Original Article

What's New in Functional and Motility Disorders in the Lower GI Tract?

Michael Camilleri

Abstract

This review addresses what is new in functional and motility disorders in the lower gastrointestinal tract: biomarkers and actionable biomarkers in irritable bowel syndrome (IBS), dietary and pharmacological treatment of abdominal pain in IBS, how to screen for rectal evacuation disorders in chronic constipation, hypotheses on the etiology of infantile colic, and lessons learned from the appraisal of an esoteric colonic motor disorder, that is, megacolon in association with multiple endocrine neoplasia type 2B. Understanding the mechanisms has moved these from idiopathic or cryptogenic disorders to organic diseases and has changed the attitude of health care providers to empathize with the suffering and legitimate pleas of millions of patients for effective therapies.

Key words

IBS, rectal evacuation disorder, chronic, diarrhea, constipation, megacolon

Michael Camilleri, M.D. M Phil (Lond), MRCP, FACP, DSc (Hon)
Mayo Clinic
Charlton 8-110
200 First St. S.W.
Rochester, MN 55905
camilleri.michael@mayo.edu

Introduction

Irritable bowel syndrome (IBS) is generally diagnosed based on symptoms of persistent abdominal pain that is associated with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M).[1] The diagnosis should rely on the clinical history so that invasive and expensive testing can be avoided. However, the diagnosis of IBS may not be easy and may involve multiple clinic and emergency room visits, extensive investigations including blood and fecal tests, and multiple radiographic and endoscopic studies to exclude inflammatory bowel diseases (IBD), celiac disease, and gastrointestinal infections. There have been significant advances in the understanding of motility and functional lower gastrointestinal disorders that augur well for optimizing management of patients with these conditions.

There is considerable evidence of abnormal peripheral mechanisms in IBS.[2] These mechanisms can be identified, in part, through biomarkers which are molecular, histologic, radiographic or physiologic characteristics that indicate a normal biological or pathological process or responses to therapeutic or non-therapeutic interventions.[3]

