Acid-Base Disturbances in Gastrointestinal Disease

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Disruption of normal gastrointestinal function as a result of infection, hereditary or acquired diseases, or complications of surgical procedures uncovers its important role in acid-base homeostasis. Metabolic acidosis or alkalosis may occur, depending on the nature and volume of the unregulated losses that occur. Investigation into the specific pathophysiology of gastrointestinal disorders has provided important new insights into the normal physiology of ion transport along the gut and has also provided new avenues for treatment. This review provides a brief overview of normal ion transport along the gut and then discusses the pathophysiology and treatment of the metabolic acid-base disorders that occur when normal gut function is disrupted.


The gastrointestinal tract is a slumbering giant with regard to acid-base homeostasis. Large amounts of H+ and HCO3− traverse the specialized epithelia of the various components of the gut every day, but under normal conditions, only a small amount of alkali (approximately 30 to 40 mmol) is lost in the stool (1,2). In contrast to the kidney, acid and alkali transport in the gut is adjusted for efficient absorption of dietary constituents rather than for acid-base homeostasis. The small amount of alkali lost as a byproduct of these transport events is easily regenerated by renal net acid excretion, which is regulated by the kidney to maintain body alkali stores. Disruption of normal gut function, however, uncovers its power to overwhelm acid-base homeostasis. Acid-base disorders can vary from severe acidosis to severe alkalosis, depending on the site along the gastrointestinal tract affected and the nature of the losses that ensue. These disruptions in acid-base equilibrium are associated with disorders of potassium balance, often leading to either hypokalemia or hyperkalemia. Major sodium and chloride losses also occur, sometimes causing life-threatening volume depletion and almost always contributing to the acid-base abnormalities.

Normal Physiology of Gut Fluid and Electrolyte Transport

During the course of each day, secretion as well as absorption of fluid and electrolytes occurs along the gastrointestinal tract. Normally 7 to 8 L of fluid is secreted each day, far exceeding dietary consumption, and almost all of these secretions, as well as any ingested fluid, are absorbed by the end of the colon (1). The gastrointestinal tract is divided into sequential segments, each with a distinct group of ion transporters and channels that interact with one another to determine the electrolyte content and volume of the fluid in the gut lumen. With the exception of the stomach and the exocrine pancreas, secretion of fluid and electrolytes occurs primarily in a subset of cells in the epithelial crypts with unique ion transport properties. Throughout the gut, fluid and electrolyte transport (both absorption and secretion) is driven primarily by Na+/K+-ATPase transport activity across the basolateral membrane of epithelial cells. Several key apical membrane electrolyte transporters participate, including Cl−/HCO3− and Na+/H+ ion exchangers and the cystic fibrosis transmembrane conductance regulator (CFTR) Cl− channel, all of which are present in many segments of the gut, and H+/K+-ATPases, which are confined to the stomach and colon (Figure 1). Disruption of function or abnormal stimulation of these ion transporters underlies a variety of gastrointestinal disorders that are associated with acid-base and electrolyte disturbances. A full description of the ion transport processes that participate in normal gut function is beyond the scope of this review, and reader is referred to other sources for more detail (1).

Mouth and Throat

Secretion of salivary fluid occurs via the parotid and salivary glands, ultimately producing a hypotonic alkaline solution when stimulated by activation of muscarinic receptors. Acinar cells secrete fluid that is similar in composition to serum, and then the secreted fluid is modified by Na+ and Cl− absorption and HCO3− secretion. The apical membrane transport proteins that alter the composition under conditions of stimulation remain to be defined, but HCO3− secretion may occur via an anion channel, possibly the CFTR Cl− channel (3). When stimulated, up to 1 L/d fluid is produced (Table 1). This alkaline secretion likely serves to protect the mucosa of the mouth, throat, and esophagus and has little impact on serum [HCO3−]. It is more than counterbalanced by gastric acid secretion in the stomach.

