

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Ernst J. Kuipers and Vincent W. Yang, Section Editors

Pathophysiology, Evaluation, and Management of Chronic Watery Diarrhea



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Chronic watery diarrhea poses a diagnostic and therapeutic challenge and is often a disabling condition for patients. Although acute diarrhea is likely to be caused by infection, the causes of chronic diarrhea (>4 weeks in duration) are more elusive. We review the pathophysiology, diagnosis, and treatment of chronic diarrhea. Drawing on recent insights into the molecular mechanisms of intestinal epithelial transport and barrier function, we discuss how diarrhea can result from a decrease in luminal solute absorption, an increase in secretion, or both, as well as derangements in barrier properties. We also describe the various extraepithelial factors that activate diarrheal mechanisms. Finally, clinical evaluation and tests used in the assessment of patients presenting with chronic diarrhea are reviewed, and an algorithm guiding therapeutic decisions and pharmacotherapy is presented.

Keywords: Diarrhea; Pathophysiology; Management.

Diarrhea poses a diagnostic and therapeutic challenge to clinicians, in part, because it has diverse etiologies. Diagnostic tests may be difficult or not readily available, a specific diagnosis may be elusive, and targeted treatment may be unavailable, leading to the need for trials of empiric therapy.

Although diarrhea may be obvious to the patient, it is important to define the basic characteristics of the diarrhea: frequency and consistency. A more quantitative approach is to determine stool weight/24 hours in a timed collection. A rational classification for evaluation of diarrhea considers acute and chronic (>4 weeks) forms. This approach emphasizes the likelihood of an infectious etiology for acute conditions, whereas chronic diarrhea is much less likely to be infectious, and other causes should be considered. An alternative classification for diarrhea is based on the appearance of the stool: fatty, inflammatory (associated with blood in the stool), or watery, as detailed elsewhere.¹

In this article, we focus exclusively on chronic watery diarrhea, reviewing the basic pathophysiology and recent advances in our understanding of intestinal mechanisms that control fluid and electrolyte transport, as well as providing a rational and parsimonious approach to the

clinical evaluation of watery diarrhea and a discussion of therapeutic options.

Intestinal Cellular Mechanisms of Fluid and Ion Transport

The amount of fluid in the stool is determined by its content of solutes. In patients with watery diarrhea, solutes are not being absorbed sufficiently, are being secreted actively into the lumen, or both. The ability, normally, to dehydrate the stool also depends on epithelial barrier function, to prevent the back diffusion of electrolytes and other solutes once they have been absorbed across the epithelium. To provide a foundation for understanding the pathophysiology of chronic diarrhea, we review our understanding of epithelial transport and barrier functions in the small intestine and colon. We confine the discussion to a consideration of the mechanisms that, when abnormal, have to contribute to diarrheal symptoms (Figure 1).

NaCl absorption

The coupled absorption of sodium and chloride ions is a prominent mechanism for the reclamation of fluid and electrolytes throughout the small and large intestines, particularly (for the former) in the period between meals.² The transport mechanism depends on paired transporters expressed on the apical membrane of villous (or surface) epithelial cells—a member of the solute carrier 9 (SLC9) family of sodium–hydrogen exchangers (NHE), and a member of the SLC26 family of anion exchangers. Depending on the precise gut segment, either SLC9A2 (also called

Abbreviations used in this paper: ATPase, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; Cg, chromogranin; cGMP, cyclic guanosine monophosphate; ENaC, epithelial sodium channel; 5-HT, 5-hydroxytryptamine; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyol; IBD, irritable bowel disease; IBS-D, diarrhea-predominant irritable bowel syndrome; NHE, sodium–hydrogen exchanger; SCFA, short-chain fatty acid; SIBO, small intestinal bacterial overgrowth; SLC, solute carrier; Sg, secretogranin.

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0016-5085/\$36.00

<http://dx.doi.org/10.1053/j.gastro.2016.10.014>

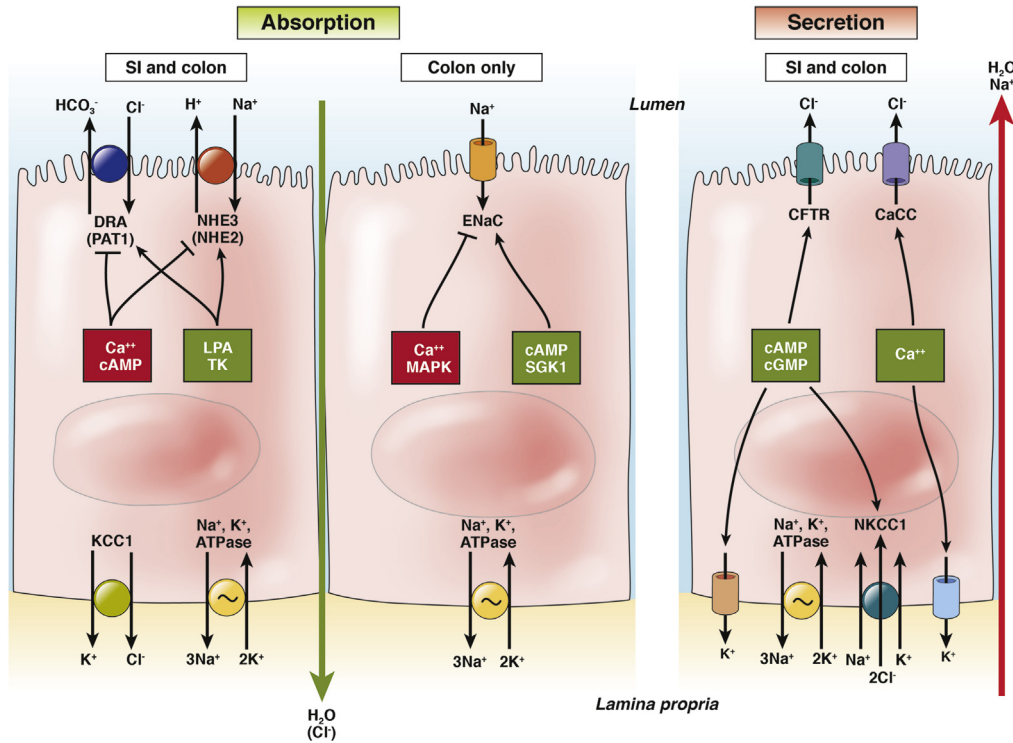


Figure 1. Cellular mechanisms accounting for intestinal absorption and secretion. Factors that reduce the amount or function of a specific transporter are shown in red boxes; those that increase levels of activity are shown in green boxes. Long vertical arrows indicate the paracellular absorption or secretion of water, with or without an appropriate counterion. LPA, lysophosphatidic acid; SI, small intestine; TK, tyrosine kinase.

NHE2) or SLC9A3 (also known as NHE3) mediate sodium-hydrogen exchange, whereas SLC26A3 (also called down-regulated in adenoma) or SLC26A6 (also called putative anion transporter 1) mediate chloride-bicarbonate exchange. Through these transporters, sodium and chloride ions enter the cell cytosol and then can be exported across the basolateral membrane via the Na^+/K^+ adenosine triphosphatase (ATPase) and a potassium chloride co-transporter, respectively.²

The activity of the apical SLC9 and SLC26 transporters is coordinately regulated, such that NHE inhibitors reduce chloride-bicarbonate exchange, and vice versa.³ Similarly, neurohumoral signals either up-regulate or down-regulate both transporters in parallel. This functional coupling results, in part, from localization of the transporters to the apical membrane in the form of macromolecular complexes that are linked (via PDZ-domain binding) to cytoplasmic regulatory proteins known as NHE regulatory factors.³ NHE regulatory factors also contain sites for phosphorylation by intracellular kinases, such as protein kinase A, which control membrane abundance of NHEs via their regulated trafficking into and out of the apical membrane.⁴ In general, SLC9 and SLC26 transporter activity is reduced by hormones that increase intracellular levels of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), or calcium, whereas it is increased by agents such as epidermal growth factor, which induce tyrosine kinase (TK)-dependent signaling.⁵ Lysophosphatidic acid (LPA) also increases SLC26A3 expression and trafficking of this transporter as well as SLC9A3 to the apical membrane.^{5,6}

Mice lacking SLC9A3 develop the equivalent of chronic diarrhea.⁷ The function and/or expression of intestinal SLC9

and SLC26 transporters also are down-regulated by a variety of inflammatory cytokines, and this may contribute to diarrhea in patients with inflammatory bowel diseases (IBDs).⁸ Similarly, single-nucleotide polymorphisms in SLC9A3 that reduce the activity of the transporter could increase susceptibility to chronic diarrhea,⁹ although this hypothesis should be tested in patients.

