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Lower and Biliary Disorders of Gut–Brain Interaction: Child and Adolescent

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Rome V provides updated criteria for pediatric disorders of gut–brain interaction, replacing age-based subdivisions with a classification based on the following regions and symptom patterns: abdominal pain disorders, defecation and anorectal disorders, and discomfort disorders. New entities were introduced, including biliary pain syndrome, centrally mediated abdominal pain syndrome, functional abdominal bloating, and proctalgia fugax. The term "infantile colic" has been replaced with "infant distress syndrome." Existing criteria for irritable bowel syndrome, functional constipation, and nonretentive fecal incontinence were revised to improve diagnostic clarity and reflect current clinical understanding. Rome V also acknowledges that disorders of gut–brain interaction may coexist with other conditions producing gastrointestinal symptoms. These updates are intended to support a more consistent diagnostic framework and guide appropriate management strategies for children and adolescents.

Keywords: Children; Adolescents; Disorders of Gut–Brain Interaction.

In this fifth iteration, the Rome V Pediatric Committees decided to depart from the age-based divisions used in Rome IV. This aligns with emerging evidence that links disorders of gut-brain interaction (DGBI) to regions and the fact that some of them may be present throughout childhood and adolescence. To facilitate conceptualization, the Lower Gastrointestinal (GI) and Biliary Disorders Committee carved out 3 distinctive groups of GI disorders: abdominal pain disorders, defecation and anorectal disorders, and discomfort disorders, as delineated in Figure 1.

Collaboratively, with the Pediatric Upper GI Committee, a strategic decision was made to include functional dyspepsia (including epigastric pain syndrome) in the upper GI chapter. This was rooted in the recognition that most of its symptoms, such as nausea and vomiting, seemingly find their origin in the upper GI tract. The Committee decided to include several new diagnostic entities within the Rome V criteria. They include biliary pain syndrome, centrally mediated abdominal pain syndrome (CAPS), proctalgia fugax (PF), and functional abdominal bloating. The Committee believes these disorders occur in children and without clear diagnostic criteria there could be unacceptable delay in diagnosis and use of inappropriate therapeutic modalities to address such conditions. It was also decided to rename "infantile colic" to "infant distress syndrome" (IDS).

H1a. Irritable Bowel Syndrome

Epidemiology

Worldwide irritable bowel syndrome (IBS) prevalence has been estimated to range from 1.9% to 10.4%.[1,2] A recent systematic review identified an overall pediatric IBS worldwide prevalence of 3% (95% CI, 2%–4%).[3] No studies have described IBS in children younger than 6 years, thus the Rome V Committee recommended 6 years as the minimum age for diagnosis.

Pediatric Irritable Bowel Syndrome Subtypes

Pediatric IBS subtype prevalence varies based on the study population. In a US-based study, subtypes were IBS-constipation (IBS-C; 48%), IBS-unclassified (40%), IBS-diarrhea (IBS-D; 8%), and IBS-mixed (IBS-M; 4%).[4] In a Sri Lankan study, the subtypes IBS-C, IBS-D, and IBS-M were almost equally distributed (27%–28%), with

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Abbreviations used in this paper: **AM, abdominal migraine; APS-NOS, abdominal pain syndrome–not otherwise specified; CAPS, centrally mediated abdominal pain syndrome; CBT, cognitive behavioral therapy; DGBI, disorders of gut–brain interaction; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; FC, functional constipation; FDr, functional diarrhea; FODMAP, fermentable, oligosaccharide, disaccharide, monosaccharide, and polyol; GB, gallbladder; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome-constipation; IBS-D, irritable bowel syndrome-diarrhea; IBS-M, irritable bowel syndrome-mixed; IDS, infant distress syndrome; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NRFI, nonretentive fecal incontinence; PENFS, percutaneous electrical nerve field stimulation; PF, proctalgia fugax; RCT, randomized controlled trial.**

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H1a. Diagnostic Criteria[a] for Irritable Bowel Syndrome

Must include *all* the following:

1. Intermittent abdominal pain on average of at least 4 days per month associated with 1 or more of the following:
   a. Related to defecation (ie, worsening or amelioration of)
   b. A change in frequency of stool
   c. A change in form (appearance) of stool
2. Abdominal pain is the predominant symptom[b]
3. After appropriate evaluation, the symptoms cannot be fully explained by other medical conditions

[a]Criteria fulfilled for at least 2 months before diagnosis.
[b]Pain should not occur solely during menses.

Table 1. Irritable Bowel Syndrome Subtypes[a]

IBS subtype	Definition
IBS-C	≥1/4 (25%) of abnormal stools type 1 or 2 and ≤25% of bowel movements with Bristol stool types 6 or 7.
IBS-D	≥1/4 (25%) of abnormal stools type 6 or 7 and ≤25% of bowel movements with Bristol stool types 1 or 2.
IBS-M	≥1/4 (25%) of abnormal stools type 1 or 2 and ≥1/4 (25%) of abnormal stools type 6 or 7
IBS unclassified	<1/4 (25%) of stools hard or lumpy with bowel movements with stool type 1 or 2 and <1/4 (25%) of bowel movements with stool type 6 or 7

[a]IBS subtypes defined according to the proportion of abnormal stool forms based on the Bristol Stool Form Scale.

IBS-M having the lowest prevalence (17.8%).[5] An Italian study reported that pediatric IBS subtypes changed in 24% over 12 months.[6]

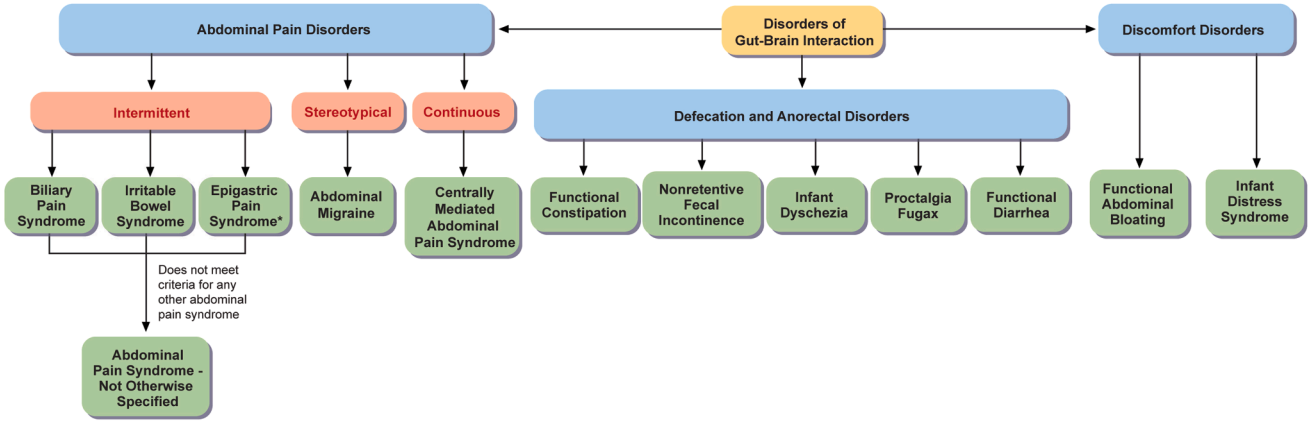
Justification for Changes in Criteria

In Rome IV, for those children with constipation, there was an attempt to differentiate functional constipation (FC) from IBS by first attempting to treat constipation.[7] However, the Rome V Committee felt that the type, dosing, and length of intervention for the treatment of FC and the amount of change in pain severity required were not well specified. Instead, the Rome V Committee proposes a shift akin to that described in the adult IBS criteria, with a focus on the predominant symptom of abdominal pain as the differentiating factor between IBS-C and FC.

