Management of functional constipation in children and adults

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Abstract | Functional constipation is common in children and adults worldwide. Functional constipation shows similarities in children and adults, but important differences also exist regarding epidemiology, symptomatology, pathophysiology, diagnostic workup and therapeutic management. In children, the approach focuses on the behavioural nature of the disorder and the initial therapeutic steps involve toilet training and laxatives. In adults, management focuses on excluding an underlying cause and differentiating between different subtypes of functional constipation — normal transit, slow transit or an evacuation disorder — which has important therapeutic consequences. Treatment of adult functional constipation involves lifestyle interventions, pelvic floor interventions (in the presence of a rectal evacuation disorder) and pharmacological therapy. When conventional treatments fail, children and adults are considered to have intractable functional constipation, a troublesome and distressing condition. Intractable constipation is managed with a stepwise approach and in rare cases requires surgical interventions such as antegrade continence enemas in children or colectomy procedures for adults. New drugs, including prokinetic and prosecretory agents, and surgical strategies, such as sacral nerve stimulation, have the potential to improve the management of children and adults with intractable functional constipation.

Functional constipation is defined as constipation without an organic aetiology and is diagnosed according to the Rome criteria[1–3]. The symptom-based Rome criteria were first developed for adults in 1989 during a consensus meeting of experts in the field of functional gastrointestinal disorders. These criteria have been updated several times and are now internationally acknowledged and used for both research and clinical purposes. The first criteria for paediatric functional gastrointestinal disorders — the Rome II criteria — were published 10 years later, in 1999. The revised Rome IV criteria— for childhood and adult functional constipation — were published in 2016 (REFS[1–3]) (BOX 1). Functional constipation, a common disorder in all age groups, shows some similarities in children and adults, but important differences exist regarding epidemiology, symptomatology, pathophysiology, diagnostic workup and therapeutic management. In this Review, we provide an overview of the literature on childhood and adult functional constipation and discuss current and future diagnostic and therapeutic management strategies.

Clinical symptoms

Symptoms of functional constipation in both children and adults include hard, infrequent bowel movements, often accompanied by symptoms of bloating and abdominal pain. Children often present with symptoms of faecal incontinence, defined as the involuntary loss of stools in the underwear after being toilet trained, which is caused by overflow of soft stools passing around a solid faecal mass in the rectum (faecal impaction)[4]. Children with functional constipation also often have urinary symptoms, such as urinary incontinence and urinary tract infections[5]. Symptoms of faecal incontinence in adults are usually the result of another underlying pathology, such as dysfunction of the pelvic floor or obstetric trauma[6,7]. Consequently, faecal incontinence is not included in the adult Rome IV criteria for functional constipation. It is important to note, however, that many adults might feel uncomfortable mentioning symptoms of incontinence and might not volunteer this information; the treating physician should, therefore, always ask about the presence of faecal incontinence. Adults often present with the sensation of incomplete evacuation or obstruction, often requiring manual manoeuvres to defaecate[3]. This symptom is rarely seen in children.

Subtypes of functional constipation

Three different subtypes of functional constipation are recognized: constipation with a normal transit, slow-transit constipation and rectal evacuation disorders. Faeces are propelled through the colon under the influence of muscular contractions of the intestinal wall.

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Key points

- Diagnosis of functional constipation is based on a thorough medical history and physical examination; additional testing is only indicated if alarm symptoms are present or conventional strategies fail.
- Functional constipation can be caused by lifestyle factors, psychological factors and behavioural factors; withholding behaviour is a key factor in the pathophysiology of childhood functional constipation, whereas adults often have dyssynergic defaecation patterns.
- In adults, additional testing is used to differentiate between different subtypes of functional constipation (normal transit, slow transit and evacuation disorders) as such information has important therapeutic consequences.
- Patients with intractable constipation should be referred to a gastroenterologist for further management; tests such as colonic transit time, anorectal manometry and a balloon expulsion test (in adults) might provide useful information.
- Surgery is a therapy of last resort; to date, no clear guidelines exist on the surgical management of functional constipation and procedures vary widely between children and adults.
- Future comparative randomized clinical trials are needed to further clarify the role of newer (prokinetic and prosecretory) pharmacological agents for the management of paediatric and adult functional constipation.

Transit marker studies and colonic scintigraphy are often used to determine colonic transit time (CTT), an indirect reflection of colonic motor function. In both children and adults, a delay in CTT has been described in a subset of patients with functional constipation and is referred to as slow-transit constipation. In children with functional constipation, 13–25% have slow-transit constipation[8]. In adults with functional constipation, the two types of delayed colonic transit most commonly described are proximal colonic transit delay characterized by slow transit in the ascending or ascending as well as transverse colon and delayed emptying of the left colon (in patients with dyssynergic defaecation)[9,10]. In a large cohort study of more than 1,400 adults presenting with functional constipation, 65% had normal-transit constipation, 30% had an evacuation disorder, and 5% had evidence of slow-transit constipation[10].

Epidemiology

Implementation of the Rome criteria has resulted in a more uniform definition of functional constipation and improved understanding of its prevalence. A 2018 systematic review and meta-analysis reported the worldwide pooled prevalence of functional constipation in children to be 9.5% (95% CI 7.5–12.1%)[11]. Although some studies have suggested that constipation is more common in boys[12], a meta-analysis reported no statistically significant difference in sex prevalence[11]. Expert opinion suggests that older children and adolescents sometimes have a long history of unrecognized functional constipation if they are not comfortable in discussing their bowel habits, as parents are usually unaware of their children's defaecation patterns. Long-term follow-up studies have shown that 25% of children who receive treatment for functional constipation as a child still experience symptoms of constipation as adults[13]. Faecal incontinence and young age of onset (that is, <1 year versus >4 years) of constipation were factors associated with poor long-term prognosis[14]. These findings contradict the commonly held belief that paediatric functional constipation always disappears before adulthood.

A 2011 meta-analysis reported that functional constipation had a prevalence of 14% in adults and was more common in women than in men (OR 2.22, 95% CI 1.87–2.62)[15]. Moreover, in adults, the prevalence of constipation seems to increase with age and is higher in elderly patients than in younger adults, possibly owing to degeneration of epithelial, muscle and neural cells of the colon and pelvic floor[16]. To support this idea, a study using ex vivo preparations of human colon found that increasing age was associated with an increased likelihood of impaired cholinergic function in the ascending colon, possibly contributing to the age-related loss of neuromuscular activity[17].

Pathophysiology

In children, an organic cause of constipation is rarely found and constipation is considered to be of functional origin in more than 95% of cases[18]. In our clinical experience, constipation secondary to a systemic disease or medication use is more common in adults than in the paediatric age group. Organic aetiologies of constipation in children and adults include intestinal conditions, anorectal conditions, metabolic and endocrine conditions and neuropathic conditions (TABLE 1). The differential diagnosis of organic causes of constipation differs substantially depending on the age at onset of symptoms. In an infant with constipation and a history of delayed passage of meconium, congenital disorders such as Hirschsprung disease, spinal cord defects and anorectal malformations should be excluded. In adolescents, an eating disorder should be excluded. In an elderly patient, degenerative diseases such as neuropathic conditions or polypharmacology often lead to constipation and should be carefully considered.

In both children and adults, the pathophysiology of functional constipation is considered to be multifactorial. Common pathophysiological factors include genetic factors, lifestyle factors (for example, diet and physical activity) and psychological disorders (FIG. 1), but some factors differ between children and adults. Adolescents with functional constipation show similarities with both children and adults but are regarded as children in this Review. Although some differences exist, elderly patients with functional constipation generally resemble younger adults and are only briefly discussed. Management of this patient population is discussed elsewhere[19].

Genetic factors

Children and adults with functional constipation often have a positive family history of constipation, so it seems plausible that genetic predisposition might have a role in the pathophysiology of the condition[6,20–22]. However, no specific genes have been linked with functional constipation and the exact role of genetic factors in its aetiology remains to be further clarified. Moreover, some studies in adults could not confirm a familial clustering of functional constipation and therefore suggested that familial aggregation might reflect an acquired aetiology associated with lifestyle and environmental factors

prevailing in certain families, rather than resulting from actual genetic factors[23].

Lifestyle factors

Diet. Dietary factors have an important role in the pathophysiology of functional constipation in both children and adults. During infancy, feeding changes, such as the transition from breastfeeding to formula feeding or the introduction of solid foods, are often a trigger for the onset of functional constipation[24]. Whether cow's milk protein allergy is associated with functional constipation is a matter of debate. A literature review of ten studies reported that a diet free from cow's milk resulted in an improvement in functional constipation in 28–78% of children[25], and so constipation is sometimes considered to be a result of a food allergy. This idea is supported by evidence of histological changes in the colonic mucosa in children with chronic constipation indicating inflammation[26]. However, current European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) paediatric guidelines state that a 2-week to 4-week trial of cow's milk avoidance should be reserved for children who do not respond to conventional strategies[27]. A low intake of fibre or fluids is known to predispose to constipation in school children, adolescents and adults[28,29]. Moreover, in adolescents with constipation, clinicians should always consider the presence of an eating disorder[30]. In patients with anorexia nervosa or bulimia, constipation can arise from insufficient food and fluid intake and these patients are at risk of laxative abuse. Early recognition of such a situation is crucial and avoids unnecessary diagnostic testing and pharmacological therapy.