Electrogenic Na^+ Absorption

In the distal colon, sodium ions are additionally absorbed without concomitant uptake of chloride. Rather, they enter the apical membranes of surface colonocytes via the heterotrimeric epithelial sodium channel (ENaC), and then they exit the colonocytes at the basolateral membrane via Na^+/K^+ ATPase. ENaC channel opening and/or membrane abundance are stimulated by neurohumoral agents that increase cAMP, but the channel is inhibited by those that increase levels of cytoplasmic calcium and/or activate mitogen-activated protein kinases.^{10,11} Acute regulation of the ENaC is mediated in large part by neural precursor cell expressed developmentally down-regulated 4-like NEDD4-2, a ubiquitin ligase whose activity results in internalization of the ENaC and its degradation by the proteasome.¹¹ Phosphorylation of NEDD4-2, either by protein kinase A or by the serum and glucocorticoid-inducible kinase, which is activated by aldosterone, reduces its binding to the ENaC and thereby increases the residence time of the channel in the apical membrane.¹² The channel's activity also is influenced positively by channel-activating protease 1, a membrane-bound protease that acts on the extracellular domains of ENaC subunits to increase the probability that the channel will be

open.¹³ ENaC activity also can be up-regulated chronically when its expression is increased by aldosterone (eg, in response to a low-salt diet) or glucocorticoids.^{14,15} There also is evidence for sodium channels other than the ENaC that contribute to absorption of the cation in the human colon.¹⁶

Mice that lack ENaCs specifically in the distal colon lose significantly greater amounts of sodium in their feces than control animals, but do not have diarrhea.¹⁴ Therefore, the ENaC-dependent mechanism for sodium absorption in the colon appears to be a salvage pathway that does not contribute significantly to water balance in health, presumably because NaCl absorption and sodium-coupled nutrient uptake are sufficient for fluid reabsorption. However, if fluid is not reclaimed adequately upstream, ENaC-dependent sodium absorption may become functionally relevant. Furthermore, the expression and function of ENaC are down-regulated in mice with colitis (serving as a model of human IBD), as well as in patients with IBD (even in macroscopically normal regions); ENaC also is down-regulated in microscopic colitis, which increasingly is appreciated as a cause of chronic watery diarrhea.^{17–21}

Chloride Secretion

Although the net vector for electrolyte transport in the healthy gut is absorptive, there is ongoing secretion to provide appropriate fluidity of luminal content to support digestion, absorption, and movement of intestinal contents along the digestive tract. Indeed, it has been estimated that the intestine itself provides approximately 1 L/day of the 8–9 L of fluid that typically traverse the gastrointestinal system. If a meal is hypertonic, it initially will draw fluid into the intestinal lumen by osmosis because the stomach does not sufficiently control the emptying of the osmotically active meal, despite the increase in pyloric resistance.²² However, secretory fluxes are driven by the active secretion of chloride ions, which occurs predominantly across crypt epithelial cells and is regulated by specific neurohormonal triggers.²³

The chloride secretory mechanism²³ involves uptake of chloride across the basolateral membrane via a sodium-potassium-2 chloride co-transporter, NKCC1. The activity of NKCC1 is driven by the low intracellular sodium concentration established by extrusion of sodium ions by the basolateral Na⁺/K⁺ ATPase. Potassium ions also are recycled across the basolateral membrane by cAMP- or calcium-activated channels; this serves to maintain the favorable electrical gradient that drives chloride exit across the apical membrane. Chloride ions that accumulate in the cytosol exit apically via regulated chloride conductances. The major pathway is via the cystic fibrosis transmembrane conductance regulator chloride channels, but there also can be a contribution from calcium-activated chloride channels, although the molecular identity of such channels remains controversial.²⁴ No matter the precise exit pathway, the net effect is to transfer chloride from the bloodstream to the intestinal lumen, with water (and sodium ions) following through the paracellular route.

Chloride secretion is stimulated by neurohumoral agents that increase levels of cAMP, cGMP, or calcium, although the

characteristics of the responses differ.²³ Cyclic nucleotide-stimulated secretion is large and sustained while the stimulus persists. Calcium-dependent secretion, on the other hand, is smaller and transient, apparently owing to a variety of inhibitory pathways intrinsic and extrinsic to the epithelium. This may allow for lubrication of the epithelium, without risking dehydration. On the other hand, when the epithelium is exposed to agonists acting through both cAMP and calcium-dependent pathways, a synergistic enhancement of secretion results. Many agents that stimulate chloride secretion simultaneously inhibit NaCl absorption, which may be relevant for the pathogenesis of secretory diarrhea.

Stimulation of active chloride secretion is an underlying pathophysiological mechanism in some acute infectious diarrheas, such as cholera or rotavirus infection (predominantly related to excessive activation of the cystic fibrosis transmembrane conductance regulator and calcium-activated chloride channels, respectively).^{25,26} However, there is evidence that certain forms of chronic watery diarrhea share a secretory component, as illustrated by the effectiveness of a chloride channel-directed therapeutic, crofelemer, in patients with human immunodeficiency virus receiving retroviral therapy.²⁷ Chloride secretion also is implicated in diarrhea associated with some neuroendocrine tumors, such as those secreting vasoactive intestinal polypeptide or serotonin (5-hydroxytryptamine [5-HT]). Chronic diarrhea in a Norwegian cohort was attributed to a gain-of-function mutation in the guanylate cyclase 2C gene, which encodes the receptor for endogenous chloride secretagogues, such as guanylin and uroguanylin. Gain-of-function mutations in this protein would be expected to cause continual increases in cGMP.²⁸

Excess bile acids also can activate chloride secretion.²⁹ Bile acid malabsorption may account for a significant proportion of patients diagnosed with diarrhea-predominant irritable bowel syndrome (IBS-D).^{30,31}

Intestinal Barrier Function

The physiologic function of the gut as a portal for the uptake of beneficial substances, while excluding pathogens and toxins, requires that paracellular transport of solutes be controlled carefully. Barrier function is provided predominantly by the tight junctions that link adjacent epithelial cells, although other intercellular junctions also contribute. The barrier is not only dynamic, but also may allow for the selective permeation of solutes through tight-junction pores.

