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The Approach to the Management of a Child with Chronic Abdominal Pain

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Abstract

Purpose of Review Abdominal pain occurs frequently in children; chronic abdominal pain affects about 15% of children. There is always an initial concern for serious organic medical conditions; these can be eliminated with careful history and physical examination, especially looking for "red flags." These children are often subjected to numerous invasive and noninvasive tests; excessive testing should be avoided. There is no evidence extensive testing improves patient outcome or satisfaction. Recent guidelines recommend celiac serology and fecal calprotectin/lactoferrin as the optimal screening tests. Anxiety is often a co-morbidity; the continued testing and lack of explanation exacerbate the symptoms and cause more dysfunction.

Recent Findings Ongoing research suggests chronic abdominal pain is a complex interaction of genetics, environmental factors including diet, changes in the microbiome, previous life events, and stresses. The gut-brain axis is now more accurately described as the microbiome-gut-brain axis. Many disturbances have been reported but it remains unclear which are causative versus reactive. Therapeutic interventions have targeted one or more of the components but rarely in a coordinated manner. A positive diagnosis and explanation of pathophysiology are crucial first steps. A holistic approach that focuses on restoration

of functioning and well-being is the best approach. A non-pharmacologic approach is the favored initial therapy; many children improve with counseling and assurance that there are no serious organic disorders. A trusting relationship with child and family is an integral part of the treatment plan.

Summary Pediatric chronic abdominal pain is commonly encountered in practice. Serious conditions can be eliminated by determining whether any of the so-called red flags are present and judicious testing. High quality evidence is lacking for many proposed treatments. Data interpretation is confounded by a high placebo response rate, even when the placebo is unblinded. The current best evidence is for non-pharmacologic treatments including cognitive behavioral therapy and hypnosis. Neuromodulation is a new, promising intervention.

Introduction

Abdominal pain is a common pediatric complaint. It is estimated to account for 2 to 4% of pediatric office visits and approximately 25% of pediatric gastroenterology consultations. The first description of this condition was by Apley and Naish in 1958 [1]. Apley's subsequent monograph remains a seminal publication [2•]. Recurrent abdominal pain (RAP) was defined as at least three episodes of pain severe enough to affect activity, over a period of no less than 3 months. This nomenclature persisted for the next forty years or so but fell into disfavor because is considered pejorative, implying psychopathologic issues in most affected children. This common condition has had several names through the years, first "recurrent abdominal pain," and then "chronic abdominal pain," followed by "functional abdominal pain." These conditions are now called pediatric functional gastrointestinal disorders—disorders of gut-brain interaction (DGBIs) [3].

A recent meta-analysis documented a worldwide prevalence of 13.5% with ranges in different populations of just over one to 41% [4–6]. Functional abdominal pain syndromes have been reported from every continent save Antarctica [7]. Numerous surveys have demonstrated how common a problem this is, but only a minority seek medical care [8, 9]. However, the financial burden to affected families and the health care system is considerable [10–12]. A series of multi-disciplinary conferences have produced the Rome Criteria for diagnosis, most recently Rome IV in 2016 [13] (Table 1). A major recent change has been decreasing the duration of symptoms necessary for diagnosis from 3 months to 2. The biopsychosocial theory has increasingly gained acceptance. It emphasizes a complex interaction of genetic, physiologic, psychologic, and environmental factors as well as the microbiome and visceral hyperalgesia [15]. The most common pain-related DGBIs are functional dyspepsia, irritable bowel, abdominal migraine, and functional abdominal pain NOS. There are often long-term physical and psychological implications [16–19].

Chronic abdominal pain frequently results in school absenteeism, interferes with daily functioning, decreases quality of life, and increases medical utilization. It is very disruptive to family life and functioning. Extensive medical evaluation in the absence of red flags rarely uncovers an organic cause much to the frustration of parents, children, and providers alike [20, 21].

This review discusses the initial evaluation, the pathophysiology as currently understood, and proposed pharmacologic and non-pharmacologic treatments. In all the diagnoses to be discussed, the role of nutrition, both in detecting micronutrient deficiencies and assuring normal growth, is crucial. The Registered Dietician is thus an integral part of the Gastroenterology team. If available, an in-clinic psychologist improves patient experience and outcomes.

