Childhood Functional Gastrointestinal Disorders: Neonate/Toddler

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In 2006, a consensus concerning functional gastrointestinal intestinal disorders in infants and toddlers was described. At that time, little evidence regarding epidemiology, pathophysiology, diagnostic workup, treatment strategies, and follow-up was available. Consequently, the criteria for the clinical entities were more experience based than evidence based. In the past decade, new insights have been gained about the different functional gastrointestinal intestinal disorders in these age groups. Based on those, further revisions have been made to the criteria. The description of infant colic has been expanded to include criteria for the general pediatrician and specific criteria for researchers. The greatest change was the addition of a paragraph regarding the neurobiology of pain in infants and toddlers, including the understanding of the neurodevelopment of nociception and of the wide array of factors that can impact the pain experience.

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Infant and toddler functional gastrointestinal disorders (FGIDs) include a variable combination of often age-dependent, chronic, or recurrent symptoms not explained by structural or biochemical abnormalities. Functional symptoms during childhood sometimes accompany normal development (eg, infant regurgitation), or they can arise from maladaptive behavioral responses to internal or external stimuli (eg, retention of feces in the rectum often results from an experience with painful defecation). The clinical expression of an FGID varies with age, and depends on an individual's stage of development, particularly with regard to physiologic, autonomic, affective, and intellectual development. As the child gains the verbal skills necessary to report pain, it is then possible to diagnose pain-predominant FGIDs.

Through the first years, children cannot accurately report symptoms such as nausea or pain. The infant and preschool child cannot discriminate between emotional and physical distress. Therefore, clinicians depend on the reports and interpretations of the parents, who know their child best, and the observations of the clinician, who is trained to differentiate between health and illness.

The decision to seek medical care for symptoms arises from a caretaker's concern for the child. The threshold for concern varies with previous experiences and expectations, coping style, and perception of illness. For this reason, the office visit is not only about the child's symptom, but also about the family's fears. The clinician must not only make a diagnosis, but also recognize the impact of the symptom on the family's emotions and ability to function. Therefore, any intervention plan must attend to both the child and the family. Effective management depends on securing a therapeutic alliance with the parents.

Childhood FGIDs are not dangerous when the symptoms and caregiver's concerns are addressed and contained. Conversely, failed diagnosis and inappropriate treatments of functional symptoms may be the cause of needless physical and emotional suffering. Disability from a functional symptom is related to maladaptive coping with the symptom. In severe cases, well-meaning clinicians inadvertently co-create unnecessarily complex and costly solutions, as well as ongoing emotional stress that promotes disability.[1]

This article provides a description, assessment, and analysis of each FGID that affects the neonate/toddler age group (Table 1). Figure 1 shows the age of presentation of FGIDs in the pediatric age group, and Table 2 shows a summary of the prevalence of FGIDs in this age group, as well as their pathophysiology and treatment. We will then review the developmental neurobiology of the pain response, as well as the assessment of pain in infants and toddlers.

I. Functional Gastrointestinal Disorders

G1. Infant Regurgitation

Reflux refers to retrograde involuntary movement of gastric contents in and out of the stomach, and is often

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Most current article

Table 1. G. Functional Gastrointestinal Disorders in Neonates and Toddlers

G1. Infant regurgitation
G2. Infant rumination syndrome
G3. Cyclic vomiting syndrome
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation

G1. Diagnostic Criteria for Infant Regurgitation

Must include both of the following in otherwise healthy infants 3 weeks to 12 months of age:

1. Regurgitation 2 or more times per day for 3 or more weeks

2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

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referred as gastroesophageal reflux.[2] When the reflux is high enough to be visualized it is called regurgitation. Regurgitation of stomach contents into the esophagus, mouth, and/or nose is common in infants and is within the expected range of behaviors in healthy infants. Infant regurgitation is the most common FGID in the first year of life.[3] Recognition of infant regurgitation avoids unnecessary doctor visits and unnecessary investigations and therapy for gastroesophageal reflux disease (GERD).[2] Infant regurgitation is distinguished from vomiting, which is defined by a central nervous system reflex involving both autonomic and skeletal muscles in which gastric contents are forcefully expelled through the mouth because of coordinated movements of the small bowel, stomach, esophagus, and diaphragm. Regurgitation is also different from rumination, in which previously swallowed food is returned to the pharynx and mouth, chewed, and swallowed again. When the regurgitation of gastric contents causes complications or contributes to tissue damage or inflammation (eg, esophagitis, obstructive apnea, reactive airway disease, pulmonary aspiration, feeding and swallowing difficulties, or failure to thrive), it is called GERD.[2]

Rationale for change in diagnostic criteria. There are minor changes from Rome III. Recently, a position paper by the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and the European Society of Pediatric Gastroenterology Hepatology and Nutrition added "bothersome symptoms" as one criterion to differentiate infant regurgitation from GERD.[3] The challenge with that definition is that quantitative methods to define "troublesome" are missing. Infants cannot communicate if they are bothered. Variations in clinician and parent interpretations of troublesome have resulted in unnecessary evaluation and treatment of many infants with regurgitation, not GERD. There is a lack of correlation between crying, irritability, and GER.[4] GER is not a common cause of unexplained crying, irritability, or distressed behavior in otherwise healthy infants.[2] Therefore, we have elected to leave "troublesome" symptoms out of the criteria.