Stomach

Digestion of many of the foods that we eat requires secretion of an acid solution into the lumen of the stomach. Secretion of this solution involves several linked transport...
of these, the gastric H+/K+-ATPase is essential for acid secretion; pharmacologic blockade of this transporter effectively blocks acidification of the gastric contents. Hydrogen ion secretion by this transporter is facilitated by K+ recycling across the apical membrane via a selective cation channel. Chloride is secreted by an as-yet-unidentified Cl− channel, yielding hydrochloric acid under conditions of stimulation. Under basal conditions, the secreted fluid is primarily NaCl. The pH and volume of gastric secretions is regulated primarily by gastrin, so maximal volume and acid secretion occurs only after a meal. At such times, the pH of the gastric fluid falls to as low as 1.0 (H+ = 100 mmol/L) and volume increases to as high as 7 ml/min. The surge in acid secretion transiently increases serum [HCO3−] by 1 to 2 mmol/L, a change referred to as the alkaline tide, once used as a test of acid secretion. The increase is transient, because the process of acid secretion itself sets in motion countervailing alkali secretion by the exocrine pancreas into the duodenum. Gastric secretion is usually 1 to 2 L/d (Table 1).

**Duodenum**

Regardless of the pH and tonicity of the gut contents that enter the duodenum, this segment of the gut restores isotonicity
through water and solute absorption, and the pH rises to 7.0. Acid is neutralized by HCO₃⁻ addition in pancreatic and biliary secretions as well as by direct secretion in Brunner’s glands along the duodenum (1). The specific ion transporters involved in duodenal HCO₃⁻ secretion remain to be defined.

**Pancreas**

Entry of the acid gastric secretions into the duodenum signals the pancreas to secrete its highly alkaline solution ([HCO₃⁻]) approximately 70 to 120 mmol/L) into the gut. The anion transporter primarily responsible for this process is an apical membrane Cl⁻/HCO₃⁻ exchanger (Figure 1). The activity of this ion exchanger is regulated by the CFTR Cl⁻ channel, which recycles Cl⁻ across the apical membrane (1,4). Under maximal stimulation, some secreted HCO₃⁻ seems to enter the lumen directly via the CFTR channel as well as by Cl⁻/HCO₃⁻ exchange (5). Pancreatic HCO₃⁻ secretion is stimulated by the hormone secretin, which is secreted when acidic fluid (pH <4.0) enters the duodenum. Thus, HCO₃⁻ secretion occurs only as a counterbalance to acid secretion in the stomach and only when this acidic fluid is passed into the duodenum. At other times, the secretion is primarily isotonic NaCl. Pancreatic secretion amounts to 1 to 2 L/d (Table 1).

**Biliary Secretion**

Although the pancreas is by far the major source of the HCO₃⁻ added to the duodenal contents, stimulation of biliary secretion by the hormones secretin and cholecystokinin also produces an alkaline solution that contains HCO₃⁻ (6). This secretion is typically approximately 1 L/d.

**Jejunum and Ileum**

This segment of the bowel both absorbs and secretes fluid, but absorption normally predominates, reducing the total gut fluid content to approximately 1 L/d by the time it enters the colon (Table 1). Absorption is driven by sodium and chloride uptake (driving water uptake) and occurs via two linked transporters, the Na⁺/H⁺ exchanger and the Cl⁻/HCO₃⁻ exchanger (Figure 1) (7,8). These two transporters take up Na⁺ and Cl⁻ from the gut lumen and secrete H⁺ and HCO₃⁻ into it. The latter two ions combine, forming H₂CO₃, which dehydrates to form CO₂ in the intestinal lumen. The Cl⁻/HCO₃⁻ exchanger in the small intestine is the “downregulated in adenoma” (DRA) gene product, also named CLD (for chloride diarrhea) (9). By the end of the ileum, Cl⁻/HCO₃⁻ exchange predominates, resulting in an alkaline solution (Table 1). Chloride secretion occurs in specialized cells in the intestinal crypts via a series of apical Cl⁻ ion channels, one of which is the CFTR channel, recycling Cl⁻ into the lumen (Figure 1). In contrast to the colon, the small intestinal secretory cells do not have an apical K⁺ channel. Potassium movement across the membrane is accounted for by passive diffusion and solvent drag, with absorption predominating (10). These absorptive and secretory processes leave the fluid that enters the colon slightly hypotonic with a [HCO₃⁻] of approximately 30 mmol/L and with a [K⁺] of 5 to 10 mmol/L (Table 1).