It is beyond the scope of this article to discuss all aspects of tight junction biology, and the reader is referred to recent reviews on this topic.^{32,33} Nevertheless, some general observations can be made. A family of claudin molecules is critical for establishing the actual permeability properties of the tight junctions, forming homotypic and heterotypic bonds with partner claudins on adjacent cells. Depending on the range of claudins expressed and their levels of expression, the junctions will be more or less leaky, or may contain charge-selective pores.³⁴ Other membrane-bound junctional components, such as occludin and tricellulin, are important in limiting macromolecular permeability across the

epithelium.³² The membrane-bound components of the tight junctions interact, via their cytoplasmic domains, with a number of adapter and regulatory proteins that influence junctional permeability.³⁵ For example, contraction of the actomyosin ring that encircles epithelial cells just below their apical poles can exert strain on the junctions that increase their permeability. Inappropriate activation of myosin light-chain kinase, which increases such contraction, may contribute to epithelial leakiness in the setting of inflammation.³⁵

Reduced effectiveness of the epithelial barrier is not sufficient to cause significant diarrhea. However, if it is coupled with defective ion transport and fluid accumulation in the lumen, the efficiency of absorptive transport may be compromised by a paracellular leak of absorbed solutes back into the luminal compartment. The resulting leak-flux diarrhea has been proposed as a mechanism of pathogenesis of IBD, but presumably could contribute to chronic watery diarrhea as well.^{32,36} Reduced tight junction expression of claudin-1 (called the *sealing claudin*) in mucosa from human ileum and ascending colon have been reported in patients with IBS-D (and, conversely, levels of claudin-1 are increased in patients with constipation).³⁷ Tight junction dysfunction also appears to contribute to the development of diarrhea after infection with *Giardia lamblia*, as well as postinfectious sequelae, at least in an animal model.³⁸ However, measurement of intestinal permeability^{39,40} in patients with chronic diarrhea should be considered as only a research tool, rather than for use in the clinic.

Secretory or Osmotic Diarrhea

Watery diarrheas are categorized as either osmotic or secretory. In patients with secretory diarrhea, stool osmolality is accounted for almost entirely by electrolytes (Na^+ , K^+ , and accompanying anions). In osmotic diarrhea, there is an unaccounted gap between the stool water electrolytes and the measured osmolality. This gap is caused by poorly absorbed molecules (eg, lactose in lactase deficiency) that draw fluid into the lumen.⁴¹ This classification has never been validated in a clinical study. A retrospective review of patients at a tertiary referral center recently showed the utility of measuring stool electrolytes and osmolality.⁴²

Watery Diarrhea Involving Motility, Inflammatory, and Combinations of Mechanisms

The importance of motility in the pathogenesis of diarrhea has been difficult to fully evaluate. There are elegant basic science techniques to elucidate the molecular mechanisms of ion transport, but only recent studies have provided insight into potential motor mechanisms involved in the development of diarrhea.⁴³ In most discussions about the basic mechanisms of diarrhea, motility generally is mentioned only briefly. Clinical studies have indicated that chronic watery diarrhea frequently has a major motility component, typically rapid transit through the gut, limiting the contact time between theoretically absorbable solutes and a normal epithelium.

There are other examples in which multiple mechanisms contribute to the development of watery diarrhea. For example, 5-HT, which is produced primarily in gut, mediates intrinsic reflexes (eg, stimulates motility, secretion, and vasodilation), and may promote inflammation that contributes to the development of diarrhea.⁴⁴

Mechanisms of Pathogenesis

A model of chronic diarrhea (Figure 2) includes effects of autocrine, luminal, paracrine, immune, neural, and endocrine factors on the paracellular pathway, epithelium, muscle, and vasculature; these can alter intestinal permeability, ion transport, and motility. Studies are underway to evaluate the effects of the microbiota on electrolyte transport and motility.

Although the archetype of chronic watery diarrhea is that produced by neuroendocrine tumors, these are exceedingly rare. More subtle abnormalities may contribute to functional diarrhea and IBS-D. IBS-D is a functional bowel disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Functional diarrhea is characterized by recurrent passage of loose or watery stools; patients with functional diarrhea should not meet criteria for IBS. Although abdominal pain and/or bloating may be present, they are not predominant symptoms.⁴⁵ Chronic pancreatitis usually is associated with a history of heavy intake of alcohol leading to significant steatorrhea; we do not discuss this process in our review of chronic watery diarrhea. If the initial screening tests provide evidence for steatorrhea, it should be included in the differential diagnosis of chronic diarrhea.

Peptides and Amines Produced by Enteroendocrine Cells, Mast Cells, or Submucosal Neurons

Several peptides and amines, such as serotonin and granins, are released from enteroendocrine cells by dietary components, bacterial metabolites of nutrients such as short-chain fatty acids (SCFAs), and endogenous chemicals such as bile acids.^{46,47} Table 1 summarizes enteroendocrine mediators that cause net fluid flux toward the lumen, either by inducing intestinal secretion or by inhibiting absorption, or both (reviewed in detail by Camilleri⁴⁸). In addition, Table 1 summarizes information that supports the potential role of intestinal secretion in the development of IBS and the neuroendocrine tumors that result in diarrhea.

Roles of Hormones and Transmitters in Functional Diarrhea and IBS-D

Chromogranins (Cg) and secretogranins (Sg) are present in secretory vesicles of nervous, endocrine, and immune cells. CgA supports the formation of secretory granules and the sorting of amine or peptide hormones to these in enteroendocrine cells, but it also exerts independent biological actions.⁴⁹ Granin release is stimulated via nicotinic cholinergic receptors. Patients with IBS with faster colonic transit have higher levels of fecal CgA, SgII, and SgIII, but

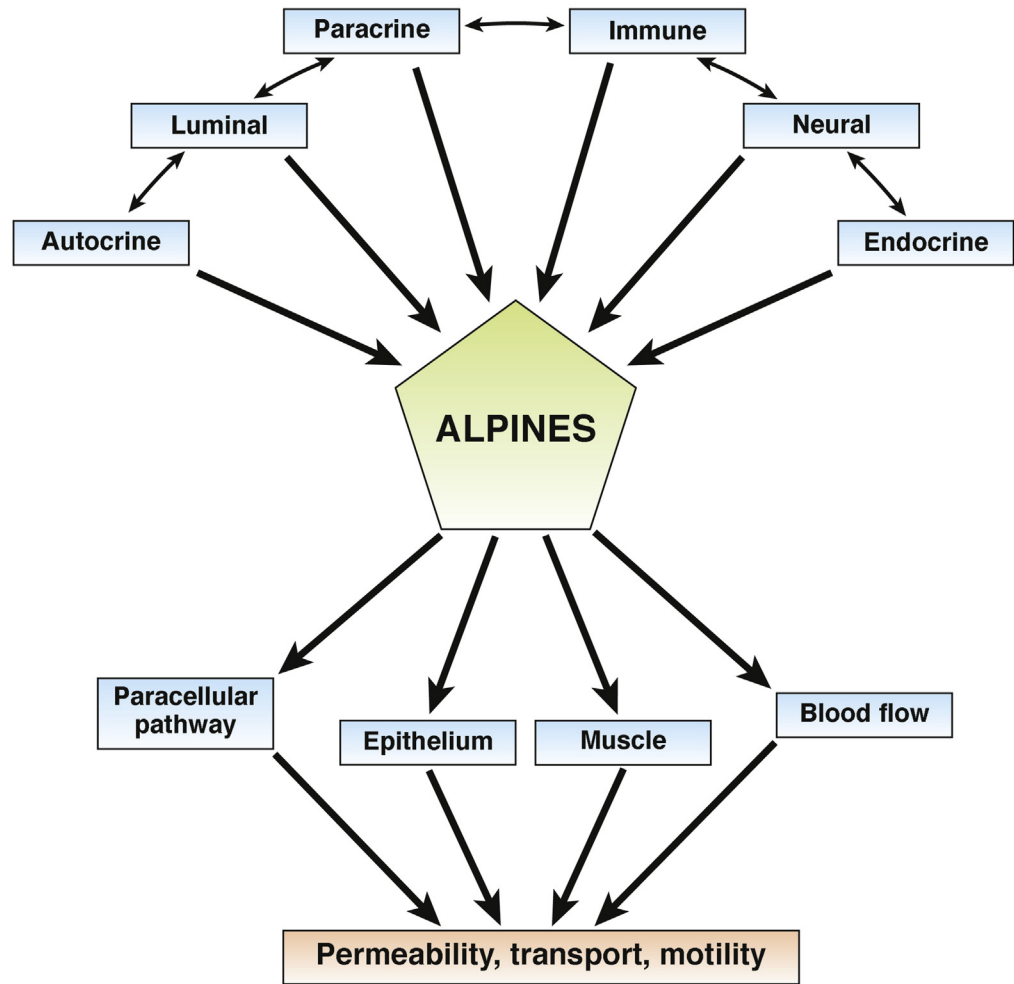


Figure 2. Interaction of mechanisms in chronic watery diarrhea. Although most reductionist research models focus on a single parameter of intestinal function, in fact there is an intricate network of agonists and effectors with a promiscuous interaction among autocrine, luminal, paracrine, immune, neural, and endocrine (ALPINES) inputs that may alter the paracellular pathway, epithelial cell function, intestinal smooth muscle, and blood flow. Diarrhea can result from a change in one or many of these pathways and alterations in permeability, transport, and motility. Figure adapted with permission from Schiller and Sellin.¹⁸⁷

