

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Irritable bowel syndrome in children: Pathogenesis, diagnosis and evidence-based treatment

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Abstract

Irritable bowel syndrome (IBS) is the commonest cause of recurrent abdominal pain (RAP) in children in both more developed and developing parts of the world. It is defined by the Rome III criteria for functional gastrointestinal disorders. It is characterized by abdominal pain that is improved by defecation and whose onset is associated with a change in stool form and or frequency and is not explained by structural or biochemical abnormalities. It is estimated that 10%-15% of older children and adolescents suffer from IBS. IBS can be considered to be a brain-gut disorder possibly due to complex interaction between environmental and hereditary factors. The diagnosis of IBS is made based on the Rome III criteria together with ruling out organic causes of RAP in children such as inflammatory bowel disease and celiac disease. Once the diagnosis of IBS is made, it is important to explain to the parents (and children) that there is no serious underlying disease. This reassurance may be effective treatment in a large number of cases. Lifestyle modifications, stress management, dietary interventions and probiotics may be beneficial in some cases. Although there is limited evidence for efficacy of pharmacological therapies such

as antispasmodics and antidiarrheals; these have a role in severe cases. Biopsychosocial therapies have shown encouraging results in initial trials but are beset by limited availability. Further research is necessary to understand the pathophysiology and provide specific focused therapies.

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Key words: Recurrent abdominal pain; Irritable bowel syndrome; Brain-gut disorder; Lifestyle modifications; Biopsychosocial therapies; Children; Rome III criteria

Core tip: Irritable bowel syndrome (IBS) is the commonest functional gastrointestinal disorder regarding which there is often limited knowledge amongst clinicians. This paper aims to address the clinical challenges that a clinician may face in managing children with IBS. Importance of the application of the Rome III criteria and a focused history is necessary to manage IBS. An evidence-based approach for managing children with IBS is highlighted in this article followed by a section on current best practice-authors' personal view. We hope the readers will find this article useful in their clinical practice.

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HISTORICAL PERSPECTIVES AND DEFINITION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) involving bowel function.

Table 1 Rome III diagnostic criteria for childhood irritable bowel syndrome

Abdominal discomfort or pain associated with 2 or more of the following (present at least 25% of the time):
Improved after defecation
Onset of symptoms associated with a change in stool frequency
Onset associated with a change in stool form alternating between diarrhea and constipation
No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the child's symptoms

The above criteria should be fulfilled at least once per week for at least 2 mo before a diagnosis of irritable bowel syndrome is made.

FGIDs are defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by any structural or biochemical abnormalities^[1,2].

One of the first references to the concept of an “irritable bowel” causing symptoms of diarrhea, abdominal pain, constipation, without any well-recognized infective cause appeared in the *Rocky Mountain Medical Journal* in 1950^[3]. This article suggested that IBS is caused by a psychosomatic or mental disorder^[3].

Recurrent abdominal pain (RAP) of childhood is an important feature of IBS. RAP was first described by Apley and Naish following their pioneering study of 1000 children in Bristol, United Kingdom^[4]. Apley defined RAP as three or more episodes of abdominal pain occurring over a period of at least 3 mo, with pain sufficient to cause some impairment of function^[4]. This definition of RAP still stands and is in current use internationally.

Prior to 1995, IBS was not recognized as a concept amongst children and these children were likely to be diagnosed as having RAP. An international group of pediatric gastroenterologists gathered together in Rome in 1995 to define the diagnostic criteria for FGIDs in childhood (including IBS) and this was published in 1999 as part of the larger Rome II criteria. The Rome II criteria were subsequently modified^[1] and the current internationally agreed diagnostic criteria for childhood IBS is known as the Rome III criteria and is shown in Table 1.

The difference between Rome II and Rome III criteria for diagnosing IBS in children is the reduction of the required duration of symptoms from 3 to 2 mo. The consensus of the committee members was that in children 2 mo better reflects clinical experience. This allows primary care physicians to diagnose IBS earlier than 3 mo and also allows 4 wk for an acute infective process and a further 4 wk to develop chronicity of symptoms^[1].

Children with IBS may experience a sense of incomplete evacuation after defecation and sit on the toilet for a long time. This symptom may not always be present in children and is therefore not part of the Rome III diagnostic criteria.

EPIDEMIOLOGY

IBS is the commonest cause of functional RAP in children in the Western world, accounting for more than

50% of cases of RAP^[5,6]. Hyams *et al*^[5] first applied the Rome I (adult) criteria for IBS to 171 children previously diagnosed with RAP in a hospital based setting and found that 68% fulfilled the adult criteria for IBS. The same group then carried out a community-based study amongst 507 middle and high school children and identified IBS in 10% children (14% amongst high school and 6% among middle school children)^[7].