Obesity and physical activity. A potential association between obesity and constipation is controversial, and paediatric and adult studies have reported conflicting data[31–34]. Along with the mechanical effects of obesity creating tension on the pelvic floor[35], decreased physical activity has also been suggested to be an important risk factor for constipation in children and adults and might contribute to the possible association between obesity and functional constipation[15,29,36–38].

Microbiome

The role of the gut microbiome in the pathophysiology of functional constipation is incompletely understood. Intestinal microbiota have been shown to differ between healthy individuals and small samples of children and adults with functional constipation, suggesting a possible role for microbial disturbances in the development of constipation; however, microbiota characteristics related to functional constipation differ between studies[39,40]. Such an association could be explained by gut microbiota having modulating effects on gastrointestinal motility as reported in animal studies[41], or by metabolites and fermentation products having osmotic effects and causing increased gas production[42]. Research is needed to unravel the role of gut microbiota in the pathophysiology of functional constipation and to optimize potential microbiota-based interventions in patients with functional constipation.

Colonic motility factors

Colonic motility dysfunction is thought to be present in a subset of children and adults with functional constipation with delayed transit time. This idea is supported by colonic manometry studies in children and adults, which report that high-amplitude propagating contractions (HAPCs) occur less frequently in patients with slow-transit functional constipation than in patients without constipation[43–46]. HAPCs are considered to be responsible for the mass movement of colonic contents in an anterograde direction and this motor pattern often occurs after a meal and upon awakening. Novel advances in manometry techniques have enabled more detailed

Box 1 | **Rome IV criteria for functional constipation**

Infants and toddlers[1]

Must have ≥2 of the following criteria for ≥1 month:

- ≤2 defaecations per week
- History of painful or hard bowel movements
- History of excessive stool retention
- History of large diameter stools
- Presence of a large faecal mass in the rectum
- ≥1 episode of faecal incontinence per week[a]
- History of large diameter stools that can obstruct the toilet[a]

Children and adolescents[2]

Must have ≥2 the following criteria for ≥1 month:

- ≤2 defaecations in the toilet per week
- History of painful or hard bowel movements
- History of retentive posturing or excessive volitional stool retention
- History of large diameter stools that can obstruct the toilet
- Presence of a large faecal mass in the rectum
- ≥1 episode of faecal incontinence per week

AND:

- Insufficient criteria for irritable bowel syndrome

Adults[3]

Must have ≥2 the following criteria for ≥3 months[b]:

- ≤2 defaecations in the toilet per week
- Lumpy or hard stools more than 25% of defaecations
- Straining during more than 25% of defaecations
- Sensation of incomplete evacuation more than 25% of defaecations
- Sensation of anorectal obstruction/blockage more than 25% of defaecations
- Manual manoeuvres to facilitate more than 25% of defaecations

AND both of the following:

- Insufficient criteria for irritable bowel syndrome
- Loose stools are rarely present without the use of laxatives

[a]In toilet-trained children.
[b]With symptom onset ≥6 months prior to diagnosis. Reproduced with permission from REFS[1–3], Elsevier.

Table 1 | **Organic aetiologies of constipation based on age at symptom onset**

Aetiology	Childhood	Adulthood (and elderly)
Intestinal conditions		
Cystic fibrosis	✓	×
Hirschsprung disease	✓	×
Neuronal intestinal dysplasia	✓	×
Intestinal carcinoma	×	✓
Stricture	✓	✓
Anorectal conditions		
Anorectal malformations	✓	×
Enterocele or rectocele	×	✓
Prolapse	×	✓
Descending perineum syndrome	×	✓
Traumatic (e.g. obstetric or surgical)	×	✓
Anismus	✓	✓
Metabolic and endocrine conditions		
Pregnancy	×	✓
Menopause	×	✓
Hypercalcaemia	✓	✓
Hypokalaemia	✓	✓
Hypothyroidism	✓	✓
Dehydration	✓	✓
Diabetes mellitus	✓	✓
Porphyria	✓	✓
Uraemia	✓	✓
Coeliac disease	✓	✓
Neuropathic conditions		
Spinal cord abnormalities	✓	×
Tethered cord	✓	×
Neurofibromatosis	✓	×
Parkinson disease	×	✓
Multiple sclerosis	×	✓
Myelodysplasia	✓	✓
Spinal cord trauma	✓	✓
Myelomeningocele	✓	✓
Botulism	✓	✓
Chagas disease	✓	✓
Autonomic neuropathy	✓	✓
Myotonic dystrophy	✓	✓
Myopathy		
Systemic sclerosis	✓	✓
Amyloidosis	✓	✓
Drugs		
Opioids	✓	✓
Calcium channel blockers	✓	✓
Anticholinergic agents	✓	✓
Antidepressants	✓	✓
Antipsychotics	✓	✓
Chemotherapeutic agents	✓	✓

visualization of colonic motor patterns and have identified several differences in expression of colonic motility patterns in healthy and symptomatic individuals, possibly uncovering pathophysiological mechanisms underlying functional constipation[47,48]. New findings suggest that the most prominent motor pattern seen in healthy adults, the retrograde cyclic motor pattern, occurs less frequently in children and adults with functional constipation[49,50]. These contractions represent a distal colonic motor pattern repetitively occurring at 2–6 cycles per minute, propagating in a predominantly retrograde direction, and increasing after a meal in healthy individuals. The clinical meaning of these findings is still uncertain.

Anorectal factors

A large subset of adult patients with functional constipation show evidence of impaired anorectal function and/or structure, resulting in difficulty in expelling stools from the rectum. These evacuation disorders, sometimes referred to as defaecation disorders, are associated with symptoms of straining, a sensation of incomplete evacuation, abnormalities of rectal sensation and manual facilitation of defaecation. However, diagnosis of evacuation disorders requires careful additional diagnostic testing. One of the most common evacuation disorders is dyssynergic defaecation, the inability to coordinate the abdominal and pelvic floor muscles to evacuate stools because of paradoxical contraction or inadequate anal relaxation[10,51]. Other (usually older) adults have rectal hyposensitivity, defined as elevated sensory thresholds to rectal balloon distention testing, associated with symptoms of constipation and faecal incontinence. A more detailed description of the diagnosis and management of anorectal disorders is provided elsewhere[52,53].

Psychological and behavioural factors

Psychological factors. An association between psychological factors and functional constipation has been reported in several studies[54–57]. In children, constipation has been reported to be more common in children with specific behavioural disorders such as autism and attention deficit disorders than in those without such disorders[58,59]. Specific psychological traits such as anxiety and depression symptoms have been reported to be more common in both children and adults with functional constipation than in healthy individuals as controls[60–62]. Moreover, stressful life events such as physical or psychological trauma might have a role in the development of functional constipation, as such events more commonly occur in children and adults with functional constipation than in their healthy peers[62–64]. The elderly population, who experience issues such as social isolation and decreased daily activity, are at particular risk of psychological causes of constipation[65].

An association between psychological factors and functional constipation might be related to the brain–gut axis (FIG. 1). In children and adults with functional constipation, sensations such as pain and abdominal distention arising from the colon are processed via afferent pathways from the enteric nervous system to the

Table 1 (cont.) | **Organic aetiologies of constipation based on age at symptom onset**

Aetiology	Childhood	Adulthood (and elderly)
Psychological conditions		
Eating disorders	✓	✓
Depression	✓	✓
Other		
Dietary protein allergy	✓	×
Immobility	✓	✓

cerebral cortex. These pathways might eventually affect brain processing and lead to psychological problems. Another idea is that psychological and emotional components might modulate colonic and rectal function via efferent pathways, resulting in gastrointestinal dysfunction[66]. To support this theory, studies using functional MRI reported that, compared with healthy individuals as controls, paediatric and adult patients with functional constipation showed different patterns of brain processing in response to rectal distention and a distinct baseline brain activity pattern[67,68].

Behavioural factors. The age of onset of functional constipation in children is usually around the time of toilet training and such cases are probably related to behavioural factors associated with this developmental phase[69]. Withholding behaviour is considered the most common cause of constipation in children[70], an important difference compared with adults in whom failure of evacuation while straining (or dyssynergic defaecation) is the cause of constipation in 25–35% of patients[10]. Stool withholding behaviour can be triggered by an experience of hard or painful stools, and is sometimes aggravated by a history of anal fissures or fear during toileting[71]. In 50% of adolescents and 40% of adults, learned behaviour to suppress the urge to defaecate is also present[72–74]. Adolescents and adults sometimes avoid bathrooms at school and work or unfamiliar places, thereby ignoring the urge to defaecate[75]. In older adults, stool retention can arise from decreased awareness of the urge to defaecate.

Stool withholding behaviour results in retained stools become harder owing to water absorption by the colonic mucosa, which makes them more difficult to evacuate, resulting in more painful defaecation. A vicious cycle of more withholding behaviour can ensue and can result in faecal impaction. Frequent faecal impactions can eventually result in the development of a megarectum and can lead to symptoms of overflow faecal incontinence, decreased rectal sensation and, ultimately, an impaired sensation and urge to defaecate[76]. Therefore, in time, repeated suppression of the urge to defaecate might eventually lead to conditions such as dyssynergic defaecation and slow-transit constipation.