Table 1. Red flags in evaluation of pediatric abdominal pain [3]

Weight loss
Vomiting
Dysphagia or odynophagia
Pain away from midline
Hematachezia or bloody stools
Nocturnal diarrhea
Growth faltering
Delayed onset of puberty
Anemia
Perianal disease
Dysmenorrhea/amenorrhea
Systemic symptoms: fever, rashes, joint pain, mouth sores
Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Anemia, weight loss, and hematachezia were most predictive of inflammatory bowel disease in single-center experience [14]

Initial Evaluation

The initial evaluation must accomplish several things. The patient and family must feel they have been heard and their concerns are taken seriously. Rapport between provider, patient, and parent must be established. Serious illnesses must be excluded (see Table 1 for "Red Flags of Serious Illness") [14, 22]. These are usually easily detected in the initial visit and appropriate testing arranged. The absence of "red flags" greatly diminishes the probability of serious organic disease. There are also well-defined risk factors for abdominal pain-related DBGIs. These include but are not limited to female gender, previous gastroenteritis, history of adverse childhood experiences, abuse and stress, poor sleep, psychologic disorders, and somatic symptoms [23].

The history should include past medical issues, family history, and inquiries about how the patient is functioning in their present circumstances. Both the patients and family should be allowed to discuss the symptoms, their impact on the child's, and family functioning.

Families may have obtained false information from on-line searches and/or social media sites but will not disclose them unless asked [24, 25]. Family history is important—they may be concerned about something as unlikely as colon cancer because "my grandmother had pain for years, until they found the cancer but by then it was too late." Growth patterns should be reviewed; slowing of previously established linear growth or weight loss may be the first indicator of inflammatory bowel disease, malabsorption or an endocrine disorder. A delay in onset or progression of puberty should also prompt further investigation.

A sense of how the child is functioning is important—how much school is being missed? Are they participating in normal activities? Are there any

stresses at home or school? Any bullying [26]? Previous lifetime adverse events including abuse have been reported in children with chronic abdominal pain [27–29]. The history must not focus only on gastrointestinal complaints; there often are multi-site pain complaints and these affect prognosis [30]. There has been recent recognition that abdominal pain and dysautonomia are more common in children with hypermobility syndrome so inquiries into joint pain, fractures or dislocations should be done [31–34].

Patients with chronic pain often use complementary and alternative medical therapies. The most common are specialized diets, herbal treatments, and chiropractic therapy [35]. This should be questioned in a nonjudgmental manner and may provide useful information about the child's treatment and response. A final caveat: there must be ample time allowed for thorough history taking and answering questions. Given the hectic pace in today's outpatient environment, it may be prudent to establish rapport, exclude "red flags," order any necessary initial studies, and schedule a follow-up appointment for detailed discussion.

A thorough examination must be conducted. A frequent comment by parents about previous encounters is "they did not do anything, just pressed on his stomach." A digital rectal examination is not universally required. However, inspection of the perianal area may reveal skin tags suggesting chronic constipation or fissures suggesting inflammatory bowel disease [36]. Contrary to popular belief, children rarely develop hemorrhoids. Such a complaint should provoke careful perianal examination

Correlation with any food should be sought. There are often self-perceived food intolerances; the most common are lactose and gluten [37]. A gluten-free or reduced diet should never be initiated prior to testing for celiac disease. Once a reduced gluten diet is initiated, it is very difficult if not impossible to diagnose celiac disease without resuming a gluten containing diet [38].

Appropriate testing should be recommended—extensive testing should be avoided [39]. There is no evidence that an extensive, invasive evaluation improves patient outcomes or satisfaction. The evidence-based studies recommended in the initial evaluation are total serum IgA, IgA tissue transglutaminase, and fecal calprotectin [40]. An explanation of gut-brain interaction should be initiated as early as possible in the evaluation. A common mistake is to proceed through a series of studies, then at the end invoke a psychological explanation for the symptoms. Acceptance and outcome are better if that discussion begins as the evaluation begins. A follow-up appointment is often required, either in person or virtually to discuss laboratory and/or radiographic results and reinforce the treatment plan. The timing and manner of the follow up can be variable depending on family's needs and wishes but usually within several weeks. The goal should be to review any testing, answer any questions, and develop a long-term plan. If the initial visit was brief due to time constraints, the follow-up should be as soon as possible. Telemedicine has made these visits more efficient. The family should be left with the sense that they can contact the pediatrician for follow-up questions and concerns.

A word of caution: constipation is a frequent cause of abdominal pain, especially in younger children. Clinicians often rely on abdominal plain

films to confirm the diagnosis. These are notoriously unreliable. A frequent report is "moderate stool in the colon." This must be interpreted in the context of the child's symptoms and the history/examination [38, 40].

A multidisciplinary holistic therapeutic regimen whose goal is restoration of normal function should be recommended. [38, 41–44]. Psychology and nutrition are valuable members of the team. It is useful to use the Rome criteria (Table 2) to identify which DBGI is being treated and to explicitly name it. An explanation of the gut-brain interaction in terms family can understand is crucial. It is important to avoid giving them the impression that "it is all in their head.". A positive diagnosis must be made and communicated to the patient and family.