Defining subtypes of IBS may help identify pathophysiological factors and tailor treatments. The subtype classification is in parallel to that used in the Rome V adult IBS diagnostic criteria (Table 1). The Committee also decided to add as exclusion criteria for cases that the pain occur solely during the menses based on 2 recent survey studies (still unpublished) that found a subset of children meeting Rome IV Criteria for IBS had pain and changes in bowel movement exclusively during menses. This is thought to be dysmenorrhea mimicking the diagnosis of IBS.

Pathophysiology

A systematic review of risk factors for abdominal pain syndromes included female sex, gastroenteritis, trauma and abuse, lifetime stress, psychological disorders, somatic symptoms, and poor sleep.[8] Having a parent with IBS was also identified as a risk factor.[9] Twin studies have found greater IBS concordance in monozygotic (17.2%–22.4%) vs dizygotic (8.4%–9.1%) twins.[10,11]



*Epigastric pain syndrome is a subtype of functional dyspepsia.

Figure 1. New classification of pediatric DGBI of the lower gastrointestinal tract. Overview of the current classification framework for pediatric DGBI on affecting the lower gastrointestinal tract.

Early life events are associated with an increased likelihood of developing pain-predominant DGBI. These include low birth weight, neonatal gastric suction, early use of antibiotics, pyloric stenosis, cow's milk protein allergy, umbilical hernia repair, and urinary tract infection.[12–17] Early childhood adverse life events such as general trauma, physical punishment, and abuse are associated with IBS.[18–21] Early life events have been found to contribute to the development of visceral hyperalgesia, primarily through preclinical models.[22]

Using rectal barostat, studies have identified that children with IBS have a lower rectal sensory threshold than controls or with other DGBI and may even have rectal distention–induced sensation that projects to other body sites (ie, a somatic referral).[23,24]

Children with IBS have been found to have increased gut permeability.[25] Using both fecal markers (ie, fecal calprotectin, fecal β-defensin-2, and fecal granins) and evaluation of mucosal biopsies, children with IBS (vs controls) were found to have increased low-grade gut inflammation.[26,27] Some but not all pediatric IBS studies have identified increased mast cells in the GI tract.[28,29]

Studies of cohorts composed primarily of those with IBS-C showed an increase in γ-proteobacteria.[30,31] Children with pain-predominant DGBI have decreased α-diversity, different β-diversity, and increased bacteria within the phylum Bacteroidetes than controls.[32] In a small cohort of children with IBS, *Flavonifractor plautii* and *Lachnospiraceae bacterium 7_1_58FAA* were associated with increased IBS abdominal pain severity.[31] Children with IBS had an increased amount of fecal steroid/sterol and bile acid metabolites compared with controls.[31]

Children with IBS may have decreased antral contraction amplitudes, slower liquid meal emptying, and may lack meal-induced decreases in rectal volume.[24,33]

More than 90% of children and adolescents with IBS identify at least 1 food that exacerbates their GI symptoms.[34,35] Fermentable, oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) carbohydrates include fructose, lactose, fructans, galactans, and polyols. FODMAPs may worsen symptoms in a subset of children with IBS.[36] The data currently do not support gluten sensitivity as a significant factor.[37]

Clinical Evaluation

Testing for celiac disease is recommended in those with IBS-D based on limited data in children with chronic abdominal pain that have suggested a higher prevalence of celiac disease in some but not all pediatric studies.[38–40] Parasitic testing should be considered based on the local context. Fecal calprotectin level is used as a screen for intestinal inflammation. In children with IBS-D there is a need to consider the possibility of carbohydrate malabsorption and assess for dietary triggers due to the increased prevalence of sucrase-isomaltase gene variants in children with chronic diarrhea.[41] In a subset of children with IBS and loose stools, bile acid malabsorption has been identified as a contributing factor.[42]

Psychological Features

Studies have reported the association between abdominal pain–related DGBI and clinically evident as well as subclinical anxiety and depression.[43–47] Anxiety and depression are as likely to follow as to precede pain[48] and are not the main factors influencing pain outcomes.[49–51] Rather than general anxiety or depression, GI-specific anxiety, cognitions, somatization, and avoidance behaviors such as pain catastrophizing[49,50] are the most important predictors of outcomes in children with abdominal pain.[52] There is also evidence that parental psychological factors play an important role.[53] In addition to pain, children with IBS can present other symptoms (eg, distention and bloating) that may have a psychological impact. Children with IBS may have increased school absenteeism, sleep disturbances, multisite pain, and functional disability.[54,55]

Treatment

Ideally, treatment should be tailored to the identified pathophysiological mechanisms, clinical presentation, and psychosocial circumstances.

Hypnotherapy and cognitive behavioral therapy. Randomized controlled trials (RCTs) have identified both short- and long-term benefits of hypnotherapy up to almost 5 years later.[56] In RCTs including children with IBS, cognitive behavioral therapy (CBT) was found to improve GI symptoms and quality of life for up to at least 1 year.[57] Other types of behavioral therapies (eg, meditation and yoga) can be useful in clinical practice but currently lack RCT evidence.

Percutaneous electrical nerve field stimulation (PENFS) is superior to sham intervention in decreasing abdominal pain.[58] This led to the US Food and Drug Administration approving this intervention for the treatment of IBS in children.[59]

Dietary interventions. The majority of lactose challenge RCTs in children with abdominal pain–predominant DGBI do not support the role of lactose as the trigger of the child's symptoms.[60] A single RCT found greater pain improvement with a 2-week fructose restriction.[61] Some RCTs have identified that a low-FODMAP diet ameliorates GI symptoms in children with IBS and DGBI.[62,63] If recommended, this diet should be implemented in the following 3 phases: restriction (no more than 4–6 weeks), reintroduction, and personalization.[64] Given concerns for abnormal eating behaviors and the potential occurrence of avoidant and restrictive food intake disorders, it is strongly recommended that a dietitian be involved in any restriction diet and that liberalization of the restriction be instrumented when possible.[65]

Probiotics. RCT data are available to support using certain probiotics, such as *Lactobacillus rhamnosus* GG, for pediatric IBS.[66–68]

Peppermint oil. A randomized, placebo-controlled trial in children with IBS identified that enteric-coated peppermint oil decreased abdominal pain severity.[69]

Psyllium. Two RCTs in children with IBS have reported that psyllium (vs placebo) is superior in ameliorating symptoms.[70,71]

Pharmacologic interventions. Despite the lack of RCT evidence, antispasmodics are often used in clinical practice for the treatment of children with IBS. A small RCT of children with functional abdominal pain compared cyproheptadine with placebo for 2 weeks and found that a greater number of children receiving cyproheptadine achieved complete resolution of pain.[72] There is contradictory data on amitriptyline.

