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Authors

Camilleri, Michael

Sellin, Joseph

Barrett, Kim

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Pathophysiology, Evaluation, and Management of Chronic Watery Diarrhea

Michael Camilleri, **Joseph H. Sellin**[*], and **Kim E. Barrett**[^]

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN

[*]Division of Gastroenterology, Department of Medicine, Baylor College of Medicine, Houston, TX

[^]Division of Gastroenterology, Department of Medicine, University of California, San Diego, La Jolla, CA

Abstract

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 (more than 4 weeks in duration) are more elusive. We review on 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 extra-epithelial factors that activate diarrheal mechanisms. Finally, clinical evaluation and tests used in assessment of patients presenting with chronic diarrhea are reviewed, and an algorithm guiding therapeutic decisions and pharmacotherapy is presented.

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 hrs in a timed collection. A rational classification for evaluation

Address for correspondence: Michael Camilleri, M.D., Mayo Clinic, 200 First St. S.W., Charlton Bldg., Rm. 8-110, Rochester, MN 55905, tele: 507-266-2305, camilleri.michael@mayo.edu.

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of diarrhea considers acute and chronic (more than 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 sufficiently absorbed, are being actively secreted 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 NHE2) or SLC9A3 (also known called NHE3) mediate sodium–hydrogen exchange, whereas SLC26A3 (also called DRA, for down regulated in adenoma) or SLC26A6 (also called PAT1, for putative anion transporter 1) mediate chloride–bicarbonate exchange. Through these transporters, sodium and chloride ions enter the cell cytosol and can then be exported across the basolateral membrane via the Na^+/K^+ 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 upregulate or downregulate 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 cAMP, cGMP, or calcium, whereas it is increased by agents such as epidermal growth factor, which induce tyrosine kinase-dependent signaling.[5] Lysophosphatidic acid 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 are also downregulated by a variety of inflammatory cytokines, and this may contribute to diarrhea in patients with inflammatory bowel diseases (IBD).[8] Similarly, single nucleotide polymorphisms in *SLC9A3* that reduce activity of the transporter could increase susceptibility to chronic diarrhea,[9] though 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 elevate 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 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 is also positively influenced 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 can also be chronically upregulated when its expression is increased by aldosterone (in response to a low-salt diet, for example) or glucocorticoids.[14,15] There is also 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] So, 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 adequately reclaimed upstream, ENaC-dependent sodium absorption may become functionally relevant. Furthermore, expression and function of ENaC are downregulated in mice with colitis, (serving as a model of human IBD) as well as in patients with IBD (even in macroscopically normal regions); ENaC is also downregulated in microscopic colitis, which is increasingly 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 1L/day of the 8–9 L of fluid that typically traverse the gastrointestinal system. If a meal is hypertonic, it will initially draw fluid into the intestinal lumen by osmosis, as 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 mechanism[23] 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 are also 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 cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels, but there can also 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 due 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 CFTR 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 HIV receiving retroviral therapy.[27] Chloride secretion is also 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 can also activate chloride secretion.[29] Bile acid malabsorption may account for a significant proportion of patients diagnosed with diarrhea-predominant IBS (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 carefully controlled. Barrier function is predominantly provided by the tight junctions that link adjacent epithelial cells, although other intercellular junctions also contribute. The barrier is not only dynamic, but may also 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 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 development of diarrhea following infection with *Giardia lamblia*, as well as post-infectious 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 almost entirely accounted for 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 due to poorly absorbed molecules (e.g. 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 demonstrated 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 provide insight into potential motor mechanisms involved in the development of diarrhea.[43] In most discussions about the basic mechanisms of diarrhea, motility is generally 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 where multiple mechanisms contribute to the development of watery diarrhea. For example, 5-hydroxytryptamine (5-HT), which is primarily produced in gut, mediates intrinsic reflexes (e.g. 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 (see 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 is usually 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 towards the lumen, either by inducing intestinal secretion or by inhibiting absorption, or both (reviewed in detail in ref. 48). In addition, Table 1 summarizes information that supports the potential role of intestinal secretion in 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 lower levels of CgB compared with healthy controls;[50] 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 can also 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 (e.g., 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 post-infectious IBS (IBS-PI),[64] and are reduced[64] or unchanged in patients with constipation-predominant IBS .[62] Rectal or colonic mucosal levels of 5-HT are increased in patients with IBS-PI.[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, retarding small intestinal transport and allowing greater absorption of solutes, fluids, and electrolytes.[66,67] Their expression is generally 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 biopsies 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 biopsies of patients with IBS-D, irrespective of mast cell numbers.[40] The proteases may increase intestinal permeability[68] and thereby contribute to diarrhea.[69,70] Serine protease activity in fecal[71] and colonic mucosal[72] supernatants from biopsies of patients with IBS-D can activate visceral afferents via proteinase-activated receptor 2,[73] as well as tachykininergic mechanisms[74]. This process could activate secretory or motor mechanisms that lead to diarrhea, although they have not been extensively studied.