lower levels of CgB compared with healthy controls⁵⁰; patients with IBS have increased duodenal CgA cell density.^{51,52} CgA-positive cells also express free fatty acid receptors that respond to SCFAs.⁵³ The role for granins in sorting and packaging neuropeptides indicates they also can affect colonic secretion and motility indirectly.^{54,55}

To provide an example of the cell products mediating intestinal secretion, we chose the amine, 5-HT, which is synthesized primarily (95%) in the gastrointestinal tract, stored in mucosal enterochromaffin cells,⁵⁶ and released in response to mechanical and chemical stimulation. 5-HT mediates intrinsic reflexes (eg, stimulation of propulsive and segmentation motility, epithelial secretion, and vasodilation) and activates extrinsic vagal and spinal afferents.⁵⁷⁻⁵⁹ Effects of 5-HT on intestinal secretion and colonic transit have been well documented in the carcinoid syndrome.^{60,61} Postprandial plasma 5-HT levels are increased in patients with IBS-D^{62,63} or postinfectious IBS,⁶⁴ and are reduced⁶⁴ or unchanged in patients with constipation-predominant IBS.⁶² Rectal or colonic mucosal levels of 5-HT are increased in patients with postinfectious IBS.⁶⁵

Other biogenic peptides that may influence intestinal secretion or absorption (detailed in Table 1) include somatostatin, peptide YY, and neuropeptide Y, all of which

increase fluid absorption and activate the ileal brake, slowing small intestinal transport and allowing greater absorption of solutes, fluids, and electrolytes.^{66,67} Their expression generally is reduced in patients with IBS-D. Conversely, IBS-D is associated with increased mucosal expression of vasoactive intestinal polypeptide and purinergic receptors, which are associated with intestinal secretion.

Serine Proteases in IBS-D

IBS is associated with increased numbers of mast cells and increased effects on afferent nerves of extracts, including proteases, from mucosal biopsy specimens of patients with IBS. Increased infiltration of mast cells in the gut mucosa of IBS patients has been reported in many, but not all, studies, as summarized elsewhere.⁴⁰ Higher levels of mast cell mediators, such as histamine or tryptase, have been observed in supernatants from colonic and jejunal biopsy specimens of patients with IBS-D, irrespective of mast cell numbers.⁴⁰ The proteases may increase intestinal permeability⁶⁸ and thereby contribute to diarrhea.^{69,70} Serine protease activity in fecal⁷¹ and colonic mucosal⁷² supernatants from biopsy specimens of patients with IBS-D can activate visceral afferents via proteinase-activated

Table 1. Altered Functions of Peripheral Hormones, Amines, and Peptides in Patients With Chronic Diarrhea

| Mechanism | Pathophysiology | Release, distribution, action | Biological and clinical correlates in IBS | Tumors causing diarrhea | Studies |
|----------------|---|---|--|---|--|
| Granins | Cg and Sg in secretory granules mobilize release of peptide hormones from enteroendocrine cells | Release of, for example, 5-HT, PYY, and SS from secretory granules | IBS-D or IBS-alternating: higher fecal CgA, SGII and III, and duodenal CgA cell density; changes not specific for IBS; higher CgA and SG associated with faster colonic transit and weakly with symptoms | | Montero-Hadjadje et al, ⁴⁹ 2009; Öhman et al, ⁵⁰ 2012; El-Salhy, ⁵¹ 2012 |
| Serotonin | Derived primarily from ECs and neurons: mediates intrinsic reflexes that stimulate motility, secretion, and vasodilation; activates extrinsic afferents that mediate extrinsic reflexes and sensation | Circulating 5-HT represents 5-HT that does not undergo re-uptake by the SERT in epithelial cells or platelets | Plasma: postprandial 5-HT increased in IBS-D and IBS-PI, reduced in IBS-C Platelet: SERT uptake disrupted in IBS-D Mucosal: 5-HT increased in IBS-C and IBS-PI Mucosal: SERT mRNA expression and immune reactivity varies between studies | Carcinoid diarrhea arises when tumor mass produces sufficient 5-HT or other peptides to induce secretion, accelerated transit and colonic hypermotility | Donowitz and Binder, ⁶⁰ 1975; Spiller et al, ⁶⁵ 2000; Mawe and Hoffman, ⁵⁹ 2013; Houghton et al. ⁶³ 2003; Atkinson et al, ⁶² 2006; Bellini et al, ¹⁷⁶ 2003; Franke et al, ¹⁷⁷ 2010; Foley et al, ¹⁷⁸ 2011; El-Salhy et al, ⁵² 2013; von der Ohe et al, ⁵¹ 1993 |
| Substance P | Derived primarily from ECs and neurons | Excitatory neurotransmitter-stimulating motility | | Co-secreted with 5-HT from carcinoid tumors | Buhner et al, ⁷³ 2009 |
| Prostaglandins | Derived primarily from immune cells and subepithelial myofibroblasts | Stimulate fluid secretion and motility | | Co-secreted with 5-HT from carcinoid tumors | |
| PYY | Derived primarily from ECs | Intraluminal PYY induces small-bowel and colon fluid/electrolyte absorption | Rectal biopsy PYY increased during acute <i>Campylobacter</i> enteritis, normal IBS-PI by 12 weeks, lower PYY in colonic mucosa in IBS | | Spiller et al, ⁶⁵ 2000; Playford et al, ¹⁷⁹ 1990; Bilchik et al, ¹⁸⁰ 1993; Bilchik et al, ¹⁸¹ 1994; Liu et al, ¹⁸² 1997 |
| NPY | Derived from enteric neurons | NPY Y2-receptor agonists reduce intestinal fluid secretion (mice) | NPY levels in both plasma and the sigmoid were lower in IBS patients than in controls | | Zhang et al, ¹⁸³ 2008; Moriya et al, ¹⁸⁴ 2010 |
| SS | Derived primarily from ECs and neurons | SS inhibits NHE1 (basolateral in enterocytes), involved in secretion of HCO ₃ ⁻ | Expression of SS in serum and colonic or rectal mucosa of IBS was higher compared with controls; SS in mucosa in IBS-C was greater than in IBS-D | | Han, ¹⁸⁵ 2013; Zachos et al, ⁵ 2005 |