Amitriptyline was significantly better than placebo in improving quality of life and right lower quadrant pain in female adolescents with IBS.[73] However, a multicenter RCT of children with abdominal pain–predominant DGBI, most of them with IBS, found no difference between amitriptyline and placebo after 4 weeks of treatment.[74] A double-blind clinical trial did not find superiority of rifaximin compared with placebo in the treatment of IBS.[75] The placebo effect is well recognized in pediatric IBS treatment trials. A multicenter crossover RCT found greater pain reduction with open-label placebo compared with hyoscyamine on an as-needed basis.[76] The importance of drug labeling in treatment success was demonstrated in a mebeverine trial.[77]

In clinical practice, medications such as loperamide and bile acid sequestrants are sometimes used to treat children with IBS-D, as they prolong transit time and reduce stool volume.[78,79] Osmotic laxatives (eg, polyethylene glycol)[80] and stimulant laxatives (eg, sennosides and bisacodyl) are considered first-line, and secretagogues (eg, linaclotide) are often used in the treatment of children with IBS-C.[81] In severe cases, multidisciplinary pain-treatment programs for children with DGBI have shown reductions in pain, improvement in functioning, and lower acute health care utilization.[82,83]

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) conducted a comprehensive review of the literature and published treatment guidelines for IBS and functional abdominal pain–not otherwise specified (FAP-NOS).[81] CBT and hypnotherapy were recommended as first-line treatments. PENFS, strain-specific probiotics, enteric-coated peppermint oil capsules, and soluble fiber (psyllium) (only for IBS) were suggested as possible treatments. Antispasmodics (eg, mebeverine and drotaverine) and antibiotics such as rifaximin were not suggested. Amitriptyline and cyproheptadine could be considered in selected cases. Restrictive diets including low-FODMAP were not suggested.[68] Specific treatments for constipation or diarrhea are recommended for specific IBS subtypes.

H1b. Abdominal Pain Syndrome–Not Otherwise Specified

Epidemiology

A recent meta-analysis reported that 1.2% of children and adolescents worldwide experience FAP-NOS, now referred to as abdominal pain syndrome–not otherwise specified (APS-NOS).[84]

H1b. Diagnostic Criteria[a] for Abdominal Pain Syndrome–Not Otherwise Specified

Must be fulfilled an average of at least 4 days per month and include *all* of the following:

1. Intermittent abdominal pain that does not occur solely during meals, defecation, or menses.
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, abdominal migraine, or biliary pain syndrome.
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition.

[a]Criteria fulfilled for at least 2 months before diagnosis.

Justification for Changes in Criteria

The committee revised the criteria to differentiate intermittent pain (APS-NOS) from constant pain (CAPS) and specified that pain in APS-NOS should not be exclusively associated with meals, menses, or bowel movements.

Pathophysiology

The pathophysiology of this disorder is multifactorial, involving psychological stress,[85,86] early life adverse events (such as trauma and medical or surgical interventions).[13,87] These and possibly other factors interact and result in abnormal brain–gut interactions,[88] visceral hypersensitivity,[89] abnormal GI motility,[90] impaired intestinal barrier function,[91] and changes in the intestinal microbiome.[32,92]

Clinical Evaluation

The history should include the type, frequency, and location of the pain, bowel habits, associated symptoms, and potential risk factors. Physical examination needs to be thorough to exclude organic causes. Although extensive testing is rarely required, investigations such as bloodwork and stool studies to screen for inflammatory diseases and celiac disease may be considered.

Psychological Features

The psychological profile of children with APS-NOS and IBS are often similar (see Irritable Bowel Syndrome section).[93]

Treatment

Therapeutic interventions include pharmacologic and nonpharmacologic approaches. Despite the lack of evidence to support the use of antispasmodics, they are frequently used for the treatment of APS-NOS. Mild cases may respond to peppermint oil.[68,69] Tricyclic antidepressants have also shown benefit in some studies,[94] along with other agents, such as cyproheptadine, domperidone,

and probiotics.[80] Among nonpharmacologic strategies, hypnotherapy, CBT,[95–97] and PENFS[98] have demonstrated efficacy. The ESPGHAN-NASPGHAN guidelines for treatment of IBS and FAP-NOS provide a strong recommendationfor CBT and hypnotherapy, and a conditional recommendation for PENFS.[68]

H1c. Biliary Pain Syndrome

Epidemiology

Most of the published pediatric literature refers to the term "biliary dyskinesia." A systematic review by Santucci et al[99] included 1833 children and adolescents with biliary dyskinesia. In 2019, Cairo and colleagues[100] conducted the largest multicenter study in North America, involving 16 institutions, and 678 patients were diagnosed with biliary dyskinesia and 78.2% were female.

Justification of Inclusion Into Pediatric Rome Criteria

Functional gallbladder (GB) and sphincter of Oddi disorders are controversial and previously only included in adult Rome criteria.[101,102] Pediatric literature is scarce, based mostly on biliary dyskinesia, with retrospective studies lacking standardized definitions[103] but reporting a rise in cholecystectomies. This gap led to the development of the first pediatric criteria on biliary-type abdominal pain. Due to limited data, these were adapted from adult criteria.[104] A key difference is the requirement for pain to be in the right upper quadrant with or without epigastric pain, helping distinguish it from functional dyspepsia.[99]

H1c. Diagnostic Criteria[a] for Biliary Pain Syndrome

Must include *all* the following:

1. Pain in the right upper quadrant with or without epigastric pain occurring on average at least 4 days per month, with all the following characteristics:
   a. Acute onset, lasting at least 30 minutes and up to several hours
   b. Episodic, with varying intervals between attacks
   c. Severe enough to lead to acute medical evaluation
2. Symptoms do not meet criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. Absence of gallstones or other structural gallbladder or biliary tract pathology
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Supportive criteria

1. Normal liver enzymes, conjugated bilirubin, and pancreatic enzymes during or within a few days of the episodes
2. Nausea and vomiting
3. Pain radiates to the back and/or right shoulder blade
4. Pain occurs postprandially
5. Pain awakens the patient from sleep

[a]Criteria fulfilled for at least 2 months before diagnosis.