Clinical evaluation. Daily regurgitation is more common in young infants than in older infants and children, and is found in higher rates in neonates.[5] A recent study of 1447 mothers throughout the United States showed a prevalence of infant regurgitation of 26% using Rome III criteria.[3] Regurgitation occurs more than once a day in 41%–67% of healthy 4-month-old infants.[2,6]
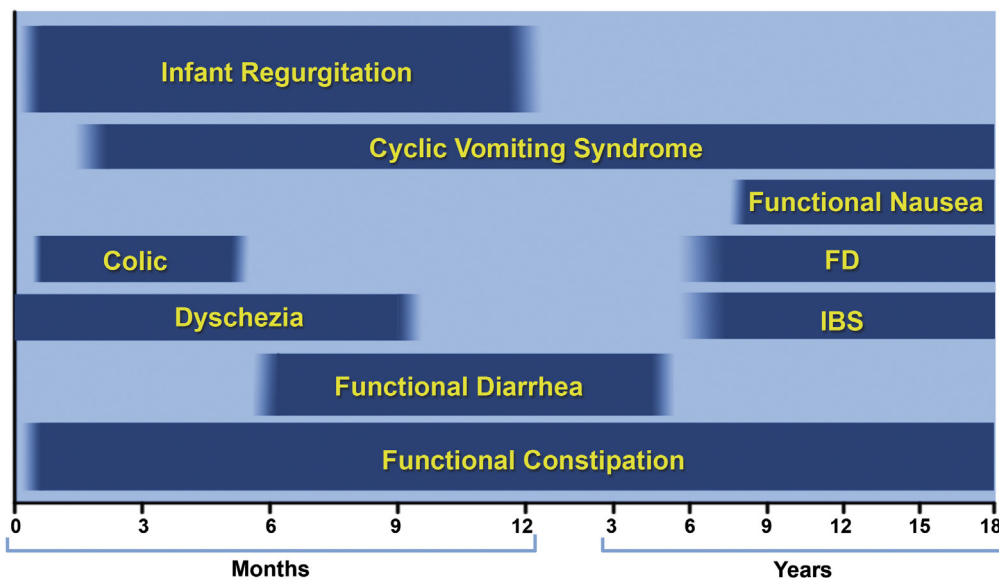

Figure 1. Age of presentation of FGIDs in pediatric patients. The bars show each diagnosis. Symptoms might begin earlier, as there is a time requirement to fulfill diagnostic criteria. IBS, irritable bowel syndrome; FD, functional dyspepsia.

Table 2. Prevalence, Pathophysiology, and Treatment of Functional Gastrointestinal Disorders in Neonates and Toddlers

Disorder	Age	Prevalence, %	Pathophysiology	Treatment	Outcome
Infant regurgitation	3 wk to 12 mo	41−67 (peak at 4 mo of age)	Small esophageal volume, overfeeding, infant positioning	Education, smaller feedings feeding thickening, positioning	Resolves in 90% by 12 mo of age
Infant rumination syndrome	3−8 mo	1.9	Emotional and sensory deprivation	Behavioral interventions, improved nurturing	Recovery with nurturing
Cyclic vomiting syndrome	Wide range	3.4	Activation of the emetic reflex and the HPA axis	Prevention of triggers, prophylactic medications, abortive medications, supportive measures	Usually resolves as child gets older but may continue or change to abdominal migraine or migraine headache
Infant colic	Early infancy to 5 mo	5−19	Results from normal developmental process Normal variations in development and temperament account for differences in crying Influence of parental perceptions	Reassurance No evidence that pharmacologic interventions are useful There is inadequate evidence whether elimination of cow's milk protein, probiotics, or herbal interventions provide viable and effective treatments These approaches remain problematic and controversial	Resolves by 5 mo of age
Functional diarrhea	6−60 mo	6−7	Dietary and motility abnormalities; increased mucosal secretion?	Education, dietary changes	Usually resolves by 60 mo of age
Infant dyschezia	Birth to 9 mo	2.4	Uncoordinated defecation dynamics	Education and reassurance, avoidance of anal stimulations and laxatives	Resolves in most cases by 9 mo of age
Functional constipation	Birth to adulthood	3−27	Results from painful defecation associated with withholding	Education, behavioral interventions, laxatives	Successful long-term treatment in 80% after first year, and increases over time

HPA, hypothalamic−pituitary−adrenal.

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Although regurgitation can occur at any age, the peak is around 4 months of age, with tapering beginning at 6 months and then declining in frequency until 12–15 months.[5]

History and physical examination may provide evidence of disease outside the GI tract, including metabolic, infectious, and neurologic conditions associated with vomiting. Prematurity, developmental delay, and congenital abnormalities of the oropharynx, chest, lungs, central nervous system, heart, or GI tract are considered risk factors for GERD.[2] Evidence of failure to thrive, hematemesis, occult blood in the stool, anemia, food refusal, and swallowing difficulties, should prompt an evaluation for GERD.[2] Assessment to exclude an upper GI anatomical abnormality, such as malrotation or a gastric outlet obstruction, should be done if regurgitation persists past the first year of life, if it started early in the neonatal period, or it is associated with bilious vomiting, dehydration, or other complications.

Treatment. The natural history of infant regurgitation is one of spontaneous improvement.[6] Therefore, treatment goals are to provide effective reassurance and symptom relief while avoiding complications. Improving the caregiver–child interaction is often aided by relieving the caregiver's fears about the condition of the infant, identifying sources of physical and emotional distress, and making plans to eliminate them. Management does not require medical interventions. There are multiple randomized trials showing a lack of benefit to the use of proton pump inhibitors in infants with regurgitation or those suspected of having GERD, mostly based on regurgitation and bothersome symptoms.[4,7] In addition, proton pump inhibitor treatment can be associated with adverse effects, mainly respiratory and GI infections.[7] Conservative measures include positioning after meals and thickened feedings. Thickened feedings and antiregurgitation formulas can decrease regurgitation in healthy infants.[8,9] While frequent smaller-volume feedings are sometimes recommended,[2] there is little direct evidence to support the efficacy of this approach. Postprandial left-sided and prone position reduces regurgitation.[10] Sleeping in prone and lateral position can increase the risk of sudden infant death syndrome. Therefore, the American Academy of Pediatrics recommends sleeping in the supine position.[11]

G2. Rumination Syndrome

Rumination is the habitual regurgitation of stomach contents into the mouth for the purpose of self-stimulation.[12] Rumination has the following clinical presentations: infant rumination syndrome, rumination in neurologically impaired children and adults, and rumination in healthy older children and adults.[12] The latter 2 presentations are not discussed in this supplement.