Table 1. Continued

| Mechanism | Pathophysiology | Release, distribution, action | Biological and clinical correlates in IBS | Tumors causing diarrhea | Studies |
|-------------------------------|--|---|---|---|--|
| Vasoactive intestinal peptide | Derived mainly from gut secretomotor neurons | Increases secretion and vasodilatation | Sigmoid mucosa and plasma levels of vasoactive intestinal peptide were higher in patients with IBS than in controls; rectosigmoid mucosal expression of vasoactive intestinal peptide increased, based on mRNA analysis | Vasoactive intestinal peptide-associated tumors (usually pancreatic) cause watery diarrhea, hypokalemia, and achlorhydria | Zhang et al, ¹⁸³ 2005; Han, ¹⁸⁵ 2013; Camilleri, ⁹⁵ 2014; Bloom et al, ⁷⁷ 1988 |
| Gastrin | Derived from parietal cells and pancreatic tumors | Intestinal secretion, some malabsorption caused by altered duodenal pH | | Gastrinoma diarrhea | Barbezat and Grossman, ⁷⁶ 1971 |
| Calcitonin | Derived from thyroid parafollicular C cells | Intestinal secretion | | Medullary cancer diarrhea | Cox et al, ⁷⁸ 1979 |
| Serine proteases | Derived from mast cells and other immune cells | Visceral hypersensitivity | Increased mast cell numbers and greater visceral afferent sensitivity to proteases from mucosa of IBS patients | Systemic mastocytosis | Buhner et al, ⁷³ 2009; Barbara et al, ¹⁸⁶ 2007 |
| Purines | P1 and P2 receptors activated by adenosine and extracellular nucleotides (eg, ATP) | P1A _{2B} receptor regulates colonic Cl ⁻ and water secretion; P2Y activates K ⁺ , Cl ⁻ , and HCO ₃ ⁻ secretion; inhibits Na ⁺ absorption | Rectosigmoid mucosal expression of P2RY4 mRNA | | Camilleri, ⁹⁵ 2014 |

CgA, Chromogranin A; EC, enteroendocrine cell; HCO₃, bicarbonate; IBS-C, constipation-predominant irritable bowel syndrome; IBS-PI, postinfectious irritable bowel syndrome; mRNA, messenger RNA; NHE1, sodium-hydrogen antiporter 1; NPY, neuropeptide Y; P1A_{2B}, purinoceptor 1A_{2B}; PYY, peptide YY; SS, somatostatin; SERT, serotonin transporter; VIP, vasoactive intestinal peptide; (NPY)-Y2, neuropeptide Y-Y2.

Adapted with permission from Camilleri.⁴⁴

receptor 2,⁷³ as well as tachykinergic mechanisms.⁷⁴ This process could activate secretory or motor mechanisms that lead to diarrhea, although they have not been studied extensively.

Hormone-Related Diarrhea in Patients With Neuroendocrine Tumor Syndromes

Patients with neuroendocrine tumors may present with chronic diarrhea that results from an increase in intestinal secretion.⁷⁵ These patients have carcinoid syndrome (predominantly through effects of 5-HT and possibly substance P on intestinal secretion⁶⁰ and motility⁶¹), Zollinger–Ellison syndrome (gastrin),⁷⁶ Verner–Morrison syndrome,⁷⁷ medullary carcinoma of the thyroid (calcitonin),⁷⁸ or systemic mastocytosis. Systemic mastocytosis is a rare myeloproliferative disorder characterized by excessive numbers of mast cells with release of serine proteases (eg, tryptase) and histamine, resulting in mildly impaired intestinal absorption.⁷⁹ Typically, diarrhea occurs when there is a sufficient mass of metastatic tumor that produces the relevant secretagogue.

Intraluminal Factors: Bile Acids and SCFAs

Enterohepatic circulation of bile acids is observed commonly in patients with ileal disease (such as Crohn's disease and radiation enteritis), patients who have undergone ileal resection, or in patients with deficiencies in production of fibroblast growth factor-19 by ileal enterocytes. Malabsorption of bile acids increases the bile acid concentration in the colon and leads to a series of effects that could result in watery diarrhea. Bile acids stimulate colonic motility⁸⁰ and transit,⁸¹ and increase colonic mucosal permeability,^{82,83} colonocyte chloride secretion, and apical Cl⁻/OH⁻ exchange.⁸⁴ Many of the effects of bile are mediated by the receptor GPBAR1 (also known as TGR5),⁸⁵ which is expressed in enteric neurons, enteroendocrine cells,⁸⁶ and primary spinal afferent and spinal neurons involved in sensory transduction.⁸⁷ GPBAR1 mediates the prokinetic actions of intestinal bile acids, is required for normal defecation in mice, and mediates colonic fluid secretion.⁸⁸ Variations in *GPBAR1* genotype were associated significantly with accelerated colonic transit at 48 hours.⁸⁹

Even in healthy adults, up to 20% of dietary starch escapes absorption in the small bowel,⁹⁰ resulting in generation of SCFAs (<6 carbon chain lengths) by colonic bacteria and increased delivery of water to the colon.⁹¹ SCFAs stimulate colonic release of 5-HT⁹² from enteroendocrine cells in rats⁹³; propionate induced chloride secretion across guinea pig distal colonic mucosa in vitro.⁵³ However, overall, SCFAs are absorbed rapidly in the colon and mostly stimulate absorption rather than secretion. SCFA profiles in fecal samples from patients with IBS-D are characterized by lower total SCFAs, acetate, and propionate, and higher n-butyrate.⁹⁴

Abnormalities in Processes That Regulate Secretion in the Colon

Increased expression of ion secretory mechanisms has been detected in the colorectal mucosa of patients with

IBS-D.⁹⁵ Guanylate cyclase 2B mediates chloride secretion in response to uroguanylin. The protein PDZ domain containing 3 associates with guanylate cyclase C and regulates cGMP production after receptor stimulation.⁹⁶ Levels of guanylate cyclase 2B messenger RNA and PDZ domain containing 3 protein are increased in mucosal biopsy specimens from patients with IBS-D.⁹⁷

Role of the Microbiome in Chronic Diarrhea

Much of the research on the microbiome has established associations, and clinical relevance of the microbiome in health and disease requires further study of the complex interactions among the microbiota, intestinal mucosa, diet, and bacterial metabolites such as butyrate and secondary bile acids.

Recent studies in animal models have provided evidence that commensal microbe byproducts can modulate the immune system, regulating intestinal inflammation. Specifically, butyrate increased generation of anti-inflammatory regulatory T cells and decreased colonic inflammation.⁹⁸ Devkota et al⁹⁹ showed that a diet high in saturated milk fat promotes taurine conjugation of bile acids, increasing the luminal availability of organic sulfur and allowing expansion of a specific sulfite-reducing bacteria (*Bilophila wadsworthia*). These bacteria were associated with an inflammatory response, mediated by cytokines from T-helper type 1 lymphocytes that increased the incidence of colitis in genetically susceptible mice.

Chronic diarrhea in cats, dogs, and human beings has been associated with an overall shift in the composition of the microbiota and its metabolic capacity.^{100–102} This so-called dysbiosis has been observed in a number of other gastrointestinal as well as systemic diseases, although most studies to date have shown correlations, rather than causality. Nevertheless, the ability of specific commensals and probiotics to beneficially influence epithelial transport and barrier properties indicates that reversing dysbiosis may be of value in chronic diarrhea.^{103,104} Dynamic changes in the diet, microbiome, bacterial metabolism, intestinal mucosa, and the immune system all could have protean effects on the gastrointestinal tract.¹⁰⁵

Motility-Related Diarrhea

Motility disorders cause diarrhea by either accelerating gastrointestinal transit (eg, postvagotomy diarrhea) or by slowing transit, thereby predisposing to small intestinal bacterial overgrowth (SIBO) (eg, scleroderma). Motility-related diarrhea can be either secretory or osmotic. The most prevalent forms of motility-related diarrheas are autonomic neuropathy¹⁰⁶ or IBS-D, associated with either accelerated colonic transit¹⁰⁷ or increased numbers of high-amplitude propagated contractions.¹⁰⁸

Rapid small-bowel transit is a relatively common finding in patients with diabetes or autonomic neuropathies, or patients who have undergone upper gastrointestinal tract surgery. A diagnosis can be made based on combined results from a hydrogen breath test and nuclear scintigraphy small-bowel transit test.¹⁰⁹ There is controversy over whether