Clinical Evaluation

A clinical history covering pain location, severity, frequency, and relation to meals and bowel habits is crucial to differentiate biliary pain syndrome from other pain-related DGBI. When the pain radiates to the epigastrium, an upper GI endoscopy may be performed at the physician's discretion. Once the suspicion of biliary pain has been raised, GB stones need to be excluded by GB and biliary tree ultrasound, complemented with magnetic resonance cholangiopancreatography. Blood tests should evaluate liver function, but GB ejection fraction studies are not recommended for diagnosis.

Treatment

Most literature focuses on the outcomes after surgical treatment, and the use of nonmedical therapies has not been emphasized (eg, antispasmodics, ursodeoxycholic acid, and neuromodulators). However, the rationale for surgery is questioned due to poor diagnostic clarity, unreliable GB ejection fraction and widely heterogeneous success rates ranging from 34% to 100%.[99] In addition, biliary dyskinesia may resolve spontaneously, with conservative treatment often showing equivalent or better outcomes than cholecystectomy in long-term follow-up.[104] Therefore, cholecystectomy should be considered only when other nonsurgical treatments have been appropriately trialed and have failed to improve symptoms. Even then, the use of surgery needs to be carefully reviewed, and patients and their families should be appropriately counseled regarding the possibility that surgery may not alleviate symptoms or may exacerbate symptoms or result in complications.

H1d. Abdominal Migraine

Epidemiology

Data suggest an abdominal migraine (AM) prevalence of approximately 1% per Rome IV Criteria,[8,105] with symptom onset at 7–8 years and being more common in girls.[106,107]

Justification for Changes in Criteria

The Rome V Diagnostic Criteria for AM remain unchanged from Rome IV. Similarly to Rome IV, the current criteria underscore that in cases of overlapping symptoms with cyclic vomiting syndrome, the predominant and most bothersome symptom will guide the primary diagnosis.

H1d. Diagnostic Criteria[a] for Abdominal Migraine

Must include *all* the following occurring at least twice:

1. Paroxysmal episodes of intense and acute periumbilical, midline, or diffuse abdominal pain lasting for 1 hour or more. Pain should be the most severe and distressing symptom.
2. Episodes are separated by at least 1 week
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. The pain is associated with 2 or more of the following:
   a. Anorexia
   b. Nausea
   c. Vomiting
   d. Headache
   e. Photophobia
   f. Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition, including cyclic vomiting syndrome.

[a]Criteria fulfilled for at least 6 months before diagnosis.

Pathophysiology

AM is among the least studied DGBI in children and adults and is part of a spectrum that includes cyclic vomiting syndrome and migraine headaches.[108] These disorders share symptoms, triggers, demographic characteristics,[109] and family history.[110] Neuronal hyperexcitability may contribute to their pathophysiology, with a lower threshold required to trigger episodes.[111] Children with AM may exhibit abnormal antral motility and slower gastric emptying.[112] Mitochondrial dysfunction is also considered a potential mechanism underlying migraines.[113]

Clinical Evaluation

Medical history should include abdominal surgeries, medications, comorbidities, family history, triggering and relieving factors, and impact on daily life. Routine evaluation should assess consciousness, hydration, vital signs, and body weight. Laboratory testing includes a complete blood count, electrolytes, glucose, kidney and liver function tests, pancreatic enzymes, and urinalysis. The evaluation may exclude other diseases associated with episodic pain such as recurrent pancreatitis; small bowel, urologic, or biliary obstruction, ovarian torsion, familial Mediterranean fever, acute intermittent porphyria, hereditary angioedema,[114] and psychiatric disorders. Psychological evaluation is important.[115]

Treatment

There are no US Food and Drug Administration–approved medications or evidence-based guidelines for treating AM in children. Education is essential to reassure families that although episodes can be severe and distressing, they are not life-threatening or indicative of serious pathology. Treatment should be individualized based on attack frequency, severity, impact on the child's life, and potential adverse effects. Treatment is based primarily on analgesics.[116] When possible, identification of triggers can prevent episodes. Children with frequent and debilitating episodes may benefit from prophylactic therapy, as some evidence suggests that antimigraine medications such as pizotifen, cyproheptadine, propranolol, and flunarizine may prevent attacks.[117] During episodes, management includes resting and sleeping, as well as oral or subcutaneous medications like pizotifen, sumatriptan, verapamil, topiramate, aprepitant, or divalproex sodium.[118] In rare unremitting cases, intravenous dihydroergotamine may be considered.[119] In addition, headache treatment strategies suggest that combining biobehavioral interventions with medical therapy may be beneficial.[120]

H1e. Centrally Mediated Abdominal Pain Syndrome

Epidemiology

Although it is common for children with DGBI to report intermittent pain, continuous pain as in the case of CAPS is much less frequent. There is no specific epidemiologic data for this diagnosis, as CAPS was not part of previous pediatric Rome Criteria.

H1e. Diagnostic Criteria[a] for Centrally Mediated Abdominal Pain Syndrome[b]

Must include *all* the following:

1. Continuous abdominal pain
2. Pain limits daily functioning[c]
3. After appropriate evaluation, the symptoms cannot be fully explained by other medical conditions

[a]Criteria fulfilled for at least 2 months before diagnosis.
[b]Centrally mediated abdominal pain syndrome is typically associated with psychosocial comorbidity, but there is no specific profile that can be used for diagnosis.
[c]Daily activities include impairment in school, social/leisure, family life, and sports.

Justification of Inclusion Into Pediatric Rome Criteria

The Rome V Committee introduced CAPS as a new pediatric diagnosis, acknowledging the existence of cases of continuous abdominal pain. Previously, this diagnosis was limited to adults only. This addition ensures diagnostic consistency across the lifespan. In adults, differently than in children, there are defined categories of CAPS. Due to the absence of pediatric epidemiologic data, the Pediatric Committee decided not to introduce these categories.

Clinical Evaluation

CAPS evaluation resembles APS-NOS, emphasizing psychological assessment to identify psychosocial influences, coping mechanisms, pain-specific cognitions, and behavioral responses. Understanding parent-child differences in pain perception is essential to better understand the patient and plan treatment.

Psychological Features

It is assumed that psychosocial factors play a more central role in symptom generation in CAPS than in other abdominal pain syndromes, although this has not been studied yet and therefore requires an in-depth evaluation.