G2. Diagnostic Criteria for Rumination Syndrome

Must include all of the following for at least 2 months:

1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue

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2. Effortless regurgitation of gastric contents, which are either expelled from the mouth or rechewed and reswallowed

3. Three or more of the following:

   a. Onset between 3 and 8 months

   b. Does not respond to management for gastroesophageal reflux disease and regurgitation

   c. Unaccompanied by signs of distress

   d. Does not occur during sleep and when the infant is interacting with individuals in the environment

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Rationale for change in diagnostic criteria. There have been no major changes from the Rome III criteria. However, given the difficulty for infants to communicate the presence of nausea, that word has been eliminated. The duration was also shortened to 2 months to be consistent with the rumination criteria for the older age groups.

Clinical evaluation. Infant rumination syndrome is rare, and has received little attention in the literature. A recent questionnaire based study of 1447 mothers showed a prevalence of 1.9%.[3] Rumination historically has been considered a self-stimulatory behavior that arises in the context of longstanding social deprivation. In the limited published literature, maternal behavior may appear to be neglectful or slavishly attentive, but there is no enjoyment in holding the baby or sensitivity to the infant's needs for comfort and satisfaction.[12]

Observing the ruminative act is essential for diagnosis. However, such observations require time, patience, and stealth because rumination can cease as soon as the infant notices the observer. No tests are necessary for the diagnosis of infant rumination syndrome.

Treatment. Historically, infant rumination syndrome responded to empathetic and responsive nurturing.

Excessive and continuous loss of previously swallowed food may cause progressive malnutrition. Behavioral therapy is useful in eliminating rumination in highly motivated adults or children with neurologic impairment. There is no information on whether those techniques are useful in infant rumination syndrome. The most humane, developmentally appropriate, and comprehensive management aims at reversing the baby's weight loss by eliminating its need for ruminative behavior. Treatment aims at helping the caregivers address their feelings toward the infant and to improve their ability to recognize and respond to the infant's physical and emotional needs.[13]

G3. Cyclic Vomiting Syndrome

Although data on clinical course in infants and toddlers are sparse, epidemiologic studies clearly report that cyclic vomiting syndrome (CVS) can occur before 3 years of age.[14,15] A study from the United States found a prevalence of CVS of 0.2%–1.0% in children and of 3.4% in toddlers

using the Rome III diagnostic criteria.[3] CVS occurs from infancy to midlife, and is most common between 2 and 7 years.[16] In a study in Ireland reporting 41 cases, the median age at onset of symptoms was 4 years, with 46% of affected children having an onset of symptoms at the age of 3 years or younger.[14] The poor recognition of the disorder leads to a timespan between the onset of symptoms and the diagnosis ranging between 1.1 to 3.4 years.[14]

G3. Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following:

1. Two or more periods of unremitting paroxysmal vomiting with or without retching, lasting hours to days within a 6-month period

2. Episodes are stereotypical in each patient

3. Episodes are separated by weeks to months with return to baseline health between episodes of vomiting

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Rationale for change in diagnostic criteria. The Rome IV committee reviewed the Rome III guidelines, NASPGHAN Cyclic Vomiting Syndrome Consensus Statement[17] and International Headache Society[18] criteria for CVS and the validation and epidemiologic data derived from their utilization. We found no studies designed for the validation of the CVS guidelines after the publication of the NASPGHAN and International Headache Society guidelines. Those guidelines require a minimum of 5 attacks of intense nausea and vomiting in any interval for a child to be considered to have a diagnosis of CVS. The NASPGHAN consensus statement considered the Rome III minimum of 2 recurrent episodes for a child to be diagnosed with CVS as lacking specificity. However, 5 recent studies using Rome III criteria conducted in infants, toddlers, children, and adolescents failed to report a significantly higher prevalence of CVS than reported previously, as would be expected if the lack of specificity was important.[19–22] The consistency of the epidemiologic data using the Rome III criteria and the narrow range of prevalence of CVS found in 4 studies (range, 0.2%–3.4%) using the Rome III criteria stands in contrast with the lack of epidemiologic data using the NASPGHAN criteria or the International Headache Society criteria. The committee agreed that, based on the important impact for the child's quality of life and family disruption derived from each CVS attack, early diagnosis is important. Therefore, the committee maintained 2 as the minimum number of episodes required. Given the difficulty for infants to communicate the presence of nausea, that word has been eliminated from the criteria.

Clinical evaluation. CVS is characterized by stereotypical and repeated episodes of vomiting lasting from hours to days with intervening periods of return to baseline health.[17] The frequency of episodes in a series of 71 patients ranged from 1 to 70 per year and averaged 12 per year.[16] Attacks may be sporadic or occur at fairly regular intervals. Typically, episodes begin at the same time of day,

most commonly during late night or in the early morning. The duration of episodes tends to be the same in each patient over time.[16] Once vomiting begins, it reaches its highest intensity during the first hours. The frequency of vomiting tends to diminish thereafter, although nausea continues until the episode ends. Episodes usually end as rapidly as they begin and are marked by prompt recovery of well being, provided the patient has not incurred major deficits of fluids and electrolytes.