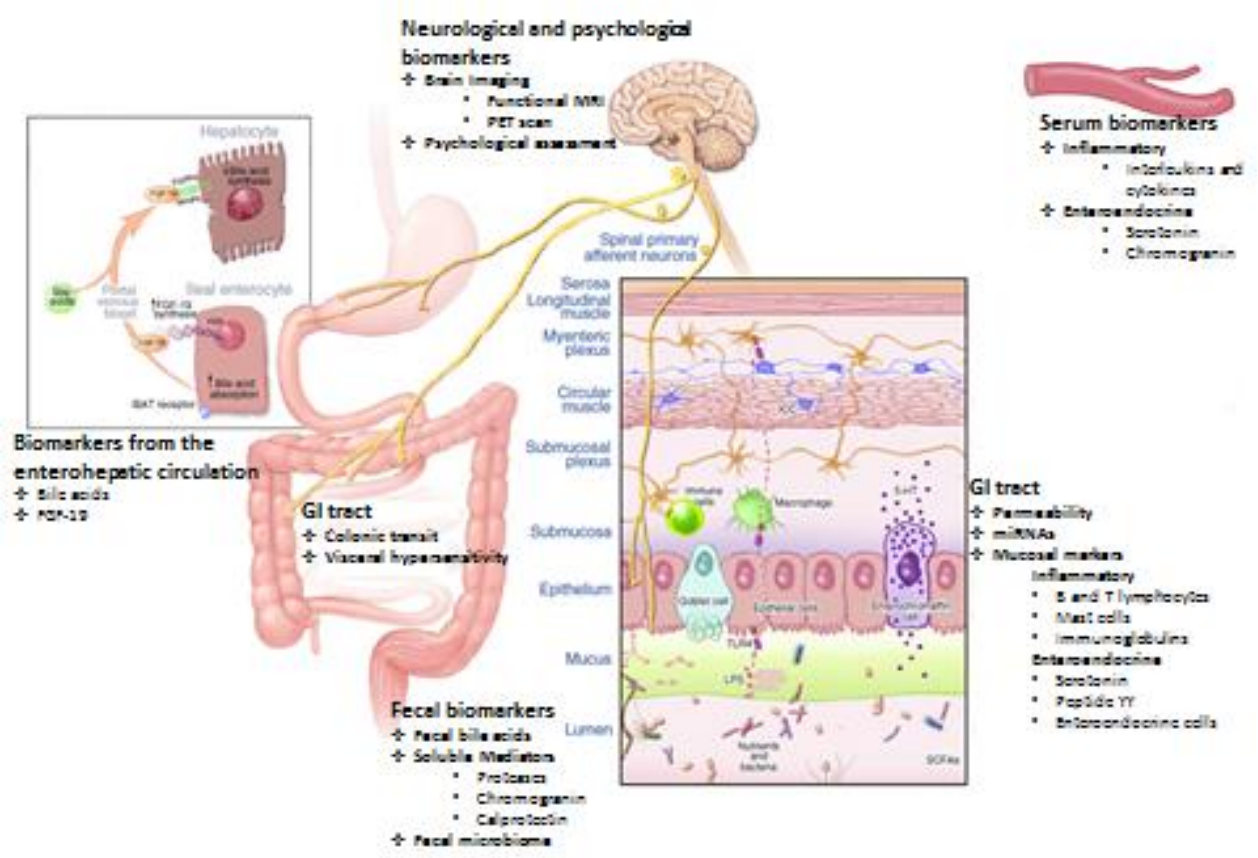
Mechanisms and Biomarkers of IBS

An ideal biomarker measures a biological substance, structure or process that influences the outcome of a disease, even though few biomarkers actually qualify as surrogate or clinical endpoints.[4]

Several biomarkers have been proposed in IBS [Figure 1], including fecal, blood, mucosal, microbial, radiological (including brain imaging), and genetic markers. IBS biomarkers' clinical utility greatly depends on our understanding of their functions in normal physiology and in the pathophysiology of IBS. A clinically useful biomarker needs to be safe, easy to measure, cost effective and actionable. The term "actionable" biomarker reflects the fact that the biomarker is helpful for the subclassification of diseases and directly impacts the selection of therapy. Validated

biomarkers may, in the future, potentially replace symptom-based criteria for IBS and aid in accurately identifying subgroups of patients beyond the symptom-based classifications, that is, bowel dysfunction and the presence or absence of significant pain.

Figure 1: *Biomarkers in IBS. Reproduced with permission from ref. 63*



Antibody panels

Antibodies to cytolethal distending toxin B (cdtB) (a toxin produced by C. jejuni) and Viniculin (component of adherens junction proteins) have been proposed for differentiating IBS-D from IBD and health.[5] However, anti-CdtB antibody was also elevated in patients with celiac disease, an important diagnosis to be differentiated in patients with suspected IBS-D. This test is now commercially available as IBSchek.

A panel of 10 markers, consisting predominantly of antibodies or inhibitors to endogenous proteins or bacteria and neurotransmitters, was used to differentiate IBS from IBD, celiac disease and functional disorders. However, the sensitivity was only 50%.[6] In addition, some of the biomarkers used in that analysis were not specific to IBS, and, thus, the test was not able to differentiate between the different subclasses of IBS. In another study, a different panel used 8 predominantly inflammatory biomarkers with a sensitivity of 88.1% and specificity of 86.5% to differentiate patients with IBS from healthy controls.[7] Differentiation from other diseases mimicking IBS with this panel requires further study.

Further validation of these markers or panels in more diverse groups will help clarify their generalizability for application as diagnostic tests.

Bile acids

In clinical practice in the United States, quantifying fecal bile acids using a 48-hour stool collection is the gold standard test for bile acid

malabsorption. Other tests for detection of bile acid malabsorption (BAM) are used in other countries; these include ^{75}Se-homocholic acid taurine (SeHCAT) retention test. Screening blood tests in development are fasting serum FGF-19, a regulator of hepatic bile acid synthesis which is low in BAM,[8] and fasting serum 7α-hydroxy-4-cholesten-3-one (C4).[9]

Several meta-analyses based on clinical studies have demonstrated that approximately 30% of patients with IBS-D has evidence of BAM.[10-12] Deoxycholic acid (DCA) and chenodeoxycholic acid (CDCA) were lower in IBS-C patients compared to healthy volunteers.[13]

Colesevelam, a bile acid sequestrant, sequestered intraluminal bile acids and increased stool consistency in IBS-D patients.[14] In the future, ileal bile acid transporter inhibitors such as elobixibat may be available for patients with constipation.