Treatment

Although specific data are lacking, multidisciplinary care is highly recommended for children with CAPS,[83,121] emphasizing collaboration with families and schools. Specialized chronic pain centers offer individualized treatment through multidisciplinary teams. Some of the treatment strategies listed in the ESPGHAN-NAPGHAN guidelines related to IBS and FAP-NOS may apply to this condition as well.[68] Brain–gut therapies are strongly recommended,[122,123] given the central sensitization that is likely present in these patients. Recommendations options are psychopharmacologic medications, PENFS,[58] and psychological approaches, such as CBT and hypnosis.[98,124] Although evidence on their efficacy in children with CAPS is needed, these therapies target the brain–gut pathway and have shown effectiveness in reducing pain and disability in other abdominal pain syndromes. Pharmacologic treatments include tricyclic antidepressants (eg, amitriptyline and nortriptyline), selective serotonin reuptake inhibitors (eg, citalopram), quaternary antidepressants (eg, mirtazapine),[125] and antiseizure medications (eg, gabapentin, pregabalin).[126,127]

H2a. Functional Constipation

Epidemiology

Constipation is a common problem worldwide. A systematic review described a mean and median prevalence in children of 14% and 12%, respectively.[128] The peak incidence of constipation occurs at the time of toilet training, and there are no sex differences.[129] There is little consensus in the literature regarding the risk factors for FC, although the low consumption of fiber, fruit, and vegetables, a positive family history, obesity, and low physical activity have been associated with an increased risk.[128]

H2a. Diagnostic Criteria[a] for Functional Constipation

1. Must include at least 2 of the following occurring in the past month:
   a. On average, 2 or fewer defecations per week
   b. On average, at least 1 episode of fecal incontinence per week[b]
   c. History of retentive posturing, straining, or inappropriate stool retention
   d. History of painful or hard[c] bowel movements
   e. Presence of a large fecal mass in the rectum
   f. History of large diameter stools
2. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
3. Does not fulfill criteria for irritable bowel syndrome

[a]Criteria fulfilled for at least 1 month before diagnosis.
[b]This criterion only applies to children who have been toilet-trained.
[c]Bristol Stool Form Scale type 1 or 2, or Brussels Infants and Toddlers Stool Scale type 1, 2, or 3 for infants.

Justification for Changes in Criteria

The committee debated whether it was beneficial to remove the term "functional" from this entity to maintain uniformity with other DGBI. It was concluded that there was no better alternative to describe this condition and that the term "functional constipation" is well accepted by patients, families, and medical providers. We changed the wording from "at least once per week" to "occurring in the past month," which brings the criteria in line with the questionnaire used and addresses the fact that some issues (eg, large fecal mass in the rectum) are not occurring every week. We eliminated "in a child of a developmental age of at least 4 years," because this entity in Rome V is no longer subdivided based on age of the patients and we added a clarification that criterion 1b applies only to patients who have been toilet-trained. Because we now have 1 set of FC criteria for children of all ages, including those who are not toilet-trained, we have eliminated "in the toilet" from criterion 1a. We added the word "straining" to the criterion 1c because stool-withholding is often misinterpreted as straining by parents. The other changes aimed at making the description less subjective. In criterion 1c we have changed the wording "excessive volitional" to "inappropriate," because the word "volitional" was not intuitive for many parents and "excessive" was subjective. The word "inappropriate" differentiates the withholding from the very appropriate behavior one expects when access to restrooms is not available. We have now clarified the wording of "hard" in criterion 1d by associating it with Bristol Stool Form Scale or Brussels Infants and Toddlers Stool Scale types. We also

removed the wording "that can obstruct the toilet" because that wording could have been related to the size and type of toilet used more than to the size of the stools. Abdominal pain is also a frequently associated symptom of FC, but its presence was not considered a criterion for FC by the Rome V Pediatric Committee. It is recognized that abdominal pain can be a consequence of constipation, as it is found in up to 65% of children who present with a defecation disorder,[130] and that many children presenting with abdominal pain improve after constipation is treated.[131] This is true for many other symptoms that are associated with constipation, such as poor appetite, early satiety, bloating, and urinary disturbances; however, none of these symptoms are believed to be either sufficient or necessary to help in the diagnosis of FC. The Committee believes that when abdominal pain is the predominant symptom and it is relieved by defecation, a diagnosis of IBS should be made.

Pathophysiology

It is estimated that pediatric constipation is functional in nature in >95% of cases. As FC is equally common in both sexes and in children with diverse socioeconomic backgrounds, dietary practices, and cultural influences,[128] the triggering event is most likely the universal instinct to avoid defecation because of pain or social reasons. Because of the withholding, the colonic mucosa absorbs water from the retained fecal mass, and the stools become progressively hard and more difficult to evacuate. This process leads to a vicious cycle of stool retention in which the rectum is increasingly distended, resulting in overflow fecal incontinence, loss of rectal sensation, and ultimately, loss of the normal urge to defecate.

Clinical Evaluation

In most cases, FC is a clinical diagnosis that can be made based on a typical history and physical examination. A careful history must be obtained to determine the timing of the passage of meconium, age at onset, stool withholding behavior, characteristics of the stools, presence of associated symptoms (eg, pain at defecation, blood on the stool or the toilet paper, fecal incontinence, and urinary symptoms), or neurologic deficits. Some parents may mistake fecal incontinence for diarrhea. The abdominal examination could identify a mobile fecal mass in the left lower quadrant and suprapubic region. External examination of the lower back and the perianal area is essential to exclude signs of spinal dysraphism, and a rectal examination is useful to assess muscle tone, consistency and amount of stool, presence of anatomic abnormalities, and size of the rectal vault. There is evidence that abdominal radiographs are neither sensitive nor specific to diagnose FC so they should only be used when clinically indicated. However, a moderate to large amount of stool found in the rectum has a high sensitivity and positive predictive value (>80%) for fecal retention as assessed by abdominal radiograph.[132] Quantification of colonic transit time with radiopaque markers may be helpful to confirm the presence of constipation in cases lacking objective data. Anorectal manometry, suction rectal biopsies, barium enema, and colonic manometry may be indicated occasionally to diagnose organic causes of constipation.

Treatment

The treatment of FC in children should be individualized and includes education, behavioral and dietary modification, and pharmacologic therapy. Education is as important as medical therapy and includes counseling families to recognize withholding behaviors and to use behavioral interventions, such as regular toileting, use of diaries to track stooling, and reward systems for successful evacuations.[133,134] Normal fiber and fluid intake is recommended.

The pharmacologic approach includes rectal or oral disimpaction and maintenance therapy to prevent the reaccumulation of feces. Both oral (laxatives and lavage solutions) and rectal (enemas and suppositories) medications can be used for fecal disimpaction.[135,136] Bekkali et al[137] reported the equal efficacy of both regimens, although fecal incontinence and watery stools were more frequent with oral laxative use. Miller et al[138] found no difference in response to polyethylene glycol or enemas at day 5 of disimpaction therapy.

