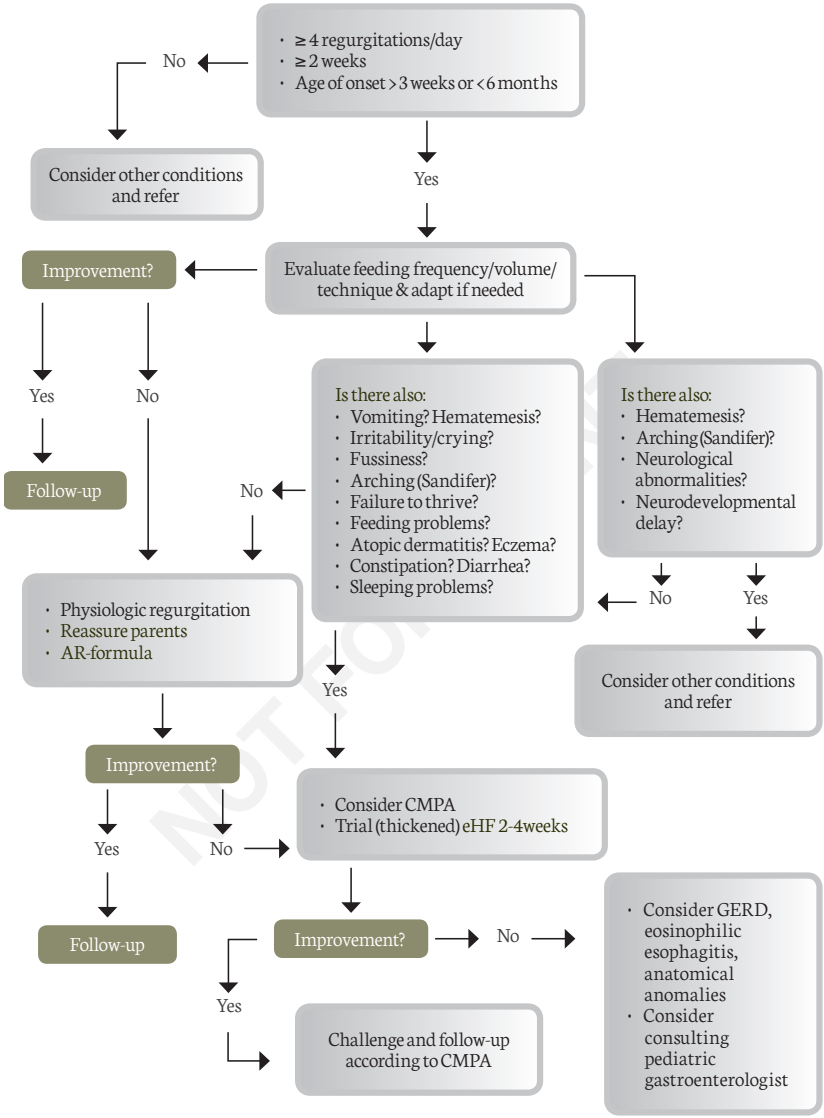
Regurgitation tends to decrease significantly between 6 and 12 months of age and to resolve spontaneously in most healthy infants by about the age of 12 months.[2,3,13] Management may entail the following (see also **Figure 4**):

Non-pharmacologic/nutritional approaches

- Provide parental education and reassurance, particularly with respect to avoidance of overfeeding, feeding frequency, and correct feeding techniques[1,2,6]
- Monitor infant growth and weight gain, particularly in cases of troublesome and frequent regurgitation or persistent vomiting[1,2]
- Consider anti-regurgitation formulas containing processed rice, corn, or potato starch, guar gum, locust bean gum, and/ or an increased casein/ whey ratio. Anti-regurgitation formulas have also been shown to reduce distress, improve sleep, and improve weight gain[2,6,12]
- Add food-grade commercial thickeners e.g. containing locust bean gum to a habitual formula[2,6]
- Consider a anti-regurgitation bed with an elevated head angle (40˚-50˚); however, the evidence for this intervention is limited[15]
- Rule out cow's milk protein allergy (CMPA) through trial elimination and reintroduction, particularly among infants with other manifestations of atopic disease such as atopic dermatitis and/or wheezing. This may be achieved through a cow's milk-free diet in the breastfeeding mother, or an extensively hydrolyzed formula in formula-fed infants[2,6,12]
- Note that the evidence that specific prebiotics or probiotics may decrease regurgitation is limited[2,16-18]

Note that there is no indication for pharmacological treatment, including proton pump inhibitors, in regurgitation, even in infants showing signs of distress.[1,2,19] If regurgitation does not resolve by the age of 12 months, further diagnostic work-up and/or referral to a pediatric gastroenterologist is recommended.[2,6]

There is broad consensus that breastfeeding should be continued in cases of infant regurgitation.



AR, anti-regurgitation; CMPA, cow's milk protein allergy; eHF, extensively hydrolyzed formula; GERD, gastroesophageal reflux disease

Figure 4. Algorithm for the management of regurgitation in formula-fed infants

Adapted and reprinted by permission from John Wiley and Sons: Vandenplas Y, Alarcon P, Alliet P, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr. 2015. doi: 10.1111/apa.12962.

Common questions from parents – how to answer*

How much spitting up is too much?

- Reassure parents that the most important concern is infant growth. If anthropometric measurements are within the normal range, there is no need for undue concern.
- Regardless of the frequency of regurgitation, ensure the parent is aware that there is no place for medication in the treatment of this condition.

What can be done if regurgitation occurs in my breast-fed baby?

- Emphasize the importance of continuing to breastfeed.
- Suggest seeking advice from a lactation consultant or doctor with special training in breastfeeding.
- In cases where there are manifestations suggestive of allergy (e.g. atopic dermatitis), a cow's milk free diet in the mother can be trialed.

My baby seems to be spitting up almost all of his feeds. What can I do?

- Regurgitation occurs frequently in infants, and is due to many factors, which includes the immaturity of the gastrointestinal tract. If it is not causing distress, reassurance and anticipatory guidance is recommended. Be careful not to overfeed. In formula-fed infants, a thickened anti-regurgitation formula may help reassure parents.

** Advice should be accompanied by a full assessment of symptoms*

Infantile colic

Definitions and diagnosis

Infants generally cry more during their first 3 months after birth than at any other time, with crying frequency peaking at 6 to 8 weeks of age. It is often difficult to tell the difference between expected crying behavior and the excessive crying condition known as "infantile colic", but the difference is related to the duration of crying and fussing, and the ability of the infant to be consoled.[20,21]

Using Rome III criteria, infantile colic is defined as episodes of irritability and inconsolable crying or fussing, *without obvious cause*, lasting for more than 3 hours per day, for more than 3 days per week, lasting at least 1 week in an infant who is otherwise well-fed and healthy.[4,5]

Crying in infants with infantile colic may be intense and accompanied by flushing of the face, drawing up of the legs, a rumbling stomach, and flatulence.[6,22] Infantile colic symptoms are most often observed in the late afternoon and evening. Symptoms typically peak at around 6 weeks of age,[6,22,23] and usually resolve spontaneously by the age of 3 to 4 months.[22]

Prevalence

Infantile colic occurs frequently during the first 3 months after birth. Studies using the Rome III criteria suggest that the prevalence of infantile colic is between approximately 6% and 20%

of infants worldwide.[7] Regional differences may be attributable to use of varying study methodologies. Infantile colic rates appear to be independent of gender, birth order, or type of feeding.[6,22-25]