**Colon**

In the colon, the fluid volume of the stool is normally reduced to <50 ml/d, and the concentrations of Na⁺ and Cl⁻ are reduced to <30 mmol/L (Table 1). Sodium chloride absorption is accomplished by the same linked transporters described for the small intestine, but, in addition, Na⁺ is absorbed via an apical membrane Na⁺ channel regulated by aldosterone (Figure 1) (11,12). The HCO₃⁻ secreted in the colon by the Cl⁻/HCO₃⁻ exchanger is consumed (along with much of the HCO₃⁻ delivered from the ileum) in buffering organic acids produced by colonic bacteria. Some of the organic anions produced by this reaction are absorbed via a linked HCO₃⁻ exchange transporter (1) (Figure 1), but the remainder are excreted and make up the 30 to 40 mmol/d of potential alkali lost in the stool despite the absence of measurable HCO₃⁻ in the stool (Table 2). The colonic absorptive epithelial cells also have a unique apical membrane H⁺/K⁺-ATPase that absorbs K⁺ and secretes H⁺ into the gut lumen (13,14), but the role of this transporter is unclear because significant net K⁺ secretion occurs in the colon, raising [K⁺] in stool water to as high as 75 mmol/L. Secretory cells in the colon contain the same apical

### Table 2. Ranges of volume and electrolyte composition in vomitus, diarrhea fluid, and ileostomy drainagea

<table>
<thead>
<tr>
<th>State</th>
<th>Volume (L/d)</th>
<th>[Na⁺] (mmol/L)</th>
<th>[K⁺] (mmol/L)</th>
<th>[Cl⁻] (mmol/L)</th>
<th>[HCO₃⁻] (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal stool</td>
<td>&lt;0.15</td>
<td>20 to 30</td>
<td>55 to 75</td>
<td>15 to 25</td>
<td>0b</td>
</tr>
<tr>
<td>Vomitus/NG drainage</td>
<td>0.00 to 3.00</td>
<td>20 to 100</td>
<td>10 to 15</td>
<td>120 to 160</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory diarrhea</td>
<td>1.00 to 3.00</td>
<td>50 to 100</td>
<td>15 to 20</td>
<td>50 to 100</td>
<td>10</td>
</tr>
<tr>
<td>Secretory diarrhea</td>
<td>1.00 to 20.00</td>
<td>40 to 140</td>
<td>15 to 40</td>
<td>25 to 105</td>
<td>20 to 75</td>
</tr>
<tr>
<td>Congenital chlorideorrhea</td>
<td>1.00 to 5.00</td>
<td>30 to 80</td>
<td>15 to 60</td>
<td>120 to 150</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>1.00 to 3.00</td>
<td>70 to 150</td>
<td>15 to 80</td>
<td>50 to 150</td>
<td>Unknownc</td>
</tr>
<tr>
<td>Ileostomy drainage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>new</td>
<td>1.00 to 1.50</td>
<td>115 to 140</td>
<td>5 to 15</td>
<td>95 to 125</td>
<td>30</td>
</tr>
<tr>
<td>adapted</td>
<td>0.50 to 1.00</td>
<td>40 to 90</td>
<td>5</td>
<td>20</td>
<td>15 to 30</td>
</tr>
</tbody>
</table>

aData primarily from reference (1).

bApproximately 30 mmol/d organic anions are lost in the stool, causing a deficit in potential alkali for the body (see text).

cNo data available.
Cl⁻ channel as in the small intestine, but, in addition, they contain several apical K⁺ channels. In colon secretory cells, Cl⁻ channel function is partially dependent on K⁺ secretion (15). Potassium secretion via these apical channels is stimulated by aldosterone, and this secretion is responsible for the increase in stool [K⁺] (16). Because of the small volume of stool water normally excreted, net daily K⁺ loss in the stool is only 10 to 15 mmol/d, but the quantity lost can easily increase if stool water volume increases.