Regarding maintenance therapy, the ESPGHAN-NASPGHAN guidelines recommend polyethylene glycol as the first-line therapy for children older than 6 months with constipation.[139] In children not improving with stool softeners, adding a stimulant laxative, such as senna or bisacodyl, to the treatment may be beneficial.[140] Recently, new classes of medications, which were approved by the regulatory agencies of many different countries for treating adult patients with chronic constipation and IBS-C, have also been tested in large RCTs in children. So far, the only compound that has been found to be superior to placebo in these pediatric trials is linaclotide, which is now approved in the United States at the dosage of 72 μg/day in patients aged 6–17 years.[141,142]

Children who fail to respond to standard medical interventions are often classified as having "refractory constipation" or "therapy-resistant constipation."[143] NASPGHAN defined refractory constipation as ongoing constipation in children who meet Rome IV Criteria for FC, who failed to improve after a minimum of 3 months of appropriate conventional therapies (daily stimulant laxatives at appropriate dosages and behavioral and biomechanical interventions) with impaired quality of life. Ongoing symptoms are defined by 2 or fewer voluntary defecations per week and/or 1 or more episodes of fecal incontinence per week.[144] Another international group defined "therapy-resistant constipation" as constipation not responding to a maximum dose of at least 2 laxatives of different classes for a minimum of 3 months with good compliance in a secondary or tertiary care facility. In these patients, interventions such as transanal irrigation enemas,[145] anorectal biofeedback,[146] pelvic physiotherapy,[147]

intra-anal botulinum toxin injection,[148] and antegrade enemas have been found to be helpful.

H2b. Nonretentive Fecal Incontinence

Epidemiology

A meta-analysis published in 2018 reported a pooled prevalence of nonretentive fecal incontinence (NRFI) of 0.4%, with a range from 0% to 1.8%.[149]

Justification for Changes in Criteria

The word "functional" was removed to maintain consistency with the other DGBI. The Committee understands that the current definition does not capture the subset of children who have never been toilet-trained and have purposeful incontinence because of emotional or psychological issues. We believe these children do not have a classic DGBI, and we have elected to exclude them from this definition by adding a statement that the incontinence should not be purposeful.

Pathophysiology

Studies using radiopaque markers found normal total and segmental transit times in children with NRFI.[150,151] The use of 3-dimensional high-resolution manometry demonstrated that children with NRFI had lower mean resting and maximum squeezing pressures and a higher threshold for the first sensation.[152] A combination of barostat and functional magnetic resonance imaging showed that children with NRFI had a higher threshold for urgency, indicating the possibility of impaired rectal sensation.[153] These findings support the hypothesis that altered brain–gut interactions play a significant role in the pathophysiology of NRFI.

Clinical Evaluation

Table 2 provides a comparison of NRFI and constipation-associated fecal incontinence.

H2b. Diagnostic Criteria[a] for Nonretentive Fecal Incontinence

Must include *all* the following in a child who has been toilet-trained:

1. Defecation into places inappropriate to the sociocultural context
2. No evidence of fecal retention
3. The incontinence should not be purposeful
4. After appropriate evaluation, the fecal incontinence cannot be explained by another medical condition

[a]Criteria fulfilled for at least 1 month before diagnosis.

Psychological Features

Constant or episodic leaking of stools into the underwear leads to significant stress in children and adolescents.[145] The pressure from peers and from family members due to the unpleasant odor is usually substantial. Thus, it is unsurprising that most children with this symptom have psychological problems, irrespective of what causes the incontinence.[155,156] They also face significant risks of child maltreatment.[154,155]

Treatment

The clinician should provide a detailed explanation to both parents and the child of the reason for the fecal incontinence, because most families present with a great deal of frustration. Patients should be instructed to sit on the toilet for approximately 5–10 minutes with appropriate seating methods at least 3 times per day, especially when they return from school, when the risk of fecal incontinence is high. One case report showed the efficacy of loperamide in treating children with NRFI.[157] There is no benefit to treating children with NRFI with laxatives, which may worsen the symptoms.[158] The use of fiber may be beneficial in certain cases.

In 1 study, although biofeedback therapy was effective in improving defecation dynamics, there was no benefit on

Table 2. Clinical Characteristics of Retentive and Nonretentive Fecal Incontinence[a]

Characteristic	Retentive fecal incontinence[b]	Nonretentive fecal incontinence[b]
Size of fecal incontinence	+	+++
Large-diameter stools	+++	–
Withholding behavior	+++	–
Night-time fecal incontinence	++	+
Enuresis	+	++
Rectal mass	+++	–
Prolonged colonic transit	++	–

[a]Comparison of clinical features commonly observed in retentive and nonretentive fecal incontinence.
[b](+) and (–) refer to the magnitude of the effect.

clinical outcomes.[159] A retrospective study showed that adding transcutaneous electrical stimulation to conventional therapy helps treat children with NRFI compared with conventional therapy alone.[160]

H2c. Infant Dyschezia

Epidemiology

A multicenter study conducted among Belgian, Italian, and Dutch children attending well-baby visits identified infant dyschezia in 71 of 1698 (4%) patients through the administration of Rome IV questionnaires.[161] Similar data have been confirmed in 2 Italian and Turkish cohorts.[162,163] Regarding the relationship with FC, Hyman and colleagues[164] reported a constipation prevalence of 4.9% among infants previously diagnosed with dyschezia.[164,165]

Justification for Changes in Criteria

No scientific evidence has been produced to require a significant change in the criteria. Considering the heterogeneity of clinical manifestations, an additional sentence was added to include "crying," "screaming," and "extreme reddening of the face" as supportive criteria.

Clinical Evaluation

The clinician must obtain an accurate clinical history that includes diet and evaluate the infant's growth. In addition, a physical examination, including a rectal examination to exclude anorectal abnormalities, is beneficial.

Treatment

Caregivers are frequently reassured by a methodical physical examination. They usually accept the explanation that the child needs to learn to relax the pelvic floor at the same time as bearing down. The caregivers are advised to avoid rectal stimulation, which produces sensory experiences that may be noxious or that may condition the child to wait for stimulation before defecating. Laxatives are usually unnecessary.

H2c. Diagnostic Criteria for Infant Dyschezia

Must include both of the following in an infant younger than 9 months:

1. Recurrent straining episodes for at least 10 minutes and visible effort to defecate before successful or unsuccessful passage of soft stools. It is often accompanied by screaming, crying, or extreme reddening of the face.
2. After appropriate evaluation, the discomfort cannot be fully explained by another medical condition.

H2d. Proctalgia Fugax

Epidemiology

An Iranian study using Rome II criteria reported a prevalence of PF of 1.8% among adolescents.[166]

Justification of Inclusion Into Pediatric Rome Criteria

The Committee agreed that cases of anorectal pain due to PF occur in children. It was decided to adopt the adult diagnostic criteria pending further studies in children. The aim is to encourage researchers to conduct epidemiologic and pathophysiological studies and formulate pragmatic management strategies.