Calprotectin

Calprotectin is a neutrophil-derived protein found in the cytosol of neutrophils; it acts as a biomarker for inflammation. Elevated fecal calprotectin helps differentiate patients with active inflammatory colitis such as IBD[15] from those with microscopic colitis.[16] Several studies in IBS patients have demonstrated similar fecal calprotectin levels compared to healthy controls[17] and patients with IBD in deep remission.[15]

A meta-analysis of 8 studies with 565 patients with IBD, 259 with IBS, and 238 healthy controls demonstrated that there was no level of fecal calprotectin that could completely exclude IBS.

Fecal calprotectin helps exclude IBD at a level <40 µg/g stool, but it is not a reliable biomarker for IBS. If IBD is excluded by imaging (e.g., colonoscopy), a high fecal calprotectin level may identify patients with immune activation as a component of the IBS mechanism.

GI motility measurements

Multiple tests are now available to evaluate gastrointestinal motility, including radiopaque marker studies, scintigraphy, and the wireless motility capsule.[18-19] In a study of 287 patients with lower functional gastrointestinal disorders, approximately 30% had abnormal colonic transit by scintigraphy: delayed transit in 22.9% of patients with IBS-C and functional constipation, and accelerated transit in 33.3% of patients with IBS-D and functional diarrhea. Discordant results were rare: 4.5% of patients with IBS-D or functional diarrhea had delayed transit at 48 hours, and 4.2% of IBS-C or functional constipation patients had accelerated transit at 24 hours.[20]

Abnormal colonic transit, measured by scintigraphy, was associated with symptoms including stool consistency, frequency of bowel movements, and ease of passage of stool.[21] Colonic transit was an independent predictor of IBS compared to healthy volunteers, with well-established normal values (GC 24 of 1.3–4.4; GC48 1.9–5.0).[22] Additionally, colonic transit with geometric center at 48 hours is an independent predictor in discriminating healthy individuals from IBS-C patients, and IBS-C patients from IBS-D patients,[23] but it does not discriminate between slow transit due to colonic dysmotility and constipation due to rectal evacuation disorders.[24]

Psychological traits

Psychological assessment has been used as a marker of illness in IBS. Psychological measures, such as the Hospital Anxiety and Depression scale, the Patient Health Questionnaire and the Perceived Stress Scale, have been added to enhance the ability of the IBS biomarker panels to differentiate IBS cases from healthy volunteers.[25]

On the other hand, psychological markers used alone are likely not sufficient to identify bowel disturbances or their severity in IBS, but they may be more closely associated with the pain/discomfort in IBS.

Actionable biomarkers in IBS

Individually, symptom-based diagnostic criteria performed modestly in the prediction of IBS,[26] and the diagnostic performance of symptom-based criteria is enhanced by additional history (e.g., nocturnal stools, somatization) and limited diagnostic tests (e.g., hemoglobin and C-reactive protein levels).[27]

A systematic review of biomarkers has appraised diverse markers.[28] Overall, the most promising biomarkers with the greatest actionability are colonic transit and bile acid secretion, as they can be measured by several methods that are applicable in clinical practice. Additionally, there are specific efficacious therapies directed at reversing the pathophysiological mechanisms

identified by those biomarkers.

Dietary and Pharmacological Treatment of Abdominal Pain in Irritable Bowel Syndrome

Abdominal pain remains the greatest unmet need in the treatment of IBS. A recent article[29] appraised the available literature on dietary, probiotics and pharmacotherapy of pain in IBS, and a summary of efficacy is provided in Table 1. The main approaches to treatment remain antispasmodics and antidepressants, and it is hoped that advances in neurobiology of pain or further understanding of the microbiome might lead to novel approaches to therapy that remain experimental even for drugs that are used off-label, such as non-sedating anti-histamines and GABA-ergic agents.