SIBO can cause chronic diarrhea. Studies have questioned a diagnosis of SIBO based on breath hydrogen or methane measurements after glucose or lactulose oral load,¹¹⁰ or small intestinal total bacterial counts of not more than 10^5 cfu/mL, or anaerobic counts not greater than 10^4 cfu/mL.¹¹¹

Management of Patients with Chronic Watery Diarrhea

Although an exact etiology usually can be determined for steatorrhea and inflammation-associated diarrhea, the causes of watery diarrhea are not always clear. Watery diarrhea therefore can present ongoing challenges for management. Patient history adequately should characterize chronic watery diarrhea. If there are any uncertainties, fecal fat should be quantified; the Sudan stain approach to quantification identifies patients with fatty diarrhea with 76% sensitivity and 99% specificity. The sensitivity of detection can be increased to 94% and the specificity to 95% by counting and size measurement of fat globules.¹¹²

Patients also should undergo testing for inflammation-associated diarrhea, which can be detected based on the serum level of C-reactive protein and fecal levels of calprotectin and lactoferrin. A systematic review reported that C-reactive protein detected inflammation-associated diarrhea with a pooled sensitivity of 49% and a specificity of 73%, whereas fecal calprotectin identified this disorder with a pooled sensitivity of 92% and specificity of 82%. Tests for

stool lactoferrin identified inflammation-associated diarrhea with a pooled sensitivity of 88% and specificity of 79%.¹¹³

If the results from these screening tests are negative, the patient is likely to have chronic watery diarrhea. The clinician then can focus on the most likely or common causes such as microscopic colitis, celiac disease, IBS-D, functional diarrhea, bile acid malabsorption, diet, motility disorders, and perhaps SIBO. Rarer conditions, such as autoimmune enteritis or Addison's disease presenting with chronic diarrhea, are beyond the scope of this discussion.

Patient History

It is important to collect a detailed history of the characteristics of a patient's diarrhea to select the best course of treatment. Although abdominal pain and diarrhea may be a common capsule summary of a case, there are substantial differences among patients with pain relieved by bowel movements (suggesting IBS-D) vs those with bloating, gas, and discomfort after meals (suggesting maldigestion and/or SIBO) or postprandial urgency and discomfort (suggesting rapid transit) (Table 2). Patients often focus on dietary factors that induce symptoms.

Specific foods often are incriminated as causes of diarrhea, some with good evidence and others less so.¹¹⁴ Patients frequently are concerned about how diet may precipitate symptoms.¹¹⁵ In assessing associations with foods, it is important to consider substances that, in

Table 2. Clinical Features in Chronic Watery Diarrhea

| Factor | Potential implications |
|---|--|
| History | |
| Family history of celiac disease, IBD, or MEN2B | Celiac disease, IBD, hormone-induced diarrhea |
| Drugs (including olmesartan) | Celiac-like disease |
| Surgery/radiation | |
| Cholecystectomy | BAD |
| Intestinal resection | Short-bowel syndrome, BAD |
| Abdominal radiation | Radiation enteritis (BAD) |
| Vagotomy, bariatric surgery | Rapid transit, motility disorder |
| Travel | |
| Immune status | Infections (eg, parasitic) |
| Common variable immunodeficiency | Opportunistic/uncommon infections |
| Diabetes | Chronic giardiasis/Norwalk virus infection |
| Associated with diabetes medications and alternative sweeteners | Rapid transit, SIBO, celiac disease, pancreatic insufficiency Metformin, acarbose, sorbitol, sugar alcohols |
| Physical examination | |
| Orthostasis, hypotension | Autonomic neuropathy (diabetes/amyloid) |
| Urticaria pigmentosa, dermatographism | Mast cell disease (mastocytosis) |
| Pinch purpura, macroglossia | Amyloidosis |
| Migratory necrotizing erythema | Glucagonoma |
| Leonine facies, flushing, heart murmur, wheezing | Carcinoid syndrome |
| Dermatitis herpetiformis | Celiac disease |
| Thyroid nodule, lymphadenopathy | Medullary carcinoma of the thyroid |
| Tremor, lid lag | Hyperthyroidism |
| Lymphadenopathy | HIV, lymphoma, cancer |
| Abdominal bruit | Chronic mesenteric ischemia |
| Hepatomegaly | Neuroendocrine tumor, amyloidosis |
| Anal sphincter weakness | Fecal incontinence |

BAD, bile acid diarrhea; HIV, human immunodeficiency virus. Adapted from Schiller et al.¹

sufficient quantities, cause diarrhea in a normal gut (eg, fructose), foods that cause diarrhea because of an underlying condition (eg, dairy products in lactase deficiency), gastrointestinal diseases that limit digestion or absorption (eg, short bowel), idiosyncratic food intolerances, and true food allergies (which are uncommon in adults). A food diary may aid in the identification of a dietary cause of diarrhea.

Poorly absorbed carbohydrates commonly are linked to diarrhea.¹¹⁴ Some monosaccharides are absorbed by facilitated diffusion with limited capacity; when the amount ingested exceeds capacity, malabsorption and diarrhea occur. Disaccharides must be split by disaccharidases, such as sucrase or lactase, which may be insufficient owing to mucosal disease or genetic down-regulation. Unabsorbed carbohydrates lead to osmotic retention of fluid in the intestine and bacterial fermentation to gases.¹¹⁶ Therefore, flatus or bloating are important clues that indicate carbohydrate malabsorption. Lactose is a common cause of diet-induced diarrhea.^{117,118} Fructose is absorbed by limited capacity facilitated diffusion.¹¹⁹ Although it may be difficult to exceed absorptive capacity with natural foods, consumption of high-fructose corn syrup may exceed the absorptive capacity of the gut.^{120,121}

Sugar alcohol malabsorption is an increasingly recognized cause of diarrhea. Sorbitol, mannitol, and xylitol are poorly absorbed non-nutritive sweeteners in items such as sugar-free chewing gum and candy; excessive intake may cause osmotic diarrhea.^{122–124} It also is important to carefully quantify the amount of caffeine consumed in coffee and energy drinks¹²⁵ because caffeine may induce diarrhea via effects on motility and cAMP-induced secretion.

The recognition that carbohydrates can cause diarrhea and other symptoms led to the development of the diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), which can reduce ingestion.¹²⁶ In a randomized trial, a diet low in FODMAP alleviated intestinal symptoms in 75% of patients with IBS.¹²⁷ However, a more recent randomized controlled trial concluded that a sensible diet was as efficacious as a low-FODMAP diet in reducing IBS symptoms.¹²⁸ A systematic review showed that a diet low in FODMAPs reduced IBS symptom severity, pain, bloating, and overall symptoms, but had no definitive benefit on diarrhea.¹²⁹

All patients with chronic diarrhea should be screened for celiac disease. Celiac disease is diagnosed based on symptoms, serology, and intestinal histology, preferably before the start of a gluten-free diet.¹³⁰ Patients can have gluten-responsive symptoms without positive results from serologic tests for celiac disease, or findings of low disease severity from pathology analysis (Marsh scores of 1 or 2).^{131–133} It is not clear when a gluten-free diet should be considered for patients with diarrhea who do not have celiac disease.¹³⁴

Fatty and fried foods frequently are implicated in the pathogenesis of watery diarrhea.¹³⁵ It is paradoxical that some foods with the highest fat content, such as ice cream, rarely are implicated in fatty food intolerance. Although fat malabsorption stimulates colonic secretion to cause diarrhea,¹³⁶ it seems that fat also may precipitate symptoms without demonstrable steatorrhea.