In a study based in a specialist gastroenterology unit in Bristol, UK (serving the same population as Apley 50 years earlier), IBS was identified as the commonest cause of RAP^[6]. Out of 103 children fulfilling the diagnostic criteria for RAP and entering the study, after extensive investigations 72 were found to have no organic pathology. Thirty-seven of these 72 children (51%) fulfilled the diagnostic criteria for IBS; making IBS the commonest cause of RAP even in a specialist hospital setting^[6]. This recent study compared to Apley had the advantage of improved screening tests (celiac serology, *Helicobacter pylori* antibody titer, inflammatory markers, serum amylase, and abdominal ultrasonography) as well as previously existing tests such as liver function tests, full blood count; urine and stool analyses. In addition to screening tests, endoscopy and oesophageal pH monitoring were performed where there was a clinical indication^[6].

In a Sri Lankan study of 1717 school children aged 10-16 years randomly selected from 4 provinces; 107 children were diagnosed with IBS symptoms as per Rome III criteria. The overall prevalence of IBS was found to be 6.23% with a higher prevalence amongst girls^[8].

In a randomized study by clustering samples in China, which involved 5403 children and adolescents aged between 6 to 18 years from 9 schools, the prevalence of IBS using the Rome II criteria was found to be 13.25% and it was higher amongst girls (male:female ratio was 1:1.8)^[9]. These studies suggest that the prevalence of IBS in children from different geographical settings is similar.

ETIOLOGY OF IBS

The exact etiology of IBS remains to be determined. The debate remains whether it is caused by hereditary or environmental factors. It is possibly due to complex interaction between both. Infection, inflammation, visceral hypersensitivity, allergy and disordered gut motility may all play a part.

In a questionnaire study with 10986 respondents (response completed by patient and their family regarding health problems) and representing 6060 twin pairs; concordance for IBS was significantly higher amongst monozygotic (17.2%) than dizygotic (8.4%) twin pairs^[10]. The same study also highlighted that having a mother or father with IBS is a stronger predictor (15.2%) than having a twin. The authors concluded that heredity contributes to IBS, but social learning has an equal or greater influence^[10]. Another study of 319 young adults with history of childhood functional abdominal pain (FAP) reported parental history of chronic pain in their childhood. It

also reported an increase in health service utilization for FAP^[11].

As there is a strong familial trend noted in IBS, there has been an ongoing interest in finding a genetic link in IBS. So far, a positive association between IBS and interleukin-10 (IL-10) polymorphism has been reported. A study in Taiwan with 94 children with IBS and 102 healthy controls, significantly lower *Escherichia coli* lipopolysaccharide-induced IL-10 production by peripheral blood mononuclear cells was noted in children with IBS although the study group concluded that this reduction in IL-10 production may not have been fully determined genetically^[12]. Patients with a mutation in a sodium channel gene (SCN5A) were found to report gastrointestinal symptoms especially abdominal pain more often, and this mutation may be a contributory factor in IBS^[13,14].

An infectious trigger for IBS may also play a role. In a prospective study of 102 children in Russia with *Giardia lamblia* detected in stool by ELISA, the prevalence of post-infectious IBS was found to be 28% in girls and 17% in boys^[15]. In a postal questionnaire survey of 576 individuals with a *Salmonella* or *Campylobacter* infection (between 2000-2009), nearly 10% of 189 individuals who responded to the questionnaire reported post-infectious IBS symptoms up to 10 years later^[16]. Similar findings were reported in another study after an outbreak of bacterial gastroenteritis (with *Escherichia coli* 0157:H7 and *Campylobacter* species) with 8 year follow-up (2002-2008) which reported increased incidence of IBS after the episode in children and adults^[17].

A prospective study recruited subjects following a large outbreak of acute gastroenteritis attributed to food-borne norovirus at the annual meeting of the Canadian Society of Gastroenterology Nurses and Associates (CSGNA)^[18]. It then documented development of post-infectious IBS symptoms. The study data showed that although after 3 mo norovirus infection produced new IBS symptoms in about 25% of case; by 6 mo the incidence was no different in infected individuals compared to healthy controls and concluded that IBS following viral gastroenteritis is a transient entity^[18].

PATHOPHYSIOLOGY OF IBS

No single clear pathophysiology has been demonstrated to date for IBS in children. Studies both in children and adults have suggested different mechanisms which may contribute to the development of IBS^[19]. IBS can be considered to be a brain-gut disorder. It is postulated that a state of dysregulation exists/occurs within the enteric and the central nervous systems in patients with IBS and this results in alteration in sensation, motility, and possibly, immune system dysfunction^[19]. It is important to consider the bidirectional brain-gut interactions, the "brain-gut axis" when considering any pharmacological interventions in IBS^[20,21].