**Acid-Base and Electrolyte Disorders**

**Vomiting and Nasogastric Drainage**

Gastric fluid typically contains 120 to 160 mmol/L Cl⁻, balanced by K⁺, Na⁺, and H⁺ (Tables 2 and 3). Under basal conditions, the cation is primarily Na⁺, and, when stimulated, the cation is primarily H⁺, the latter rising to as high as 100 mmol/L (1). Potassium concentration remains at approximately 10 mmol/L in both settings. Loss of this Cl⁻-rich solution through either vomiting or nasogastric drainage causes major Cl⁻ losses, with variable H⁺ loss as well. Any H⁺ loss abruptly increases serum [HCO₃⁻] while simultaneously abrogating the signal to the pancreas to secrete HCO₃⁻ into the duodenum. The result is metabolic alkalosis, initiated by the H⁺ loss but sustained by disproportionate loss of Cl⁻, a chain of events that leads to greater depletion of body Cl⁻ stores than of other electrolytes (17). The abrupt increase in serum [HCO₃⁻] leads to some HCO₃⁻ loss in the urine initially, but this anion rapidly disappears, and urine pH falls despite a sustained increase in serum [HCO₃⁻]. Initial loss of Na⁺ is also rapidly followed by a rise in K⁺ excretion, leading to secondary K⁺ depletion and hypokalemia. In the new steady state, alkalosis and hypokalemia are sustained until gastrointestinal Cl⁻ losses are stopped and body stores are repleted (17–19). The renal mechanisms that lead to a sustained increase in renal H⁺ secretion remain incompletely defined but likely involve stimulation of H⁺ secretion in the collecting duct (20). Although extracellular fluid volume and K⁺ depletion normally contribute to sustaining the alkalosis, these events are neither necessary nor sufficient (19,21–23). Loss of H⁺ in the gastric contents also contributes to the alkalosis, but a similar pattern can be seen with Cl⁻ loss without accompanying loss of H⁺ (e.g., with diuretic agents that block Cl⁻ reabsorption in the loop and early distal tubule). The metabolic alkalosis induced by nasogastric drainage or vomiting can be severe. With continued losses, serum [HCO₃⁻] may rise to as high as 80 mmol/L with a concomitant fall in serum [Cl⁻] (24). In fact, in patients with serum [HCO₃⁻] >45 mmol/L, gastric losses are virtually always the precipitating cause. A characteristic feature of the urine electrolytes in the metabolic alkalosis caused by gastric losses is a [Cl⁻] <10 mmol/L, a finding that can aid in the diagnosis of surreptitious vomiting. Treatment with isotonic saline and/or KCl corrects the disorder, and reversal of the initial cause of the upper gastrointestinal losses prevents its recurrence (Table 4). If continued losses cannot be prevented, then pharmacologic inhibition of the gastric H⁺/K⁺-ATPase will ameliorate this form of metabolic alkalosis (25), but whether it can prevent the disorder remains to be determined.

**Diarrhea**

For acid-base and electrolyte abnormalities to occur in diarrheal states, the volume of fluid lost must be sufficiently large to overcome the kidney’s ability to adjust excretion to maintain acid-base equilibrium. When losses are sufficiently large, the disorder that develops is determined by the specific electrolyte

<table>
<thead>
<tr>
<th>Gastrointestinal Disorder</th>
<th>Acid-Base Disorder</th>
<th>Potassium</th>
<th>Extracellular Fluid Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting, nasogastric drainage</td>
<td>Metabolic alkalosis</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Diarrhea states</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholera</td>
<td>Metabolic acidosis</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>other infectious</td>
<td>Metabolic acidosis</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>autoimmune</td>
<td>No significant disorder⁵</td>
<td>Normal⁴</td>
<td>Normal⁴</td>
</tr>
<tr>
<td>congenital chloridorrhea</td>
<td>Metabolic alkalosis</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Villous adenoma of colon</td>
<td>No significant disorder</td>
<td>Metabolic alkalosis or metabolic acidosis</td>
<td>Normal or low</td>
</tr>
<tr>
<td>Laxative abuse</td>
<td>No significant disorder⁶</td>
<td>Metabolic acidosis</td>
<td>Low</td>
</tr>
<tr>
<td>Pancreatic/biliary drainage</td>
<td>when losses high and sustained</td>
<td>Normal or high</td>
<td>Low</td>
</tr>
<tr>
<td>Ileostomy drainage</td>
<td>Metabolic acidosis</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Short bowel</td>
<td>Metabolic acidosis⁷</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

