

are watershed zones where two arterial circulations terminate.

- **Angiodysplasia** is a malformation of submucosal and mucosal blood vessels and a common cause of lower intestinal bleeding in those older than 60 years of age.
- **Diarrhea** can be characterized as secretory, osmotic, malabsorptive, or exudative.
- The malabsorption associated with **cystic fibrosis** is the result of pancreatic insufficiency, leading to inadequate pancreatic digestive enzymes, and deficient luminal breakdown of nutrients.
- **Celiac disease** is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains. The malabsorptive diarrhea in celiac disease is due to loss of brush border surface area, including villous atrophy, and, possibly, deficient enterocyte maturation as a result of immune-mediated epithelial damage.
- **Environmental enteropathy** is prevalent in areas with poor sanitation. It is estimated to affect more than 150 million children worldwide and may contribute to a very large number of childhood deaths.
- **Lactase deficiency** causes an osmotic diarrhea due to the inability to break down or absorb lactose. The autosomal recessive form is rare and severe; the acquired form usually presents in adulthood and is common.
- **Autoimmune enteropathy** is an X-linked disorder characterized by severe persistent diarrhea and autoimmune disease that is caused by mutation in *FOXP3* gene, resulting in defective function of regulatory T cells.
- **Abetalipoproteinemia** is a rare autosomal recessive disease due to a mutation in microsomal triglyceride transfer protein that is required for enterocytes to process and secrete triglyceride-rich lipoproteins.

## Infectious Enterocolitis

*Enterocolitis can present with a broad range of symptoms including diarrhea, abdominal pain, urgency, perianal discomfort, incontinence, and hemorrhage (Table 17-8).* This global problem is responsible for more than 2000 deaths each day among children in developing countries and greater than 10% of all deaths before age 5 worldwide. Bacterial infections, such as enterotoxigenic *Escherichia coli*, are frequently responsible, but the etiology varies with age, nutrition, and host immune status as well as environmental influences (Table 17-8). For example, epidemics of cholera are common in areas with poor sanitation, as a result of inadequate public health measures, natural disasters, such as floods and earthquakes, or war. Pediatric infectious diarrhea, which may result in severe dehydration and metabolic acidosis, is commonly caused by enteric viruses.

### Cholera

***Vibrio cholerae* are comma-shaped, gram-negative bacteria that cause cholera, a disease that has been endemic in the Ganges Valley of India and Bangladesh** for almost all of recorded history. Since 1817, seven great pandemics have spread along trade routes to large parts of Europe, Australia, and the Americas, but, for unknown reasons

these pandemics resolved and cholera retreated back to the Ganges Valley. Cholera also persists within the Gulf of Mexico but causes only rare cases of seafood-associated disease; this occurs because shellfish and plankton can be reservoirs of *Vibrio* bacteria.

There is a marked seasonal variation in the incidence of cholera in most climates due to rapid growth of *Vibrio* bacteria at warm temperatures. While the bacteria can be present in food, the infection is primarily transmitted by contaminated drinking water. Thus, cholera can become rampant in areas devastated by natural or man-made disasters, such as earthquakes or war, that threaten sewage systems and drinking water supplies. For example, the January 2010 Haitian earthquake led to a cholera epidemic that began in October 2010. At the end of the first year, more than 5% of the population was affected. More than half of the cases required hospitalization and approximately 1% were fatal. In all, the cholera epidemic in Haiti accounted for more than half of worldwide cholera cases and deaths reported to the World Health Organization in 2010 and 2011.

**Pathogenesis.** Despite the severe diarrhea, *Vibrio* organisms are noninvasive and remain within the intestinal lumen. While cholera toxin, encoded by a virulence phage and released by the *Vibrio* organism, causes disease, the flagellar proteins, which are involved in motility and attachment, are necessary for efficient bacterial colonization. Hemagglutinin, a metalloproteinase, is important for bacterial detachment and shedding in the stool. The mechanism by which cholera toxin induces diarrhea is well understood (Fig. 17-27). Cholera toxin is composed of five B subunits and a single A subunit. The B subunit binds GM1 ganglioside on the surface of intestinal epithelial cells, and is carried by endocytosis to the endoplasmic reticulum, a process called retrograde transport. Here, the A subunit is reduced by protein disulfide isomerase, and a fragment of the A subunit is unfolded and released. This peptide fragment is then transported into the cytosol using host cell machinery that moves misfolded proteins from the endoplasmic reticulum to the cytosol. Such unfolded proteins are normally disposed of via the proteasome, but the A subunit refolds to avoid degradation. The refolded A subunit peptide then interacts with cytosolic ADP ribosylation factors (ARFs) to ribosylate and activate the stimulatory G protein  $G_s\alpha$ . This stimulates adenylate cyclase and the resulting increase in intracellular cAMP opens the cystic fibrosis transmembrane conductance regulator, CFTR, which releases chloride ions into the lumen. Chloride and sodium absorption are also inhibited by cAMP. The resulting accumulation of chloride, bicarbonate, and sodium within the intestinal lumen creates an osmotic driving force that draws water into the lumen and causes massive diarrhea. Remarkably, mucosal biopsies show only minimal histologic alterations.

**Clinical Features.** Most individuals exposed to *V. cholerae* are asymptomatic or develop only mild diarrhea. In those with severe disease there is an abrupt onset of watery diarrhea and vomiting following an incubation period of 1 to 5 days. The voluminous stools resemble rice water and are sometimes described as having a fishy odor. The rate of diarrhea may reach 1 liter per hour, leading to