In a prospective study of 98 children who underwent upper or lower GI endoscopy, serotonin (5-HT) signaling

was noted to be altered in IBS with diarrhea but not in functional dyspepsia^[22]. In another study of 93 children (aged 7-10 years) with symptoms of FAP or IBS, evidence of increased GI permeability and low-grade GI inflammation were detected; the latter related to the degree to which pain interfered with activities when compared to healthy control ($n = 52$)^[23].

A study of 35 children (aged 10-17.6 years) who fulfilled criteria for IBS demonstrated that abdominal pain is associated with visceral hypersensitivity and abnormal perception of visceral sensations^[24]. Studies suggest that patients with IBS describe gut stimuli as being unpleasant or painful at lower intensity levels when compared with non-IBS individuals and this is likely to be neurological in origin^[19,25].

In another study of 10 children with 10 age-matched controls, fecal short-chain fatty acid (SCFA) profile of patients with diarrhea predominant IBS (IBSD) was found to have lower concentrations of total SCFA, acetate, and propionate and a higher concentration and percentage of n-butyrate. Fecal flora from these patients produced less SCFA in an *in vitro* fermentation system in response to incubations with various carbohydrates and fibers. Differences in SCFA production by colonic bacterial flora in patients with IBSD may be related to the development of GI symptoms^[26].

A recent study in the United States looked at the intestinal microbiomes in stool samples ($n = 71$) obtained from 22 children with IBS (diagnosed by Rome III criteria) and 22 healthy controls^[27]. Children who received antibiotics, probiotics, or steroids (oral or inhaled) within 6 mo of sampling were excluded. Stool samples were analyzed using 16S metagenomics by PhyloChip DNA hybridization and deep 454 pyrosequencing. Specific microbiome signatures were associated with pediatric IBS suggesting important association between GI microbes and IBS in children. Children with IBS were characterized by a significantly greater percentage of the class Gammaproteobacteria *Haemophilus parainfluenzae* being a prominent component of this group. It is postulated that the microbiome signature approach may prove to have a diagnostic role in the future^[19,27-29].

HISTORY TAKING AND CLINICAL PRESENTATION

The most important step in making a diagnosis of IBS is to elicit a detailed history and compare symptom concordance with the Rome III criteria (Table 1). Children and adolescents generally present with RAP along with change in bowel frequency and/or consistency associated with abdominal pain. The pain is classically relieved following defecation. Children with IBS may report a sense of incomplete evacuation (often sitting on the toilet for a long time); however this is not by itself diagnostic of IBS. It is important to enquire about symptoms of bloating and an urgency to go to the toilet as well as the location of pain which is usually central peri-umbilical but may

Table 2 Red flag symptoms

Night time pain or diarrhea
Recurrent unexplained fever
Recurrent or worsening rectal bleeding
Joint pains
History of weight loss and poor growth
Family history of inflammatory bowel disease
Persistence of severe vomiting or diarrhea
Unexplained pallor
Stools that may be difficult to flush away
Delay in onset or progression of puberty

involve the lower abdomen.

Parents sometimes describe their child as a “little worrier”^[30]. Older children and adolescents sometimes report that symptoms get worse during periods of emotional stress so it is important to explore psychological issues at school such as bullying, oncoming exams or at home such as financial difficulties, recent parental separation or divorce or ill-health. It is important to ask if there is history of recent gastrointestinal infection as this may be associated with onset of IBS symptoms. This may be particularly relevant in children with diarrhea predominant IBS^[31].

It is important to enquire if there is a family history of IBS amongst parents or siblings. An anxiety state may be present in children and also in parents of children presenting with features suggestive of IBS^[31-34]. Studies have reported that IBS patients in comparison to healthy controls have higher scores for anxiety, hostile feelings, sadness, depression, interpersonal sensitivity and sleep disturbance^[25] and these issues should be explored while eliciting the history.

It is essential to specifically enquire about “red flag” symptoms as these may indicate serious underlying organic pathology^[21]. The “red flag” symptoms are listed in Table 2. Very occasionally an organic pathology may co-exist with IBS as the latter is relatively common.

If any or combination of the above symptoms are elicited from the history, appropriate investigations are necessary to exclude underlying organic pathology.