⁵Unless diarrhea is severe, then metabolic acidosis, volume depletion, and hypokalemia.
⁶May have minor increase in serum [HCO₃⁻].
⁷p-Lactic acidosis.
that increases cAMP levels by permanently activating adenylyl
Vibrio cholera

cussed next. The patho-
and hypokalemia. When diarrhea is severe, lactic acidosis may
metabolic acidosis and hypokalemia when severe enough (par-
With larger losses, any form of diarrhea will lead to a significant fall in extracellular fluid volume, reducing GFR and limiting the ability of the kidney to help correct the abnormalities. This pattern of events most commonly occurs with tissue hypoperfusion (27). The pathophysiology of these diarrhea states is less well defined, but both increased secretion and absorption seem to contribute. Enterotoxin obtained from pathogenic *E. coli* activates guanylyl cyclase, which increases cyclic GMP levels, stimulating Cl− secretion in intestinal epithelial cells (33).

**Other Bacterial Diarrheas.** Entero-pathic *Escherichia coli* and other bacteria and viruses can cause diarrhea, producing metabolic acidosis and hypokalemia when severe enough (particularly in young children and infants). The pathophysiology of these diarrhea states is less well defined, but both increased secretion and absorption seem to contribute. Enterotoxin obtained from pathogenic *E. coli* activates guanylyl cyclase, which increases cyclic GMP levels, stimulating Cl− secretion in intestinal epithelial cells (33).

**Short bowel syndrome.** The diarrhea in short-bowel syndrome is caused by the bacterium *Vibrio cholera*. This intestinal pathogen produces a toxin that increases cAMP levels by permanently activating adenylyl cyclase in intestinal crypt cells, producing a sustained activation of the apical membrane CFTR Cl− channel and thereby leading to excessive Cl− secretion into the ileum and colon (28,29). The increase in Cl− secretion in turn stimulates the apical Cl−/HCO3− exchanger, increasing stool [HCO3−]. The increase in anion secretion results in increased paracellular Na+ and water entry, resulting in high-volume diarrhea that contains a large amount of HCO3−, as well as Na+, Cl−, and K+ (Table 2). The clinical presentation is severe volume depletion, hyperchloremic metabolic acidosis, and hypokalemia. Oral hypotonic electrolyte solutions are effective first-line therapy for this disorder and have been shown to reduce mortality significantly (Table 4) (1,30,31). Oral intake of 75 to 100 ml/kg body wt is recommended (1). When oral rehydration fails to keep up with losses, vigorous intravenous volume repletion with added potassium and bicarbonate can be life-saving. The CFTR channel is central to the pathophysiology of this disorder, because blockade of the channel by a specific inhibitor completely prevents the effect of cholera toxin on rat intestinal fluid secretion (32). The hope is that a clinically useful inhibitor of the CFTR channel could eventually become an adjunct to the management of cholera (27), but no suitable inhibitor has yet been developed. A second approach shown to be effective in experimental animals is activation of the calcium-sensing receptor, which hastens breakdown of cAMP and thereby decreases the stimulation of secretory channels in intestinal epithelial cells (33).

**Cholera.** The diarrhea in cholera is caused by the bacterium *Vibrio cholera*. This intestinal pathogen produces a toxin that increases cAMP levels by permanently activating adenylyl cyclase in intestinal crypt cells, producing a sustained activation of the apical membrane CFTR Cl− channel and thereby leading to excessive Cl− secretion into the ileum and colon (28,29). The increase in Cl− secretion in turn stimulates the apical Cl−/HCO3− exchanger, increasing stool [HCO3−]. The increase in anion secretion results in increased paracellular Na+ and water entry, resulting in high-volume diarrhea that contains a large amount of HCO3−, as well as Na+, Cl−, and K+ (Table 2). The clinical presentation is severe volume depletion, hyperchloremic metabolic acidosis, and hypokalemia. Oral hypotonic electrolyte solutions are effective first-line therapy for this disorder and have been shown to reduce mortality significantly (Table 4) (1,30,31). Oral intake of 75 to 100 ml/kg body wt is recommended (1). When oral rehydration fails to keep up