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 secretion[60] and motility[61]), 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 (e.g., 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 commonly observed 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 motility[80] 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 significantly associated 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 (less than 6 carbon chain length) by colonic bacteria and increased delivery of water to the colon.[91] SCFAs stimulate colonic release of 5-HT[92] from enteroendocrine cells in rats;[93] propionate induced chloride secretion across guinea pig distal colonic mucosa in vitro.[53] However, overall, SCFAs are rapidly absorbed 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 (GUC2AB) mediates chloride secretion in response to uroguanylin. The protein PDZ domain containing 3 (PDZD3) associates with guanylate cyclase C and regulates cGMP production following receptor stimulation.[96] Levels of *GUC2AB* mRNA and PDZD3 protein are increased in mucosal biopsies 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 al demonstrated 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.[99]

Chronic diarrhea in cats, dogs, and humans 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 could all have protean effects on the gastrointestinal tract.[105]

Motility-related diarrhea

Motility disorders cause diarrhea by either accelerating gastrointestinal transit (e.g. post-vagotomy diarrhea) or by slowing transit, thereby predisposing to small intestinal bacterial overgrowth (SIBO; e.g. scleroderma). Motility-related diarrhea can be either secretory or osmotic. The most prevalent forms of motility-related diarrheas are autonomic neuropathy[106] or IBS-D, associated with either accelerated colonic transit[107] 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 10^5cfu/mL, or anerobic counts not above 10^4cfu/mL.[111]

Management of Patients with Chronic Watery Diarrhea

Although an exact etiology can usually be determined for steatorrhea and inflammation-associated diarrhea, the causes of watery diarrhea are not always clear. Watery diarrhea can therefore present ongoing challenges for management. Patient history should adequately 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 should also undergo testing for inflammation-associated diarrhea, which can be detected based on serum level of c-reactive protein (CRP) and fecal levels of calprotectin and lactoferrin. A systematic review reported that CRP detected inflammation-associated diarrhea with a pooled sensitivity value of 49% and specificity of 73%, whereas fecal calprotectin identified this disorder with a pooled sensitivity value of 92% and specificity of 82%. Tests for stool lactoferrin identified inflammation-associated diarrhea with a pooled sensitivity value of 88% and 79% specificity.[113]

If the results from these screening tests are negative, the patient is likely to have chronic watery diarrhea. The clinician can then 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 post-prandial urgency and discomfort (suggesting rapid transit) (see Table 2). Patients often focus on dietary factors that induce symptoms.

Specific foods are often incriminated as causes of diarrhea, some with good evidence and others less so.[114] Patients are frequently concerned about how diet may precipitate symptoms.[115] In assessing associations with foods, it is important to consider substances that, in sufficient quantities, cause diarrhea in a normal gut (e.g., fructose), foods that cause diarrhea because of an underlying condition (e.g., dairy products in lactase deficiency), gastrointestinal diseases that limit digestion or absorption (e.g. short bowel), idiosyncratic food intolerances, and true food allergies (uncommon in adults). A food diary may aid in the identification of a dietary cause of diarrhea.