Parental factors

Parental factors also have an important role in the pathophysiology and prognosis of childhood functional constipation. Certain parental characteristics, for instance neuroticism and depression, and parental rearing attitudes, such as overprotection and attitudes that foster a high or low degree of autonomy, are reported to be associated with constipation and faecal incontinence[77,78]. In such circumstances, a family-based approach might be of benefit.

Diagnosis

Functional constipation is a clinical diagnosis made according to the Rome IV criteria (BOX 1). In children and adults presenting with constipation, a thorough medical history and complete physical examination can be sufficient to establish the diagnosis. Identification of alarm symptoms, which differ between children and adults (BOX 2), raises the suspicion of underlying organic conditions[27,52]. In children, alarm symptoms include signs of congenital abnormalities, stunted growth and symptoms suggestive of sexual abuse. In adults, alarm symptoms are those indicative of a colonic malignancy such as unintentional weight loss, recent change in bowel function, rectal bleeding or anaemia. A stepwise approach for the initial diagnosis and management of children and adults with functional constipation is provided[27,79] (FIG. 2).

Physical examination

In both children and adults, a thorough physical examination consists of examination of the abdomen and inspection of the perianal region. A digital rectal examination (DRE) is not always necessary for the diagnosis of functional constipation in children already fulfilling two Rome IV criteria[27]. In adults, however, a DRE is mandatory to exclude a mechanical obstruction such as a tumour or mass, and to evaluate anal sphincter and pelvic floor functions. When performed by an experienced physician, a DRE can provide information about sphincter function and is sometimes used to identify pelvic floor dyssynergia[80]. The most useful factors to assess during a DRE in adults are absence of perineal descent on straining, high resting anal sphincter tone, tenderness of the anal sphincter and pelvic floor and paradoxical contraction of the pelvic floor when simulating the effort associated with straining to expel the examining finger from the rectum and anal canal. These DRE findings are significantly correlated with objective parameters obtained with anorectal manometry (including resting anal sphincter pressure, anorectal difference pressure) and balloon expulsion time[81].

Additional diagnostic testing

In children and adults, diagnostic procedures are only recommended in the presence of alarm symptoms (BOX 2) or if conventional therapeutic strategies fail. Diagnostic testing is more common in adults than in children and is used to exclude organic causes of constipation and to distinguish between the different subtypes of functional constipation (normal-transit constipation, slow-transit constipation or an evacuation disorder)[52]. In adults, these subtypes of constipation have different therapeutic implications and the correct diagnosis is therefore critical. In children, however, the evaluation of defaecation dynamics for the diagnosis of evacuation

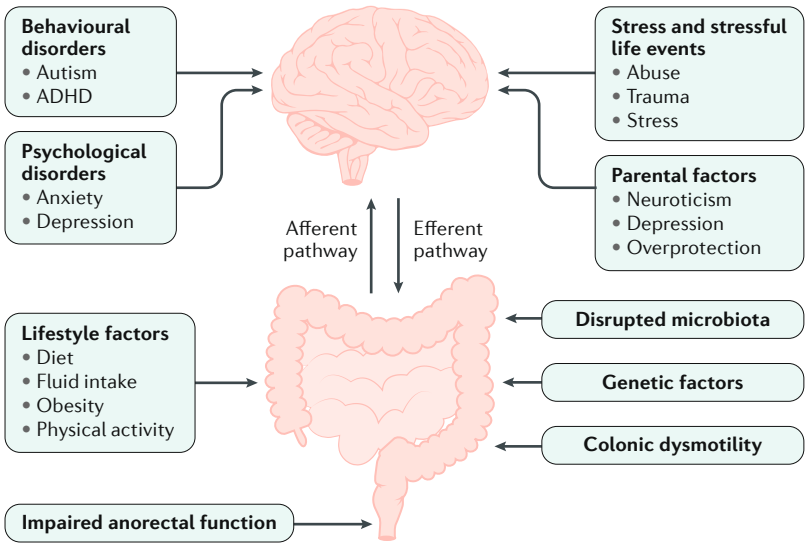

Fig. 1 | **Pathophysiological factors of functional constipation in adults and children.** An overview of the multifactorial aetiology of paediatric and adult functional constipation, including lifestyle factors and motility factors. Psychological and behavioural factors are associated with functional constipation via the efferent (carrying signals from the brain to the gut) and afferent (carrying signals from the gut to the brain) pathways of the brain–gut axis. ADHD, attention-deficit/hyperactivity disorder.

disorders can be challenging as it requires the child to understand the test procedure and cooperate fully. As functional constipation usually results from withholding behaviour, in young children differentiating between subtypes of constipation is of less importance in clinical practice. In adolescents, dyssynergic defaecation is more common than in young children and should be ruled out in those who fail conventional treatment.

The most frequently used additional tests for childhood and adult constipation include laboratory testing, radiography, calculating colonic transit time, anorectal manometry, colonic manometry, contrast enema, the balloon expulsion test and defaecography. A more detailed description of the diagnosis (and management) of anorectal disorders is described elsewhere[52,53].

Laboratory testing. A complete blood count, biochemical profile, thyroid function and coeliac screening are only performed in the presence of alarm symptoms (BOX 2). The need for routine screening for cow's milk allergies and hypercalcaemia in children with functional constipation is not supported by current literature[27,82]. Serological testing for coeliac disease and thyroid function is indicated in children and adults with short stature or unexpected weight loss, persistent gastrointestinal symptoms or a positive first-degree family history[83,84]. Moreover, coeliac disease testing should be considered in adults with IBS[84].

Radiography. An abdominal X-ray to demonstrate an excessive colonic faecal load is still often used in an attempt to diagnose constipation[85]. The use of routine X-ray for the diagnosis of constipation is not recommended in children, however[27]. A systematic review showed a high variance in specificity and sensitivity of abdominal radiography in the detection of faecal impaction in children[86]. More importantly, it exposes patients to unnecessary radiation[87].

In adults, if abdominal CT or abdominal radiography has been performed for another indication (such as investigation of bloating or pain), the images could be used to obtain supportive evidence for clinically suspected rectal evacuation disorders by measuring the appearance of a rectal or pelvic gas shadow or stool located above the pelvic floor (approximately corresponding to the level of the ischial spines)[88]. A rectal gas area >900 mm^2 on a CT scan, the scout film of a CT scan or a plain abdominal radiograph has been reported to have 75% accuracy for predicting rectal evacuation disorder and might be useful for determining whether a patient should be referred for anorectal manometry or MRI defaecography[89]. Further replication of these findings at other centres is awaited. CT scanning should be avoided if possible, however, especially in young fertile women, as it exposes patients to a relatively high level of radiation compared with other tests for rectal evacuation disorders.

Colonic transit time. CTT is usually assessed using ingestion of radiopaque markers and is calculated based on the number and location of the remaining intra-abdominal markers visualized on abdominal X-ray images at specific intervals after ingestions. Another method of determining CTT is scintigraphy, which involves ingestion of a radioisotope to assess colonic transit[90]. Studies have shown that scintigraphy is an effective tool in differentiating between normal and abnormal colonic motor function in both children and adults with severe constipation, and that it is well tolerated in both paediatric (≥6 years) and adult patients[91,92]. However, to date, scintigraphy in children is less widely used than in adults since it is not widely available, is more expensive than a radiopaque marker transit test, and normative values in the paediatric population are lacking. CTT can also be calculated by tracking the movement of a radiation-free wireless motility capsule. A limitation for its use in children is that it requires a relatively large capsule to be swallowed[93] and only one study has shown its feasibility in children with upper gastrointestinal complaints[94]. This device is currently predominantly used in adults in the academic setting, where it seems to provide results comparable to radiopaque markers[93,95].

If the diagnosis of functional constipation is unclear in children presenting with faecal incontinence, CTT can be used to discriminate between faecal incontinence associated with functional constipation and that caused by functional nonretentive faecal incontinence[96,97].

In both children and adults, a delayed CTT indicates slow-transit constipation[98,99]. However, (segmental) colonic slow transit can also result from withholding behaviour in children[100] and from rectal evacuation disorders in adults[101]. Regional CTT (that is, the measurement of transit in specific colonic segments) has been used to differentiate between evacuation disorders and slow-transit constipation[102], but a 2017 study could not confirm these findings and showed that regional CTT

could not be used to exclude evacuation disorders in adults with chronic constipation[103]. Therefore, the use of the marker transit method to differentiate rectal evacuation disorder from slow-transit constipation is not recommended; further tests such as the balloon expulsion test or anorectal manometry are needed. It is hypothesized that faecal impaction might delay colonic motility, making it challenging to differentiate between slow-transit constipation and an evacuation disorder[27,104,105]; however, the limited evidence on the effect of routine bowel cleansing on CTT results remain contradictory.