### Table 4. Treatment of gastrointestinal disorders that disrupt acid-base and electrolyte homeostasis

<table>
<thead>
<tr>
<th>Gastrointestinal Disorder</th>
<th>Treatment</th>
<th>Unproven and Potential Future Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Isotonic saline</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Nasogastric drainage</td>
<td>KCl, Reverse underlying cause</td>
<td>Blockade of CFTR Cl− channel, Ca2+ receptor agonists</td>
</tr>
<tr>
<td>Cholera</td>
<td>Oral electrolyte solutions, Isotonic saline,</td>
<td>Blockade of CFTR Cl− channel, Ca2+ receptor agonists</td>
</tr>
<tr>
<td></td>
<td>NaHCO3, KHCO3</td>
<td></td>
</tr>
<tr>
<td>Infectious diarrhea</td>
<td>Oral electrolyte solutions, Isotonic saline,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NaHCO3, KHCO3</td>
<td></td>
</tr>
<tr>
<td>Congenital chloridorrhea</td>
<td>Oral NaCl and KCl supplements</td>
<td></td>
</tr>
<tr>
<td>Increased ileostomy drainage</td>
<td>Isotonic saline, NaHCO3 when serum [HCO3−] is</td>
<td></td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>Limit carbohydrate intake</td>
<td></td>
</tr>
</tbody>
</table>

...
authors concluded that mild to moderate metabolic alkalosis is present in patients with more extensive involvement, review of their data indicates that mean arterial [HCO₃⁻] 26 mmol/L, was within the normal range even in these patients and was only 2 mmol/L higher than in patients with lesser involvement.

**Congenital Chloridorrhea.** In this disorder, high-volume watery diarrhea begins at birth (38,39). The disorder is caused by a loss of function mutation in the downregulated in adenoma (DRA or CLD) gene, leading to an absence of any function gut Cl⁻/HCO₃⁻ exchange (40,41). As a result of the absence of Cl⁻ absorption and HCO₃⁻ secretion, the diarrhea fluid contains primarily Na⁺, Cl⁻, and K⁺ (Table 2). As discussed previously, gastrointestinal losses with Cl⁻ that essentially equal or exceed [Na⁺] + [K⁺] lead to disproportionate Cl⁻ depletion, producing metabolic alkalosis through effects on renal acid and K⁺ excretion. Concomitant NH₄⁺ losses in the diarrhea fluid may also contribute to the development of metabolic alkalosis (2), but the disorder is sustained unless the Cl⁻ losses can be replaced (Table 4). Management of the continued fluid and electrolyte losses is obviously a difficult problem, so patients with this disease usually have sustained metabolic alkalosis and are chronically volume depleted. In a single case report, inhibition of the gastric H⁺/K⁺-ATPase, using omeprazole, reduced stool volume dramatically in a patient with congenital chloridorrhea, providing a promising new tool for managing this disorder (42).

**Villous Adenoma.** Little is known about the ion transport pathways that are stimulated or inhibited by these rare tumors, but they produce a copious secretion with Na⁺ and Cl⁻ concentrations approaching those of serum (Table 2) (43). The unusual rate of fluid secretion by these tumors is not a feature of the cases with metabolic alkalosis even though renal function may be markedly impaired. The normal fluid contains primarily Na⁺-rich fluid, significant metabolic acidosis does not occur. When acidosis is severe, treatment should also include replacement of extracellular fluid volume with isotonic saline (Table 4).

**Laxative Abuse**

Long-term laxative ingestion with the intent to increase stool volume causes increased and unregulated losses of K⁺ (44,45). If this excess loss is not counterbalanced by a concomitant increase in dietary K⁺ intake, then body K⁺ stores will become depleted, a change that causes hypokalemia and some H⁺ shift into cells, raising extracellular fluid [HCO₃⁻] (18). The increase in [HCO₃⁻] may be sustained by the effect of K⁺ depletion to increase renal NH₄⁺ production and excretion. The major clinical feature of laxative abuse is hypokalemia; clinically significant metabolic alkalosis, if present, is usually mild in the absence of concomitant bulimia (44,45). If laxative abuse induces excessive diarrheal losses, then metabolic acidosis can of course occur, as with any severe diarrhea (45).