Signs and symptoms that might accompany cyclic vomiting include pallor, weakness, increased salivation, abdominal pain, intolerance to noise, light and/or odors, headache, loose stools, fever, tachycardia, hypertension, skin blotching, and leukocytosis.[17]

Patients with CVS frequently have a maternal history of migraine headaches and commonly progress to migraine headaches themselves. The matrilineal history of migraines suggests a mitochondrial dysfunction. Individuals related through the maternal line carry an identical mitochondrial DNA sequence. In addition to genetic factors, psychosocial factors have also been associated with CVS in children. Episodes of CVS may be triggered by excitement, stress, or anticipatory anxiety. A high prevalence of internalizing psychiatric disorders (especially anxiety disorders) was found in children with CVS and their caregivers.[23]

There are no tests to diagnose CVS. The working team agreed with the clinical evaluation proposed in the NASPGHAN guidelines of CVS for children 2−18 years of age.[17] There is a higher likelihood of neurologic and metabolic diseases explaining the vomiting episodes in children with early onset of symptoms. Evaluation depends on the physician's confidence in making a symptom-based diagnosis and the likelihood of identifying an underlying condition.

The differential diagnosis of CVS includes GI, neurologic, urologic, metabolic, and endocrine conditions having similar presentations during at least part of their courses.[24] The NASPGHAN guideline recommends a basic metabolic profile (electrolytes, glucose, blood urea nitrogen, creatinine) in all patients before the administration of intravenous fluids, and upper GI series to exclude malrotation and anatomic obstructions. Because serious underlying metabolic and anatomic disorders must be considered in toddlers, the occurrence of CVS under the age of 2 years should prompt metabolic or neurologic and anatomical testing.

Treatment. Treatment goals are to reduce the frequency and severity of episodes, and establish a protocol for rescue therapy in home and hospital settings. Prevention is the goal in patients whose episodes are frequent, severe, and prolonged. Conditions that trigger episodes may be identified, and avoided and treated.[17] Prophylactic daily treatment with cyproheptadine or pizotifen in children younger than 5 years are the first-line drugs, but amitriptyline or propranolol have also been used. Erythromycin, which improves gastric emptying, as well as phenobarbital, have also been reported to be effective in the prevention of the attacks.[25] These medications succeed in reducing the frequency of, or eliminating, episodes in many children.[17]

Early in the episode it might be helpful to begin an oral acid-inhibiting drug agent to protect esophageal mucosa and

dental enamel, and lorazepam for its anxiolytic, sedative, and antiemetic effects. Intravenous fluids, electrolytes, and H_2-histamine receptor antagonists or proton pump inhibitors are administered until the episode is over. Complications arising during cyclic vomiting episodes include water and electrolyte deficits, hematemesis mostly due to prolapse gastropathy, peptic esophagitis and/or Mallory-Weiss tears, deficits in intracellular potassium and magnesium, hypertension, and inappropriate secretion of antidiuretic hormone.

G4. Infant Colic

Understanding infant colic requires an appreciation of the development of the infant, the dyadic relationship with the caregiver, and the family and social milieu in which they exist.[26] Infant colic has been described as a behavioral syndrome in 1- to 4-month-old infants involving long periods of crying and hard-to-soothe behavior. The crying bouts occur without obvious cause so that their unexplained nature is one of the main reasons for caregivers' concerns.[27] Prolonged crying is more likely to occur in the afternoon or evening and tends to resolve by 3 to 4 months of age or, in the case of babies born prematurely, 3 to 4 months after term.[28] On average, crying peaks at about 4–6 weeks and then steadily diminishes by 12 weeks.[29] Most cases of colic probably represent the upper end of the normal developmental "crying curve" of healthy infants and there is no proof that the crying in such cases is caused by pain in the abdomen or any other part of the infant's body. Nevertheless, caregivers often assume that the cause of crying is abdominal pain of GI origin. Despite the lack of proof that infant colic is caused by a functional GI disturbance, infants with colic are often referred to pediatric gastroenterologists. Familiarity with infant colic is therefore necessary to help families and to avoid diagnostic and therapeutic misadventures.

G4. Diagnostic Criteria for Infant Colic

For clinical purposes, must include all of the following:

1. An infant who is <5 months of age when the symptoms start and stop

2. Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers

3. No evidence of infant failure to thrive, fever, or illness

"Fussing" refers to intermittent distressed vocalization and has been defined as "[behavior] that is not quite crying but not awake and content either." Infants often fluctuate between crying and fussing, so that the 2 symptoms are difficult to distinguish in practice.

For clinical research purposes, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:

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1. Caregiver reports infant has cried or fussed for 3 or more hours per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician

2. Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept, 24-hour behavior diary

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Rationale for change in diagnostic criteria. The Rome III report included a version of the Wessel et al's "rule of threes" criteria, which stipulated that colic crying had to start and stop suddenly and occur for 3 or more hours/day for at least 3 days in a week.[30] Recent research has found that these criteria fail to meet the requirements for an effective clinical diagnostic scheme[31] because:

1. They are arbitrary. There is no evidence that infants who cry more than 3 hours per day are different from infants who cry 2 hours and 50 minutes per day.[32]

2. They are culturally dependent. Infants in some cultures cry more than in others.[33]

3. They are impractical to use. Caregivers are often reluctant to keep behavior diaries for 7 days.

4. The rule of threes focuses on crying amount, but the amount of crying has been found to distress caregivers less than its prolonged, hard-to-soothe, and unexplained nature.[34] The duration of unsoothable crying bouts was most strongly associated with caregiver reports of daily frustration, more so than the amounts infants cried.[34]

5. Few studies have assessed whether colic crying bouts start suddenly or sound abnormal, but the available evidence does not support this.[35,36]

Ultimately, criteria and methods that allow the infant behaviors involved in colic to be measured objectively are highly desirable.