Anorectal manometry. Anorectal manometry, which provides information about the neuromuscular function of the rectum and anal sphincter complex, is the most commonly performed motility test in young children presenting with constipation. In children, the test is often used to exclude Hirschsprung disease by assessing the presence of the recto-anal inhibitory reflex[27]. The test is indicated in infants with early onset of symptoms, delayed passage of meconium and a positive family history of Hirschsprung disease (BOX 2). However, children with a high suspicion of Hirschsprung disease should instead be referred for rectal suction biopsy. Parameters measured by anorectal manometry considered to be helpful in adults and children with constipation are resting pressure, squeeze pressure, rectal sensation and recto-anal inhibitory reflex (TABLE 2). In adults, the most common indication for anorectal manometry is to provide information on the anal sphincter pressure and defaecation technique in order to exclude dyssynergic defaecation[53]. The main drawback of the use of anorectal manometry for evaluating defaecation dynamics in children is that patients need to be awake and cooperative during the test. In young children, anorectal manometry is sometimes performed with the use of sedation or general anaesthesia. However, some anaesthetics can substantially reduce the anal resting pressure, which alters the test results[106]. Anorectal manometry is only performed in specialized centres, usually in an academic setting.

Colonic manometry. Interpretation of colonic manometry includes the evaluation of the presence and characteristics of HAPCs after a meal or after chemical stimuli (for example, stimulant laxatives)[107]. Although mostly performed in children in an academic setting, colonic manometry is a useful tool in both children and adults with intractable constipation to exclude neuromuscular motility disorders of the colon associated with slow-transit constipation[108,109]. Colonic manometry can be used in children and adults to identify colonic motility disorders and to evaluate the extent of colonic dysmotility, which can have consequences for medical and surgical management[107,110]. Owing to ethical concerns, normative data in the paediatric age group are lacking, complicating the interpretation of manometry studies in children. Furthermore, colonic manometry still remains an invasive test that is only performed in specialized clinics and hospitals, with wide variations in study protocols between centres[111].

Box 2 | **Alarm symptoms of constipation**

Alarm symptoms in children

- History
  - Delayed passage of meconium
  - Early onset (<1 month old)
  - Positive family history for Hirschsprung disease, coeliac disease or hypothyroidism
  - Blood in the stools
  - Ribbon stools
  - Fever
  - Bilious vomiting
- Physical examination
  - Failure to thrive
  - Severe abdominal distention
  - Abnormal anal or cremasteric reflex
  - Abnormal position of anus or gluteal cleft
  - Extreme fear of anal exam
  - Scars on anus
  - Anal fissures or haematoma
  - Abnormal neurological exam
  - Hair tuft on spine
  - Sacral dimple
  - Abnormal thyroid gland
  - Eczema

Alarm symptoms in adults

- History
  - Change in bowel habits
  - Unexplained iron deficiency anaemia
  - Recent sudden onset of symptoms
  - Blood in the stools
  - Unintentional weight loss
  - Family history of colon cancer or inflammatory bowel disease
  - Rectal tenesmus
- Physical examination
  - Abdominal or rectal mass
  - Cachexia
  - Jaundice
  - Lymphadenopathy
  - Abnormal thyroid gland

Contrast enema. Contrast studies of the colon can be useful to exclude anatomical abnormalities such as masses, megacolon and megarectum in both children and adults. In paediatric patients with severe refractory symptoms this test is sometimes used to guide surgical interventions by providing information on the anatomy and colonic length and dilatation[112].

Colonoscopy. Endoscopy is not recommended in the investigation of children with functional constipation[83]. In adults, routine colonoscopy is not warranted and should only be considered in patients with alarm symptoms that could indicate malignancy (for example, sudden change of bowel habits, bloody stools, unexpected weight loss, family history of colon cancer or inflammatory bowel disease, and unexplained anaemia) and those who are not up to date with colon cancer screening after the onset of constipation[52].

Balloon expulsion test. The balloon expulsion test is a reliable method to screen for pelvic floor dyssynergia in adults. This test is not commonly performed in young

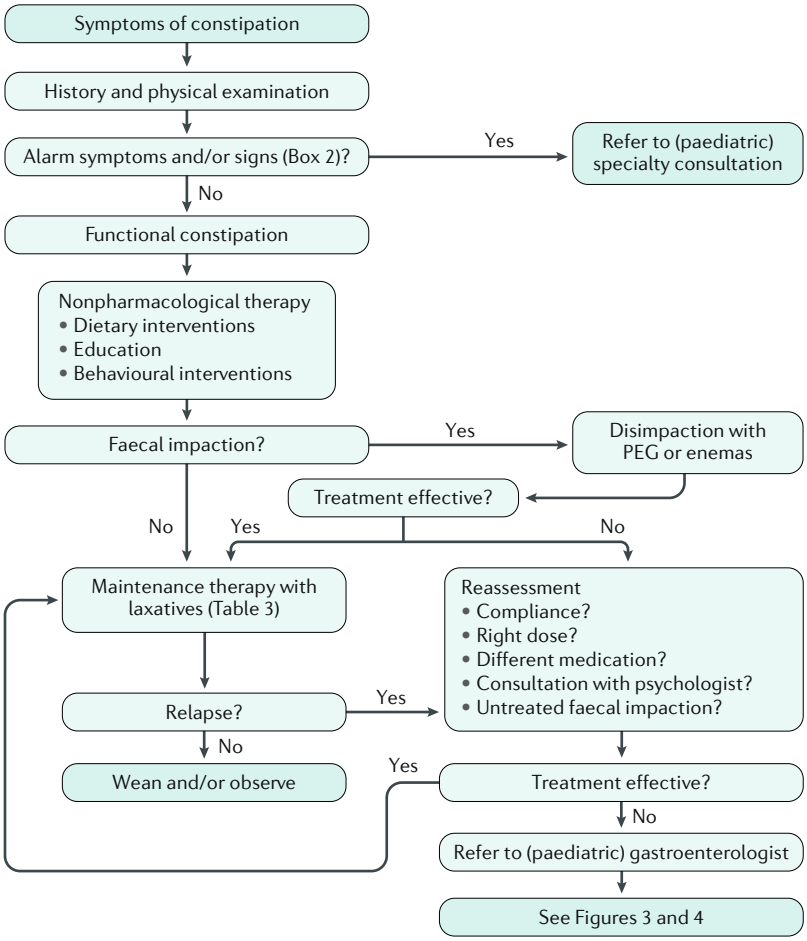

Fig. 2 | **Algorithm for initial presentation of symptoms of constipation.** A suggested stepwise approach for the evaluation and treatment of children and adults presenting with constipation. PEG, polyethylene glycol. Modified with permission from REF.[79], Wiley-VCH, and REF.[27] (Tabbers, M. M. *et al.* Evaluation and treatment of functional constipation in infants and children: Evidence-based recommendations from ESPGHAN and NASPGHAN. *J. Pediatr. Gastroenterol. Nutr.* **58**, 258–274, 2014), Wolters Kluwer.

children (that is, <5 years of age)[113] because it requires a high level of cooperation by the patient[114]. In adults, a 40- to 50-ml balloon is normally evacuated in less than 60 s (REF.[115]).

Defaecography. Defaecography is indicated in adults when the results of anorectal manometry and rectal balloon testing are inconsistent with clinical symptoms[116]. Defaecography is seldom performed in children as it requires patient cooperation and because of the large exposure to radiation. Defaecography includes imaging of the anorectum and attempted defaecation after infusing barium contrast into the rectum. This test provides dynamic information on pelvic floor function and assessment of the effectiveness of rectal evacuation[52]. Moreover, the test is also used to identify anatomical abnormalities such as rectocele, enterocele and (uterovaginal) prolapses and to follow up on surgical corrections of such abnormalities[116]. MRI defaecography is an alternative to defaecography and provides more detailed information on anorectal function during defaecation without the disadvantage of radiation. This test is usually avoided in younger children because it requires children to lie still for several minutes and can involve sedation; also, it is not widely available[116].

Management

In both children and adults, nonpharmacological management is the first step in the treatment of functional constipation. This step includes education and lifestyle adjustments such as dietary recommendations, regular physical activity and advice on toileting posture and behaviour. An overview of the management of functional constipation in children and adults is provided[27,79] (FIGS 2,3,4).

Dietary interventions

Dietary recommendations, including the need for a normal fibre and fluid intake, are the first interventions in the treatment of constipation. According to the recommendations of the ESPGHAN/NASPGHAN guidelines for children with functional constipation, an increase in fibre intake above the normal requirements is not beneficial, so a normal intake of fibre is advised[27]. Most children and adults fail to meet the daily fibre recommendations (0.5 g/kg per day for children aged >5 years[117], and 14 g per 1,000 kcal in adults[118]); however, so fibre intake should be addressed[119,120]. Two systematic reviews in adults with functional constipation reporting on the efficacy of fibre supplementation found that fibre supplementation showed beneficial effects over placebo or no treatment and is therefore recommended[121,122].

Prebiotics and probiotics (for example *Bifidobacterium* and *Lactobacillus* species) have been suggested as a potential treatment modality for functional constipation and have been reported to have a positive effect on colonic transit and defaecation frequency[123,124]. However, owing to the large heterogeneity in studies and lack of randomized controlled trials, several systematic reviews including multiple studies in children and adults found limited evidence for the role of prebiotics and probiotics in the treatment of functional constipation[125–130].

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (a FODMAP diet), which restricts the intake of poorly absorbable carbohydrates, has been found to be helpful in adults and children with IBS[131]; however, no data are yet available on the effect of such a diet in patients with functional constipation. Furthermore, this diet has limitations for its use, particularly in the paediatric population, owing to the risk of dietary deficiencies and difficulties with dietary adherence[132].