CLINICAL SUBTYPES AND DIFFERENTIAL DIAGNOSIS OF IBS

Three clinical subtypes of IBS are encountered in clinical practice: diarrhea predominant IBS is termed as IBSD, constipation predominant IBS is termed as IBSC and IBS with alternating diarrhea and constipation is termed as IBSA. The clinical subtypes are not rigid classification and cross-over from one type to another may be seen during the course of treatment. It is useful, depending on the presenting stool pattern, to assign the children to a clinical subtype as the management in part will depend on the subtypes of IBS.

EXAMINATION OF CHILDREN WITH IBS

The history taking should be followed by a thorough

physical examination including plotting the height and weight on an age and sex appropriate growth chart. A confirmed documented significant weight loss should be considered as a red flag sign and is unlikely to be due to IBS^[21]. Signs of anemia, jaundice, mouth ulcers, skin rash or arthritis should also be specifically looked for and suggest organic pathology. It is useful to ask the child to point with one finger where the pain is worse and is most frequently felt. In IBS this is often centered around the umbilical region. Inspection of the abdominal wall for scars, distension or masses is necessary. Prominent juicy perianal skin tags or fistulae are indicative of Crohn's disease.

Great care should be taken to rule out any organomegaly, tenderness and/or abdominal mass in the right iliac fossa. If the child is too tense, distraction may be needed in such cases and discussing about other aspects of their life such as school, friends or even a planned holiday may be helpful.

DIAGNOSING CHILDREN WITH IBS

In the absence of a definitive laboratory or radiological diagnostic test, IBS remains a clinical diagnosis. We suggest following investigations to rule out other serious gastrointestinal disorders: serological screening for celiac disease, inflammatory markers (ESR, C-reactive protein, plasma viscosity or orosomucoid) likely to be raised in inflammatory bowel disease (IBD), liver function tests (low serum albumin in IBD) and full blood count (unexplained anemia, blood loss in IBD). In developing countries it is especially important to send a stool sample for microscopy and culture with specific request to look for ova, cyst and parasites (including *Giardia*).

The diagnosis of IBS is made after exclusion of organic causes of abdominal pain and bowel changes based on history and examination particularly ensuring that no red flag symptoms are present (Table 2). These organic causes include lactose intolerance, celiac disease and IBD. Symptoms concordant with the Rome III criteria should help clinicians to make a positive diagnosis of IBS and avoid unnecessary investigations.

Specialist investigations such as gastrointestinal endoscopy or radiological evaluation should be reserved for difficult cases where the diagnosis may not be clear from the history, and/or physical examination suggest pathology. These investigations if indicated should be best carried out by pediatric gastroenterologists.

DIFFERENTIAL DIAGNOSES

It is important to differentiate IBS from other causes of RAP by matching symptom concordance with the Rome III criteria for childhood FGIDs^[1]. Those with epigastric pain or discomfort not relieved by defecation are classified as functional dyspepsia. Abdominal migraine causes self-limiting episodes of severe abdominal pain interspersed with pain free periods^[1]. The remaining group of children whose pattern of abdominal pain does not fit into the above groups is classified as FAP. If other symp-

toms such as headache and limb pain are reported this is labeled as FAP syndrome. Amongst the latter group there are some children with abdominal pain but no other GI symptoms whose pain is made worse by exercise. This pain can be musculoskeletal in origin and may represent the pediatric equivalent of adult abdominal wall pain. Constipation also needs to be considered as it may be associated with overflow spurious diarrhea which may mimic an alternating constipation and diarrhea pattern seen in IBSA.

EVIDENCE BASED TREATMENT FOR CHILDREN WITH IBS

The aim for any therapeutic intervention in IBS should be to improve the quality of life. This includes ensuring the child's pain is minimized and stool consistency and frequency are normalized. The most important step in managing children with IBS is to explain the diagnosis to parents (and the child if age appropriate), explain strategies to cope with stress and provide reassurance that there is no serious underlying disease.

Wherever available and feasible, multidisciplinary team approach should be used to deal with the complex interplay of biopsychosocial factors considered to be involved in the development of IBS in children. It is important to explain the expected benefits of any therapy and give a realistic overview about its expected outcome to parents (and children) before commencing the intervention. Drugs may be needed to treat symptoms including modulating abnormalities in sensorimotor function of enteric nervous system. Following therapeutic interventions have been used in children with IBS, the evidence base for their use is discussed in the next section: (1) dietary interventions; (2) probiotics; (3) drug therapy → peppermint oil, tegaserod, antispasmodics, anti-diarrheal agents, antibiotics; and (4) biopsychosocial therapy → hypnotherapy, cognitive behavior therapy, yoga, acupuncture.

Dietary interventions

Dietary interventions form an important strategy in managing children with IBS. It is important to note that parents generally accept dietary treatment more willingly than drugs.