Clinical evaluation. About 20% of infants are reported by caregivers to have the prolonged periods of crying known as colic.[37] However, the prevalence of infant colic is influenced by caregivers' perceptions of the intensity and duration of crying bouts,[37,38] the method by which data on crying are collected, the well being of the caregivers,[39] and culturally influenced infant care practices.[33]

In a study of all afebrile infants presented to a pediatric hospital over a year because of crying, irritability, colic, screaming, or fussiness, just 12 of 237 (5.1%) were found to have a serious underlying organic etiology.[40] Most of the infants with organic disease were visibly unwell on clinical examination and tests for urinary tract infections were recommended in such cases. Behaviors associated with colic (eg, prolonged crying, unsoothable crying, facial expressions appearing to show pain, abdominal distension, increased gas, flushing, and legs over the abdomen) are not diagnostic

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clues indicative of pain or organic disease, but they do help to explain caregivers' concerns.[30,41]

Time-limited therapeutic trials have been recommended to confirm possible etiologies of prolonged crying: elimination of cow's milk from the breastfeeding mother's diet or switching to a protein-hydrolysate formula if the infant is formula fed.[42] Elimination of cow's milk from the mother's diet remains controversial because there are no data on how often this is successfully implemented. Despite widespread use of treatments for gastroesophageal reflux to reduce infant crying, there is no evidence that GERD causes infants to cry, or and there is evidence that treatments for reflux are ineffective in reducing crying.[43]

The satiated infant's response to nonanalgesic, non-nutritive soothing maneuvers, such as rhythmic rocking and patting 1 to 3 times per second in a quiet, nonalerting environment, may quiet the baby who might nevertheless resume crying as soon as it is put down.[44] Demonstration that a common maneuver of this kind quiets the infant supports a diagnosis of colic as well as providing caregiver reassurance.

Treatment. In >90% of cases, treatment consists not of "curing the colic," but of helping the caregivers get through this challenging period in their baby's development.[45] Clinicians need to evaluate caregiver vulnerabilities, such as depression and lack of social support, and to provide continuing availability to the family.[30,46] Making an assessment of the infant's crying at the referral point can help to reassure caregivers and provide useful diagnostic information, particularly when this is combined with a discussion of normal babies' crying patterns. Prospectively kept logs of crying and other behavior, such as the Baby's Day Diary, are the most accurate and validated tools.[47] Questionnaire assessments, such as the Crying Patterns Questionnaire, are more subjective but easier for caregivers to complete with clinician support and sufficiently accurate for screening purposes.[48,49] These assessments can be obtained free of charge for clinical use from the original authors.[32,50]

There is recent evidence from several randomized controlled trials that particular probiotic supplements (eg, *Lactobacillus reuteri* DSM 17938) can reduce infant crying relative to controls.[51,52] However, no benefits were found in a recent large-scale fully blinded trial[47] and a systematic review of this evidence found an equal number of trials in which probiotic supplements had not ameliorated crying.[53]

If attempts to control a baby's crying are unsuccessful, anxiety and frustration may develop, leading to caregiver exhaustion.[54,55] This may be more likely when the caregiver relationship is unsupportive.[56] This stressful state can impair the caregiver's ability to soothe the infant and cause doubts about their competence as a caregiver.[56] The emergence of adversarial or alienated feelings toward the unsoothable infant lowers the threshold for "shaken baby syndrome" and other forms of abuse.[34] Infant colic may then present as a clinical emergency.

G5. Functional Diarrhea

Population-based studies show that the defecation frequency declines with age from a mean of 3.0 per day at 4 weeks to 1.3 per day at 4 years.[57,58] Defecation frequency is higher in breastfed infants compared with formula-fed infants, but there is no difference in stool frequency between preterm and term-born infants.[58–60] Breastfed infants usually have softer stools than formula-fed infants and they are more often yellow in color.[61] Approximately 97% of 1- to 4-year-old children pass stool 3 times daily to once every other day.[60,62] Many children are ready to start toilet training at the age of 21 to 36 months. Initiation of toilet training before the age of 27 months does not lead to earlier completion of toilet training, but it is also not associated with constipation, stool withholding, or stool toileting refusal.[63]

Functional diarrhea is defined by the daily painless recurrent passage of 3 or more large unformed stools for 4 or more weeks with onset in infancy or preschool years. There is no evidence of failure to thrive if the diet has adequate calories. The child appears unperturbed by the loose stools and the symptom resolves spontaneously by school age. Functional diarrhea has been called chronic nonspecific diarrhea, or toddler's diarrhea previously.

G5. Diagnostic Criteria for Functional Diarrhea

Must include all of the following:

1. Daily painless, recurrent passage of 4 or more large, unformed stools
2. Symptoms last more than 4 weeks
3. Onset between 6 and 60 months of age
4. No failure to thrive if caloric intake is adequate

Rationale for change in diagnostic criteria. In a US survey, 11.7% of the children (mean age 1.4 years; range, 0.4–3 years) were reported by their caregivers as having 3 stools per day. Twenty-seven percent of the children had very soft stools, 4.5% had watery stools, 1.5% had undigested food in the stools, and 22.1% started after 6 months of age.[3] Based on these data, the committee decided to increase the number of stools from 3 to 4 stools per day. Furthermore, about 25% of mothers reported that their young children pass stools when asleep, so this criterion is no longer required because of its low specificity.

Clinical evaluation. Functional diarrhea is the leading cause of chronic diarrhea in an otherwise well child. According to the Rome III criteria, 2.4% of infants <1 year and 6.4% of toddlers aged 1–3 years presented with functional diarrhea.[3]

Small intestinal transport is not defective in children with functional diarrhea. Water and electrolyte secretion and glucose absorption are normal and steatorrhea is absent.[64] Nutritional factors are reported to play key roles in the pathogenesis of toddler's diarrhea. Overfeeding, excessive fruit juice consumption, excessive carbohydrate (fructose) ingestion with low fat intake, and excessive sorbitol intake have been reported in children with functional diarrhea.[65,66] In patients with functional diarrhea, food fails

to interrupt the fasting migrating motor complex (MMC), so there is a lack of postprandial motility in the small intestine.[67]

The evaluation of children with chronic diarrhea includes identifying factors that may cause or exacerbate diarrhea, such as past enteric infections, laxatives, antibiotics, or diet. In toddlers with functional diarrhea, typical stools contain mucus and/or visible undigested food. Often stools become less solid with each bowel movement during the day. The physical examination focuses on height, weight, and signs of malnutrition, diaper rash, and fecal impaction.