Education and behavioural therapy

Counselling of children and parents is crucial in the treatment of childhood constipation, including education about the role of withholding behaviour and the concept of overflow incontinence. A structured toilet-training programme with a reward system, instructing the child to attempt to defaecate at least two or three times daily (after each meal), has been found to prevent the occurrence of faecal impaction and to decrease the risk of faecal incontinence[133]. For children, parental

Table 2 | **Parameters measured by anorectal manometry in patients with constipation**

Parameter	Children	Adults
Resting pressure	High resting anal sphincter pressure (>90 mmHg) is highly suggestive of hypertonic sphincter and withholding behaviour	If performed correctly with a cooperative patient, high resting anal sphincter pressure (>90 mmHg) and highly negative anorectal pressure differential (more negative than −50 mmHg) could be suggestive of rectal evacuation disorder
Squeeze pressure	Only performed when cooperative	High squeeze sphincter pressure can be caused by concurrent anal fissure
Rectal sensation	Only performed when cooperative; reduced rectal sensation is most often a result of megarectum owing to prolonged faecal retention secondary to withholding behaviour	Reduced rectal sensation in most patients presenting with constipation (rather than faecal incontinence) is most often a result of megarectum owing to prolonged faecal retention secondary to a rectal evacuation disorder; ideally, rectal hyposensitivity should be confirmed with rectal barostat procedure
Recto-anal inhibitory reflex	The most common reason for an absent recto-anal inhibitory reflex is Hirschsprung disease	The most common reason for an absent recto-anal inhibitory reflex is megarectum

child-rearing attitudes towards faecal incontinence, such as frustration and overprotection, should be discussed as they can be associated with constipation[77]. In children who also have behavioural problems, behavioural therapy should be considered[134].

In adolescents and adults, including the elderly, behavioural therapy is mainly focused on restoring the mechanisms of normal defaecation and is recommended in patients with functional constipation caused by dyssynergic defaecation[52]. In such adults, behaviour modifications such as taking time to defaecate and promptly responding to the urge to defaecate are needed to prevent impairment of rectal sensation and function.

Biofeedback training and physiotherapy are interventions aimed at gaining better control over the pelvic floor muscles that have a role in the process of defaecation. Biofeedback training is not routinely recommended in young children with functional constipation owing to insufficient evidence, partly because of the heterogeneity between studies in children[135]. A randomized controlled trial (RCT) including 53 children suggested that pelvic floor physiotherapy in addition to standard medical therapy is more successful in the treatment of functional constipation than is standard medical therapy alone[136]. However, more research is necessary to confirm these promising findings.

In adults and adolescents, biofeedback training is beneficial in patients with functional constipation and dyssynergic defaecation[137]. Several RCTs have demonstrated that in adults with constipation biofeedback therapy is superior to placebo or standard treatment approaches including diet, education and laxatives[138–140]. In the elderly population in particular, sensory training in patients with abnormalities of rectal sensation is beneficial and can help to facilitate stooling[137].

Pharmacological interventions

Pharmacological treatment of children with functional constipation involves two steps: faecal disimpaction followed by maintenance therapy. Faecal disimpaction can be achieved with high-dose oral polyethylene glycol (PEG) or enemas containing active ingredients such as sodium phosphate, sodium lauryl sulfoacetate or sodium ducosate. Both options are equally effective in children; however, not all children tolerate rectal enemas and the oral route is, therefore, recommended in this population, despite high-dose PEG being associated with an increased risk of faecal incontinence[27]. After successful disimpaction, maintenance therapy is advised to prevent repeat accumulation of stools. Faecal disimpaction is less often required in adults, but the approaches are similar and commonly used oral treatments include large doses of PEG or magnesium citrate. Alternatives to enemas in children and adults are suppositories containing glycerine or bisacodyl.

Osmotic laxatives are the first-choice maintenance therapy recommended for functional constipation[27,52]. PEG is the osmotic agent of choice for both children and adults owing to its effectiveness and perceived safety[141,142]. Safety issues with respect to the long-term use of PEG in children have, however, now been raised owing to reports of associated behavioural problems and the detection of potential neurotoxins (ethylene glycol and diethylene glycol) in PEG 3350 (REF.[141]). Investigating these concerns, a 2018 study found no sustained elevated blood levels of these neurotoxins in children who received daily PEG 3350 compared with healthy individuals as controls[143]. The FDA is currently still investigating these potential safety issues, but stated that no action is currently required based on the available data.

Other frequently used laxatives are mineral oil (a lubricant) and milk of magnesia (magnesium hydroxide). If symptoms persist, stimulant laxatives such as bisacodyl or senna are recommended in clinical guidelines in both children and adults[27,52]. The pharmacological agents most commonly used for the treatment of functional constipation are listed in TABLE 3.

Health care professionals report adherence to therapy as one of the most challenging aspects of treating children and adults with functional constipation[144]. A cross-sectional survey study of 115 children treated with PEG showed that only 37% of patients were compliant with therapy[145]. Even among those who adhere to treatment,

some will remain symptomatic. A systematic review reported that 40% of children treated for functional constipation were still symptomatic after 6–12 months of treatment[146]. Long-term follow-up studies (median follow-up of 11 years) show that 25% of children still experience symptoms of constipation as adults[13] and many continue to have severe symptoms[14]. Long-term follow-up studies in adults with functional constipation are lacking, but more than half of adult patients report to be dissatisfied with their current treatment owing to lack of efficacy and adverse effects[147–149]. Thus, novel pharmacological treatments for functional constipation are needed.

New pharmacological interventions

Over the past few years, several new therapeutic agents have been proposed and some approved for the management of functional constipation.

These novel drugs show promise in the treatment of functional constipation, but as pharmacokinetics and pharmacodynamics might differ between children and adults owing to differences in physiology and mechanisms of drug clearance[150], extrapolation of data regarding safety and efficacy generated from adults to the paediatric population requires great care. Outcome measures can differ widely between studies in paediatric and adult populations. For example, faecal incontinence is usually an important endpoint in paediatric studies, whereas the occurrence of this symptom is negligible in adults with functional constipation. Moreover, the lack of high-quality placebo-controlled RCTs, especially in the paediatric population, make it challenging to explore the benefits of these newer treatment strategies. The costs of these novel drugs, in comparison with the relatively inexpensive available agents, should also be taken into account. More comparative studies, including cost–effect analyses, between the relatively new and expensive agents and the available conventional laxatives are needed to elucidate their role in clinical practice. Recommendations for the design of future clinical trials are provided elsewhere[151].

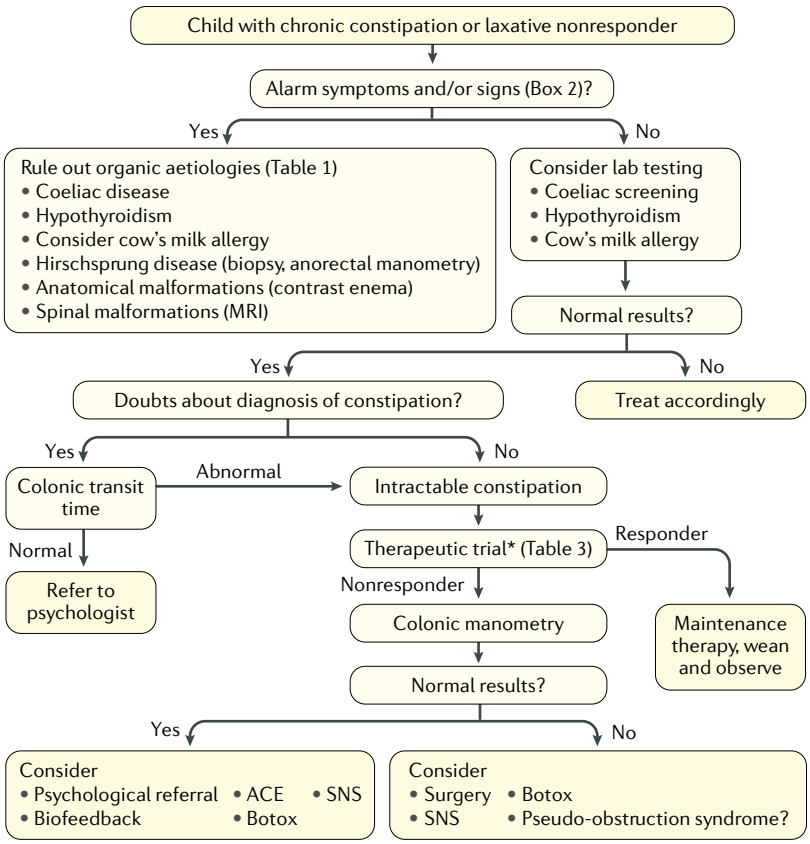

Fig. 3 | **Algorithm for children referred to a paediatric gastroenterologist with chronic functional constipation.** A suggested stepwise approach for the evaluation and management of children with chronic functional constipation who do not respond to conventional strategies. ACE, antegrade continence enema; SNS, sacral nerve stimulation. *Assess compliance and dosage, use of other medication and combination therapy. Modified with permission from REF.[79], Wiley-VCH, and REF.[27] (Tabbers, M. M. *et al.* Evaluation and treatment of functional constipation in infants and children: Evidence-based recommendations from ESPGHAN and NASPGHAN. *J. Pediatr. Gastroenterol. Nutr.* **58**, 258–274, 2014), Wolters Kluwer.