Pathophysiology

Higher internal anal sphincter thickness and increased contractile activity with a more significant number of anal ultraslow wavers have been reported in patients with PF.[168,169]

Clinical Evaluation

The pain in PF is characterized by a sudden onset of severe cramping or stabbing pain in the rectum that lasts from seconds to several minutes and disappears completely. A thorough history and physical examination can help inform the diagnosis. Due to the typical and transient nature of the pain, limited diagnostic testing may be considered to rule out other GI or inflammatory conditions. Suggested tests include complete blood count, metabolic panel, C-reactive protein, fecal calprotectin, colonoscopy, and anorectal manometry.

Treatment

Most children are managed with a simple explanation of the transient and benign nature of the disorder. Treatment is indicated in severe cases only. In adults, persistent symptoms can be treated with local application of 0.2% glyceryl trinitrate or 2% diltiazem at the onset of symptoms.[169] Inhaled salbutamol has been shown to reduce the duration of pain episodes.[170] Other medical interventions include clonidine, amyl nitrate, low-dose intravenous

H2d. Diagnostic Criteria[a] for Proctalgia Fugax

Must include *all* the following:

1. Intermittent pain localized to the anorectum and unrelated to defecation
2. Pain generally lasts from seconds to minutes
3. There is no anorectal pain between episodes
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical conditions

[a]Criteria fulfilled for at least 2 months before diagnosis.

lidocaine, and local botulinum toxin injection.[171–173] There is insufficient evidence to use biofeedback therapy in PF.[174]

H2e. Functional Diarrhea

Epidemiology

Functional diarrhea (FDr) prevalence is approximately 2%[175–180] in children and 3.6%–5.3% in adults.[181]

Justification for Changes in Criteria

The Rome V Criteria expanded the diagnostic age range for FDr up to 18 years based on studies showing its presence in school-aged children and adolescents.[182,183] Given age-related differences in stool frequency, Rome V now provides separate criteria based on age and recommends using the Bristol Stool Form Scale (types 6–7) and Brussels Infant and Toddlers Stool Scale (types 5, 6, or 7), depending on the age group.[184,185]

Clinical Evaluation

With Rome V extending the age range for FDr diagnosis up to 18 years, distinguishing FDr from IBS-D in older children is now necessary. The key differentiator is the presence and pattern of abdominal pain. FDr is characterized by diarrhea without significant pain, whereas IBS-D presents with pain as the predominant symptom. However, symptom overlap may exist, and clinicians should assess which feature predominates.

Evaluation should begin with an age-appropriate clinical history that explores symptom onset and its relationship with GI infections, dietary changes, stressors, new medications, or supplements. Special attention should be given to ruling out conditions such as celiac disease, inflammatory bowel disease, malabsorption syndromes (eg, sucrase–isomaltase deficiency), and infectious causes. The physical examination should specifically assess hydration, nutritional status, and alarm signs (Table 3).[186,187] In most cases, the likelihood of an underlying organic disease can be reasonably excluded through basic bloodwork and stool tests.

Treatment

Because there are no randomized trials for FDr treatment in children, recommendations are based on expert opinion and adult studies. Most toddlers and preschoolers do not require medical therapy. In older children, treatment depends on symptom severity and impact on quality of life. Reassurance, education on bowel habits, and addressing caregiver concerns are essential. Dietary evaluation is recommended—especially reduction of juice and fructose intake in young children.[188,189] A low-FODMAP diet may be trialed in older children. Other treatments include loperamide,[79] bile acid sequestrants (eg, cholestyramine),[78] and 5-hydroxytryptamine type 3 antagonists when symptoms are persistent.

H3a. Functional Abdominal Bloating

Epidemiology

Functional abdominal bloating is a recent addition to the pediatric Rome Criteria. Despite that consultations for abdominal distention and bloating are common in neurogastroenterology practice, there has been little epidemiologic research in children. The only study exclusively focused on children found that 36% of children with FAP also experienced bloating.[190]

H2e. Diagnostic Criteria[a] for Functional Diarrhea

Must include *all* the following:

1. Passage of an average of 4 or more painless bowel movements daily in children younger than 4 years or more than 2 bowel movements daily in children 4 years or older, with at least 25% of stools being unformed[b]
2. Onset between 6 months and 18 years of age
3. Does not meet criteria for functional constipation, diarrhea-predominant irritable bowel syndrome, and nonretentive fecal incontinence
4. After an appropriate evaluation, the diarrhea cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months before diagnosis.
[b]Bristol Stool Form Scale or Brussels Infants and Toddlers Stool Scale type 6 or 7 in infants/children with diapers.

H3a. Diagnostic Criteria[a] for Functional Abdominal Bloating

Must include *all* the following:

1. Intermittent bloating and/or distention occurring on average at least 4 days per month; abdominal bloating and/or distention predominate over other symptoms[b]
2. There are insufficient criteria for a diagnosis of irritable bowel syndrome, functional constipation, functional diarrhea, aerophagia, or postprandial distress syndrome
3. After appropriate evaluation, the bloating cannot be fully explained by another medical condition

[a]Criteria fulfilled at least 2 months before diagnosis.
[b]Mild pain related to bloating may be present as well as minor bowel movement abnormalities.

Table 3. Alarm Features in Functional Diarrhea[a]

Alarm feature
Unintentional weight loss
Malnutrition
Delayed puberty
Growth delay
Loss of appetite
Dehydration
Nocturnal diarrhea
High-volume diarrhea
Recurrent, bilious, or nocturnal vomiting
Hematochezia
Hematuria or proteinuria
Association with abdominal pain
Edema
Abdominal distension
Abdominal tenderness
Ileus
Renal failure
Fever
Skin rash or joint involvement
Expulsion of parasite
Anemia
Thrombocytopenia
Elevated white blood cells
Elevated calprotectin, C-reactive protein, and erythrocyte sedimentation rate
Family history of inflammatory bowel disease, celiac disease, or colorectal neoplasia

[a]Systemic, clinical, and laboratory alarm features that should prompt further evaluation in children presenting with functional diarrhea.

Justification of Inclusion Into Pediatric Rome Criteria

Functional abdominal bloating is a newly recognized diagnostic category. Given the lack of pediatric criteria and the need for guidance in children and adolescents seeking diagnosis, the Pediatric Committee hopes that the new criteria will drive pediatric research efforts. To harmonize diagnostic criteria with adults, functional abdominal bloating criteria closely resemble the adult diagnosis.