In children fulfilling the criteria for functional diarrhea, a malabsorption syndrome would be unexpected. Chronic diarrhea as the sole symptom in a thriving child makes cystic fibrosis and celiac disease unlikely.

Treatment. No medical interventions are necessary, but an evaluation of fruit juices and fructose intake with subsequent dietary advice to normalize and balance the child's diet is recommended. Furthermore, effective reassurance of the caregivers is of paramount importance. A daily diet and defecation diary helps to reassure caregivers that specific dietary items are not responsible for the symptom. Many families accept effective reassurance readily. The morbidity associated with functional diarrhea may be related to the caloric deprivation caused by the misuse of elimination diets.[68] This can be related to an anxious caregiver's inability to accept the functional diarrhea diagnosis, or a clinician's attempt to assuage the caregiver's anxiety.

G6. Infant Dyschezia

Infants with dyschezia strain for many minutes, scream, cry, and turn red or purple in the face with each effort to defecate. The symptoms usually persist for 10−20 minutes. Stool passes several times daily. In the majority of infants, the symptoms begin in the first months of life, and resolve spontaneously in the majority of children after 3−4 weeks.

G6. Diagnostic Criteria for Infant Dyschezia

Must include in an infant <9 months of age:

1. At least 10 minutes of straining and crying before successful or unsuccessful passage of soft stools

2. No other health problems

Justification for changes in diagnostic criteria. The age that infant dyschezia can still be present has been changed from 6 to 9 months based on a recent prospective study.[69] The unsuccessful attempt to defecate was added to the criteria based on this study, which found that caregivers reported other defecation-related symptoms, especially extreme reddening of the face and straining without subsequent defecation.

Clinical evaluation. A population based study in the Netherlands showed that at the age of 1 and 3 months, dyschezia was present in 3.9% and 0.9% of the infants, respectively. At the age of 9 months, the symptoms of

another 0.9% were consistent with a diagnosis of dyschezia.[69] A recent questionnaire-based study of 1447 mothers showed a prevalence of 2.4% in the first year of life.[3]

Failure to coordinate increased intra-abdominal pressure with relaxation of the pelvic floor results in infant dyschezia.[30] The examiner performs a history including diet; conducts a physical examination, including rectal examination, to exclude anorectal abnormalities; and charts the infant's growth.

Treatment. The child's caregivers require effective reassurance to address their concerns that their child is in pain and that there is no pathologic disease process that requires intervention in their infant.

Parents usually accept the explanation that the child needs to learn to relax the pelvic floor at the same time as bearing down. To encourage the infant's defecation learning, the caregivers are advised to avoid rectal stimulation, which produces artificial sensory experiences that might be noxious, or that might condition the child to wait for stimulation before defecating. Laxatives are unnecessary.

G7. Functional Constipation

Functional constipation (FC) is often the result of repeated attempts of voluntary withholding of feces by a child who tries to avoid unpleasant defecation because of fears associated with evacuation.[70] Withholding behavior leads to stool retention that leads the colon to absorb more water, creating hard stools. In the first years of life, an acute episode of constipation due to a change in diet may lead to the passage of dry and hard stools, which may cause painful defecation. In toddlers, the onset of constipation may coincide with toilet training, when excessive caregiver pressure to maintain bowel control and/or inappropriate techniques, such as the use of regular toilets that do not allow sufficient leg support, can lead to stool withholding.

G7. Diagnostic Criteria for Functional Constipation

Must include 1 month of at least 2 of the following in infants up to 4 years of age:

1. 2 or fewer defecations per week

2. History of excessive stool retention

3. History of painful or hard bowel movements

4. History of large-diameter stools

5. Presence of a large fecal mass in the rectum

In toilet-trained children, the following additional criteria may be used:

6. At least 1 episode/week of incontinence after the acquisition of toileting skills

7. History of large-diameter stools that may obstruct the toilet

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Rationale for change in diagnostic criteria. The change in criteria to differentiate between toilet-trained or not toilet-trained children is based on data suggesting that the majority of toddlers younger than 2.5 years are not toilet trained.[63,71] In addition, recognition of fecal incontinence in infants and toddlers wearing diapers is unreliable.

Clinical evaluation. The prevalence of constipation in the first year of life is 2.9% and increases to 10.1% in the second year of life, with no difference between boys and girls.[72,73] A cohort study from Brazil reported a constipation prevalence of 27% at the age of 24 months.[74]

The presentation of functional constipation (FC) in infants and toddlers varies. Only a minority of infants with FC defecates <3 times/week and exhibit bloody stools.[75] These infants have hard stools >90% of the time and almost half of them may exhibit pain during defecation, stool withholding behavior, and rectal impaction. Eighty-six percent of the toddlers with FC have either 2 bowel movements weekly or hard, painful bowel movements and at least one of the other Rome III criteria for functional constipation.[76] Fecal incontinence more than once per week is the most common symptom found in these children.