Prosecretory agents. Prosecretory agents such as lubiprostone, linaclotide and plecanatide modulate epithelial channels in the gut, promoting the intestinal secretion of fluids and enhancing stool volume, resulting in an improvement in gastrointestinal transit[152].

Lubiprostone induces intestinal fluid secretion by activating the CIC-2 chloride channel and cystic fibrosis transmembrane conductance regulator[153,154]. Multiple RCTs in adults with functional constipation have shown that this drug is safe and increases bowel movement frequency[155–158]. Only one study in the paediatric population has been published — an open label noncontrolled study showing that 4 weeks of treatment with lubiprostone resulted in increased defaecation frequency in 127 children with functional constipation[159]. However, in early findings (published in abstract form) from a double-blind, placebo-controlled, multicentre study, 12 weeks of treatment with lubiprostone in children with functional constipation did not result in a statistically significant improvement in bowel movement frequency (to more than three times per week) over control treatment (placebo). Lubiprostone was safe and well tolerated and had statistically significant beneficial effects on secondary outcome points, such as straining, stool consistency and pain during defaecation[160,161].

Linaclotide promotes intestinal fluid secretion by activating the guanylate cyclase C receptor. It improves defaecation frequency in adults with functional constipation and is approved for use in the United States and Europe[162,163]. Plecanatide is a new guanylate cyclase C receptor agonist approved in the United States that is well tolerated in adults[164,165]. A double-blind phase III RCT in adults with functional constipation showed that 12 weeks of plecanatide was associated with a substantial improvement in bowel movement frequency, stool consistency and abdominal symptoms compared with placebo[166]. The most frequently reported adverse effects were diarrhoea and urinary tract infections[164,166]. No data are available on the use of linaclotide and plecanatide in the paediatric population.

Serotonergic agents. A number of 5-hydroxytryptamine 4 (5-HT_4) agonists have been developed to treat functional constipation. Serotonin (5-HT) is a central and enteric neurotransmitter that binds to the 5-HT_4

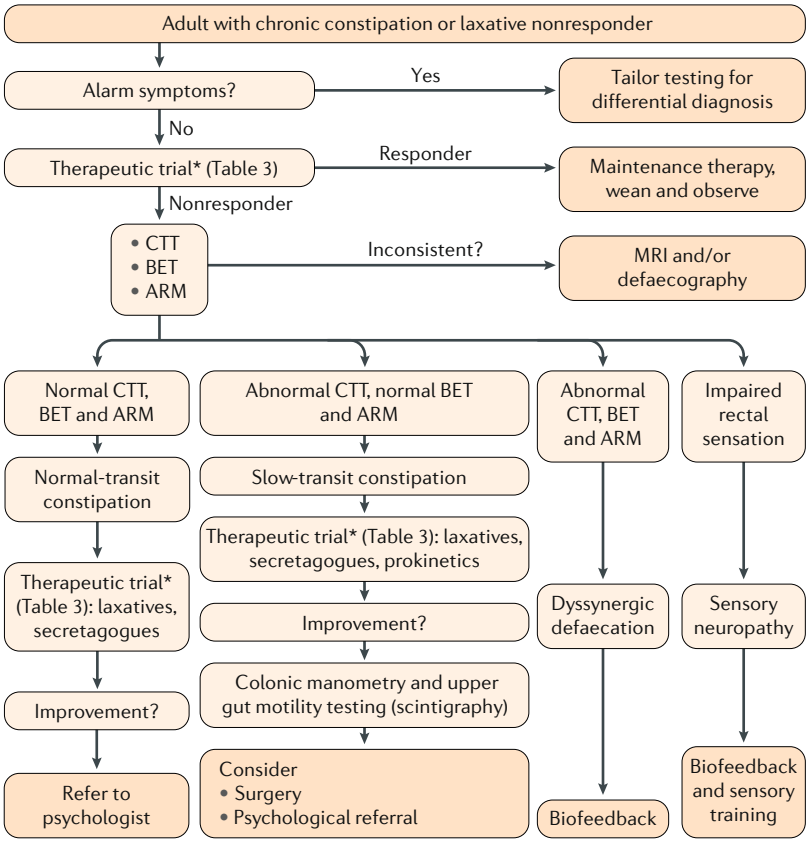

Fig. 4 | **Algorithm for adults referred to a gastroenterologist with chronic functional constipation.** A suggested stepwise approach for the evaluation and management of adults with chronic functional constipation who do not respond to conventional strategies. ARM, anorectal manometry; BET, balloon expulsion test; CTT, colonic transit time. *Assess compliance and dosage, use of other medication and combination therapy. Modified with permission from REF.[79], Wiley-VCH, and REF.[27] (Tabbers, M. M. *et al.* Evaluation and treatment of functional constipation in infants and children: Evidence-based recommendations from ESPGHAN and NASPGHAN. *J. Pediatr. Gastroenterol. Nutr.* **58**, 258–274, 2014), Wolters Kluwer.

receptors in the gut, increasing the release of acetylcholine and resulting in an increased secretion and gut motility[167]. Moreover, serotonin also increases motility by initiating the gastrocolic reflex by stimulating the afferent nerves in the mucosa[168].

Prucalopride is a highly selective serotonin 5-HT_4 receptor agonist which functions as a prokinetic agent. In adults with functional constipation, prucalopride has been reported to be tolerable and safe without the occurrence of cardiovascular adverse effects[169,170], which were reported after use of other prokinetic agents such as cisapride and tegaserod[171,172]. In a 2016 systematic review including multiple RCTs, prucalopride successfully increased the number of bowel movements per week in adults with chronic functional constipation[173]. Only two published studies have evaluated the effect of prucalopride in children with functional constipation and the results have been less successful. One open-label, nonplacebo-controlled study showed that prucalopride was associated with an improvement in defaecation frequency, stool consistency and faecal incontinence frequency in 37 children with functional constipation after 8 weeks of treatment[174]. However, a placebo-controlled RCT in 213 children with functional constipation did not find a statistically significant improvement in bowel movement and frequency of faecal incontinence[175]. It is conceivable that this result reflects the high prevalence of stool withholding in children with functional constipation; a prokinetic drug would not be expected to overcome withholding behaviour. This finding is also consistent with the observation that prucalopride was not superior to PEG 3350 in a study in adults with functional constipation who had dominant symptoms consistent with rectal evacuation disorders (98% showed straining ≥25% of the time, >95% had a sense of incomplete rectal evacuation ≥25% of the time, >50% had a sense of anal blockage on ≥25% of defaecations, and >15% performing manual disimpaction in ≥25% of defaecations)[176].

Velusetrag and naronapride are selective 5-HT_4 receptor agonists not yet approved by the FDA that have been shown to increase bowel movement frequency in adults with chronic constipation in phase II studies[177,178]. No published studies have investigated the use of these agents in children.

Bile acids. Endogenous deconjugated bile salts increase fluid secretion and colonic motility. Normally, bile salts are reabsorbed into the small intestine via the apical ileal bile acid transporter and ~5% pass into the colon where they are deconjugated and dehydroxylated. Chenodeoxycholic acid, a primary bile acid, was shown to be effective in improving stool consistency in adults with IBS[179]. In children with functional constipation, Hofmann et al.[180] showed an altered faecal chenodeoxycholic acid profile, suggesting a possible role of bile acids in the pathophysiology of functional constipation but, to date, no studies on the use of bile acids have been performed in children with functional constipation. Elobixibat, an ileal bile acid transporter inhibitor, has been shown to increase defaecation frequency and accelerate CTT in several phase III studies in adults with functional constipation[181–183]. Two large, multicentre phase III trials, ECHO 1 and ECHO 2, were terminated early because of a distribution issue with the trial medication. Moreover, long-term safety issues concerning a theoretical risk of colorectal cancer owing to increased bile acid concentration exposure needs to be investigated, although currently available evidence is reassuring[184]. Paediatric studies of elobixibat are yet to be performed.

Cholinesterase inhibitors. Acetylcholinesterase inhibitors such as pyridostigmine increase gastrointestinal motility by increasing the availability of acetylcholine. Pyridostigmine has been used for the treatment of small cohorts of adults with severe slow-transit constipation[185,186]. One published case series of pyridostigmine in four children with gastrointestinal motility disorders suggested a beneficial effect on defaecation frequency in one patient with chronic constipation[187].