Poorly-absorbed carbohydrates are commonly 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 due 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 nonnutritive sweeteners in items such as sugar-free chewing gum and candy; excessive intake may cause osmotic diarrhea.[122–124] It is also important to carefully quantify the amount of caffeine consumed in coffee and energy drinks,[125] since caffeine may induce diarrhea via effects on motility and cAMP-induced secretion.

The recognition that carbohydrates can cause diarrhea and other symptoms led to 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 symptoms of IBS.[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 are frequently implicated in the pathogenesis of watery diarrhea.[135] It is paradoxical that some foods with the highest fat content, such as ice cream, are rarely implicated in fatty food intolerance. Although fat malabsorption stimulates colonic secretion to cause diarrhea,[136] it seems that fat may also 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 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 are usually unremarkable, but there may be occasional findings that can lead to a specific diagnosis (see 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 supect the diagnosis.[152,153] These include factors such as patient age, sex, and use of high risk medications such as proton-pump inhibitors, non-steroidal 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 biopsies even with normal-appearing colonic mucosa. This practice may need to be revisited after the clinical introduction of tests for bile acid-associated diarrhea, since 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 are rarely examined by upper gastrointestinal endoscopy for chronic watery diarrhea. In a pathology review of 28,000 duodenal biopsies, Carmack and Genta found only celiac disease and mild lymphoctic duodenitis—none of the rare causes of chronic diarrhea that 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 hrs of stool collection; normal stool weight is 200g/24 hrs with less than 7g

fat), yet this is the standard for assessing steatorrhea. A fresh stool sample is necessary to differentiate secretory from osmotic diarrhea. Stool weight greater than 1000g/24 hrs leads to a different diagnostic approach (a search for a possible neuroendocrine cause) than a value of 300g/24 hrs. Approximately 25% of patients referred specifically for a diarrhea evaluation actually have normal stool weight (Sellin J, unpublished observations). The 48 hr stool collection test can also 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 level of 5-hydroxyindoleacetic acid. However, due to 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 should therefore almost never 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 malabsorption. Bile acid malabsorption is identified based on the results of administration of a bile acid sequestrant, or when possible, measuring serum levels of 7α-hydroxy-4-cholesten-3-one or fibroblast growth factor 19, fecal level of 48 hr bile acid (available through reference laboratories), or 7-day retention of ^{75}Se-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 to 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 is generally 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 are usually given hydrogen breath tests using glucose or lactulose as substrates. However, these tests detect SIBO with varying levels of sensitivity and specificity,[162–166] so 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 increased 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 is seldom performed.

Algorithm for evaluation of chronic diarrhea

Figure 3 shows a proposed algorithm for 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 on hematology group), 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 excess fecal fat and calprotectin. Colonoscopy and biopsy are usually performed according to recommendations for colorectal cancer screening. Intractable watery diarrhea may require colonic biopsy analysis, 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.[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 (e.g. loperamide, 2– 4 mg, as many as 4 times/day), with pre-prandial 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 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.[173]

Deodorized tincture of opium and morphine are significantly more potent, but are necessarily 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 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 or ciprofloxacin, should therefore be considered. Agents that act intraluminally (fiber, pectin, and calcium) may be particularly 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 3.

Future Directions

Despite diagnostic and therapeutic challenges, it is possible to manage most patients with chronic watery diarrhea. It is important to increase our understanding of mechanisms of pathogenesis, 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 demonstrated the complex interactions among these factors. For example, rapid colonic transit is associated with altered microbiota in rats[174] and with dysbiosis[175] and fecal bile acids[161,175] in humans; 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.