FC is a clinical diagnosis that can be made on the basis of a typical history and physical examination. Withholding behavior may lead to the passage of large stools, which can cause anal fissures, especially in the first 2 years. The painful evacuation of a fecal mass often leads a terrified child to try to avoid further bowel movements. Blood in the stools alarms caregivers, but does not cause clinically important blood loss. Fecal incontinence (involuntary passage of fecal material) can occur in toddlers who accumulate a large rectal fecal mass. Loose stool that accumulates around the fecal mass may be involuntary extruded as the infant passes gas. Physical examination provides reassurance to the clinician and caregivers that there is no disease. The physical examination includes assessing the size of the rectal fecal mass, which is judged for height above the pelvic brim with bimanual palpation on either side of the rectus sheath. When the history is typical for FC, the perineum should be inspected, but a digital rectal examination may not be necessary until a treatment trial fails, there is uncertainty in the diagnosis, or there is suspicion of an anatomic problem.

The differential diagnosis of constipation in infancy includes anatomic obstructions, Hirschsprung's disease, spinal problems, and other metabolic and neuroenteric abnormalities. More than 90% of healthy term infants and <10% of infants with Hirschsprung's disease pass their first meconium before 24 hours of life.[58,77] Therefore, a rectal suction biopsy is necessary in an infant with delayed passage of meconium by 24 hours who has accompanying symptoms (vomiting, food refusal, abdominal distension, fever, failure to thrive, blood in stool) to rule out Hirschsprung's disease.[78] Another rare defecation disorder is internal anal sphincter achalasia, but in contrast to Hirschsprung's disease, ganglion cells are present in rectal suction biopsies but the rectoanal inhibitory reflex is absent.[79]

Treatment. In infants, symptoms improve with early intervention. The shorter time that the symptoms persist, the higher likelihood of treatment success.[80] Education for caregivers and the child is the first step in treatment.[70] The child and family appreciate a clinician who thoroughly assesses the history and physical examination, then explains the evolution of the problem, the absence of worrisome disease, and safe and effective management. The clinician addresses the myths and fears by sharing information: The child has FC, one of the most common problems in pediatrics; FC is not dangerous and it resolves when the child gains confidence and trusts that defecation will not cause pain; for toddlers, toilet training will not proceed smoothly until the child's fear of painful defecation resolves; caregivers who are anxious must understand that coercive toilet training tactics are likely to backfire into a struggle for control.

Recently, evidence-based recommendations for the treatment of FC have been made by the European Society of Pediatric Gastroenterology Hepatology and Nutrition/NASPGHAN.[70] Treatments that soften stools and assure painless defecation are an important part of the treatment. To date, however, large well-designed randomized clinical trials evaluating the effect of any dietary supplement or laxative in infants and toddlers with FC are still lacking. The key to effective maintenance is assuring painless defecation until the child is comfortable and acquisition of toilet learning is complete. For the maintenance phase of treatment, stool softeners are continued for months to years.

There is limited published information on the treatment of infant constipation with probiotics.[81,82]

Inconsistent data exist about the role of cow's milk protein allergy in FC. Iacono et al[83] were the first to show that 78% of children affected by constipation and cow's milk protein allergy improved after cow's milk protein elimination diet. In contrast, others were not able to confirm this association in patients affected by chronic constipation.[84] However, a history of cow's milk allergy in the first year of life was associated with FC in childhood (odds ratio = 1.57; 95% confidence interval: 1.04−2.36).[85] The recent published guideline on FC suggests consideration of a 2- to 4-week trial of hypoallergenic formula in those infants and toddlers in whom laxative treatment failed.[70]

Most experts favor a daily nonstimulant laxative, such as polyethylene glycol, lactulose, or milk of magnesia, which slowly softens the mass until the child chooses to pass it days or weeks later.[70] The goal of stool softening is to assure painless defecation until FC resolves. For preschool children, behavior modification utilizing rewards for successes in toilet learning is often helpful. A child can earn "stars" for a chart with each successful defecatory effort.

II. Neurobiology of Pain in Infants and Toddlers

Because pain is a complex symptom often associated with FGIDs, an understanding of the neurodevelopment of nociception and of the wide array of factors that may impact the pain experience, and an appreciation for pain

assessment in infants and toddlers is important for the clinician addressing functional pain in children. The model that most individuals use to understand pain is that of acute pain in which the pain functions as a signal of anatomic or biochemical pathology. The underlying assumption is that if the pathology is addressed, the pain will dissipate. This model is simplistic because it does not account for the various elements that contribute to the interpretation and response to nociceptive information. The acute pain model is inappropriate in addressing functional pain, in which the pain does not serve a warning function, but is itself the illness (Figure 2).

Development of Nociceptive and Pain Pathways

Data from neonatal animals and human infants suggest that preterm infants have nociceptive systems in place at birth.[86] Cutaneous innervation is already present at 8 weeks of gestational age, afferent synapses to the spinal cord by 10 weeks, and lamination in the spinal cord by 15 weeks. By 20 weeks, there is reflex motor withdrawal to a noxious stimulus. Thalamo-cortical projections are present by 24 weeks and somatosensory evoked potentials after cutaneous stimulation are present by 29 weeks gestational age. Nociceptive circuitry is functional by 30 weeks gestation. Recent work measuring cortical hemodynamic activity in the somatosensory cortex suggests that by 24 weeks, the impact of a noxious stimulus is identifiable in the brain.[87] Infants have a lower pain threshold that increases with age and, as a result, they may respond to routine handling, such as diaper changes, similarly to invasive procedures. Additionally, they lack descending inhibitory control, a key element in modulating the pain experience, and therefore lack the ability to put the pain experience in perspective. It appears, therefore, that not only are preterm and term infants capable of cortical level pain processing, but they may experience painful stimuli differently and more intensely then others.[88]

The fact that infants experience pain is evident in their immediate response to noxious stimuli. Preterm and term infants display measurable physiologic responses, such as increased heart rate, respiratory rate, blood pressure, and decreased oxygen saturation. They produce cortisol and stress hormones in response to pain. They also display distinct behavioral responses to noxious stimuli, such as specific facial expressions and patterns of movement.[89]

Another important consideration is the long-term impact of pain in the newborn and its relationship to the subsequent development of altered pain perception, particularly as it relates to functional abdominal pain. Infants and toddlers exposed to painful events, such as early surgery, may be predisposed to visceral hyperalgesia.[90,91] There are a number of studies that have examined the impact of early painful procedures/neonatal intensive care unit admission on the subsequent development of chronic abdominal pain. It appears that pyloric stenosis or allergic colitis may predispose infants to development of chronic abdominal pain.[92]

In addition to physical trauma, Barreau et al,[93] attempting to identify the impact of emotional trauma, demonstrated that neonatal maternal deprivation in rodents triggered changes in the colonic epithelial barrier and mucosal immunity.