Transanal irrigation

Transanal irrigation is a treatment typically used in children with functional constipation who are unresponsive to pharmacological treatment[188]. During transanal

Table 3 | **Pharmacological agents for childhood and adult functional constipation**

Drug	Evidence	Adverse events	Dosage in children	Dosage in adults
Osmotic laxatives				
Lactulose	Improvement of symptoms of mild to moderate constipation; safe to use in pregnancy and young children	Abdominal gas, bloating and cramping	7 months to 18 years: 1–2 g/kg per day in 1–2 doses	12–24 g per day
Polyethylene glycol without electrolytes: PEG 4000	Improves consistency and frequency of stools, and straining	Diarrhoea and abdominal distention	Maintenance: 0.3–0.8 g/kg per day; disimpaction: 1–1.5 g/kg per day (for maximum of 7 days)	Maintenance: 10–20 g per day; disimpaction: 80 g per day (for maximum of 3 days)
Polyethylene glycol with electrolytes: PEG 3350	Improves consistency and frequency of stools, and straining	Diarrhoea and abdominal distention	Maintenance: 0.3–0.8 g/kg per day; disimpaction: 1–1.5 g/kg per day (for maximum of 7 days)	Maintenance: 10–20 g per day; disimpaction: 80 g per day (for maximum of 3 days)
Milk of magnesia (magnesium hydroxide)	Evidence of efficacy is poor	Diarrhoea; excessive use, particularly in elderly patients and those with renal insufficiency, might lead to electrolyte disturbances	2–5 years: 0.4–1.2 g per day; 6–11 years: 1.2–2.4 g per day; 12–18 years: 2.4–4.8 g per day	2–5 g per day
Lubricants				
Mineral oil (liquid paraffin)	Evidence supports efficacy of mineral oil, but quality of studies is poor	Skin irritation and reduced absorption of fat-soluble vitamins; be vigilant for lipid pneumonitis with aspiration if ingested in reclined body position	1–3 ml/kg per day (maximum 90 ml per day	15–45 ml per day
Stimulant laxatives				
Bisacodyl (diphenylmethane)	Evidence supports effect on improvement of symptoms	Diarrhoea and abdominal pain	3–10 years: 5 mg per day in 1 dose before bedtime; >10 years: 5–10 mg per day in 1 dose before bedtime	5–10 mg per day in 1 dose in the evening
Sodium picosulfate (diphenylmethane)	Evidence supports effect on improvement of symptoms	Diarrhoea and abdominal pain	4–5 years: 3 mg; >6 years: 4–6 mg per day in 1 dose	4–6 mg per day in 1 dose
Senna (anthraquinone)	Clinical experience suggests that senna is effective and well tolerated, but no large randomized trials have been performed	Diarrhoea and abdominal pain; in young children, senna could induce dermatitis	2–6 years: 2.5–5 mg/day in 1–2 doses; 6–12 years: 7.5–10 mg/day in 1–2 doses; >12 years: 15–20 mg/day in 1–2 doses	185–370 mg per day
Prosecretory agents				
Lubiprostone	Limited evidence in children; improvement of stool frequency and consistency, and reduced straining and bloating in adults	Nausea	Off-label use	24 μg twice daily
Linaclotide	Limited evidence in children; improvement of stool frequency and consistency in adults	Diarrhoea	Off-label use	145–290 μg per day
Plecanatide	Limited evidence in children; improvement of symptoms in adults	Diarrhoea	Off-label use	3–6 mg per day
Serotonergic agents				
Prucalopride	Limited evidence in children; improvement of stool frequency, consistency and straining in adults	Headache, nausea, diarrhoea and abdominal pain	Off-label use	1–2 mg per day
Rectal laxatives				
Bisacodyl	Evidence supports beneficial effect on faecal impaction	Abdominal pain and anal discomfort	3–10 years: 5 mg per day in 1 dose before bedtime; >10 years: 5–10 mg per day in 1 dose before bedtime	5–10 mg per day in 1 dose in the evening

Table 3 (cont.) | **Pharmacological agents for childhood and adult functional constipation**

Drug	Evidence	Adverse events	Dosage in children	Dosage in adults
Rectal laxatives (cont.)				
Sodium phosphate	Evidence supports beneficial effect on faecal impaction	Water and electrolyte disturbances, especially in young children and elderly; do not use in patients with suspicion of Hirschsprung disease	2.5 ml/kg (maximum of 133 ml per dose)	133 ml per dose
Sodium docusate	Evidence supports effect on faecal impaction	Abdominal pain and anal discomfort	<6 years: 60 ml; >6 years: 120 ml	120 ml
Sodium lauryl sulfoacetate	Evidence supports effect on faecal impaction	Abdominal pain and anal discomfort	1 month to 1 year: 2.5 ml/dose (=0.5 enema); 1–18 years: 5 ml/dose (=1 enema)	5 ml/dose (=1 enema)

irrigation, a catheter or cone is inserted into the rectum to infuse water, thereby flushing the colon, resulting in a thorough clean out. Transanal colonic irrigation is well established for use in patients with neurogenic bowel disorders and anorectal malformations[189,190]. Data on the efficacy of transanal irrigation in patients with a functional aetiology of constipation is limited. In paediatric cohort studies, including small populations of children with functional constipation, transanal irrigation has been suggested to be effective in the treatment of faecal incontinence and constipation symptoms[191–194] and high parental satisfaction has been reported[195].

Similar results have been described in adults with functional constipation. A study that surveyed 102 adults with functional constipation showed that patients perceived the use of transanal irrigation as effective and safe[196]. Thus, when lifestyle and medical strategies fail, transanal irrigation should be considered as a valuable therapeutic alternative for children and adults with functional constipation.

Surgical interventions

Surgery for functional constipation is regarded as a therapy of last resort and is only considered when maximal conventional therapies have failed and symptoms are greatly disrupting quality of life[27,52]. To date, surgical approaches differ widely between physicians[111]. Generally, a step-up approach is used to decide between the different surgical procedures, beginning with the strategy that is least invasive. A systematic review summarizing current surgical strategies for children has been published elsewhere[197]. In adults, the steps in the algorithms leading to consideration of laparoscopic colectomy with ileorectostomy have been summarized elsewhere[198], including in a consensus guideline from Canada[199].

Antegrade continence enemas. Antegrade continence enemas (ACEs) can be used to achieve antegrade colonic irrigation. ACEs enable flushing of fluids with or without added laxatives through an external opening into the colonic lumen. The most commonly utilized procedures to establish an ACE are the percutaneous cecostomy and the Malone appendicocecostomy. ACE surgery is considered minimally invasive and good clinical outcomes have been reported in children[197]. Although it has been suggested that patients with colonic dysmotility had lower success rates than patients without colonic dysmotility[200,201] after ACE, King et al.[202] showed that ACEs were successful in 81% of 42 children with slow-transit constipation. By comparison, reported success rates in adults with functional constipation are much lower. Two studies in adults with functional constipation reported a success rate of 42% and 50%, respectively[203,204]. Moreover, in adults, stoma stenosis is common in patients who have undergone ACE surgery and patients often require further surgical revision[205].

Ostomies and resection. When minimally invasive surgical therapies fail in children and adults (that is, in cases of intractable functional constipation), ileostomy, colostomy or total colectomy are considered. However, the decision regarding the type of surgical procedure to perform remains challenging and differs widely between centres. Colonic manometry is sometimes used before surgery to identify colonic inertia and to determine the extent of colonic dysmotility[108,206,207]. Results of manometry can help in guiding the extent of colonic resection. Moreover, motility testing can discriminate between patients who would benefit from a colostomy (short, distal segment) and those who need an ileostomy (long colonic segment) and can be valuable in deciding the need for and timing of diversion[206,208,209].

In children, the decision regarding surgery type is often based on the presence of dysmotility and colonic dilation based on manometry and contrast enema results[205]. In the presence of a megarectum or megasigmoid, a rectosigmoid resection has been shown to be effective in children[205]. Children with colonic dysmotility or slow-transit constipation can benefit from a total or subtotal colectomy, sometimes in combination with an ACE[52,210]. A study involving 37 children with intractable functional constipation who were treated with either ileostomy, colostomy, sigmoid resection or subtotal colectomy at a single centre reported a high postoperative parental satisfaction rate of 91%[211].

In adults, surgical options are available for patients with slow-transit constipation or evacuation disorders but published evidence is limited[212–215]. Adults with normal-transit functional constipation are less likely than those with slow-transit constipation or evacuation disorders to benefit from surgery, and diagnosis of the

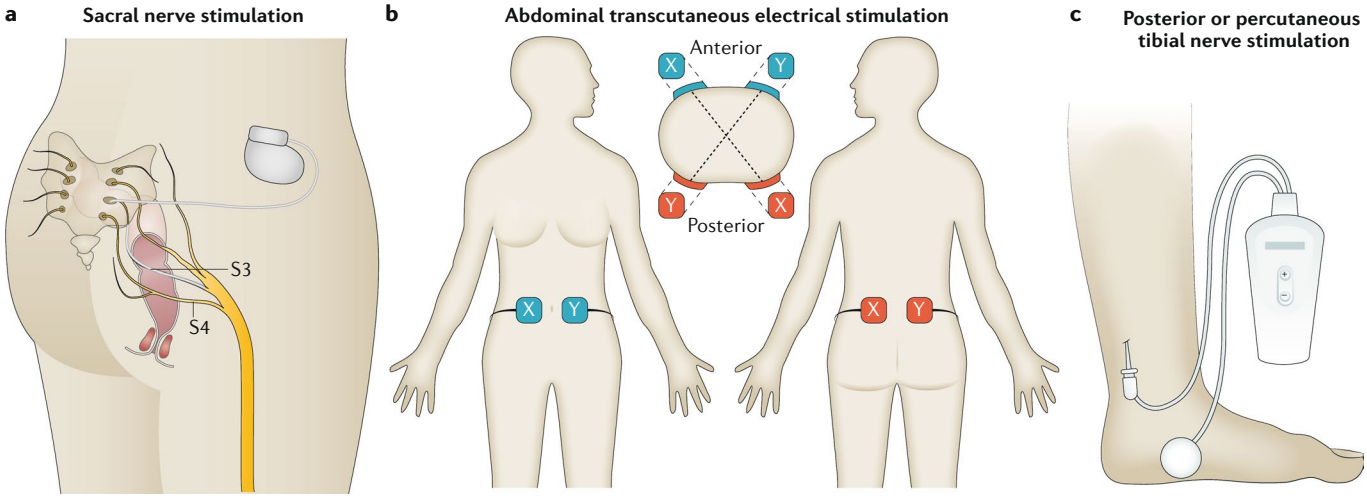

Fig. 5 | **Different methods of neuromodulation for functional constipation. a** | Sacral nerve stimulation involves the subcutaneous placement of a stimulator device with a lead into the sacral foramen, stimulating the sacral nerves S3 and S4. **b** | Abdominal transcutaneous electrical stimulation includes stimulation of electrode pads applied across the skin of the abdomen and lower back. **c** | Posterior or percutaneous tibial nerve stimulation involves (bilateral) stimulation of the posterior tibial nerve by inserting a needle electrode at the level of the medial malleolus, indirectly stimulating the sacral nerves. Panel **a** adapted from REF.[253], Springer Nature Limited. Panel **b** adapted with permission from REF.[254], Elsevier.