Causes

Despite its frequency, the exact causes of infantile colic remain unclear.[6] Many studies have found no clear intestinal or other abnormalities in infants with infantile colic.[26] Underlying disease is found in only approximately 5% of infants who present with persistent crying,[27] and some researchers consider infantile colic behavior to be associated with immaturity of the central nervous system causing disorganized, unstable cyclic behavior.[28] However, several gastrointestinal, psychosocial, and neurodevelopmental imbalances have been suggested as contributory factors[29] (**Table 1**). In the vast majority of infants, the cause of infantile colic is likely to be complex and multi-factorial.[22]

Infantile colic frequently co-exists with feeding difficulties,[30] and may be exacerbated by an unfavorable climate created by parental inexperience and anxiety, which may increase the risk of poor infant-parent interaction and insecure attachment.[22,28,31] However, there appears to be no association between infantile colic incidence and factors such as family history, socioeconomics, infant gender, or types of feeding.[22]

Table 1. Possible pathogenic contributors to infantile colic[6,22,28,29]

Category	Comments
Central nervous system	Disorganized, unstable behavior and an inability to self-soothe or fall asleep may be based on immaturity of the central nervous system, rather than an underlying gastrointestinal disorder. Central nervous system abnormalities, infantile migraine, or subdural hematoma may also contribute.
Gastrointestinal	
Altered gastrointestinal function/motility	Temporary episodes of nervous system dysregulation may affect infant gastrointestinal motility during the first few weeks of life, although cause-and-effect studies are inconsistent. Some studies have demonstrated an association between an imbalance of certain gastrointestinal hormones such as motilin and ghrelin and infantile colic. Constipation may also contribute to infantile crying.
Gut microbiota imbalance	Appropriate microbial colonization may be a prerequisite for physiological mucosal immune function, and studies have demonstrated that differences in the composition of *Lactobacillus* species in the gastrointestinal tract may influence the onset of infantile colic. Such imbalances are also thought to adversely affect gastrointestinal development, which can in turn lead to compromised gastrointestinal barrier function and a lack of food tolerance. Some studies in breast-fed infants with infantile colic indicate that specific probiotics may reduce crying episodes.
Food intolerance/ hypersensitivity	Increasing evidence suggests that food intolerance may be associated with infantile colic. Approximately 25% of infants with moderate or severe infantile colic symptoms may have cow's milk-dependent infantile colic, and some studies have shown resolution in some breast-fed infants with the exclusion of cow's milk protein from the maternal diet. In other infants, standard cow's milk formulation should be substituted with a protein-hydrolysate formulation.
Low lactase activity/transient secondary lactose intolerance	A failure to incompletely break down all dietary lactose allows significant amounts to enter the large bowel, where *Bifidobacteria* and *Lactobacilli* bacteria ferment it to produce lactic acid and gasses. These gasses are hypothesized to cause distension of the colon, which may cause pain; lactic acid and lactose may also alter osmotic pressures in the gastrointestinal tract, drawing water into the bowel and causing further distension.
Other	Reflux, constipation, or rectal fissure may also contribute to infantile crying.
Infections	Viral illnesses, otitis media, urinary tract infection, and meningitis should be excluded.
Trauma	Abuse, bone fractures, and a foreign body in the eye/corneal abrasion should be excluded.

Impact

FGIDs, and as such infantile colic, tend to be benign in nature and self-limiting in the vast majority of infants.[22]

Despite the fact that infant crying and sleep problems often spontaneously resolve, excessive crying has been associated with postnatal depression, both as a cause and as a consequence, and can negatively affect family dynamics by:[32,33]

- Disrupting parent relationships, sleep, and family routines
- Provoking feelings of anger/frustration, despair, and incompetence
- Reducing face-to-face interaction with the infant
- Precipitating parental stress and difficulties with concentration.

Importantly, studies also show that excessive crying can significantly increase the risk of non-accidental injury to an infant.[32,33] Healthcare professionals should watch out carefully for signs of family distress and assess the family's coping resources.[29] A lack of adequate information regarding the cause of infantile colic and effective management strategies can significantly add to levels of parenting stress;[28] thus, parents need support during this difficult period, and to be reassured that functional digestive disorders like infantile colic occur frequently and should resolve naturally within a few months. Once infantile colic resolves, evidence shows very little lasting effect on levels of maternal anxiety and depression.[29]

Furthermore, infantile colic has been shown to impose a substantial economic burden due to the need for healthcare provision and loss of parental work time.[34,35]

Some studies show no differences in various behavior parameters at the age of 12 months between infants who previously had infantile colic and those who did not.[29] However, there is also some evidence to suggest that children who displayed infantile colic symptoms during infancy may display a more difficult temperament and academic difficulties in later childhood, although long-term data are lacking.[22,36] Some evidence suggests that infantile colic may be associated with the development of functional gastrointestinal problems, recurrent abdominal pain, allergic disorders, and migraine during adolescence,[37-39] although the literature is inconclusive, and causality is very difficult to prove.

Even though infantile colic resolves by definition at 3 to 4 months of age, it can cause appreciable distress to infants and parents with pending long-term consequences for the wellbeing of both.[4,27,40,41] Indeed, even excessive crying that does not fit the criteria for infantile colic can be very distressing and tiring for parents.

Management

There are no standard treatment regimens for infantile colic.[6] Systematic reviews and meta-analyses show a lack of conclusive evidence of most interventions for infantile colic, mostly due to challenges in trial design and reporting of results.[42-45]

In the first instance, parents need to be reassured that infantile colic typically resolves spontaneously by 3 to 4 months of age, and

that it is a benign and self-limiting condition that, when present without any other symptoms, is not a cause for concern.[25,29]

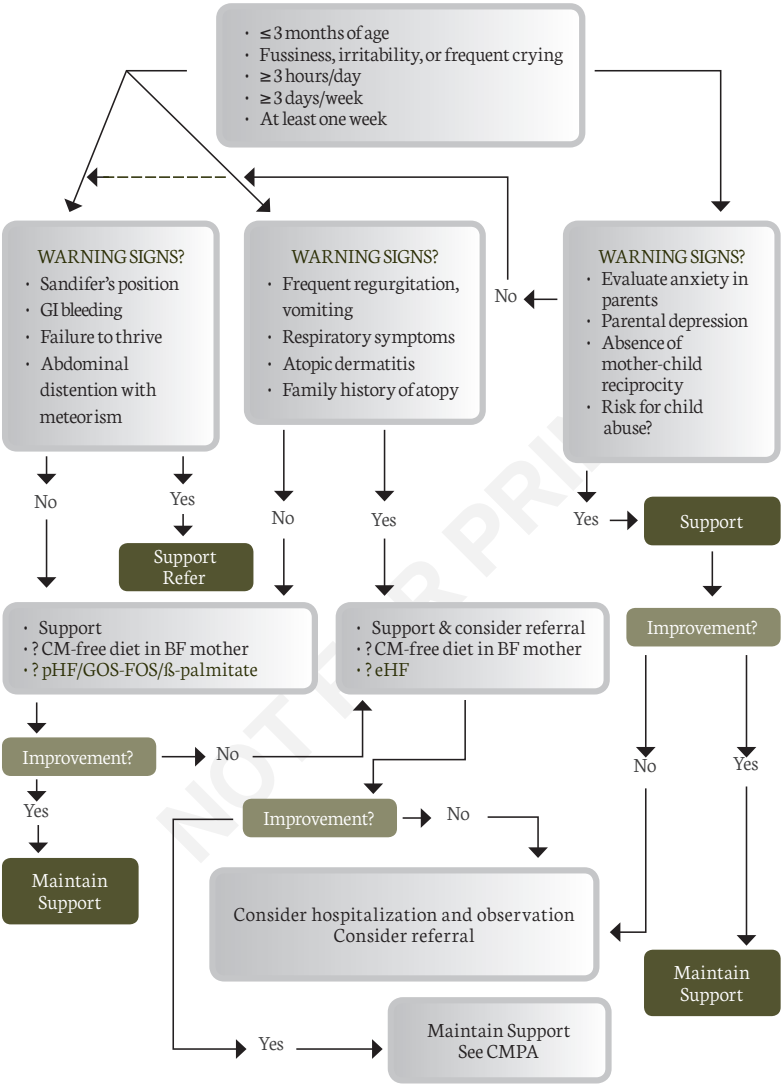
Healthcare professionals may suggest additional methods for soothing the infant. Studies of infants with infantile colic have shown that holding, breastfeeding, walking, and rocking may be effective calming tools in up to 87% of colicky infants; swaddling may also be effective.[46,47] **Breastfeeding mothers should be encouraged to continue breastfeeding.**