Pain Assessment in Infants and Toddlers

In adults and older children who are intellectually intact, self-report of pain is the gold standard. Typically, a numeric rating scale in which pain can be quantified is used.[94] This addresses pain intensity only, and not the quality of the pain, but is often the cornerstone of clinical pain care. For children aged between 3 and 8 years,
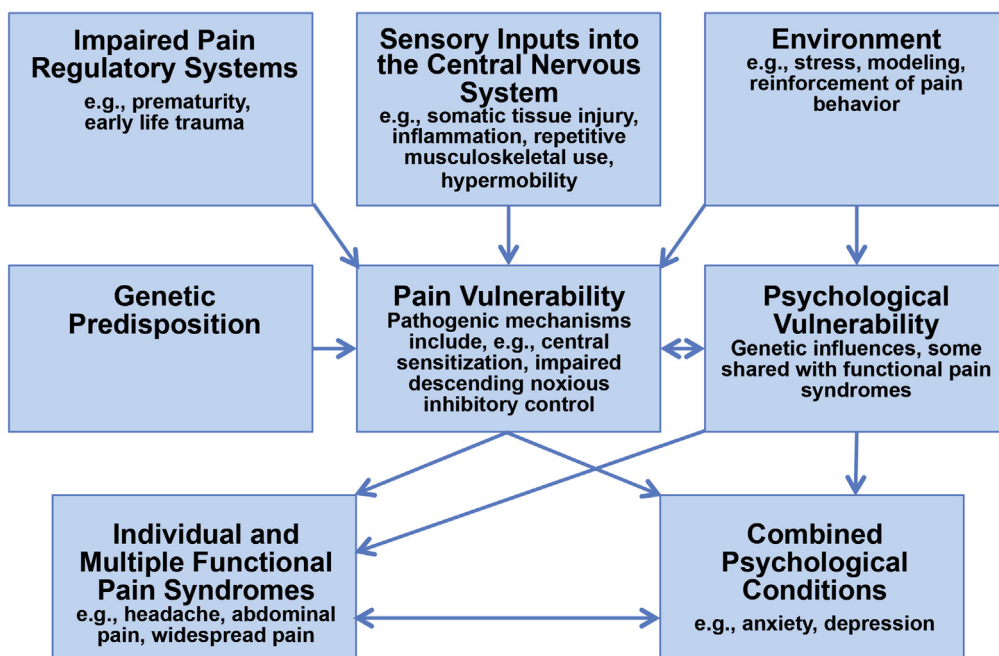

Figure 2. Proposed pathophysiology of functional pain. From von Baeyer and Champion,[95] adapted with permission.

modifications of the numeric rating scale are often used. These are typically cartoon faces of individuals in pain. They require the child to have the intellectual sophistication to appreciate differences in size and apply them to internal sensations.

Infants and most toddlers do not have that capability, however. Although caregivers may play a vital role in conveying their perception of the child's level of discomfort, it is helpful as well to have techniques that may allow us proxies for direct verbal reporting from the child. A number of techniques have been developed to serve in that capacity. These include evaluation of various behaviors associated with pain (facial action, body movement, cry, consolability) and physiological indicators (heart rate, blood pressure, oxygen saturation, galvanic skin response measurements). Individually, these markers lack specificity, but a number of composite measures that link together various elements have become the standard of care in managing acute pain in infants and young children.

More recently, investigators have used near infrared spectroscopy and somatosensory evoked potentials in an attempt to intuit a "pain signature." Slater et al[87] compared the results of a behavioral pain assessment (Preterm Infant Pain Profile) with near-infrared spectroscopy in a group of preterm babies undergoing heel stick. They reported that almost one-third of the babies demonstrated evidence of a cortical hemodynamic response without evidence of a behavioral response. As a result, they suggested that the typically used instruments to clinically assess newborn pain may be inaccurate.

Even more complicated than the assessment of acute pain in newborns is the measurement of chronic pain in which many of the expected behaviors may not be present. Currently, however, there is no instrument available for infants and toddlers to assess chronic pain. The challenges around chronic pain assessment in young children further complicate our attempt to identify and categorize pain-predominant functional disorders in this vulnerable population.

Recommendations for Future Research

1. Epidemiological cross-cultural studies are needed to ascertain the impact on quality of life, and medical consultation across cultures.

2. Pathophysiology in the majority of FGIDs in young children is still poorly understood and multicenter prospective genetic, metabolic, and neurophysiologic characterizations of large numbers of patients are needed.

3. Among key questions for research is what the primary outcome measures should be for trials that seek to resolve it.

4. Validated measures, especially for infant crying and pain assessment, are needed. These will help to clarify the relationship between colic and pain and to distinguish the specific infant behaviors underlying caregiver's perceptions of infant colic.

5. Prospective studies are needed to show the efficacy of different diets in infants and toddlers with FGIDs.

6. Studies to show that anticipatory guidance and efforts to intervene at the pediatrician office will have an impact are required.

7. Recent limited information has suggested that there is a possibility that other, not as well-defined, functional GI problems in neonates and toddlers may need to be considered, particularly those related to feeding disorders.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.02.016.

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