Table 1: *Efficacy of interventions on the relief of symptoms in IBS: Relative risk (RR) or odds ratio (OR) and confidence interval (CI) based on systematic reviews and meta-analyses. Reproduced with permission from ref. 29*

Intervention	Parameter	RR or OR	Ref. #
Dietary or Probiotics or Antibiotics			
Bran, ispaghula and unspecified fiber	Abdominal pain	RR 0.87 (0.76-1.00)	49
Low FODMAP diet	Abdominal pain	OR 1.81 (1.13-2.88)	50
Probiotics	Global improvement	SEM: -0.25 (-0.36, -0.14)	51
Probiotics: combination of E. coli + Enterococcus faecalis OR E. coli alone	Abdominal pain	RR 1.96 (1.14-3.36)	52,53
Rifaximin	Global improvement	OR 1.57 (1.22-2.01)	54
Rifaximin	Bloating	OR 1.55 (1.23-1.96)	54
Antispasmodics			
Peppermint oil	Global improvement	RR 2.23 (1.78-2.81)	55
Antidepressants			
Antidepressant therapy	Global improvement	RR 0.66 (0.57-0.78)	56
	Abdominal pain	RR 0.62 (0.43-0.88)	56
Antidepressant therapy	Global improvement	RR 0.67 (0.58-0.77)	57,58
Antidepressant therapy	Abdominal pain	RR 0.62 (0.43-0.88)	57,58
Drugs Targeting Specific Gastrointestinal Receptors			
Alosetron	Abdominal pain and discomfort	RR 1.30 (1.22-1.39)	59
	Overall risk difference	0.13 (0.1-0.16)	59
Alosetron	Abdominal pain and discomfort	RR 1.23 (1.15-1.32)	60
	Global improvement	RR 1.5 (1.40-1.72)	60
Ondansetron	Adequate relief response	RR 4.7 (2.6-8.5)	61
Linaclotide	Adequate relief response	RR1.95 (1.3-2.9)	62
	Abdominal pain	RR 1.58 (1.02-2.46)	62