A recent Cochrane review^[35] included seven studies comparing dietary interventions with placebo. Two studies which compared fiber supplements with placebo and had 83 participants, found that the pooled odds ratio for improvement in the frequency of abdominal pain was 1.26 (0.25-6.29). Two studies compared lactose-containing diet with lactose-free diet in 90 participants, but no definite conclusion could be drawn from the way the data was presented. A comparison between *Lactobacillus* GG and placebo was made in 3 trials, and these gave a pooled odds ratio for improvement of symptoms as 1.17 (95%CI: 0.62-2.21). The Cochrane review conclusion was that there is a lack of high quality evidence on the effectiveness of dietary interventions^[35].

Another meta-analysis included 3 randomized controlled trials (RCTs) selected by searching MEDLINE, EMBASE and the Cochrane Library and included 167 children aged 5-17 years^[36-39]. This compared use of dietary fiber supplements with placebo for abdominal pain-related FGIDs in children^[36]. The reviewers concluded that there is lack of evidence to support the supplementation with fiber as a dietary manipulation for treating children with FGIDs^[36].

Fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) may play a role in triggering gastrointestinal symptoms in IBS patients^[40]. The effect of low FODMAP diet was prospectively evaluated using a symptom questionnaire amongst 90 children with IBS with a mean follow up of 15.7 mo. Abdominal pain, bloating, flatulence and diarrhea were significantly improved amongst participants while on low FODMAP diet ($P < 0.001$ for all)^[41].

A recent randomized controlled trial in Italy^[2] involved treating 60 children (aged 8-16 years) with IBS and RAP with either partially hydrolyzed guar gum (PHGG) or fruit juice. Improvement was seen in 43% children ($n = 30$) given PHGG compared with 5% in control group ($n = 30$) given fruit juice, with normalization of bowel movements in IBS subgroups which was statistically significant. Improvement in abdominal pain was noted but was not statistically significant. Benefit from PHGG was largely seen in IBSA group; similar findings were also reported in an earlier observational study^[2,42].

Probiotics

Probiotics have shown some promising results in adult studies with validated efficacy with no reported adverse effects^[43,44]. A study of VSL#3 (a probiotic containing 8 beneficial species of bacteria) demonstrated beneficial effect in reducing flatulence scores and retarded colonic transit in patients with IBS and bloating^[45].

In an observational study in Germany with 203 children (66 boys, 137 girls) aged 4 to 18 years (mean 10.5 ± 4.5 years) treated with Symbioflor 2 (contains the natural intestinal bacterium *E. coli*) for an average of 43 d, the treatment was well tolerated and no adverse events were reported^[46]. The key IBS symptoms (abdominal pain, stool frequency) as well as the other symptoms (bloating, mucous and blood in stool, need for straining at stools, urge to defecate) improved significantly during treatment and the global assessment of therapy was found to be altogether positive as reported by parents and doctors^[46].

In a double-blind, placebo controlled, crossover trial conducted in 5 pediatric tertiary care centers (4 in Italy and 1 in India); 59 children (aged 4-18 years) were randomized to receive either VSL#3 or a placebo for 6 wk. VSL#3 was superior to placebo both in primary (subjective assessment of relief of symptoms) and secondary endpoints (abdominal pain/discomfort, abdominal bloating/gassiness and family assessment of life disruption)^[47].

Another randomized double-blind, placebo controlled trial involved 141 children (aged 5-14 years) treated with *Lactobacillus rhamnosus* GG (LGG) or placebo for 8 wk

and then further followed up for 8 wk^[48]. At entry and at the end of the trial, children underwent a double-sugar intestinal permeability test. Children treated with LCG showed reduction in abnormal permeability results post treatment. When compared with baseline, children who received LGG reported a significant reduction in both frequency and severity of abdominal pain. At 12 wk, success was achieved in 48 children in LGG group as compared to 37 in placebo group ($P < 0.03$)^[48].

A systematic review of RCTs by Spiller on the effectiveness of probiotics postulated that their beneficial effects are due to enhancement of gut barrier function, inhibition of pathogen binding and modulating gut inflammatory response. They may also reduce visceral hypersensitivity associated with both inflammation and psychological stress. Probiotics can also alter colonic fermentation and stabilize colonic microbiota^[49].