There is usually no need for medical treatment, and there is a lack of firm evidence supporting the use of both prescription and non-prescription medical approaches.[1,25] Specifically, there is no evidence to support the use of proton pump inhibitors, dicycloverine, cimetropium, simethicone or dicyclomine in infants with infantile colic.[42,48,49]

Nevertheless, various management approaches may be considered, including (see also **Figures 5 and 6**):

Non-pharmacological approaches:

- Carefully examine to rule out organic disease[1]
- Rule out warning signs such as vomiting, back arching /Sandifer syndrome, gastrointestinal bleeding, failure to thrive as well as disproportionate parental anxiety, parental depression, lack of bonding, and signs of child abuse[1]
- Evaluate the feeding technique. One study has shown that prolonged emptying of one breast before feeding from the other, as opposed to draining both breasts equally at each feed, may reduce the incidence of infantile colic in the first 6 months after birth[50]
- If parents smoke, they should be advised to stop smoking; several studies have identified parental smoking as a risk factor for infantile colic[51,52]
- Exclude the possibility of CMPA[1,33]
  - Identify symptoms such as eczema, wheezing, and family history of atopy
  - Advise the mother to avoid cow's milk for 2-4 weeks while breastfeeding
- For exclusively breast-fed infants, the suspected food (i.e. cow's milk) is eliminated from the mother's diet[53]
- In formula-fed infants, consider reducing dietary lactose, e.g. by providing a formula with low lactose or fermented formula with lactase in cases of suspected transient secondary lactose intolerance.[54,55] However, reduction in lactose is at this point not routinely recommended due to a lack of conclusive evidence.[22,48,56] Infants whose colic is caused by factors other than transient secondary lactose intolerance can expect no relief[22]
- Consider dietary support in formula-fed infants with partial protein hydrolysate formula with beta-palmitate and prebiotic mixtures of short chain galacto-oligosaccharides (scGOS) and long chain fructo-oligosaccharides (lcFOS)[57]
- Consider treatment of breast-fed infants with the probiotic *Lactobacillus reuteri* DSM 17938. The evidence to support this approach is, however, controversial. Three independent double-blind randomized controlled trials consistently showed reduced crying in exclusively breast-fed infants.[58-60] However, a larger randomized controlled trial showed no significant benefit among breast-fed and formula-fed infants in Australia.[43] Reviews and meta-analyses on the topic have concluded that the evidence for the use of *L. reuteri* in formula-fed infants is insufficient and needs further evaluation[43,61,62]
- Note that the evidence to support alternative or herbal treatments such as chiropractic care, spinal massages, fennel extract, peppermint extract, or sucrose solutions is limited[29,63-67]
- Refer for further work-up and observation if there is no improvement after dietary adjustments[1]



BF, breastfeeding; CM, cow's milk; CMPA, cow's milk protein allergy; eHF, extensively hydrolyzed formula; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; pHF, partially hydrolyzed formula

Figure 5. Algorithm for the management of colic in infants

Adapted and reprinted by permission from John Wiley and Sons: Vandenplas Y, Alarcon P, Alliet P, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr. 2015. doi: 10.1111/apa.12962.

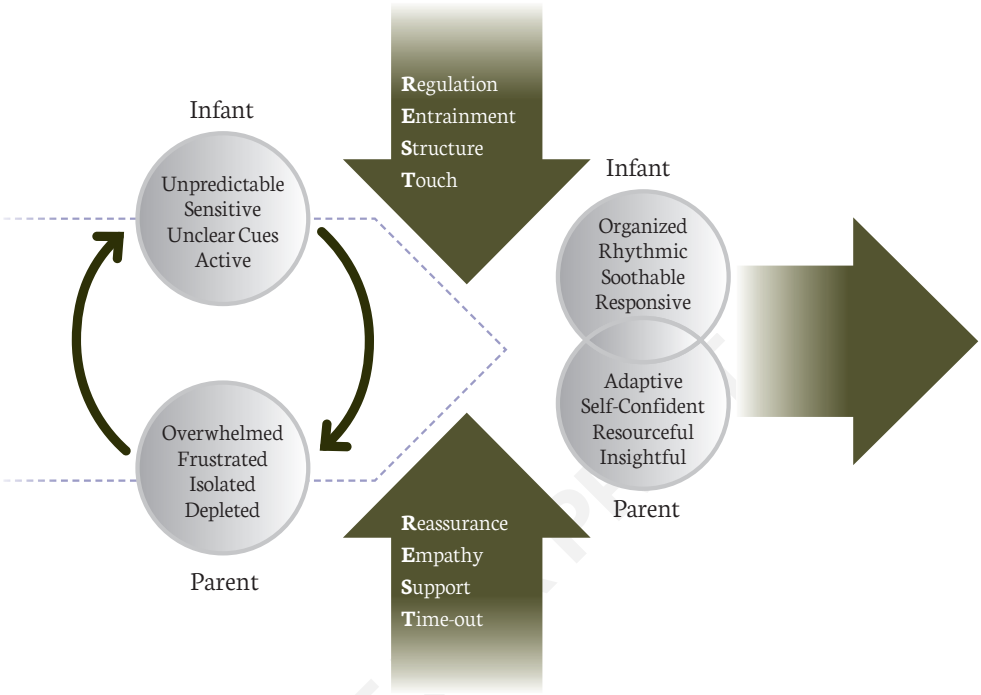


Figure 6. Theoretical model of infant irritability and support requirements in infants and parents

Reproduced by permission from Wolters Kluwer Health, Inc: Keefe MR. Irritable infant syndrome: Theoretical perspectives and practice implications. ANS Adv Nurs Sci. 1988;10(3):70-78.

Empowering parents of infants with infantile colic

Along with reassurance and support, practical suggestions for parents to try might include the following:

- Minimizing stimulation by placing the infant in a safe environment to give both the infant and parents appropriate rest
- Burping
- Swaddling in cloth
- Shifting positions; for example, try walking around carrying the infant face-down, with a hand under his or her stomach
- Using a little quiet 'white noise' such as turning on a fan or running an appliance nearby
- Rocking the infant in a rocking chair, infant seat, or stroller; if not too tired, take a drive
- Skin-to-skin contact and/or gentle massage
- Placing the infant in a sling
- Maintaining correct routines where possible
- Keeping as calm as possible; unsettled behavior may be exacerbated by a stressed, anxious parent
- Taking a short time out by leaving the infant with a trusted spouse or family member
- Phoning a local helpline or visiting the doctor or nurse if concerned

Interventions that are to be avoided, or where evidence is unsubstantiated, include:[68-70]

- Proton pump inhibitors, dicycloverine, cimetropium, or dicyclomine
- Defoaming agents such as simethicone
- Acupuncture
- Herbal compositions (e.g. "gripe water")
- Any foods (e.g. honey) or beverages that are not suitable for infants

Common questions from parents – how to answer*

Why won't my baby stop crying? There must be something seriously wrong?