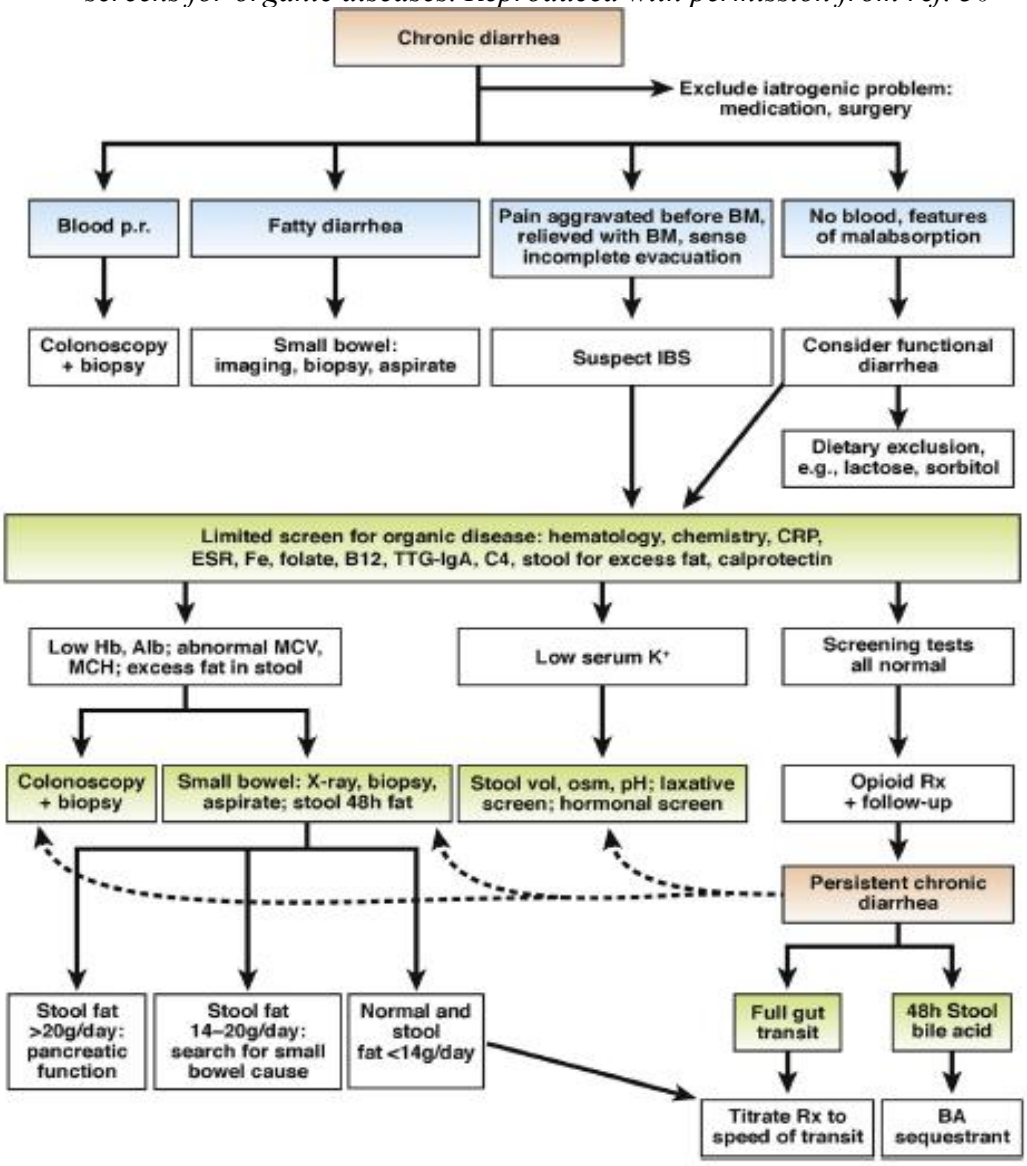
Chronic Diarrhea

Algorithm for evaluation of chronic diarrhea

Figure 2 shows a proposed algorithm for the diagnosis of chronic diarrhea.[30]

It is important to appraise the presence of rectal bleeding, features of malabsorption, or symptoms of IBS from the patients' histories. If there are no rectal blood or features of malabsorption, a limited screen for organic disease may include hematology and chemical analyses, and tests to measure C-reactive protein, erythrocyte sedimentation rate, serum iron, folate, vitamin B12, tissue transglutaminase-IgA (to detect celiac disease), serum level of 7α-hydroxy-4-cholesten-3-one or fibroblast growth factor 19 (if available, to detect bile acid diarrhea), and examinations for excess fat or calprotectin in a random stool sample. In addition, colonoscopy and biopsy are usually performed according to recommendations for colorectal cancer screening, or in patients with intractable watery diarrhea to exclude microscopic colitis. American Gastroenterological Association guidelines specify the importance of excluding celiac disease, hyperthyroidism, IBS, and medication use (e.g. non-steroidal anti-inflammatory drugs, aspirin, proton-pump inhibitors, clozapine, and acarbose) when considering the possibility of microscopic colitis.[31]

Figure 2: *Algorithm for management of chronic diarrhea. Patients undergo an initial evaluation based on different symptom presentations, leading to selection of patients for imaging, biopsy analysis, and limited screens for organic diseases. Reproduced with permission from ref. 30*



The next steps in the management algorithm are guided by results of the initial screen for organic disease. The next steps include further specific tests when features indicate IBD or malabsorption. When results from all tests are normal and suggest chronic watery diarrhea typically without hypokalemia, opioid therapy should be tested (e.g. loperamide, 2–4 mg, as many as 4 times/day), with preprandial dosing for patients with prominent postprandial diarrhea. If the diarrhea persists, patients should be formally tested for bile acid malabsorption or given a trial of bile acid sequestrants if the tests for BAM are unavailable (e.g. 48h total fecal BA, or ^{75}SeHCAT retention at 7 days; measurement of colonic transit will make it easier to select subsequent therapies. Tests for small intestinal bacterial overgrowth (SIBO- still best achieved by small bowel aspirates and culture) should be considered when there is evidence of malabsorption from the screening tests for organic disease, such as hypoalbuminemia or positive qualitative fecal fat.

Management based on pathogenesis of chronic diarrhea

The principles of management are accurate diagnosis and treatment of the specific factors that are causing the chronic diarrhea. Dehydration and severe electrolyte abnormalities are uncommon in patients with chronic watery diarrhea, but, when they occur, should be addressed with oral rehydration therapy.