Chronic abdominal pain often persists into adulthood, resulting in ongoing morbidity and decreased quality of life [17, 45, 46]. Pediatricians should do everything possible to interrupt this cycle [16]. Predictors of persistence into adulthood include extra-intestinal somatic symptoms and depressive symptoms at initial evaluation. Age, gastrointestinal symptoms, and severity of pain were not predictive [46]. There have been several recent excellent reviews of treatment of pediatric disorders of brain-gut interaction [47–51].

Anxiety is often a comorbidity. There is a bidirectional relationship between anxiety and pain. Anxiety is common in children with DBGID's [52–58]. There is often discordance between parent and child on the presence and significance of anxiety [59–61]. Standardized screening tools are helpful in identifying the relative role of anxiety [62].

It is also important to note that studies of treatments in DGBI's often have a high placebo response rate [63]. Nurko, using an open label placebo approach, demonstrated a substantial response even when the patient and family knew they were being given an inert substance [64•]. A crucial component of therapy is an initial positive diagnosis and establishing a therapeutic relationship.

We will briefly discuss the more common, potentially serious conditions that may present with acute or chronic pain and the best initial approach.

Inflammatory Bowel Disease

Inflammatory bowel disease is a topic too broad to be fully covered here. It must be considered in the patient presenting with abdominal pain especially if there are bloody stools, diarrhea, or tenesmus. Growth failure may be present; however, it may not have been recognized by family or other providers. Obesity does not preclude the diagnosis of IBD [65, 66]. Standard laboratory studies (hemoglobin, platelet count, albumin, and sedimentation rate) are normal in twenty percent of children and adolescents with proven inflammatory bowel disease [67]. If there is any suspicion, fecal calprotectin, a very sensitive marker of intestinal inflammation, is helpful in determining next steps [68, 69]. Symptoms of IBD and irritable bowel syndrome often overlap; calprotectin is helpful in differentiating them [40]. The normal concentration is less than 50 micrograms/gram of stool; 50–100 microgram results should be repeated. Levels above 150 micrograms warrant referral to gastroenterology to exclude inflammatory bowel disease. The initial examination should also look for extra-intestinal manifestations such as mouth ulcers, arthritis, erythema nodosum, and perianal lesions.

Table 2. Rome IV Criteria for pediatric pain-related functional gastrontestinal disorders [3]

Functional nausea: must include all of the following (present for at least two months)

1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition

Functional vomiting: must include all of the following (present for at least two months)

1. On average, one or more episodes of vomiting per week
2. Absence of self-induced vomitng or criteria for an eating disorder or rumination
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition

Functional dyspepsia – must include one or more of the following bothersome symptoms at least 4 times a month for at least two months prior to diaggnosis.

1. Postprandial fullness
2. Ealy satiation
3. Epigastric pain or burining not associated with defecation
4. After appropriate evaluation, the symptom cannot be fully explained by another medical conditon

Irritable bowel syndrome: Must include all of the following

1. Abdominal pain at least 4 days per months associated with the following:
    a. Related to defecaton
    b. A change in frequency of stool
    c. A change in form (appearance) of stool
2. In children with constipation and abdominal pain, the pain does not resolve with resolution of the constipation (children in whom the pain reoslves have functional constipation not IBS)

Abdominal migraine: must include all of the following at least twice:

1. Paraxysmal episodes of intense, acute periumbilical pain, midline or diffuse abdominal pain lasting 1 hour or more (should be most severe and distressing symptom)
2. Episodes are separated by weeks or months
3. Pain is incapacitating and interferes with normal activities
4. Steotypical pattern in individual patient
5. Pain is associated with two or more of the following:
    a. Anorexia
    b. Nausea
    c. Vomiting
    d. Headache
    e. Photophobia
    f. Pallor

Ater appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Functional abdominal pain – not otherwise specified

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating and menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical evaluation

Initial evaluation of suspected inflammatory bowel disease usually includes upper and lower endoscopy, and cross-sectional imaging (usually MR enterography). Treatment in the modern era often involves biologic agents such as antitumor necrosis factor agents. There is still a limited role for corticosteroids, 5-aminosalicylate compounds, and immunomodulator therapy. Nutrition therapy has had increasing interest in the treatment of Crohn's disease [70].