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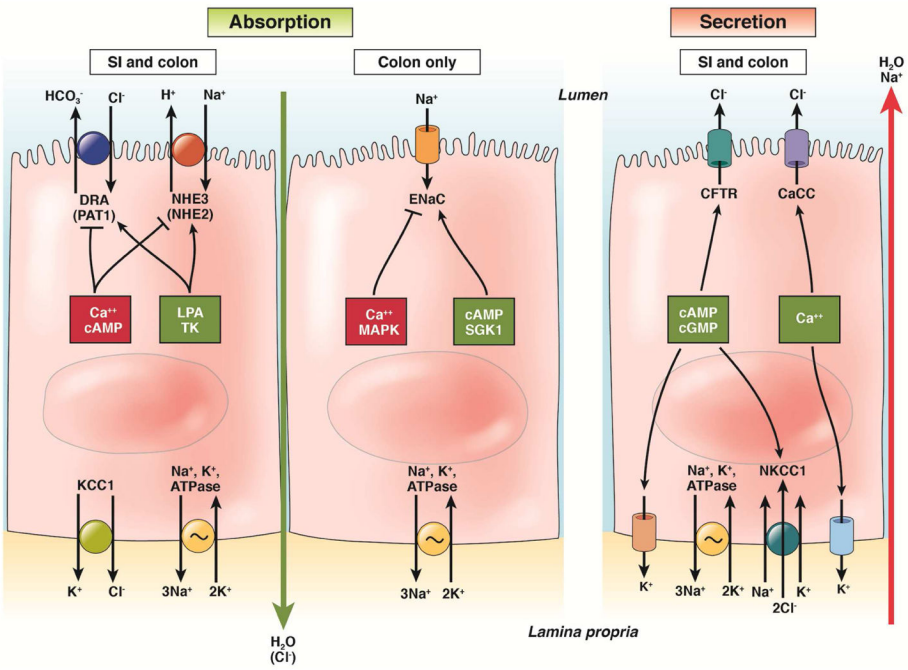

Figure 1. Cellular mechanisms accounting for intestinal absorption and secretion

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.

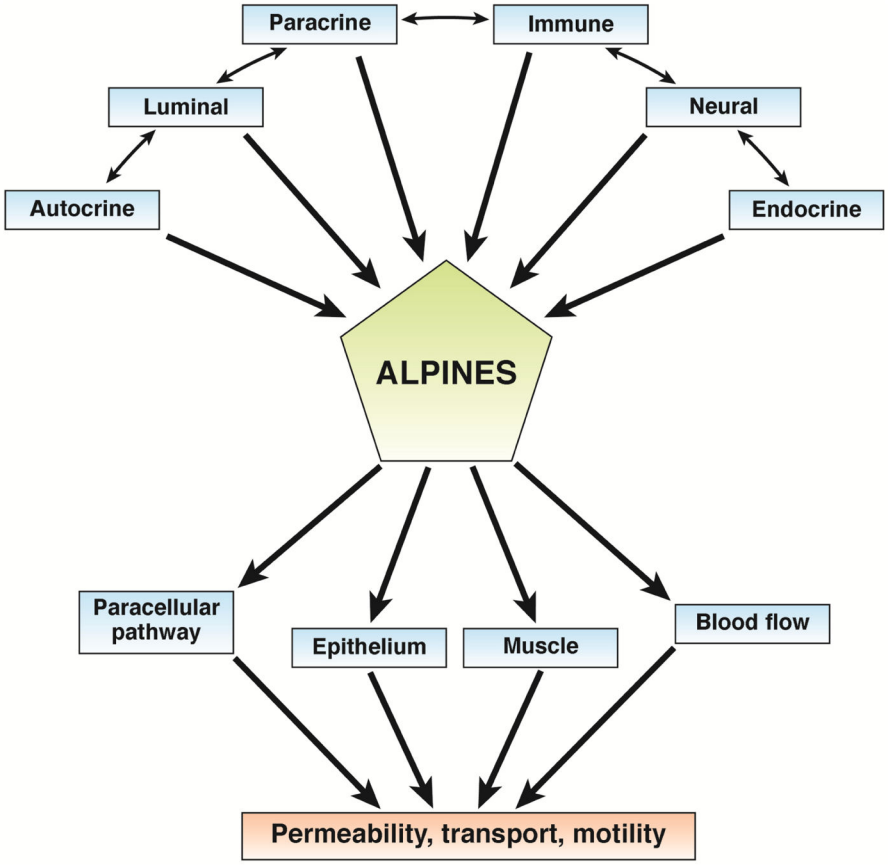

Figure 2. Interaction of mechanisms in chronic watery diarrhea

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 from ref. 187, Schiller LR, Sellin JH. Diarrhea. In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th ed. Feldman M, Friedman LS, Brandt LJ, Eds. Elsevier:New York, 2015, pp. 221–241 (permission not required by Elsevier, as Dr. Sellin is author of original work and of this work).