Treating the factors that cause the disorder is more specific, such as with budesonide for microscopic colitis or a bile acid sequestrant for patients with diarrhea, and is certainly more intellectually satisfying. However, when that is not possible to direct treatment to a specific etiological mechanism, it is important to relieve symptoms with non-specific therapies that address the secretory and motor components of chronic diarrhea. Opioids are the mainstay of treatment and, when given in a scheduled regimen, are generally safe. However, a recent report found that high doses of loperamide can induce toxic cardiac arrhythmias and death.[32]

Table 2: *Summary and Dosages of Drugs Used in Treatment of Chronic Watery Diarrhea. Reproduced with permission from ref. 30*

Drug class	**Agent**	**Dose**
Opiates (μ-opiate receptor selective)		
	Diphenoxylate	2.5–5 mg, 4 times/day
	Loperamide	2–4 mg, 4 times/day
	Codeine	15–60 mg, 4 times/day
	Opium tincture	2–20 drops, 4 times/day
	Morphine	2–20 mg, 4 times/day
	Eluxadoline	100 mg twice daily (μ-opioid agonist and δ-opioid antagonist) for IBS-D
Adrenergic α2 receptor agonist		
	Clonidine	0.1–0.3 mg 3 times/day; Weekly patch
Somatostatin analogue		
	Octreotide	50–250 μg 3 times/day (subcutaneously)
Bile acid-binding resin		
	Cholestyramine	4 g daily or up to 4 times/day
	Colestipol	4 g daily or up to 4 times/day
	Colesevelam	1875 mg up to twice daily
Fiber supplements		
	Calcium polycarbophil	5–10 g daily
	Psyllium	10–20 g daily
Soluble fiber	Pectin	2 capsules before meals
Calcium		1000 mg twice or 3 times daily
Serotonin 5-HT_3 receptor antagonists		
	Alosetron	0.5-1.0 mg twice daily
	Ondansetron	2-8 mg twice daily

Deodorized tincture of opium and morphine are significantly more potent, but should not be prescribed for the indication of chronic watery diarrhea. Clonidine has been used to relieve the autonomic neuropathy associated with diabetic diarrhea, but may provide only limited benefit because of associated orthostatic hypotension. Use of the trans-dermal approach for clonidine may result in control of diarrhea without significant postural hypotension. Chronic intermittent antibiotics are the mainstay of treatment for well-proven SIBO. Several antibiotics have been shown to be equally effective.[33] Although rifaximin is frequently prescribed, its use is limited by its high cost and regulatory approval for 3 courses, each of 2 weeks duration. Less expensive alternatives, such as metronidazole, doxycycline or ciprofloxacin, should therefore be considered. Agents that act intraluminally (fiber, pectin, and calcium) may be helpful in patients with small volume diarrheas. In some cases, a cocktail of agents with different mechanisms is required.

These and second-line approaches to use when first-line treatments fail are presented in Table 2.