Ask the parent how long the infant cries, to ascertain whether the duration of crying is in fact excessive. Encourage the parent to keep a diary of the infant's crying behavior and possible triggers. Assure the parent that a certain amount of crying is normal. If excessive, reassure the parent that infantile colic occurs frequently, that infants grow out of infantile colic symptoms within a few months, and that infantile colic is not associated with any long-term adverse effects.

What can I do to stop my baby's crying?

The most important thing is for parents to stay calm, as infants are highly sensitive to a parent's anxiety. Try various methods of soothing your child (see box). Keep the infant in a smoke-free environment, as parental smoking has been associated with infantile colic.

** Advice should be accompanied by a full assessment of symptoms*

Functional constipation

Definitions and diagnosis

Stool frequency in healthy infants is dependent upon age and method of feeding. Bowel movement frequency varies from more than four stools per day during the first week after birth to around two stools per day at 2 years of age, and around one per day at 4 years of age.[71] However, a diagnosis of constipation may be complicated by that fact that it is perfectly normal for healthy breast-fed infants to go a week

(or, in exceptional cases, up to 3 weeks) without defecating, while other infants may defecate up to 12 times a day.[6] Healthcare professionals should be aware of normal defecation patterns in order to be able to differentiate between normal and abnormal presentation.

In the majority of cases, no underlying medical condition is found, and constipation is referred to as "functional".[35]

The Rome III criteria define functional constipation in early life (up to 4 years of age) as fulfilling at least two of the following criteria for at least one month:[4,5,35]

- Two or fewer defecations per week
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools.

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety, which may disappear immediately following passage of a large, firm stool.[5,35]

Diagnostic approaches include:[35]

- Excluding underlying conditions by taking a thorough history

- Physical examination (focus on growth parameters; abdominal examination e.g. muscle tone, distension, fecal mass; and inspection of the perianal and lumbosacral regions)
- A trial of an extensive hydrolysate formula if CMPA is clinically suspected.

Prevalence

Estimates of the prevalence of infant functional constipation vary, presumably as a result of differences in study designs and populations, and differences in definitions of functional constipation versus constipation with underlying pathology. Studies estimate the overall prevalence of functional constipation during the first year after birth to be approximately 3%–14%,[7,35,71,72] with the prevalence increasing during the second year after birth.[7,72] Boys and girls appear to be affected with equal frequency.[72] One study that distinguished between infants in terms of feeding type showed an incidence of hard stools in only 1% of breast-fed infants, compared with 9% of infants fed with a standard formula without prebiotics.[73]

Constipation accounts for approximately 3% of consultations with pediatricians and up to 25% of referrals to pediatric gastroenterologists.[71]

Causes

Constipation is a common complaint among infants, especially when switching from human milk to formula or to solid food.[6,73] The younger the infant, the higher the likelihood of an anatomical

or organic cause, although functional constipation remains the most frequent cause at any age, accounting for 97% of all infant constipation cases.[72]

The pathogenesis of functional constipation is not completely understood. A frequent cause appears to be an acquired behavior of withholding bowel movements after an experience of painful defecation; the rectal mucosa continually absorbs water from the withheld stools, resulting in a hard fecal mass that is difficult and painful to pass. Functional constipation can thus become a persistent cycle.[71]

Factors leading to painful defecation in the first months after birth are unclear; however, functional constipation has been found to be more frequently associated with formula feeding, while breastfeeding has been shown to be a protective factor for the development of constipation in the first 3 months after birth.[71]

Constipation has been shown in some infants to be related to the intake of cow's milk protein or the use of palm oil as the main source of fat in infant formulas.[35,73] In addition, research suggests constipation may be associated with an altered intestinal gut microbiota.[74] Beneficial commensal bacteria produce short chain fatty acids through fermentation of human milk oligosaccharides in the gastrointestinal tract; short chain fatty acids have many benefits, including stimulation of intestinal motility.[75]

Impact

Functional constipation tends to be benign in nature and self-limiting in the majority of infants.[1] However, in a subset of children, functional constipation may persist into adulthood.[76]

Management

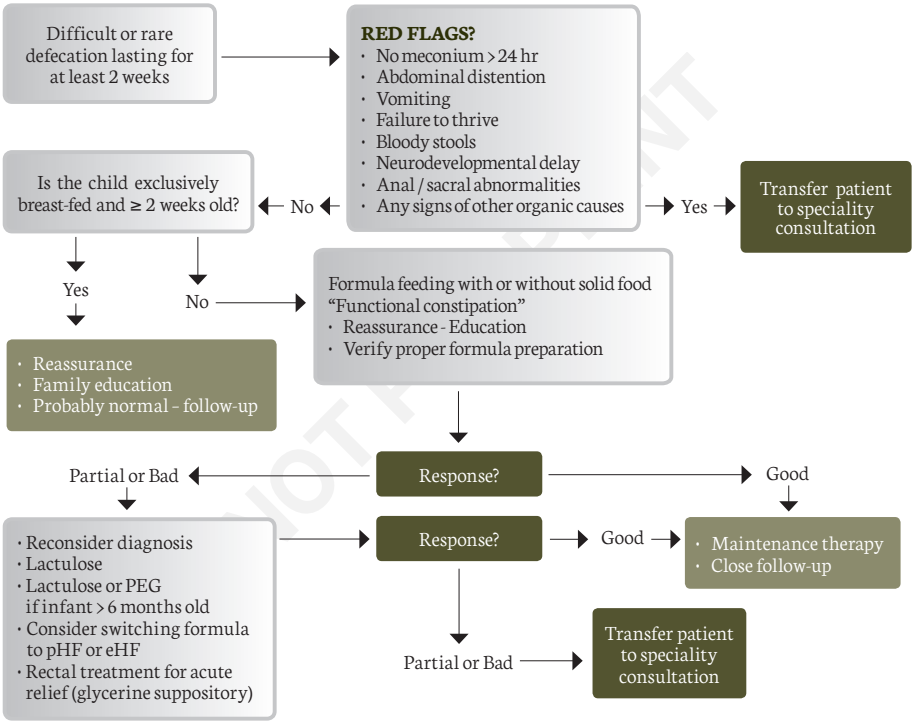
A full medical history, including patterns of meconium passage after birth, should be obtained. Failure to pass meconium within 24 hours after birth should raise suspicion of Hirschsprung's disease or cystic fibrosis.[35] In addition, digital rectal examination should be performed to evaluate perianal sensitivity, anal caliber, position and tone, the presence of anal wink, fissure, or prolapse.[4,6,35]

If the likelihood of an underlying organic condition is low, reassurance and close follow-up should be sufficient.[6] However, intervention to relieve symptoms may be required, even if the symptoms do not fulfill the Rome III criteria presented above.