Celiac Disease

Celiac disease is an autoimmune response to gluten in genetically predisposed patients. Patients may be asymptomatic or have multiple gastroenterological complaints. Growth failure may be present. Risk factors include a positive family history, Trisomy 21, other autoimmune disease, Turner syndrome, and Williams' syndrome. Otherwise, screening should be reserved for symptomatic patients. Unfortunately, symptoms may be vague and include non-specific abdominal pain, both diarrhea and/or constipation, fatigue, arthralgia, and mouth ulcers. Unexplained iron deficiency may also be present since iron is absorbed in the duodenum and proximal jejunum, frequent sites of involvement.

Current recommendations are to screen appropriate patients with total serum IgA and IgA tissue transglutaminase (TTG). Patients must be on a gluten containing diet for diagnostic tests to be valid. Total serum IgA is necessary because an IgA antibody is measured, and celiac disease is more common in patients with IgA deficiency. IgG gliadin antibodies are less sensitive and specific and should not be the first choice.

There is currently some controversy about how to approach a positive TTG. The European approach is that if the TTG is greater than 10 times the upper limits of normal, an endomysial antibody is obtained and genetic phenotype (presence of DQ2 and DQ8 haplotype is determined). If present, the diagnosis is confirmed, and patient placed on gluten free diet [71]. In North America, the tendency is still to perform endoscopy and duodenal biopsy for confirmation [72]. Traditionally celiac disease has been considered to cause diarrhea and weight loss; recently, it has been seen in overweight children and those with a history of constipation. An experienced dietician is crucial in educating families in the nuances of the gluten free diet [73–76].

Functional Constipation

Constipation is a common cause of abdominal pain. Diagnosis can usually be diagnosed from history but occasionally the family is unable to quantitate the stooling history. Additional tests or radiographs are rarely required. The initial therapy is usually polyethylene 3350 (PEG) disimpaction followed by a maintenance regimen of PEG and a stimulant such as senna. A regular regimen of sitting on the toilet at designated times, usually after meals, can be helpful. Adequate fiber (age plus 5 g per day) and hydration are helpful. Referral to gastroenterology should be considered if there is no response. Some patients may require an inpatient clean-up. Pelvic floor physical therapy may be helpful [77]. A potential red flag is delayed passage of meconium at birth—that raises

the possibility of Hirschsprung's disease [42, 78–80]. If there is suspicion of Hirschsprung's or there has been no response to therapy, additional testing may be considered . At that point, diagnostic options include a water-soluble contrast enema, anorectal manometry, or a rectal biopsy. These are usually not necessary unless there are other concerns, or the patient is refractory to treatment. Colonic manometry is reserved for truly refractory cases.

Note that abdominal pain may be associated with functional constipation, but it is not a diagnostic necessity. The diagnosis of irritable bowel syndrome requires abdominal pain as well as irregular defection. It is often misdiagnosed as functional constipation [40, 81].

Pain Predominant Functional Disorders: Disorders of Brain-Gut Interaction (DBGI)

The Rome IV publication lists four pain predominant disorders: functional dyspepsia, abdominal migraine, irritable bowel syndrome and functional abdominal pain [2•] (Table 2).

Functional dyspepsia is defined as bothersome nausea as the predominant symptom, occurring at least twice a week and generally not related to meals. It is not consistently associated with vomiting and after appropriate evaluation, the nausea cannot be fully explained by another medical condition. Criteria must be fulfilled for at least two months prior to the diagnosis. The pathophysiology is unknown but there may be systemic symptoms such as sweating, dizziness, pallor, and tachycardia [3].

Abdominal migraine is a difficult diagnosis to confirm. It is important to note that the diagnosis requires the attacks be stereotypical in the patient and that there are weeks to months of symptom-free intervals.

The diagnosis of irritable bowel syndrome requires both abdominal pain and a change in bowel frequency or stool consistency. Irritable bowel syndrome can be divided into subtypes: constipation predominant, diarrhea predominant, or mixed. Use of the Bristol stool chart to describe stool consistency helps classification.

Treatment of Pain Predominant Functional Disorders: Disorders of Brain-Gut Interaction (DBGI)

Treatment can be divided into pharmacologic and non-pharmacologic approaches .They are not mutually exclusive; often a combination gives the best results.

Non-pharmacologic Treatment

Non-pharmacologic treatments have been used in all the pediatric gastrointestinal pain predominant disorders. High-quality evidence is scanty, but

many patients believe they are helpful. The best evidence is for cognitive behavioral therapy and hypnosis.

Non-pharmacologic therapies can be divided into psychological, dietary, and neuromodulation. It has been hypothesized that DGBI's are strongly associated with stress, anxiety, and depression. The child's coping skills are crucial in determining how they will respond to stress. Those with tendency to catastrophize do not do as well [54, 82]. Screening for anxiety and functional disability as part of the initial identifies affected children and helps frame the conversation [55, 56].