Another recent systematic review and meta-analysis^[45,47,48,50-53] performed to investigate the quantity and quality of the current evidence regarding the effect of different probiotics strains in the treatment of FGIDs in children and adolescents found probiotics to be more effective than placebo in the treatment of patients with abdominal pain-related FGID, especially with respect to patients with IBS. A meta-analysis of 6 RCTs selected by searching MEDLINE, EMBASE, CINAHL, the Cochrane Library, trial registries and proceedings of major meetings^[47,48,51,53-55] compared use of LGG with placebo for abdominal pain-related FGIDs ($n = 457$) in children including 3 RCTs involving IBS specifically ($n = 167$)^[54]. It concluded that children treated with LGG had moderate increase in treatment success with abdominal pain-related FGIDs and this was particularly marked in children with IBS^[54].

Drug treatment

A Cochrane review concluded that only weak evidence exists regarding beneficial effects of pharmacological agents in providing relief from symptoms in FAP in children^[20]. Evidence relating to some of the pharmacological agents that have been used is discussed here:

Peppermint oil: exerts an antispasmodic action via menthol [main component of peppermint oil (PO)] and acts as a calcium antagonist and results in anti-flatulent action, the exact mechanism of which currently remains unexplained. A review has been carried out of 16 clinical trials investigating the use of 180-200 mg enteric-coated PO in irritable IBS or RAP including 1 study in children^[56]. Nine out of 16 studies were randomized double blind cross over trials, five had a randomized double blind parallel group design and two were open labeled studies. Placebo was used in 12 studies and anticholinergics were used as comparator in three studies. Adverse events reported with PO were very specific, but generally mild and transient and included typical GI effects like heartburn and anal/perianal burning or discomfort. The review concluded that 1-2 enteric coated capsules (180-200 mg)

daily over 2-4 wk may be the first drug of choice for patients with IBS and constipation and diarrhea^[56].

Tegaserod: is a selective 5-HT₄ (serotonin) receptor agonist which has shown improvement in children (and adults) with IBSC and chronic idiopathic constipation. A Cochrane review, which included randomized or quasi-randomized controlled trials comparing tegaserod with placebo, no treatment or any other intervention, showed some improvement in overall symptomatology and frequency of bowel movements in those with IBSC or chronic constipation^[57]. However, due to its significantly increased risk of cardiovascular ischemic events, tegaserod is not licensed in many countries^[58] and is not recommended.

Antispasmodics agents: Have been shown to have a role in IBSD and attenuate heightened baseline and postprandial contractility. Mebeverine is licensed in the United Kingdom and is generally well tolerated; and can be used on an as required basis before meals. A systematic review^[59] which searched medical databases and all relevant literature from 1965 to June 2009 for any placebo-controlled clinical trials of mebeverine, identified 14 relevant papers (8 were randomized trials with 555 patients) and concluded that mebeverine is mostly well tolerated with no significant adverse effects; however, its efficacy in global improvement of IBS was not found to be statistically significant^[59].

In a recent randomized study from Turkey involving 78 children (selected out of a total of 345 children aged 4-18 years who were diagnosed with IBS on basis of Rome III criteria), clinical recovery was seen in 94.9% of 39 children treated with trimebutine maleate at the end of 3 wk when compared to the non-medicated group where spontaneous recovery was seen in only 20.5% children^[60]. Children in this study predominantly had IBSC and the authors concluded that trimebutine maleate is an effective agent for treating childhood IBS.

Anti-diarrheal agents: Have a limited role in managing children with IBS but may be tried in children with IBSD where diarrhea and increased bowel frequency interferes with activities of life. Loperamide, an opiate analogue, is most commonly used and acts by stimulating inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and intestinal secretion. Adult studies have found loperamide to be effective in reducing diarrhea in IBS patients but did not alleviate symptoms of abdominal pain.

Antibiotics: Role of antibiotics in treatment of children with IBS remains controversial. The only rationale behind antibiotic therapy is to eradicate small intestinal bacterial overgrowth. The big question remains as to what antibiotic to use as haphazard prescription of antibiotic therapy may not be effective and will lead to antibiotic resistance. In an adult (aged ≥ 18 years) study improvement in resolution of symptoms (bloating, abdominal

pain, and loose or watery stools.) were noted in IBS patients treated with Rifaximin for at least 2 wk^[61]. Similar beneficial results were later replicated in a study of 50 children with IBS symptoms whose visual analogue scale (VAS) score to evaluate symptoms (abdominal pain, constipation, diarrhea, bloating, flatulence) showed improvement and normalization of lactulose hydrogen/methane breath test (66% cases) after 1 month treatment with 600 mg of Rifaximin^[62].