Suggested pharmacologic and non-pharmacologic approaches are listed below (see also **Figure 7**):

Non-pharmacological approaches:	Pharmacological approaches:
• Add dietary fiber up to normal requirement[6,77] • If appropriate for age, ensure normal fluid intake, including juices that contain sorbitol (e.g. prune, pear, and apple juices)[1,6,77,78] • Consider infant formula containing partially hydrolyzed proteins and/or prebiotics (such as a mixture of scGOS/lcFOS)[1,6] • Lactulose has been shown to relieve constipation[77,78] but causes flatulence in a subgroup of infants[1]	• Polyethylene glycol (PEG) with or without electrolytes for 3 – 6 days[1,35] ➢ PEG is registered in most countries from the age of six months onwards, and has been shown to be at least as effective as lactulose, and to cause fewer side effects ➢ For maintenance, ESPGHAN/NASPGHAN recommends continuing with therapy for at least 2 months, and to discontinue only once the infant is symptom-free for at least one month • Enemas once daily for 3 – 6 days if PEG is not sufficient or available, and acute relief or disimpaction is required[35] • Milk of magnesia (after careful consideration as additional or second-line treatment)[1,35]

Persistent functional constipation cases accompanied by pain, irritability, or decreased appetite should be referred to a pediatric gastroenterologist. Of these persistent cases, 50% can be expected to recover with no ongoing need for laxative treatment after 6 to 12 months.[35]



BF, breastfeeding; eHF, extensively hydrolyzed formula; FF, formula feeding; PEG, polyethylene glycol; pHF, partially hydrolyzed formula

Rare defecation: < 1 / 3 days in FF and < 1 / 7 days in BF

Figure 7. Algorithm for the management of constipation in infants

Adapted and reprinted by permission from John Wiley and Sons: Vandenplas Y, Alarcon P, Alliet P, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr. 2015. doi: 10.1111/apa.12962.

Empowering parents of infants with functional constipation

- Parental education is the most important aspect of management. It is important to engage parents and offer reassurance and follow-up.[35]
- Explain to parents that functional constipation is one of the most frequent benign digestive problems seen in early life. It usually disappears over time, and dietary changes may be sufficient to address the symptoms.[6]
- Encourage parents to keep a stool frequency diary to track patterns and improvements.

Common questions from parents – how to answer*

What changes to diet can help relieve my baby's constipation? Is fiber or fluid intake important?

- Normal intake of fluid and fibers is recommended. Excessive intake has not been shown to be effective.
- Prebiotic oligosaccharides in combination with other ingredients such as beta-palmitate and protein hydrolysates have been shown to soften the stools in constipated infants.[79,80]
- Prolonged administration of lactulose and PEG (> 6 months of age) for several weeks/months may be considered.
- Extensive protein hydrolysates may be indicated if CMPA is suspected.

** Advice should be accompanied by a full assessment of symptoms*

Dyschezia

Definitions and diagnosis

Dyschezia is different from constipation. Rome III criteria describe dyschezia as bouts of straining or crying lasting at least 10 minutes before passing soft, rather than hard stools, in otherwise healthy infants.[4,5] Dyschezia tends to develop in the first 6 months after birth and can occur several times a day.[72,77]

Prevalence

The prevalence of infant dyschezia is difficult to ascertain because an incorrect diagnosis of constipation is very common among infants referred to a gastroenterologist.[81] Two studies have reported the true prevalence of dyschezia in infants according to Rome III criteria. In a recent US cross-sectional study, the prevalence was 2% among infants under 12 months.[7] A recent prospective study in 1,292 infants in the Netherlands showed that 3.9% fulfilled the Rome III criteria for dyschezia at 1 month and 0.9% at 3 months. However, this study showed much higher parent-reported rates of dyschezia symptoms that did not strictly fulfill the Rome III criteria at an age of 1 and 3 months (17.3% and 6.5%, respectively).[82]

Causes

Dyschezia tends to be a self-limiting condition and appears to be related to immature gastrointestinal and pelvic floor muscle activity undermining proper co-ordination with increased abdominal pressure.[81]

Impact

Pain and difficulties in defecation can cause significant distress to infants and their caregivers.[72]

Management

Evidence suggests infants with minor, self-limiting dyschezia invariably improve over several weeks without specific intervention.

Non-pharmacological approaches:

- Observation[78]
- Reassurance regarding the benign nature of the condition[72,77,78]
- Parental education[72]
- Discourage parents from attempting rectal stimulation, to avoid perpetuation of dyschezia[72,77]

Functional diarrhea

The absorption and secretion of water and electrolytes within the gastrointestinal tract is a finely balanced, dynamic process; diarrhea may occur when this balance is lost.[83]

Gastrointestinal infections can result in osmotic, secretory, or inflammatory diarrhea.[84] Acute diarrhea in infancy is most often due to infections, which should be excluded first during diagnostic work-up. Infectious agents may result in damage to the gastrointestinal mucosa (e.g. in cases of rotavirus) or produce toxins (e.g. in cholera), causing diarrhea symptoms. Infectious diarrhea may become chronic infectious diarrhea in several instances, such

as infections caused by cytomegalovirus, cryptosporidium or giardia.[83]

Chronic diarrhea in developing countries is frequently associated with persistent intestinal infections and has a high case/fatality ratio. However, in developed countries, chronic diarrhea typically takes a more benign course with a broader range of probable causes.[84] CMPA, fructose or lactose intolerance, celiac disease, and even cystic fibrosis are relatively frequent causes of chronic diarrhea in developed countries. Antibiotics may in some cases cause diarrhea due to microbial dysbiosis.[83-85]

This section will focus primarily upon *functional diarrhea* of no known underlying cause in otherwise healthy infants. This would refer to cases where all the aforementioned causes have been ruled out.

Definitions and diagnosis

The frequency of bowel movements in healthy infants is highly variable,[83] complicating the diagnosis of infantile functional diarrhea. A diagnosis of functional diarrhea in infants and toddlers by Rome III criteria requires all of the following:[4,5]

- Daily painless, recurrent passage of three or more large, unformed stools
- Symptoms lasting more than 4 weeks
- Onset of symptoms that begin between 6 and 36 months of age

- Passage of stools that occurs during waking hours
- No failure-to-thrive where caloric intake is adequate.

Frequently referred to in the past as "toddler's diarrhea", functional diarrhea in children typically starts in the toddler age group; a diagnosis below the age of two years is not frequent.[84]

In theory, functional diarrhea is an elimination-diagnosis. In children with healthy weight gain and no underlying pathology, the most probable diagnosis is functional diarrhea.[84] Possible causes of chronic diarrhea should be excluded based on the general condition of the child, the predominant features of diarrhea, and intestinal dysfunction. In thriving infants with chronic diarrhea, it is not necessary to rule out every possible cause of chronic diarrhea.

Diagnostic work-up should start with age (current age, and age at onset), nature of onset, feeding and weight patterns, and family history. Examination of the stool (watery, presence of blood/mucus, presence or absence of undigested food particles, steatorrhea) can give valuable information on malabsorption or inflammation patterns. This should be followed by a stepwise investigative approach to minimize invasiveness to the child and to avoid unnecessary costs.[84] It is important to take a balanced approach based on clinical findings: avoid unnecessary tests but not at the cost of missing an organic, treatable cause of chronic diarrhea.

Prevalence

Studies on the prevalence of functional infant diarrhea are scarce, and complicated by the large number of underlying

non-functional causes, especially infections. A large study in infants in Italy showed a 4% incidence of functional diarrhea in infants from birth to 6 months of age.[9] A US cross-sectional study showed a prevalence of functional diarrhea according to Rome III criteria of 2% among infants under 12 months of age and 6% in toddlers aged 1-3 years.[7]

Impact

Chronic diarrhea may result in impairment of both physical and intellectual development.[83,86] However, given the low study numbers, the complexity of the diagnosis, and symptomatic overlap with other etiologies, there is no conclusive evidence on the long-term impact of functional diarrhea. By definition, functional diarrhea does not have a negative impact on development.