How to Screen for Rectal Evacuation Disorders in Chronic Constipation

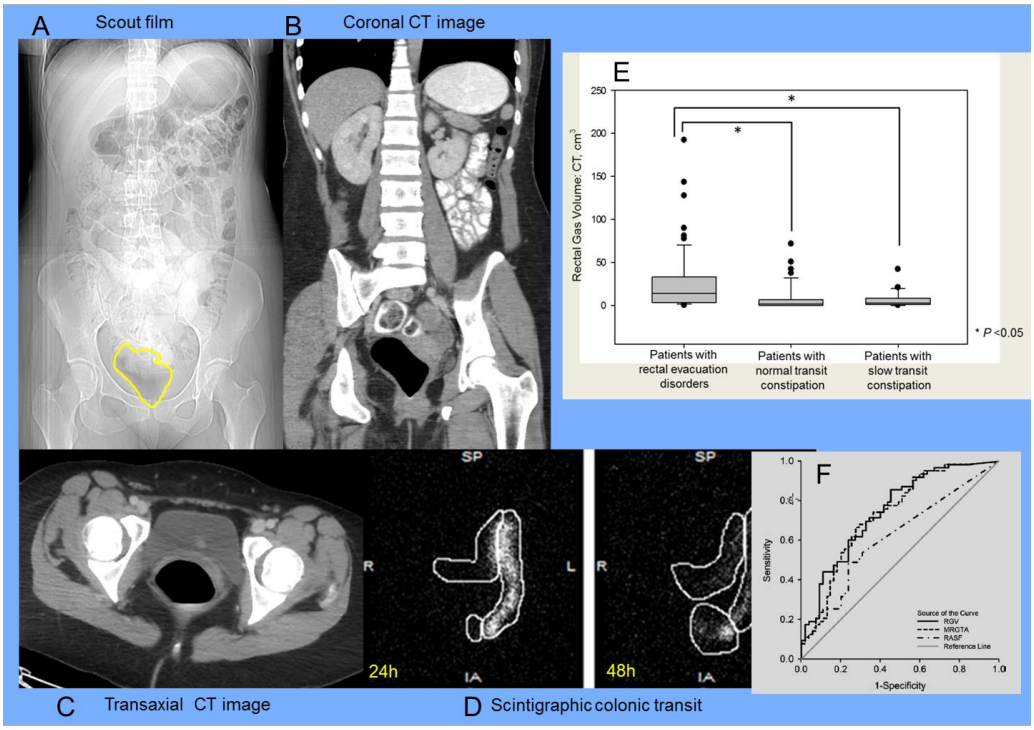
Rectal evacuation disorders account for approximately one-third of patients presenting with constipation in gastroenterology practice.[34] A recent population-based study showed that defecatory disorders are relatively common in the community, with the sex-adjusted incidence rate being 5-fold higher in women than in men.[35] The most effective therapeutic approach to refractory constipation with rectal evacuation disorders is biofeedback therapy or pelvic floor retraining.[36] To avoid laxative overuse in constipated patients with rectal evacuation disorders and to optimize treatment in these patients, an accurate diagnosis for rectal evacuation disorders is needed. Currently, the diagnosis for rectal evacuation disorders is based on anorectal manometry and evacuation tests (balloon, barium or MR defecography), which are not generally available in internal medicine or gastroenterology practices. Unfortunately, there is also considerable discordance among tests used for the diagnosis of rectal evacuation disorders,[37] and also there is lack of standardization for the balloon expulsion test.

Therefore, in addition to careful clinical evaluation[38] including digital rectal examination which is best for dyssynergic defecation,[39] an easily accessible diagnostic tool with high specificity to select the patients with suspected rectal evacuation disorders is desirable prior toreferral for specialized tests to confirm the diagnosis. There are several clinical pointers in the history and examination that can be used, to identify dyssynergic defecation.[39] A carefully performed digital rectal examination by a highly experienced expert is a good screening test, with 75% sensitivity and 87% specificity.[39] However, it is operator dependent and even gastroenterologists fail to perform the rectal examination for a variety of reasons.[40] Therefore, there is need for a test that can corroborate the clinical impression and support referral for specialized anorectal testing. One test that is often performed to exclude other diseases in patients presenting with constipation is abdominal and pelvic computerized tomography (CT).

In 118 patients [(102 females) who underwent CT abdomen and pelvis among >1500 patients with constipation evaluated by a single experienced gastroenterologist over 20 years], there were 63 with rectal evacuation disorders, 17 with slow transit constipation (STC), and 38 with normal transit constipation (NTC), based on the sum of the evidence from clinical findings and results of laboratory or radiological investigations.[41] Using abdomen and pelvis CT, the rectal gas volume and maximal rectal gas transaxial area (MRGTA) were significantly greater in constipated patients with rectal evacuation disorders than in those without rectal evacuation disorders.[41] Assessment of rectal gas area or volume on abdominal imaging may indicate rectal evacuation disorders in patients with constipation. At ~90% specificity for rectal evacuation disorders, the rectal gas volume of 20 or 30mL or MRGTA of 10cm^2 on CT have a positive predictive value of ~75%, and rectal area on scout film of >9cm^2 has a positive predictive value of ~69% [Figure 3].[41]