Amitriptyline: Amitriptyline (AMI), a tricyclic antidepressant (TCA), has been found to be effective in adults with IBS in producing global improvement, increasing feelings of well-being, reducing abdominal pain, and increasing satisfaction with bowel movements. The beneficial effects of antidepressants can be explained by partial increments in the central pain threshold. Other mechanisms by which antidepressants might exert their effects include anticholinergic effects (may result in improvement of diarrhea), regulation of GI transit and peripheral anti-neuropathic effects. In a randomized double-blind placebo controlled trial of 33 participants (24 females) aged 12 to 18 years, it was found that patients who received amitriptyline were more likely to experience improvement from baseline in overall quality of life at 6, 10, and 13 wk ($P = 0.019, 0.004$, and 0.013)^[63]. They also reported reduction in IBS-associated diarrhea at 6 and 10 wk, a reduction in periumbilical pain at 10 wk, and a reduction in right lower quadrant pain at 6, 10, and 13 wk^[63].

Biopsychosocial modifying therapies

Hypnotherapy: Studies have shown that hypnotherapy may produce a beneficial effect in children with IBS which persists for at least five years after cessation of therapy^[64-68]. A randomized controlled study which compared hypnotherapy ($n = 27$) with standard medical treatment ($n = 23$) and followed up for a mean duration of 4.8 years showed that 68% of children in the hypnotherapy group remained in remission as compared to only 20% in the control group^[64]. It is postulated that hypnotherapy normalizes altered visceral sensation, reduces colonic phasic contractions and reverses the patients' negative thoughts about their condition. Another prospective randomized controlled trial in Germany^[69] with 38 children aged 6 to 12 years evaluated a brief hypnotherapeutic-behavioral intervention program in 20 children (recruited for therapy) and compared their response to a waiting list condition ($n = 18$, served as control). Children in the treatment group reported a significantly greater reduction of pain scores and pain-related disability (55%) than children of the waiting list condition (5.6%)^[69].

A recent systemic review which included three RCTs comparing hypnotherapy to control treatment with sample sizes between 22 to 52 children found that all trials demonstrated statistically significant improvement in abdominal pain scores in hypnotherapy group^[70]. While one trial reported statistically significant improvement in the quality of life, two trials reported improvement in

school attendance and the benefit was persistent even after 1 year of completion of therapy. The authors go on to recommend hypnotherapy as the first line in the management of children with IBS^[70].

Cognitive behavioral therapy: Many children with IBS receive psychological interventions^[70]. A Cochrane review which included six trials conducted in children aged between 5 to 18 years with RAP comparing Cognitive behavioral therapy (CBT) with standard therapies such as dietary interventions, pharmacological interventions, *etc.* concluded that CBT may be a useful intervention for children with RAP and IBS^[71]. However, the evidence remains weak and behavioral therapies are beset by unavailability of therapists and the need for multiple numbers of sessions.

Yoga: Yoga can be considered as a form of behavioral therapy and consists of general relaxation exercises, breathing exercises, focused training for abdominal relaxation and positive reinforcement by focusing thoughts on a single topic and good experiences. In a pilot study^[72], 20 children aged between 8-18 years were trained Hatha yoga by a children's yoga teacher and received 10 yoga sessions and also practiced at home. Yoga exercises were found to be effective in children with RAP and IBS resulting in significant reduction of pain intensity and frequency^[72].

Acupuncture: This is considered to relieve pain by release of endogenous opiates and triggering of serotoninergic inhibitory pathways. A study compared differences in the therapeutic effect of Tianshu acupuncture (ST 25) ($n = 20$) and Dachangshu acupuncture (BL 25) and western medication with Trimebutine maleate ($n = 20$). Acupuncture was found to relieve symptoms of IBS and was reported to be superior to medication^[73].

A recent Cochrane review which included 17 randomized controlled studies (including the one above) with 1806 adult participants, greater benefits were reported by participants treated with acupuncture as compared to the two antispasmodic drugs (pinaverium bromide and trimebutine maleate). However, five sham-controlled RCTs comparing acupuncture with sham acupuncture showed no significant difference^[74].

Current best practice-authors' personal view

There is no universally proven therapy that will work in all children with IBS. We start with a detailed focused history of the symptoms including family, social and educational history of the child and make enquiries regarding other members in the family who may be suffering from IBS or other FGIDs. Use of Rome III criteria and targeted enquiries regarding the possible presence of red flag signs are also made.

This is followed by a thorough physical examination and review of growth and development including pubertal assessment where appropriate and an assessment of

child's mental status.

Basic investigations are carried out to rule out organic causes. Our practice is to do a full blood count, liver and renal function test, inflammatory markers, amylase, celiac screen and in cases of diarrhea a stool culture and stool reducing substances. Specialist investigations such as ultra sound scan of abdomen, MRI scan, gastrointestinal endoscopy, colonic transit test, *etc.*, are only carried out if organic pathology is suspected and the test is appropriate.