Management

Non-pharmacological approaches:

- No specific therapy required in otherwise healthy and thriving infants[4]
- Change diapers frequently to avoid diaper rash
- Observe if symptoms other than those stated under 'Definition and Diagnosis' become apparent during follow up. These must be considered warning signs, and other causes of diarrhea must be excluded during clinical work up[1]

Flatulence

Causes

The presence of a certain amount of gas in the digestive tract is to be expected. However, when there is excessive build up, certain signs and symptoms may be present such as abdominal distension, pain causing intense fussiness/crying, flatulence, soft stools, frequent regurgitation, and diarrhea.[6]

Excess abdominal gas may be due to improper feeding techniques causing swallowing of air, low gastrointestinal lactase activity, secondary lactose malabsorption, or fructose malabsorption,[6,87] causing a large amount of hydrogen gas production as a byproduct of fermentation.

Management

Excessive gas usually resolves within a few months.

Non-pharmacological approaches: [6,54,55,88-91]

- Reassurance
- Physical examination
- Evaluation of feeding technique
- Short trial of a lactose-free or lactose-reduced diet or fermented infant formula may be introduced in children with flatulence

Food allergy: cow's milk allergy

Definitions and diagnosis

Infants may present with a diverse range of symptoms triggered by allergy to specific food proteins. These symptoms can be gastrointestinal, cutaneous, respiratory, or cardiovascular.[92] Considering the wide range of distinct immune pathologies and organs that can be affected, a spectrum of disease falls under the umbrella of food allergies. Gastrointestinal symptoms of food allergy needs to be distinguished from non-immunological intolerance reactions to food constituents (see next section); symptoms may be difficult to distinguish due to a diverse and overlapping spectrum of manifestations and underlying causes.[87]

There is no simple diagnostic test for food allergy. The current recommendation is a doubled-blind, placebo-controlled food challenge.[92] Clinical diagnosis, however, may in many cases rely first upon clinical improvement with removal of the suspected allergen from the diet, and relapse upon re-exposure. Gastrointestinal biopsies may provide further diagnostic clues where necessary.[87]

Cow's milk protein allergy (CMPA) is the most frequent cause of food allergy among infants and young children globally.[93] General symptoms of CMPA may include regurgitation, chronic diarrhea or vomiting, feeding difficulties, unsettled behaviors, sleep pattern disturbance, failure to thrive, and atopic symptoms such as skin manifestations (e.g. rash/dermatitis), respiratory symptoms (e.g. wheezing), or urticaria. Upper and lower gastrointestinal

pathologies include mucosal inflammation, ulceration, small intestinal villous damage, changes in intestinal permeability, gastrointestinal motility abnormalities, enterocolitis, and proctocolitis.[6,87]

Prevalence

Studies show a variable prevalence of food allergy; one large meta-analysis focusing on cow's milk, egg, peanut, and seafood allergy in children showed an overall prevalence of 3.5%.[93] A rise in the prevalence of food allergies has been observed in recent years, in both developed and developing countries.[94,95]

CMPA affects approximately 2%–3% of infants under the age of 2 years,[96,97] while studies of peanut allergy, for example, in the US and UK indicate a prevalence of about 1%.[94]

Approximately 50% of infants have been found in observational cohort studies to grow out of CMPA by 1 year of age, meaning that they have developed tolerance towards cow's milk protein.[87,98,99] However, while most children outgrow allergies to milk, egg, wheat, and soy, other allergies such as peanut, treenut, fish, and shellfish allergies often persist into adulthood.[94]

Causes

The causes of food allergy are complex and multifactorial; genetic predisposition, environmental factors, and health status are important modulating factors. However, it is not known why in some infants the immune system is triggered and fails to develop tolerance towards otherwise harmless food antigens.[100]

Gut microbial dysbiosis has been hypothesized to be associated with the development of food allergies. As a healthy gut microbiota is essential for the proper development of the immune system in infancy, disruption of appropriate gastrointestinal colonization and microbiota establishment may interfere with the immune training process, leading the immune system to over-react to harmless antigens, including food proteins.[101]

Impact

Nutritional deficiency and growth impairment may occur if food allergy is not diagnosed early.[6,87] In addition, infants with CMPA have an increased risk of developing other allergies in later life.[102]

Food allergies in children also have a heavy impact upon family quality of life. Families may experience major disruption to daily routines, and practical planning must be done to ensure avoidance of all allergenic foods and cross-contamination while holidaying, traveling, and eating away from home.[103]

In addition, the health economic burden of food allergy is significant.[103]

Management

In the case of CMPA, cow's milk needs to be eliminated from the diet (see also **Figure 8**).

Non-pharmacological approaches

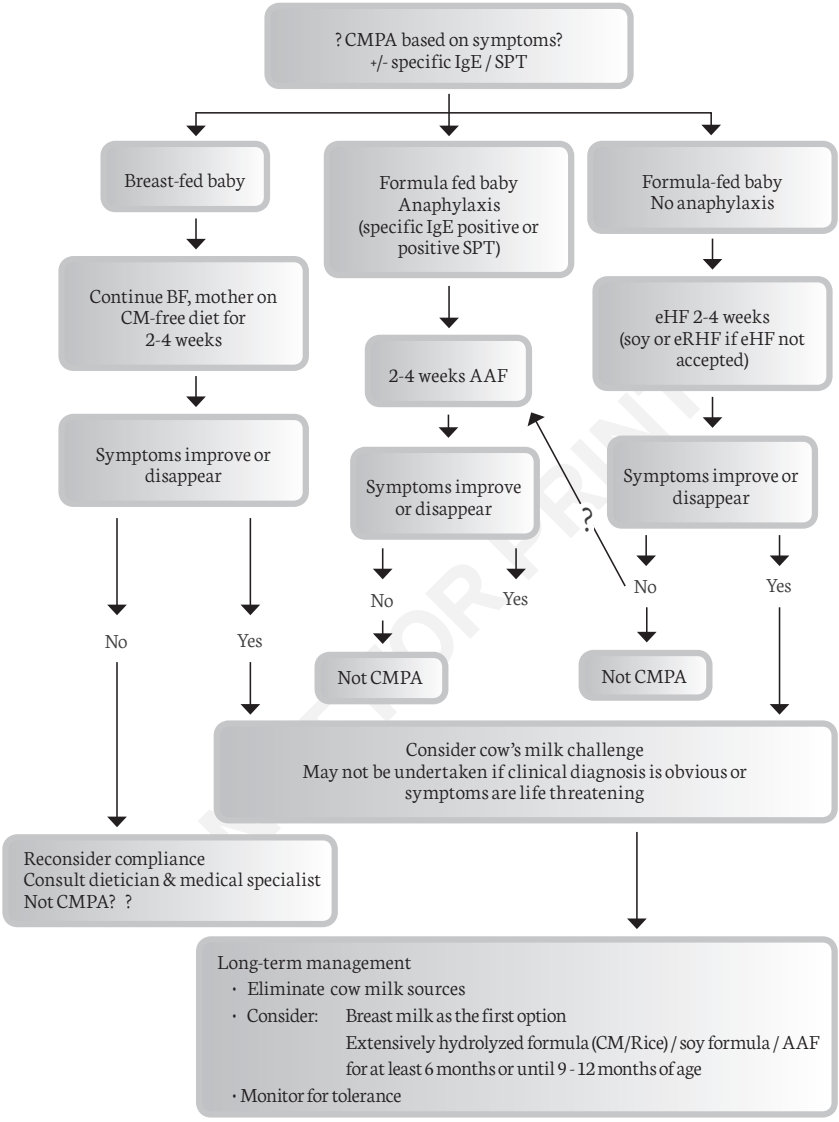
Eliminate cow's milk from the diet

- Breast-fed infants:
  - Eliminate all dairy products from the maternal diet[96]
- Formula-fed infants:
  - Change to an extensively hydrolyzed cow's milk based protein formula[87,104,105]
  - Change to extensively hydrolyzed rice protein-based formula or soy infant formula as an alternative if the extensively hydrolyzed cow's milk based formula is not available, too expensive, or if the infant refuses to drink it[106-110]
  - In infants presenting with anaphylactic reactions, amino acid based formula rather than extensively hydrolyzed formula is recommended[105]

Note: Current systematic reviews and meta-analyses indicate that in infants younger than 6 months, the prevalence of allergies to soy and IgE sensitization to soy could be lower than previously reported.[104,107,108] ESPGHAN guidelines concluded that soy formula cannot be recommended for the prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance, and should not be used in infants with food allergy during the first 6 months after birth. If soy protein formula is considered for therapeutic use for food allergy after the age of 6 months, tolerance to soy protein should first be established by clinical challenge.[111]

The nutritional burden of food avoidance is important in the growing child, and it is essential that suitable alternatives or supplements are provided to ensure normal growth.[112] In addition, any dietary restrictions should be employed only when there is a strong indication to do so, and under adequate supervision, given that the inappropriate implementation of such restrictions may reduce quality of life for the infant and his or her family, impair growth, and result in unnecessary costs.