Food allergies (an immune response to specific foods) can cause diarrhea and other symptoms. Food intolerances are not immune-based and are more common.¹³⁷ Epidemiology studies have reported that 1%–2% of adults have a bona fide food allergy; children have a higher incidence.^{138–141} Certain foods more frequently cause allergic reactions. Recent studies have linked banana, avocado, walnut, and kiwi to a latex food allergy syndrome.^{142,143} Although true food allergy is uncommon in adults, it should be considered when other allergic features are present, such as hives. Some patients who are allergic to food have increased fecal levels of tryptase and eosinophilic cationic protein, without increased levels of fecal calprotectin.^{144,145}

Physical Examination

Results from physical examination of patients with watery diarrhea usually are unremarkable, but there may be occasional findings that can lead to a specific diagnosis (Table 2). In the absence of alarm signs such as weight loss, clinicians face the dilemma of how far to pursue a potential diagnosis through testing before making a diagnosis of IBS-D and/or functional diarrhea based solely on symptom criteria. Whether (and when or how many) tests are worthwhile depends on progression of the disorder. The literature is replete with arguments for and against testing for thyroid status, lactose intolerance, and celiac disease,^{146,147} whereas consensus favors testing for celiac disease in all patients with chronic diarrhea. One challenge in evaluating chronic watery diarrhea is that, beyond some basic tests, many published testing strategies are not readily available. We focus on the most clinically relevant tests.

Colonoscopy and endoscopy. The diagnostic yield of colonoscopy for chronic watery diarrhea has been reported to range from 2% to 15%.^{148–150} The most common diagnosis is microscopic colitis, with IBD generally a distant second. Although a recent meta-analysis suggested that colonoscopy may have limited benefit in detecting microscopic colitis in patients with IBS,¹⁵¹ scoring systems have been developed that can guide the clinician to suspect the diagnosis.^{152,153} These include factors such as patient age, sex, and use of high-risk medications such as proton-pump inhibitors, nonsteroidal anti-inflammatory drugs, and serotonin reuptake inhibitors. Although there is debate about whether isolated right-sided microscopic colitis is a real or common entity, it is reasonable to perform a complete colonoscopy and to take random right- and left-sided biopsy specimens even with normal-appearing colonic mucosa. This practice may need to be revisited after the clinical introduction of tests for bile acid-associated diarrhea because microscopic colitis, and, to a lesser extent, collagenous colitis, are associated with bile acid malabsorption,¹⁵⁴ and such patients appear to respond well to bile acid sequestration.¹⁵⁵

Patients rarely are examined by upper gastrointestinal endoscopy for chronic watery diarrhea. In a pathology review of 28,000 duodenal biopsy specimens, Carmack and Genta found only celiac disease and mild lymphocytic duodenitis—none of the rare causes of chronic diarrhea that

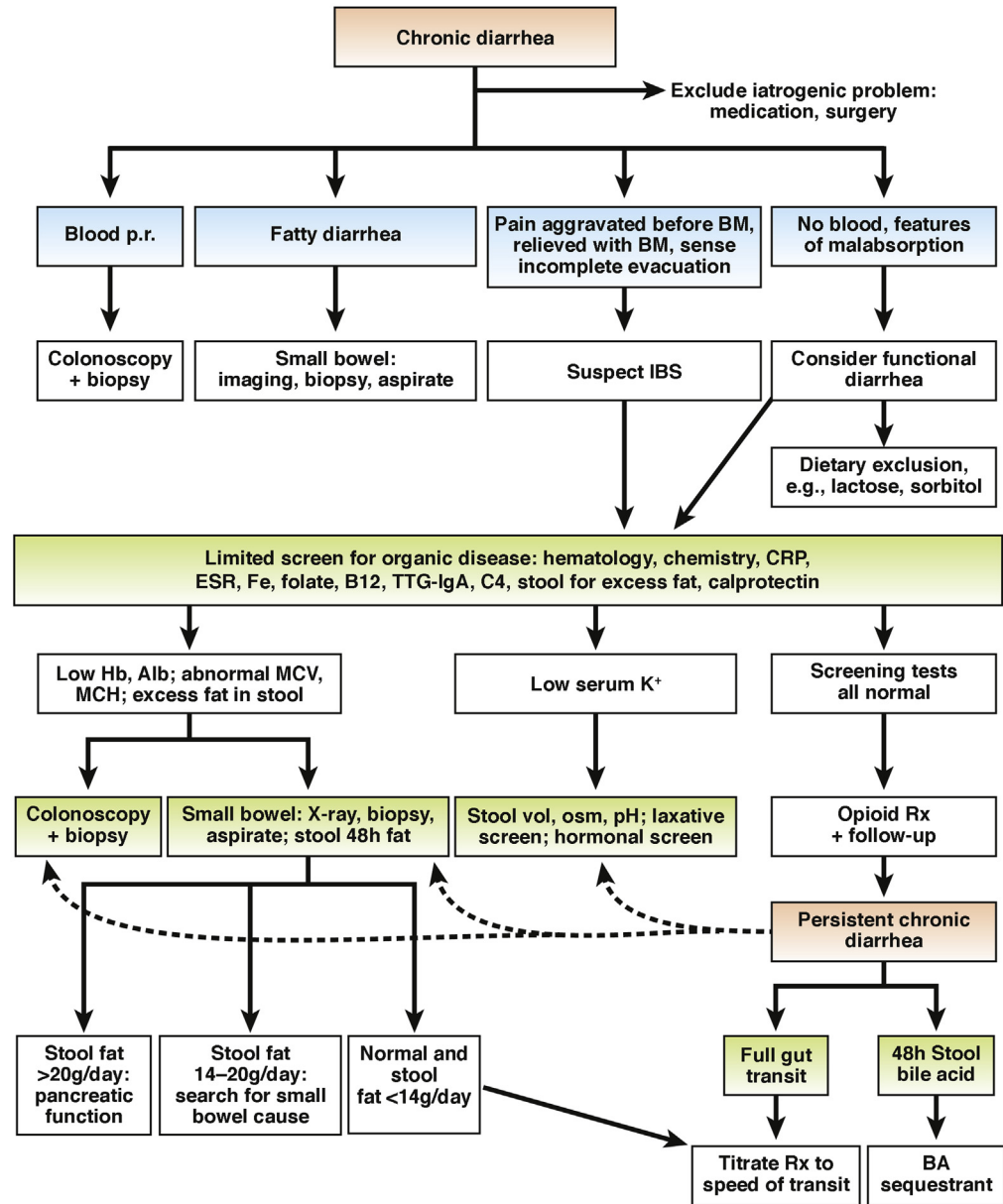


Figure 3. Algorithm for management of chronic diarrhea. Patients undergo an initial evaluation based on different symptom presentations, leading to selection of patients for imaging, biopsy analysis, and limited screens for organic diseases. Alb, albumin; BA, bile acid; BM, bowel movement; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; osm, osmolality; Rx, prescription; TTG, tissue transglutaminase; vol, volume.

may be diagnosed based only on small-bowel biopsy, such as Whipple’s disease.¹⁵⁶ Therefore, if results are negative from serologic tests for tissue transglutaminase IgA (assuming the patient is not IgA-deficient), upper gastrointestinal endoscopy with biopsy analysis would provide only limited benefit. Patients with villous atrophy limited to the duodenal bulb are significantly less likely to present with diarrhea than traditional celiac disease.¹⁵⁷

Timed stool collection. Neither patients nor laboratory technicians relish in the timed stool test (48–72 hours of stool collection; normal stool weight is 200 g/24 h with <7 g fat), however, this is the standard for assessing steatorrhea. A fresh stool sample is necessary to differentiate secretory from osmotic diarrhea. Stool weight greater than 1000 g/24 h leads to a different diagnostic approach (a search for a possible neuroendocrine cause) than a value of 300 g/24 h. Approximately 25% of patients referred

specifically for a diarrhea evaluation actually have a normal stool weight (Sellin J, unpublished data, 2016). The 48-hour stool collection test also can be used to measure fecal bile acids.¹⁵⁸

Blood tests for neuroendocrine tumors. Hormone-secreting tumors are rare causes of secretory diarrhea, typically detected by measuring serum levels of chromogranin, gastrin, vasoactive intestinal polypeptide, or calcitonin, as well as urine levels of 5-hydroxyindoleacetic acid. However, because of the rarity of these tumors and low pretest probability, many positive results from these tests (especially borderline results) turn out to be false positives.¹⁵⁹ These tests therefore almost never should be considered early in the course of an evaluation.