Pathophysiology

Bloating and distention can result from gas accumulation at various levels of the GI tract.[191] In adults, gas retention in the small bowel and colon can trigger symptoms, particularly in those with visceral hypersensitivity.[192] Poor intestinal tone may also lead to gas buildup, with increased wall tension causing symptoms even without visible distention. Carbohydrate intolerance and the ingestion of poorly absorbed fermentable carbohydrates result in an increased volume of water, gas production, and bloating.[193] Fatty meals and lipid infusions in the small intestine also exacerbate gas retention.[194] Dysbiosis, small intestinal bacterial overgrowth,[195] abdominophrenic dyssynergia, pelvic floor dysfunction,[196] and impaired gas clearance[197] may further contribute to bloating. Behavioral factors, such as voluntary stool retention, may also result in distention and bloating.[198]

Clinical Evaluation

Abdominal bloating and distention should be differentiated during consultation as their etiology and pathophysiology may differ. Potential organic causes of both

bloating and distention include small bowel bacterial overgrowth, celiac disease,[199] congenital sucrase-isomaltase deficiency, and other malabsorption disorders.[195] Evaluation should encompass dietary history, bowel movement frequency, stool consistency, posture, surgical history, family history of GI diseases, and behavioral factors like air swallowing. Given the broad differential, clinicians should rely on judgment and targeted tests when appropriate, such as abdominal radiographs, hydrogen breath tests,[200] and in some cases, evaluation of GI motility[201] to refine the diagnosis.

Treatment

Identifying the underlying cause of bloating or distention helps guide individualized treatment, which may include dietary changes, microbiome modulation, promotion of gas evacuation, antifoaming agents such as simethicone, treatments targeted to alleviate visceral perception, and in some patients with abdominal distention, biofeedback to improve the tone of the abdominothoracic wall and in selected cases to treat pelvic floor dissyinergia.[202]

H3b. Infant Distress Syndrome

Epidemiology

Two meta-analyses of more than 50 studies from 17 countries demonstrated that the average fuss or cry duration in the first 3 months of life ranges from 1 to 2 hours per day. Thereafter, it may drop to 30 to 60 minutes per day.[203,204] Using the Rome IV criteria, where infant colic was defined as crying and fussing for 3 or more hours per day for 3 or more days per week, the prevalence varies from 1.9% to 19.2%, and was more frequent in the Americas than in Europe and Asia, with a peak between 1 and 2 months of age.[180,205] Fussing refers to intermittent distressed vocalization and has been defined as "not quite crying but not awake and content either."[150] Infants often fluctuate between crying and fussing, so the 2 symptoms are difficult to distinguish in practice.

H3b. Diagnostic Criteria for Infant Distress Syndrome

For clinical purposes, must include *all* the following:

1. An infant who is younger than 5 months of age when the symptoms start
2. Recurrent and prolonged periods of infant crying and fussing reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

H3b. Criteria for Clinical Research in Infant Distress Syndrome

For clinical research, infants must fulfill the diagnostic criteria as described above and they must fulfill at least 1 of the following criteria:

1. Crying duration of >3 hours per day for children up to 6 weeks of age or >2.5 hours for older children (75th percentile for age) for at least 3 days per week
2. Daily life and well-being of at least 1 of the caregivers are severely impacted by the crying

Justification for Changes in Name and Criteria

IDS is a new name proposed by the Rome V Committee in lieu of the term "infant colic." The Rome V Committee agrees that this syndrome of excessive crying in infancy belongs to the DGBI group because there is evidence for a role of both brain and gut in its pathophysiology. However, the term "colic" suggests that the pain arises in the colon, which has not been proven to date. Hence, a more general name for excessive crying in infancy was formulated to emphasize the visible distress of the infant, resulting in the term "infant distress syndrome." Rome IV Criteria stipulated those symptoms had to stop before the age of 5 months. However, some infants still cry excessively after the age of 5 months, and therefore this criterion has been modified.[203,204] The third criterion in Rome IV, stating that the absence of failure to thrive, fever, or illness was a prerequisite, seemed a random choice of symptoms and the new criteria have been made consistent with those of other DGBI. In Rome IV, only children with a crying duration of at least 3 or more hours per day for at least 3 days per week were included in clinical research.[206] The Rome V committee, however, agreed that this criterion of 3 hours was arbitrary and that many infants present to the pediatrician with excessive crying of a duration of less than 3 hours per day but with severe impact on at least 1 of the caregivers.

Pathophysiology

The pathophysiological mechanisms underlying IDS are still poorly understood, but IDS is likely to be a multifactorial disorder with GI, neurologic, and psychosocial disturbances.[207] The pathogenesis of excessive crying may be closely related to the development of the GI microbiome with higher levels of *Proteobacteria*, lower amounts of *Bifidobacteria* and *Lactobacillus*, and decreased bacterial diversity in IDS than in control infants.[208,209] Antibiotic treatment in the first week of life has been associated with both gut dysbiosis and an increased risk of infant colic.[210,211] A diminished capacity to regulate crying episodes, greater reactivity to sensory stimuli, neurobiological differences in the development of the amygdala, and disorders in the biorhythm have been suggested as contributing neurologic factors, although studies can be contradictory.[212,213]

Psychological Features

There is strong evidence linking parental depression and anxiety to IDS.[214,215] Maternal anxiety has been consistently found to be both a preceding and concurrent condition of excessive crying, but subsequent anxiety is not, suggesting that maternal anxiety is a potential risk factor for subsequent IDS. However, depression seems to be a result of IDS, with excessive crying and maternal depression exacerbating simultaneously in a vicious cycle.[214] Paternal depressive symptoms during pregnancy are also associated with excessive infant crying, possibly related to genetics, bonding problems, or contextual stressors.[216]

Clinical Evaluation

In studies of afebrile infants who presented with crying or fussiness, only a small minority had an underlying organic etiology, such as a urinary tract infection.[217,218] A thorough history and physical examination are the cornerstones of evaluating the crying infant, and afebrile infants with excessive crying in the first few months of life should undergo urine evaluation.[218] Red flags that have been proposed for identifying organic disorders include extreme or high-pitched cry; lack of a diurnal rhythm; symptoms starting after 4 months of age; frequent regurgitation, vomiting, or diarrhea; weight loss; maternal drug ingestion; and an abnormal physical examination.[219] Given the association between parental psychopathology and excessive crying, as well as the stress-inducing nature of a child's excessive crying, it is advisable to include questions on parental stress and feelings of anxiety and depression.

Treatment

The cornerstone of helping infants with IDS is to validate the infant's symptoms and the emotional burden of the parents, reassure the parents that their child is healthy, and educate them about the self-limited nature of IDS and the need for support by family members. Education on the interplay of biopsychosocial factors that generate and maintain IDS may be helpful. Parent training programs, with or without soothing techniques, can reduce crying times for infants compared with controls, but more studies are needed.[220]

Probiotics may reduce crying time in infants with IDS. *Limos lactobacillus reuteri* is the most studied agent, showing a reduction of 64.6 minutes in daily crying without obvious adverse effects.[216,221] Evidence for the effectiveness of dietary modifications to treat IDS is scarce and presents a significant risk of bias.[222] However, removing cow's milk from the infant's diet or from the maternal diet in those who are breastfed may be beneficial. Findings regarding the effects of manual therapy, chiropractic care, and osteopathy on crying time are controversial, preventing their use from being recommended.[223] In addition, the evidence for using lactase, sucrose, glucose, simethicone, herbs, acupuncture, and proton pump inhibitors is very weak.[224]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2026.01.036.

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