Most children with immunoglobulin E-mediated CMPA ultimately achieve tolerance following an appropriate therapeutic elimination diet and controlled reintroduction into the diet.[104]



AAF, amino acid based formula; BF, breastfeeding; CM, cow's milk; CMPA, cow's milk protein allergy; eHF, extensively hydrolyzed formula; eRHF, extensive rice hydrolysate formula; SPT, skin prick test

Figure 8. Algorithm for the management of cow's milk protein allergy in infants

Adapted and reprinted by permission from John Wiley and Sons: Vandenplas Y, Alarcon P, Alliet P, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr. 2015. doi: 10.1111/apa.12962.

Immune-mediated enteropathies: celiac disease

Definitions and diagnosis

In general, childhood celiac disease is not often diagnosed during infancy; the median age of childhood diagnosis is 4 years, and most cases are diagnosed in adulthood.[113] In infants with celiac disease, symptoms tend to have a more aggressive presentation, and include chronic diarrhea, constipation, failure to thrive, abdominal distention, and vomiting.[113-115]

Celiac disease-focused histology and serology, along with a HLA-DQ2/DQ8 screening test, may be useful diagnostic tools in assessing for possible celiac disease before eliminating gluten from the diet.[87,114]

Prevalence

There is little information currently available on the precise prevalence of celiac disease in children with suggestive symptoms.[115] The prevalence in the general population is thought to be approximately 1%,[116] but some studies suggest a prevalence as high as 3%.[117,118] While the prevalence has always been lower in Asian countries, it appears to be increasing in parallel with changing diets and an increase in gluten consumption.[119]

Causes

Gluten is a protein composite found in grains, particularly wheat. Celiac disease is an immune-mediated systemic disorder. Reactions are elicited by gluten and related prolamines in genetically susceptible individuals, and characterized by the presence of a

variable combination of gluten-dependent clinical manifestations, celiac disease-specific prevalence of DQ2 or HLA-DQ8 haplotypes, and enteropathy.[87] In celiac disease, dietary gluten causes inflammation of the small intestine, which may affect absorption of important nutrients such as iron, folate, and calcium.[120] Studies and surveys among adults and children with celiac disease that follow a gluten-free diet also revealed that approximately 20%–40% of them have nutritional complications. These complications include imbalances of protein-energy ratio, and deficiencies of dietary fiber, mineral, and vitamin intakes.[121-125]

Management

Non-pharmacological approaches:

- Life-long avoidance of gluten-containing foods in the diet[87]
- Where necessary, incorporate suitable alternatives or supplements into the child's diet to ensure normal growth and development[112]

Food intolerances

Food intolerances, unlike food allergies, do not involve the immune system.[103,126] Symptoms of nutrient intolerances (e.g. fructose malabsorption) are similar to those of food allergy (intermittent, food-associated diarrhea, abdominal distension, pain, and perianal excoriation from acidic stools) but usually without atopic manifestations.[6,87]

While it is important to avoid the food component to which the infant is allergic, most individuals with non-allergic food

intolerances should be able to include small amounts of the food or substance in their diet with no adverse effects.[103]

Fructose malabsorption

Definitions and diagnosis

Fermentation of unabsorbed fructose by intestinal bacteria causes gas production, abdominal pain, and diarrhea.[87]

Prevalence

Fructose malabsorption is a rare condition, which only causes symptoms if an exaggerated amount of fructose is consumed – for instance, when the child drinks a lot of apple juice. Symptoms occur subsequent to the ingestion of fructose, and are thus easy to recognize.

Causes

Causes of fructose malabsorption are largely unknown. As fructose malabsorption has such a high prevalence in young children, there is some debate as to whether this condition is in fact a distinct disease state or a normal variant.[87]

Impact

Families who have a young child with a food intolerance, just as families with children who have a food hypersensitivity, experience higher levels of stress and concerns in daily life compared with families without these challenges.[112]

Management

Non-pharmacological approaches:

- Elimination of high-fructose fruits (apple, pear, watermelon, dried fruit), fruit juice, and honey from the diet[87]

Symptoms tend to improve with age, and a low-fructose diet may usually be relaxed over time.[87]

Beneficial effects of specific dietary factors and other non-pharmacological approaches

In treating digestive problems in infants, it is important to avoid the use of drugs and invasive procedures where possible. Nutritional treatments are generally the preferred option. Clearly, the ideal approach is prevention, by providing the infant with the nutrition required to develop and maintain a healthy gastrointestinal tract. **Breastfeeding remains the gold standard for infant nutrition.**

Fiber and fluids

A central component of healthy nutrition is ensuring that the growing infant receives sufficient quantities of fluids and dietary fiber, both of which help ensure regular bowel movements. Dietary fiber is a collective term for a range of indigestible carbohydrates that have several health benefits, especially in terms of promoting gastrointestinal health.[127]

Many dietary fiber components are partially or completely fermented by the gut microbiota. As described and in **Chapter 1**, fermentation of indigestible carbohydrates produces short chain fatty acids, which can be directly absorbed by the gastrointestinal tract, thus offering a way to extract energy from indigestible carbohydrates, and also act to lower the pH in the large intestine, stimulating bowel movement. Meanwhile, by increasing the water content of the stools, these carbohydrates also become incorporated into the stool, increasing its mass while softening its consistency. All these effects help to increase stool weight while reducing the transit time through the large intestine, increasing the frequency and ease of defecation.[127]

In newborn infants, all dietary fiber and fluid are provided by milk, whether human milk or formula. Human milk naturally contains dietary fiber in the form of human milk oligosaccharides. Conventional cow's milk-based formula does not contain human milk oligosaccharides, which is one reason why formula-fed infants tend to have a higher incidence of constipation.[6]

Probiotics and prebiotics

One approach to managing digestive disorders in infants is to supplement the diet with prebiotics and/or probiotics designed to promote gut health,[128] as discussed in the first Essential Knowledge Briefing.