Majority of children will improve with a positive diagnosis of IBS (based on Rome III criteria) with counseling, education about IBS and personalized pain, stress and other management advice and need no other treatment. It is important to spend time with the patient and their family in explaining the diagnosis of IBS, categorically mention that all the investigations done so far have been negative and that there is nothing seriously wrong with their tummy and it will improve.

For a small subset of patients with severe disabling symptoms finding an effective treatment will remain a challenge and few strategies may need to be tried before symptom control is achieved. Lack of a single proven intervention for all cases highlights the complexity of psycho-pathophysiology of IBS.

We favor an integrated bio-psycho-social approach. It is important to educate the family about IBS and address emotional or environmental issues that may be triggering symptoms of IBS and/or making them worse. The need to achieve may be leading to stress and counseling may be necessary. Clinicians need to invest time early in the diagnosis in exploring and addressing other issues such as bullying at school, difficulties in relationship with parents or peers, unrealistic academic expectations, *etc.*

A dietary history including type and amount of food and drinks taken should be recorded and appropriate changes to the diet suggested involving the dietician if needed. High fiber diet may have a beneficial role in IBSC while diet low in fiber may be beneficial in patient with IBSD. It is important to explain that a high fiber diet is often associated with intestinal gas production, increased cramps and flatulence and may not be tolerated by some patients. If there is a suspicion of dairy intolerance, lactose free diet may be useful; a trial of 2-4 wk should be enough to get a response. A trial of PHGG may be beneficial in patients with IBSA in regulating stool type and frequency.

Probiotics such as VSL#3 or LGG are safe to use and are worth considering especially when IBS symptoms have been triggered off by an episode of gastroenteritis.

Social individualized support for child and family may be necessary in difficult cases. A multi-disciplinary team comprising of pediatric gastroenterologist, dietician, social care, education, psychologist, will be necessary in such cases and the chances of achieving success are better. Financial difficulties that a family may be facing are also worth exploring and addressing. It is also important to involve parents in supporting their children with IBS

for positive reinforcement and distraction. The positive effect of distraction was evident from a randomized controlled study where symptom complaints of pain by children (aged 8-16 years) with FAP ($n = 104$) and well children ($n = 119$) nearly doubled in the group where parents were trained to give attention and were reduced by half in the distraction group^[75].

Pharmacotherapy: There is only limited evidence regarding effectiveness of pharmacological treatments. Smooth muscle relaxants such as peppermint oil and trimebutine may be helpful in children where abdominal pain or spasms are a major problem. In difficult cases with low mood or severe symptoms, membrane stabilizer such as low dose amitriptyline may be necessary. Loperamide on a required basis is useful in children with IBSD. Antibiotics should be reserved for cases where there is strong suspicion of small intestinal bacterial overgrowth or giardiasis.

Biopsychological therapy: Hypnotherapy and CBT have shown promising results in selective cases^[76]. Yoga or acupuncture may also be beneficial. However all these need specialist trained pediatric therapists who may not be easily available in most centers. The lack of trained therapists may be solved by such therapies being delivered by pre-recorded therapies in DVDs to be used at home. This suggestion is supported by a study of 34 children aged 6-15 years with FAP^[77] who were randomly assigned to receive standard medical care with or without self directed home-based audio-recorded guided imagery hypnotherapy treatment. Guided imagery treatment plus medical care was reported to be superior (63.1% as compared to standard medical care only (26.7% successful) for the treatment of abdominal pain in FGIDs, and treatment effects were sustained over a long period (6 mo after completion of therapy)^[77].

Future direction: IBS no longer remains a condition thought to be affecting adults and adolescents only and is being increasingly recognized as a common condition in young children in developing and more developed countries. There is a need for research to fully understand the pathophysiology of IBS in children. There is a need to understand subsets of IBS so as to deliver specifically targeted effective treatments. There is also a need for well planned randomized placebo controlled evaluations of pharmacological, psychological and other biopsychosocial therapies in children with IBS taking into account subsets of RAP and IBS.

CONCLUSION

IBS remains a clinical diagnosis of exclusion and can sometimes present a challenge because of the nature and range of associated symptoms and their interpretation amongst parents and pediatricians. A detailed focused history and use of Rome III criteria helps to clarify uncer-

tainties about the diagnosis. Investigations should be kept to the minimum and used for selected cases to exclude other serious pathologies that may present with similar features. Successful management of IBS in children involves the biopsychosocial approach with enough time initially spent at explaining and reassuring the child and the parents. Therapy needs to be individualized to patient needs and it is important that the expected benefits and possible side-effects are explained to the family before initiating therapy. In difficult cases a multi-disciplinary team approach is needed.

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