Many families have self-diagnosed food intolerances: the most common are lactose and gluten. Celiac disease should be excluded. Non-celiac gluten sensitivity may cause symptom; the only diagnostic test is withdrawing gluten to see the response, then reintroduce it [83]. The FODMAPS diet (low in fermentable oligosaccharides, disaccharides, monosaccharides, and polys) has been recommended for irritable bowel syndrome. There is no high-quality evidence that it is helpful. It is difficult but not harmful. A recent review failed to find high-quality evidence that various dietary manipulations including FODMAPs, fructans, fructose restriction, inulin serum-derived bovine immunoglobulin, and vitamin D supplementation were effective. There was low-quality evidence that fiber led to higher treatment success [84].

The most effective non-pharmacologic therapies are cognitive behavioral therapy, either in person or remotely [85]. Hypnosis has also been shown to be effective [86–88]. Yoga has produced mixed results but in general exercise is helpful [89, 90]. Poor sleep affects pain and its perception, so sleep evaluation and therapy may be helpful [91].

Although not strictly non-pharmaceutical, herbal therapy has gained attention. High-quality evidence is lacking but there are suggestions that peppermint oil, Iberogast, cannabis, fennel, and licorice may be helpful [92]. A caution about cannabis, besides the obvious legal questions in some jurisdictions, was shown. Cannabis has been reported to calm the gastrointestinal tract but chronic use in susceptible individuals may in result in prolonged vomiting, the so-called hyperemesis cannabis [93•].

Neuromodulation is a promising frontier. Kovacic reported a study in 115 children with chronic abdominal pain. Half were treated with neuromodulation via an ear device, the others had the device but sham treatment. The treated group had a reduction in worst pain at baseline and follow-up [94•]. Santucci and coworkers used a similar protocol: treated patients had improved resting and evoked pain and nausea as determined by a water load test. They also had improved sleep, less disability, pain catastrophizing and anxiety after four weeks of treatment. Some retained benefit 6 to 12 months later [95].

Pharmacologic Treatment

Pharmacologic interventions purport to target different components of the gut-brain axis, gastrointestinal tract, central nervous system, or a combination. In general, high-quality studies are lacking in children. Koterink et al. reviewed available pharmacologic therapies and concluded: "there is no evidence to support routine use of any pharmacologic treatment. Peppermint oil, cyproheptadine and famotidine might be potential interventions but well-designed trials are needed"[49]. Antispasmodics such as hyoscyamine and dicyclomine have been used but the evidence base is inadequate.

Antidepressant therapy with tricyclic medications or SSRIs has had mixed results. Their use may improve sleep that in turn may improve intestinal symptoms. Mirtazapine has been used in adults but pediatric data are lacking. A retrospective review showed greater response to SSRIs than tricyclics [96]. A large randomized clinical trial did not demonstrate that amitriptyline was superior to placebo, mainly because of high placebo rate [97]

Irritable bowel, especially with constipation, may require a different therapeutic approach, including calcium channel activators such as lubiprostone or guanylate cyclase-c agonists such as linaclotide. Linaclotide has recently been FDA approved for children ages 6–18. Some of these agents have been tested and found to be safe in children but they are not yet approved by the FDA for use under age 18 [40, 98, 99]. Insurance coverage may still be an issue. Diarrhea predominant irritable bowel may respond to rifaximin or other antibiotic therapy for possible small bowel bacterial overgrowth.

In summary, abdominal pain is a frequently encountered pediatric complaint, serious conditions (almost always heralded by red flags) must be eliminated. There should be a complete thorough history and physical examination. There must be allowed for the family to ask questions and develop understanding. It is crucial that a positive diagnosis be made and given. Too often the family walks away thinking they have been told "it is all in their head." Detailed explanation, at the child's and families' level, of gut brain interactions and its permutations is important. The Rome criteria can be useful when discussing diagnosis with the family.

Then, the art of medicine becomes paramount. Patient and family must feel that they have been heard and taken seriously. Their concerns and fears must be elicited and discussed. The impact on the child and family must be acknowledged. The focus must become restoring the child's functioning including returning to school. Underlying stresses such as school performance and bullying must be addressed.

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Compliance with Ethical Standards

Conflict of Interest
Michael K. Farrell declare that he has no conflict of interest, Leslie Farrell declare that she has no conflict of interest. Peter R. Farrell declare that he has no conflicts of interest.

Human and Animal Rights and Informed Consent
Michael K Farrell participated in studies about anxiety in pediatric abdominal pain. These studies were reviewed and approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. No studies with animals were conducted by any of the authors.

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