correct subtype of functional constipation is therefore crucial for the surgical management of adults with constipation. In adults with slow-transit constipation who do not have dyssynergic defaecation, a colectomy might be useful when the functional constipation is refractory to all nonsurgical treatment[205,213]. Success rates of 50–100% after total abdominal colectomy in adults with ileorectal anastomosis have been described[216]. Unfortunately, a wide variation in the definition of success (satisfaction, patient report, symptoms, and so forth) was used in these studies. A systematic review showed high satisfaction rates of 86% in adults with slow-transit constipation after a colectomy procedure[217]. Upper gastrointestinal motility disorders in patients with intractable constipation can negatively influence outcomes after the colectomy procedure and should therefore be ruled out[218].

For adults with pelvic floor dyssynergia who are unresponsive to conservative therapy, therapies to improve dyssynergia such as biofeedback should be considered before subtotal colectomy. In adults with rectal anatomical abnormalities (for example, prolapse or rectocele), repair of the outlet obstruction is recommended[216]. An ileostomy should be considered as a last resort[52].

Neuromodulation

Over the past two decades, developments have resulted in the growing use of neuromodulation as a viable treatment strategy for patients with intractable functional constipation. Available strategies of neuromodulation include sacral nerve stimulation (SNS), abdominal transcutaneous electrical stimulation (TES) and posterior or percutaneous tibial nerve stimulation (PTNS) (FIG. 5). SNS involves the subcutaneous placement of a stimulator device with a lead into the sacral foramen, stimulating the sacral nerves S3 and S4 (FIG. 5a). The efficacy of SNS on both urinary and faecal incontinence in paediatric and adult patients is well established[219–223], but its mechanism of action and role in the treatment of constipation symptoms is less clear[221,224]. SNS is hypothesized to be effective because of its influence on anorectal function at a peripheral and central level[225]. Small cohort studies in children with functional constipation have shown promising effects of SNS on defaecation frequency[226,227]. A long-term follow-up study in children with heterogeneous aetiologies of constipation showed no statistically significant improvement in defaecation frequency after 2 years of SNS treatment; however, faecal incontinence rates decreased from 72% to 20%[228].

In adults, SNS for functional constipation has been available for a longer period, but results have been conflicting. Several studies have shown its efficacy in improving defaecation frequency in patients with normal-transit functional constipation, slow-transit functional constipation and rectal evacuation disorders[229–233]. Furthermore, one long-term study in adults with functional constipation showed that improvement in bowel movement frequency and sensation of incomplete emptying was sustained at over 60 months of follow-up[234]. However, results of an RCT comparing SNS with sham stimulation in adults with slow-transit constipation showed no benefit of SNS over sham stimulation on defaecation frequency after 3 weeks, 1 year and 2 years of follow-up[235,236].

Although SNS is considered a minimally invasive surgical procedure, high rates of device-related adverse events have been reported including pain, haematoma, infection, and displacements of the leads, sometimes requiring surgical revision[237]. SNS remains a specialized and expensive procedure and more prospective studies with long-term follow-up are needed to provide

a better assessment of the efficacy and safety of SNS as a treatment for constipation.

Abdominal TES and PTNS use noninvasive or minimally invasive methods of stimulation. TES involves stimulation of electrode pads applied across the skin of the abdomen and lower back (FIG. 5b). The stimulation is usually performed by trained physiotherapists, but is now available in a home-based setting[238]. In an RCT comparing 4 weeks of TES with 4 weeks of sham stimulation in children with slow-transit constipation, CTT and quality of life scores improved substantially, but defaecation frequency did not improve[239,240]. Colonic manometry studies showed an increase in HAPCs after 2 months and 7 months of TES in eight children with slow-transit constipation[241]. One long-term follow-up study found that 33% of children with slow-transit constipation had statistically significant improvement in bowel movement consistency and faecal incontinence after 2 years of treatment with TES[242]. A randomized study comparing 4 weeks of TES with 4 weeks of sham TES in adults with slow-transit constipation showed that defaecation frequency significantly increased (from 3.71 per week at baseline to 5.64 per week after 4 weeks of treatment, $P < 0.05$) with TES treatment[243].

PTNS involves (bilateral) stimulation of the posterior tibial nerve by inserting a needle electrode at the level of the medial malleolus (FIG. 5c), indirectly stimulating the sacral nerves. Findings from studies investigating PTNS in children with faecal and urinary incontinence[244,245] and adults with constipation[246–249] remain conflicting and this treatment modality is currently reserved for the academic setting. Future studies are needed to determine the efficacy of these treatment modalities on functional constipation.

Future therapies

Novel alternative therapies including acupuncture and faecal microbiota transplantation have been suggested to show potential for the treatment of adults with functional constipation. However, current guidelines do not yet support the use of these treatments in the management of functional constipation and more studies are needed.

Acupuncture. Several Chinese studies have been published on the use of acupuncture for adults with chronic constipation[250]. A randomized, parallel, sham-controlled study of 1,075 adults with functional constipation showed major improvements in spontaneous bowel movement frequency (an increase of 1.76 bowel movements per week, 95% CI 1.61–1.89) in the acupuncture group compared with the control group after 8 weeks of treatment[251]. Long-term follow-up of these patients was not included in this study.

Faecal microbiota transplantation. Owing to possible alterations in the gut microbiota in patients with functional constipation, faecal microbiota transplantation (that is, the administration of faecal bacteria from a healthy donor into the intestinal tract of a recipient) has been suggested as a possible therapy for constipation. One study showed promising short-term improvements in defaecation frequency, CTT and quality of life in 52 adults with slow-transit constipation. However, after 12 weeks of therapy these effects were no longer seen[252].

Conclusions

Functional constipation is highly prevalent in children and adults. Many predisposing factors, including lifestyle and psychological abnormalities, are similar in children and adults, but there are important pathophysiological differences. Children with functional constipation often have symptoms of faecal incontinence, and childhood functional constipation usually results from withholding behaviour. Therefore, in children, there is little need for additional diagnostic testing. Parental influences and behavioural disorders are predisposing factors and children often benefit from family-based strategies including a structured toilet-training programme and behavioural interventions. By contrast, adults with functional constipation present with infrequent and hard bowel movements and less often report symptoms of incontinence. In adults, additional testing is often indicated to identify underlying disorders and to establish a diagnosis of normal-transit constipation, slow-transit constipation or pelvic floor dysfunction, which has therapeutic consequences.

The first-choice therapies for both children and adults with functional constipation include lifestyle interventions and osmotic laxatives. However, some patients do not benefit from these drugs, partly because of low compliance rates. New pharmacological interventions that target the pathophysiology of functional constipation have been well investigated in adults; however, data in children are limited and contradictory. Several types of neuromodulation strategies have shown promise in functional constipation. If conventional management fails, surgery might be beneficial. To date, no clear guidelines exist on the surgical management of functional constipation and procedures vary widely between children and adults.

Differences in response to conventional strategies such as biofeedback therapy and pharmacotherapy, and different surgical outcomes after neuromodulation and ACE surgery, suggest that childhood functional constipation is a different entity from adult functional constipation. Comparing findings from clinical trials between children and adults with functional constipation is challenging owing to age-related differences in drug pharmacokinetics and pharmacodynamics, differences in paediatric and adult Rome IV criteria, and differences in primary endpoints in studies (such as the component of faecal incontinence in children but not in adults). High-quality placebo-controlled RCTs with uniform diagnostic criteria are needed to explore the benefits of new treatment strategies for children and adults with intractable constipation. Finally, long-term follow-up studies are needed to improve our understanding of the prognosis and disease course of functional constipation.

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Author contributions
M.H.V. researched data for the article. All authors were involved in the writing and review/editing of the manuscript before submission.

Competing interests
M.A.B is a consultant for Shire, Norgine, Coloplast, Danone, Takeda, Allergan, FrieslandCampina, and Novalac. The remaining authors declare no competing interests.

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