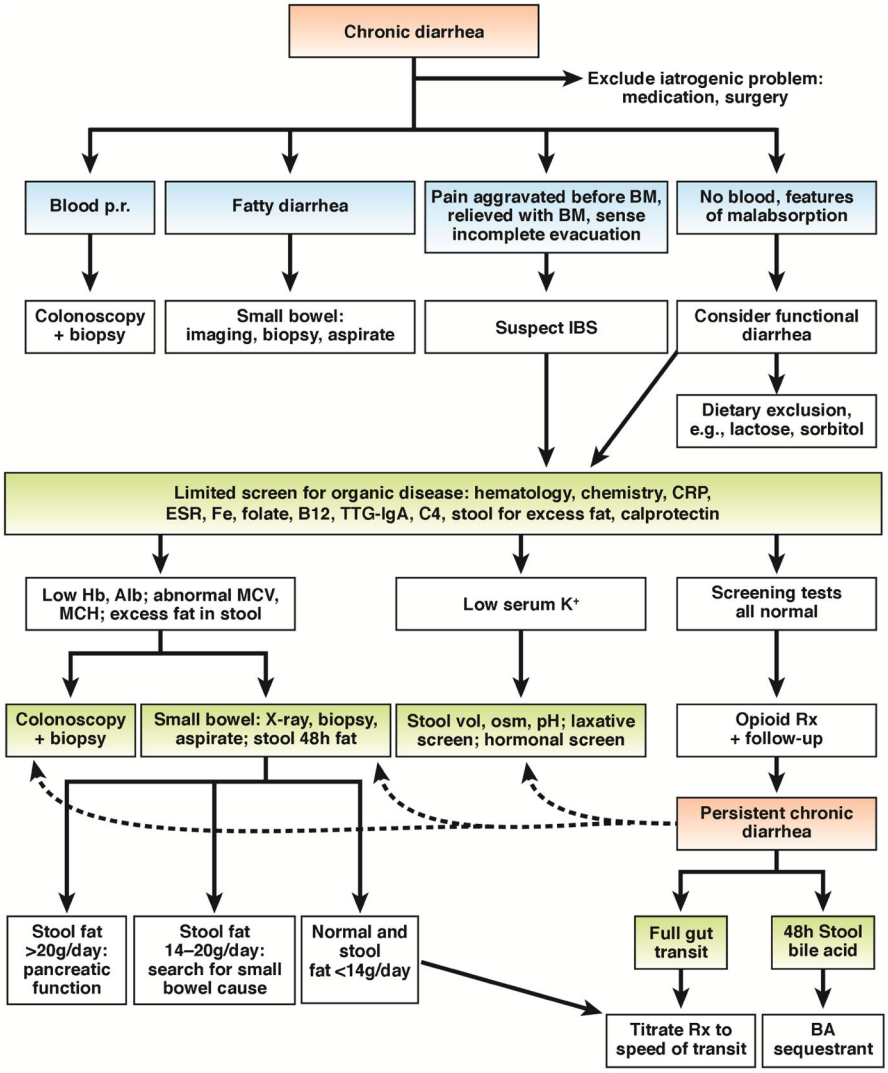

Figure 3. Algorithm for management of chronic diarrhea

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.