Tests for bile acid diarrhea. A systematic review of 36 studies (5028 patients) found that 22.5% of patients with chronic functional diarrhea or IBS-D have bile acid

Table 3. Summary of Drugs Used in Treatment of Chronic Watery Diarrhea

| 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 α 2-receptor agonist | | |
| | Clonidine | 0.1–0.3 mg, 3 times/day; weekly patch |
| Somatostatin analogue | | |
| | Octreotide | 50–250 μ g, 3 times/day (subcutaneously) |
| Bile acid-binding resin | | |
| | Cholestyramine | 4 g/day for up to 4 times/day |
| | Colestipol | 4 g/day for up to 4 times/day |
| | Colesevelam | 1875 mg up to twice daily |
| Fiber supplements | | |
| | Calcium polycarbophil | 5–10 g/day |
| | Psyllium | 10–20 g/day |
| Soluble fiber | Pectin | 2 capsules before meals |
| Calcium | | 1000 mg, 2–3 times day |
| Serotonin 5-HT ₃ -receptor antagonists | | |
| | Alosetron | 0.5–1.0 mg, twice daily |
| | Ondansetron | 2–8 mg, twice daily |
| Chloride ion channel inhibitor | | |
| | Crofelemer ^a | 125 mg, twice daily |

^aindicated for HIV-related non-infectious diarrhea.

malabsorption. Bile acid malabsorption is identified based on the results of administration of a bile acid sequestrant, or when possible, measuring serum levels of 7 α -hydroxy-4-cholesten-3-1 or fibroblast growth factor 19, fecal level of 48-hour bile acid (available through reference laboratories), or 7-day retention of ⁷⁵Se-labeled 23-seleno-25-homotaurocholic acid (available in some countries).¹⁶⁰ Patients with bile acid malabsorption have increased small-bowel permeability, borderline faster colonic transit, a higher proportion of chenodeoxycholic acid in stool bile acids, and higher fecal levels of fats compared with patients with IBS-D without increased bile acid excretion.¹⁶¹ The prevalence of bile-acid diarrhea is estimated to be similar to that of celiac disease, so it is logical to screen for this condition in patients with chronic watery diarrhea. Unfortunately, most of the tests for bile acid malabsorption are not available outside research settings.

Evaluation for SIBO. SIBO generally is caused by anatomic or functional abnormalities of the intestine, such as strictures, achlorhydria, motility disorders, or scleroderma. Diarrhea, bloating, and weight loss are classic symptoms related to SIBO. The diagnostic standard, quantitative culture of intestinal aspirates,¹⁶² is uncommonly performed in practice. Instead, patients usually are given hydrogen breath

tests using glucose or lactulose as substrates. However, these tests detect SIBO with varying levels of sensitivity and specificity,^{162–166} therefore they are not reliable and can produce conflicting positive or negative results in patients with IBS-D.^{115,167–171} These tests do not have sufficient diagnostic accuracy for clinical decision making.

The sensitivity and specificity of tests for IBS-D detection can increase by simultaneous measurement of intestinal transit by scintigraphy, to determine whether the hydrogen signal arises from the small bowel or colon.^{111,114} However, such simultaneous testing seldom is performed.

Algorithm for Evaluation of Chronic Diarrhea

Figure 3 shows a proposed algorithm for the diagnosis of chronic diarrhea. It is important to determine patients' histories of rectal bleeding, features of malabsorption, or symptoms of IBS. If there are no blood or features of malabsorption, a limited screen for organic disease may include hematology analyses, chemical analyses, and tests to measure C-reactive protein, erythrocyte sedimentation rate, serum iron, folate, vitamin B12 (typically if there are abnormal red blood cell indices in the hematology group), tissue transglutaminase IgA (to detect celiac disease), serum level of 7 α -hydroxy-4-cholesten-3-1 or fibroblast growth factor 19 (if available, to detect bile acid diarrhea), and excess fecal fat and calprotectin. Colonoscopy and biopsy usually are performed according to recommendations for colorectal cancer screening. Intractable watery diarrhea may require colonic biopsy analysis to exclude microscopic colitis. American Gastroenterological Association Institute guidelines specify the importance of excluding celiac disease, hyperthyroidism, IBS, and medication use (eg, nonsteroidal anti-inflammatory drugs, aspirin, proton-pump inhibitors, clozapine, and acarbose) when considering the possibility of microscopic colitis.¹⁷²

The next steps in the management algorithm are guided by results of the initial screen for organic disease and include further specific tests when features indicate IBD or malabsorption. When results from all tests are normal and suggest chronic watery diarrhea, opioid therapy should be tested (eg, 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 tested for bile acid malabsorption; measurement of colonic transit will make it easier to select subsequent therapies. Tests for SIBO should be considered when there is evidence of malabsorption from tests for organic disease.

Management Based on Pathogenesis of Chronic Diarrhea

The principles of management are accurate diagnosis and treatment of the specific factor that causes 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, it is important to reduce symptoms with nonspecific therapies that address the secretory and motor components of chronic diarrhea. Opioids are the mainstay of treatment and, when given per a scheduled regimen, generally are safe. However, a recent report found that high doses of loperamide can induce toxic cardiac arrhythmias and death.¹⁷³

Deodorized tincture of opium and morphine are significantly more potent, but necessarily are prescribed with stringent precautions. Although these medications are generic, recent increases in price have limited their use. Clonidine has been used to relieve the autonomic neuropathy associated with diabetic diarrhea, but could provide only limited benefit because of associated orthostatic hypotension. Chronic intermittent antibiotics are the mainstay of treatment for well-proven SIBO. Several antibiotics have been shown to be equally effective.¹¹¹ Although rifaximin frequently is 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 or ciprofloxacin, therefore should be considered. Agents that act intraluminally (fiber, pectin, and calcium) may be particularly helpful in patients with small-volume diarrhea. 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 3.

Future Directions

Despite diagnostic and therapeutic challenges, it is possible to manage most patients who have chronic watery diarrhea. It is important to increase our understanding of pathogenesis mechanisms, for patients and for the field of research. Many investigators have focused on what proportions of patients have specific factors, such as bile acid malabsorption, but the relative importance of individual etiologies of watery diarrheas cannot be resolved until a comprehensive study simultaneously assesses multiple factors. Recent research has shown the complex interactions among these factors. For example, rapid colonic transit is associated with altered microbiota in rats,¹⁷⁴ and with dysbiosis¹⁷⁵ and fecal bile acids^{161,175} in human beings; further integrated research is required. Advances in our understanding of epithelial biology, as well as interactions of the microbiota with host physiology (including neurohormonal factors and organic anions), should yield targeted therapies for chronic diarrhea.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2016.10.014>

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Conflicts of interest

These authors disclose the following: Michael Camilleri has received support for single-center research studies from Salix, Novartis, and NGM Biopharmaceuticals for studies in diarrheal diseases; and Joseph Sellin has participated in clinical trials related to inflammatory bowel diseases. The remaining author discloses no conflicts.

Funding

Work from the authors' laboratories have been supported by grants from the National Institutes of Health (R01-DK92179 to M.C. and AI077661 to K.E.B.), and an unrestricted grant from the Estratest/Shape Up settlement fund (K.E.B.).

Received July 22, 2016. Accepted October 11, 2016.

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