**Ileostomy Drainage**

Patients with well-functioning ileostomies have daily fluid losses of 0.5 to 1.0 L and adapt to these obligatory losses through subtle changes in salt and water intake, as well as changes in urine volume and electrolyte and acid excretion (46–48). When ileostomy drainage abruptly increases, the resultant salt and water losses can easily produce symptomatic volume depletion. In this setting, either metabolic acidosis or metabolic alkalosis may occur (46,48–51). The development of metabolic acidosis is not surprising because ileostomy fluid [HCO₃⁻] is usually higher than in plasma (Table 2), causing disproportionate alkali loss. Metabolic acidosis is almost always accompanied by hyperkalemia, reflecting that K⁺ is not secreted in the ileum and therefore the losses contain little K⁺ (Table 2). In addition, renal K⁺ excretion is impaired by the associated volume depletion.

Metabolic alkalosis is a more surprising outcome of increased ileostomy drainage and seems to occur much less commonly. In a few cases, this disorder has been severe, with serum [HCO₃⁻] >40 mmol/L (48,51). In these cases, the electrolyte content of the losses has been characterized by Cl⁻ concentrations that are almost equal to [Na⁺], and both are higher than are normally seen in ileostomy fluid. Because disproportionate Cl⁻ loss is the most common cause of metabolic alkalosis, this characteristic likely accounts for the disorder. The cause of the high [Cl⁻] in the ileal drainage remains unclear but seems most likely due to impaired ileal Cl⁻ absorption (48). The alkalosis is sustained by the associated volume depletion, which impairs any changes in renal acid excretion that might ameliorate the disorder. In contrast to the patients with metabolic acidosis, hyperkalemia is not a feature of the cases with metabolic alkalosis even though renal function may be markedly impaired. The normal or slightly low serum [K⁺] likely reflects K⁺ losses in the urine in response to metabolic alkalosis as well as to transcellular K⁺ shifts.

The fist line of treatment of either disorder is vigorous repletion of extracellular fluid volume with isotonic saline (Table 4). When acidosis is severe, treatment should also include replacement of alkali stores with HCO₃⁻. If K⁺ depletion is present, then appropriate potassium replacement should be undertaken as well.

**Short Bowel Syndrome**

In patients who have undergone jejunooileal bypass surgery for weight reduction or who have a shortened small intestine connected to the colon for other reasons, undigested glucose delivery to the colon is increased, providing a substrate for bacteria that metabolize this sugar to lactic acid (1,52). This bacterial metabolic process produces D- and L-lactic acid, both of which are readily absorbed into the circulation. Humans have the enzyme machinery to metabolize L-lactic acid rapidly, but D-lactic acid is only slowly metabolized. Absorption of sufficient D-lactic acid results in a characteristic syndrome of mental confusion and metabolic acidosis with an increased anion gap. Because only L-lactate is measured in the usual laboratory test for lactic acid, no elevation in lactate will be detected despite the increased anion gap acidosis. With mass
spectrometry or chromatography methods that detect both p- and l-lactic acid, the elevated p-lactate levels will be evident (2). The symptoms and acidosis clear spontaneously with time as the p-lactic acid is gradually removed from the circulation by metabolism, but the syndrome will recur after eating another high-carbohydrate meal. Once recognized, the disorder is easily treated by limiting the carbohydrate content of the diet (Table 4). Because of many problems with jejunoileal bypass, of which this disorder is only one, the operation is no longer performed for weight loss.

Conclusions
Disruption of normal bowel function as a result of infection, inflammation, complications of surgical procedures, or hereditary and acquired transport abnormalities uncovers its critical importance for acid-base, electrolyte, and fluid volume homeostasis. The nature of the acid-base disorder that develops is directly dependent on the electrolyte composition of the fluid that is lost as well as by the magnitude of the losses. Regardless of whether metabolic acidosis or alkalosis develops, the disorder is sustained only when the losses are large enough to impair renal homeostatic mechanisms and maintenance of fluid and electrolyte balance through increased oral intake. The mainstay of the acute treatment for all sustained disorders of acid-base equilibrium that are induced by abnormal gastrointestinal losses is vigorous extracellular fluid volume repletion, with appropriate adjustments in the electrolyte composition of the replacement fluids to reflect specific losses. The long-term approach is to correct the underlying gastrointestinal disorder if possible. Our hope is that advances in our understanding of ion transport along the gut will provide new avenues for the treatment of disorders that disrupt its function. Gastrointestinal disorders provide an experiment in nature that has shed light on the normal transport properties of the gut as well as uncovered its importance in acid-base and electrolyte homeostasis.

Disclosures
None.

References