Prebiotics comprise indigestible oligosaccharides such as scGOS and lcFOS that can stimulate the growth and proliferation of these beneficial bacteria in the gastrointestinal tract, with positive

health effects.[129] Prebiotic oligosaccharides added to infant formula have been shown to alter the composition of the infant gut microbiota, making it more similar to that of breast-fed infants.[129] When added to formula, prebiotic oligosaccharides can produce more frequent and softer stools, and reduce digestive discomfort in formula-fed infants.[130]

Other dietary manipulations

As discussed, the infant diet can also be modified in various other ways to help treat digestive disorders. For example, formula thickened with locust bean gum or starches that are specifically designated for the usage in infant formula may help to relieve regurgitation.[6] Whey based partially hydrolyzed formula with low levels of lactose may alleviate symptoms of digestive discomfort in cases when CMPA is not suspected. When CMPA is suspected, an extensive hydrolysate formula is recommended.[6]

Digestive disorders in infants can be distressing for both infants and parents, not least because they can lead to pain, discomfort, and excessive crying. In many cases, however, modifications to the infant's diet may be sufficient to alleviate many of the most troubling symptoms,[1] leading to happier infants and more relaxed parents.[32]

Healthcare professional-parent interaction: Best practices in a nutshell

- As a healthcare professional, securing a positive relationship with parents fosters trust and helps ensure effective management of infant digestive problems. Since parents know their child best and can report their observations, it is necessary to engage them fully in the care of their infant.
- Parental education, support and reassurance are important aspects of managing functional digestive disorders in infants. Parents need to be reassured that, in most cases, there is no obvious underlying cause and that the symptoms will naturally resolve after a few months. It is helpful to suggest measures to settle the infant, including behavioral and nutritional input.
- Parents should be advised that pharmaceutical treatments are not usually recommended for infants, unless no other options are available.

Chapter highlights

- Infant functional gastrointestinal disorders, such as regurgitation, infantile colic, functional constipation, and functional diarrhea, have no obvious underlying pathology and should naturally resolve over time.
- Regurgitation and vomiting are clinical manifestations of GER; other manifestations of GER may include persistent crying, irritability, back-arching, and sleeping problems. Management approaches include avoidance of overfeeding and feeding in the prone position, ruling out food allergy, and offering nutritional support in persistent cases.
- Infantile colic is characterized by intense, inconsolable crying and fussing which has no clear underlying cause. Infantile colic may be extremely distressing for parents, and has been reported to be associated with postnatal depression and poor parent-infant bonding in a subset of infants. Along with exclusion of possible underlying causes, a key management approach includes parent support and education.
- Functional constipation often begins during the first year after birth, especially during the weaning period. It may be self-perpetuating due to acquired behavior of withholding bowel movements after episodes of painful defecation. Although the evidence is very limited, some studies also suggest involvement of microbiota dysbiosis in functional constipation. Management approaches may include reassurance, infant formula containing hydrolyzed protein and prebiotics or probiotics, glycerin suppositories, behavioral therapy, and pharmacologic disimpaction treatments such as laxatives. Probiotics have been shown to increase stool frequency but to not change consistency. Prebiotics oligosaccharides, which constitute a form of dietary fiber, have been shown on the contrary to soften stools in infants.

- Dyschezia is distinct from constipation and is characterized by pain preceding the passing of soft stools. It usually improves over several weeks without intervention.
- Diarrhea may be functional or have an underlying cause, either infectious or non-infectious. In otherwise healthy, thriving infants, diagnosis and treatment should be carefully balanced.
- Excessive gas may be caused by improper feeding techniques, transiently low GI lactase activity/secondary lactose malabsorption, or fructose malabsorption. Management approaches are similar to those for infantile colic, and dietary lactose intake can be transiently reduced in formula-fed infants.
- Food allergies, such as CMPA, and nutrient intolerances such as gluten or carbohydrate intolerances, can cause a range of digestive symptoms including chronic diarrhea, failure to thrive, abdominal distention, and vomiting, along with atopic manifestations in cases of allergy. Elimination and re-exposure is both a diagnostic and a management approach.
- Dietary supplementation with probiotics and/or prebiotics with documented efficacy may be considered in some cases to help manage some digestive disorders in infants.

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CHAPTER 5

Future directions

While this Essential Knowledge Briefing has considered several gastrointestinal conditions separately, there are common threads in the issues determining the future direction of the treatment strategies. These issues are the focus of on-going and future research in the area of FGIDs in infants, and involve the collection of reliable FGID prevalence data, the long-term health impact of FGIDs in infants, and the development of new dietary ingredients to promote gut health.

Collection of data

High-quality prevalence data on a global level is necessary to provide accurate estimates of disease burden and to provide baseline data to measure the impact on future health outcomes. At the moment, much of the relevant data were published several decades ago, and the lack of congruence in study design, study populations, infant age parameters, and definitions make it difficult to draw firm conclusions.

Collection of reliable data according to agreed or standardized criteria are required to obtain more accurate estimates than those currently available. In addition, differences in feeding methods and other contributory factors should be adjusted for when collecting data for global estimates.

Moreover, global standardization of criteria and classifications are needed. For example, dyschezia, which is considered a functional disorder in its own right, may frequently be classified as infantile colic or constipation. Improved awareness and education with

respect to diagnosis and classification are necessary on a global scale.

Evaluation of long-term health impact

Studies on the prevalence and long-term health outcomes of are limited.

As discussed in **Chapter 4**, some evidence suggests that infantile colic may be associated with future health problems, including gastrointestinal disorders, migraine, and behavioural/developmental problems. However, further well-designed, prospective studies are required to establish the precise nature of this association, and it is acknowledged that causality may be very difficult to prove.

Data on the long-term effects of other frequent FGIDs such as regurgitation and constipation indicates an association with long-term health outcomes. Whether these associations are specific, or whether FGIDs as such constitute an early traumatic event, or both, is of interest and warrants further investigation.

While infantile colic and regurgitation usually resolve without treatment, this is less likely to be the case with functional constipation. Some evidence suggests that functional constipation in infants may be associated with future gastrointestinal problems, and preliminary data suggests improved outcomes with early treatment. However, the evidence is not well established, and prospective studies are sorely needed to confirm these associations.

In the case of functional diarrhea in infants, expert consensus is that functional diarrhea occurring before the age of 12 months appears to have no long-term consequences. Likewise, dyschezia is not thought to be associated with subsequent onset of functional constipation or other gastrointestinal symptoms. However, again, good quality prospective studies are needed.

Development of new dietary ingredients

A significant fraction of the literature surrounding FGIDs was published before the commercial introduction of infant formulas containing prebiotic and probiotic agents. These novel dietary ingredients introduced in the past decade may have had a significant impact on the prevalence and outcomes of some of the symptoms discussed above.

Based on our ever-increasing understanding of the composition of a healthy gut microbiota and its importance for health, along with the encouraging clinical leads supporting the use of pre-, pro- and synbiotics, it is important for both clinicians and researchers to further explore existing and new concepts such as fermented infant formula and their impact on short- and long-term health.

Parental support: The role of healthcare professionals

As discussed in **Chapter 4**, FGIDs such as infantile colic and constipation can be very distressing for parents and caregivers. Healthcare professionals have an important role in counseling parents with regard to the expected natural history of these disorders, and the need for a conservative approach to treatment in

most cases. Education and counseling should be offered wherever necessary, particularly in cases of postnatal depression or risk of harm to the infant, and for first-time parents without experience in infant care.

In acknowledgement of the parenting difficulties associated with FGIDs, it is very important that easily accessible support mechanisms are put in place alongside clinical management procedures, to ensure optimal outcomes for both the infant and his or her family.

Ultimately, future directions in infant FGID management, whether in research, the development of novel strategies, or parental support infrastructure, must be based on the overarching objective of optimizing gut health in early life. Pursuing knowledge in the right directions will help direct the child's first steps towards a healthier life journey and provide parents with a more fulfilling parenting experience.

GUT HEALTH IN EARLY LIFE is an educational series highlighting gut health during the first 1000 days, a critical period of human development which provides the foundation for lifelong health and wellbeing.

IMPLICATIONS AND MANAGEMENT OF GASTROINTESTINAL DISORDERS is the second book in the series and provides the latest updates in the prevalence, causes, impact, diagnosis and management of common functional gastrointestinal disorders and digestive problems in pregnancy and infancy.

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