***Figure 3**: Scout film (upper left), coronal image (upper middle) and cross-sectional image on CT (lower left) from a 44 year-old female with rectal evacuation disorder. The rectal gas volume was 77.5mL and maximum rectal gas area was 22.2cm^2. Patients with rectal evacuation disorder have retention of isotope in the left colon at 24 and 48h (lower middle). Data for the three groups (upper right) are summarized and show higher RGV in patients with RED compared to NTC and STC. ROC curves (lower right) of rectal gas volume, maximal rectal gas area, and area of rectal gas (vertical) on the 2-dimensional abdominal film (scout) to identify a rectal evacuation disorder. Note the two approaches have similar performance characteristics. Reproduced with permission from ref. 41.*

RGV, rectal gas volume; MRGTA, maximum rectal gas transaxial area; RGA on scout, area of rectal gas on the 2-dimensional abdominal film (scout)



Hypotheses on the Etiology of Infantile Colic

Infantile colic is a syndrome characterized by recurrent irritability and inconsolable crying and screaming, accompanied by clenched fists, drawn-up legs, and a red face. It usually starts in the second or third week after birth, and peaks at 5 to 8 weeks of age. It generally stops spontaneously by 4 months of age. The prevalence is estimated to be between 5% and 28%.[42] A recent review identified three hypotheses for the etiology of infantile colic. First, immaturity of hepatic synthesis, reduced intraluminal levels of bile acids, and impaired ileal absorption of bile acids in the neonate result in malabsorption of fat and other nutrients, with potential for secondary effects on colonic microbial flora. A second hypothesis proposes that the colonic microbial flora are abnormal and result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon. Third, immaturity of the enteric nervous system (ENS) may lead to abnormal motor and sensory functions of the intestine and colon.[43] Given the reversal of symptoms by 4 months of age, the concept that colic results from a dysmaturity of one of these digestive processes seems compelling.

Overall, the literature provides evidence for interaction among these three mechanisms. Understanding these potential mechanisms may lead to the introduction of diagnostic procedures that should enhance the selection or individualization of therapy for infantile colic.

Lessons from an Esoteric Motility Disorder

The most recognized gastrointestinal motility disorders presenting in neonates or infancy are congenital hypertrophic pyloric stenosis (which is easily managed by surgical pyloromyotomy and has undergone limited investigation of the genetic mechanisms) or Hirschsprung's disease which is associated with several genetic abnormalities in Ret

kinase, endothelin B and its receptor, and SOX10 pathways.

On the other hand, multiple endocrine neoplasia type 2B (MEN2B) is an autosomal dominant syndrome caused by germline activating mutations of the RET proto-oncogene (typically at the M918T locus). It is associated in all patients with medullary thyroid cancer, and mucosal neuromas, and less frequently with phaeochromocytoma. Ganglioneuromas associated with megacolon are characterized by an increased number of ganglion cells and nerve fibers in all layers of the bowel wall.[44] The ganglioneuromas can lead to loss of bowel tone, distension, segmental dilation and, ultimately, megacolon.

Megacolon is characterized on imaging studies by a permanently enlarged colon diameter which is greater than 6.5 cm at pelvic brim, greater than 8 cm in the ascending colon, or greater than 12 cm in the cecum.[45] Infants with MEN2B frequently experience gastrointestinal symptoms,[46] with constipation and intermittent diarrhea being the most frequently reported.[47] Sixty percent of patients have prominent lips and 100% of patients have neurofibromas on their tongue, particularly the anterior two-thirds of the tongue. This physical finding should be sought, and plain abdominal radiograph should be conducted in patients presenting with abdominal pain, constipation, bloating and distension, as they may identify megacolon or rectal evacuation disorders (see above) which may be mistaken for chronic functional gastrointestinal disorders and yet could be eminently treatable by laparoscopic colectomy or retraining of the pelvic floor respectively. Indeed, 5 of 7 recently reported patients with megacolon associated with MEN2B underwent colectomy with excellent outcomes.[48] Among these 7 patients with megacolon and MEN2B, 2 patients also had esophageal achalasia and 1 had a Zenker's diverticulum; therefore, patients should be screened for esophageal dysmotility and treated according to the diagnosis.

Conclusion

There have been significant advances in the understanding of motility and functional lower gastrointestinal disorders that augur well for optimizing management of patients with these conditions. Perhaps, it is most important to recognize that understanding the mechanisms has moved these from idiopathic or cryptogenic disorders to organic diseases and has changed the attitude of health care providers to empathize with the suffering and legitimate pleas of millions of patients for effective therapies.

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