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	References
Granins	Cgs and Sg in secretory granules mobilize release of peptide hormones from enteroendocrine cells	Release of, for example, 5-HT, PYY, somatostatin (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		[49] Montero-Hadjadje 2009; [50] Ohman 2012; [51] El-Salhy 2012
Serotonin	Derived primarily from EC 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 serotonin transporter (SERT) in epithelial cells or platelets	*Plasma* postprandial 5-HT elevated in IBS-D and IBS- PI; reduced in IBS-C; *Platelet* SERT uptake disrupted in IBS-D; *Mucosal* 5-HT elevated 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	[60] Donowitz and Binder 1975; [65] Spiller 2000; [59] Mawe, Hofmann 2013; [63] Houghton 2003; [62] Atkinson 2006; [176] Bellini 2003; [177] Franke 2010; [178] Foley 2011; [52] El-Salhy 2013; [61] von der Ohe 1993
Substance P	Derived primarily from EC and neurons	Excitatory neurotransmitter stimulating motility		Co-secreted with 5-HT from carcinoid tumors	[73] Buhner, Schemann 2009
Prostaglandins	Derived primarily from immune cells and subepithelial myofibroblasts	Stimulate fluid secretion and motility		Co-secreted with 5-HT from carcinoid tumors	
Peptide YY (PYY)	Derived primarily from EC	Intraluminal PYY induces small bowel and colon fluid/electrolyte absorption	Rectal biopsy PYY elevated during acute *Campylobacter* enteritis; normal IBS-PI by 12 weeks; lower PYY in colonic mucosa in IBS		[65] Spiller 2000; [179] Playford 1990; [180] Bilchik 1993; [181] Bilchik 1994; [182] Liu 1997
Neuropeptide Y (NPY)	Derived from enteric neurons	NPY Y2 receptor agonists reduce intestinal fluid secretion (mice)	NPY levels in both plasma and the sigmoid slower in IBS patients than controls		[183] Zhang 2008; [184] Moriya 2010
Somatostatin (SS)	Derived primarily from EC 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 higher compared with controls; SS in mucosa in IBS-C greater than in IBS-D		[185] Han 2013; [5] Zachos 2005
Vasoactive intestinal peptide	Derived mainly from gut secretomotor neurons	Increases secretion and vasodilatation	Sigmoid mucosa and plasma levels of vasoactive intestinal peptide higher in patients with IBS than controls; rectosigmoid mucosal expression of	Vasoactive intestinal peptide-associated tumors (usually pancreatic) cause watery diarrhea, hypokalemia, achlorhydria	[183] Zhang 2005; [185] Han 2013; [98] Camilleri 2014; [77] Bloom 1988

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Mechanism	Pathophysiology	Release, distribution, action	Biological and clinical correlates in IBS	Tumors causing diarrhea	References
			vasoactive intestinal peptide increased, based on mRNA analysis		
Gastrin	Derived from parietal cells and pancreatic tumors	Intestinal secretion, some malabsorption caused by altered duodenal pH		Gastrinoma diarrhea	[76] Barbezat and Grossman 1971
Calcitonin	Derived from thyroid parafollicular C cells	Intestinal secretion		Medullary cancer diarrhea	[78] Cox 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	[73] Buhner 2009; [186] Barbara 2007
Purines	P1 and P2 receptors activated by adenosine and extra- cellular nucleotides e.g., ATP	$P1A_{2B}$ receptor regulates colonic Cl^- and water secretion; P2Y activates K^+, Cl^-, HCO_3^- secretion; inhibits Na^+ absorption	Rectosigmoid mucosal expression of *P2RY4* mRNA		[98] Camilleri 2014

Note: (adapted from reference 44, Camilleri M. J Physiol 2014;592:2967-2980)

Enteroendocrine cells (EC), serotonin (5-HT), peptide YY (PYY), somatostatin (SS), serotonin transporter (SERT), post-infectious IBS (IBS-PI), neuropeptide Y (NPY), sodium-hydrogen antiporter 1 (NHE1), bicarbonate (HCO3), constipation-predominant irritable bowel syndrome (IBS-C), vasoactive intestinal peptide (VIP)

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	Bile acid diarrhea (BAD)
intestinal resection	Short bowel syndrome, BAD
abdominal radiation	Radiation enteritis (BAD)
vagotomy, bariatric surgery	Rapid transit, motility disorder
Travel	Infections e.g. parasitic
Immune status	Opportunistic/uncommon infections
Common variable immunodeficiency	Chronic giardiasis/Norwalk virus infection
Diabetes	Rapid transit, SIBO, Celiac disease, pancreatic insufficiency
Associated with diabetes medications and alternative sweeteners	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

Note: Adapted from reference 1, Schiller LR, et al. J Gastroenterol Hepatol 2014;29:6-25

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 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