Gastroenteritis

Christina Quigley and Xi Jiang

Introduction to Gastroenteritis

Diarrheal disease is responsible for significant morbidity and mortality worldwide, with nearly 1.7 billion cases [1] and at least two million deaths per year, many resulting from consumption of contaminated food [2]. Acute infectious gastroenteritis is defined as disorder of the physiological functions of stomach, small, and large intestine (see chapter "Overview" under part "Gastrointestinal tract") due to inflammation of the digestive tract, resulting from bacterial, viral, or parasitic infections (Fig. 1). Noninfectious gastroenteritis may also occur after ingestion of certain types of food and medicines but is less common. Common symptoms include diarrhea, vomiting, abdominal pain, headache, nausea, fatigue, and occasionally fever and chills [3]. Infectious gastroenteritis can occur year-round, but bacterial cases are seen more commonly in warm or summer months because bacterial pathogens can replicate *in vitro* after contamination of food or water. These diseases are more common in developing nations where sanitation conditions are poor and visitors to these nations commonly develop traveler's diarrhea. Viral pathogens are not able to replicate *in vitro*, but tend to survive longer in cold conditions, which facilitates their spread via person-to-person contact. Therefore, viral diseases are more common in the fall/winter seasons when people are indoors more often [4].

C. Quigley • X. Jiang (✉)
Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, MLC 7017,
3333 Burnet Ave., Cincinnati, OH 45229, USA
e-mail: christina.quigley@cchmc.org; jason.jiang@cchmc.org

Pathophysiology of Gastroenteritis

Bacteria

Normal bacterial flora populates the gut, increasing in numbers from the stomach to the distal colon (see chapter "Overview" under part "Gastrointestinal tract") [5]. These bacteria are helpful to the human host by fermenting unused energy substrates; training the immune system; preventing growth of harmful, pathogenic bacteria; regulating the development of the gut; producing vitamins, like vitamin K_2; and metabolizing estrogen and androgen hormones [6].

Bacterial gastroenteritis can result from invasion of the gut mucosal surface, attachment to mucosal surfaces and release of toxins, or by toxin production in food prior to ingestion.

Invasive bacterial strains, such as *Shigella* and *Campylobacter* sp., usually lead to mucosal ulceration (see chapter "Peptic ulcer disease"), abscess formation, and inflammation, which can occur due to invasion of the gut alone, but are exacerbated by toxin production [7]. This process results in severe diarrhea due to secretion of water and electrolytes, sometimes containing mucus and/or blood in the feces with fever, abdominal pain, and rectal tenesmus (a feeling of incomplete defecation), known as dysentery [4].

E. Lammert, M. Zeeb (eds.), *Metabolism of Human Diseases*,
DOI 10.1007/978-3-7091-0715-7_22, © Springer-Verlag Wien 2014

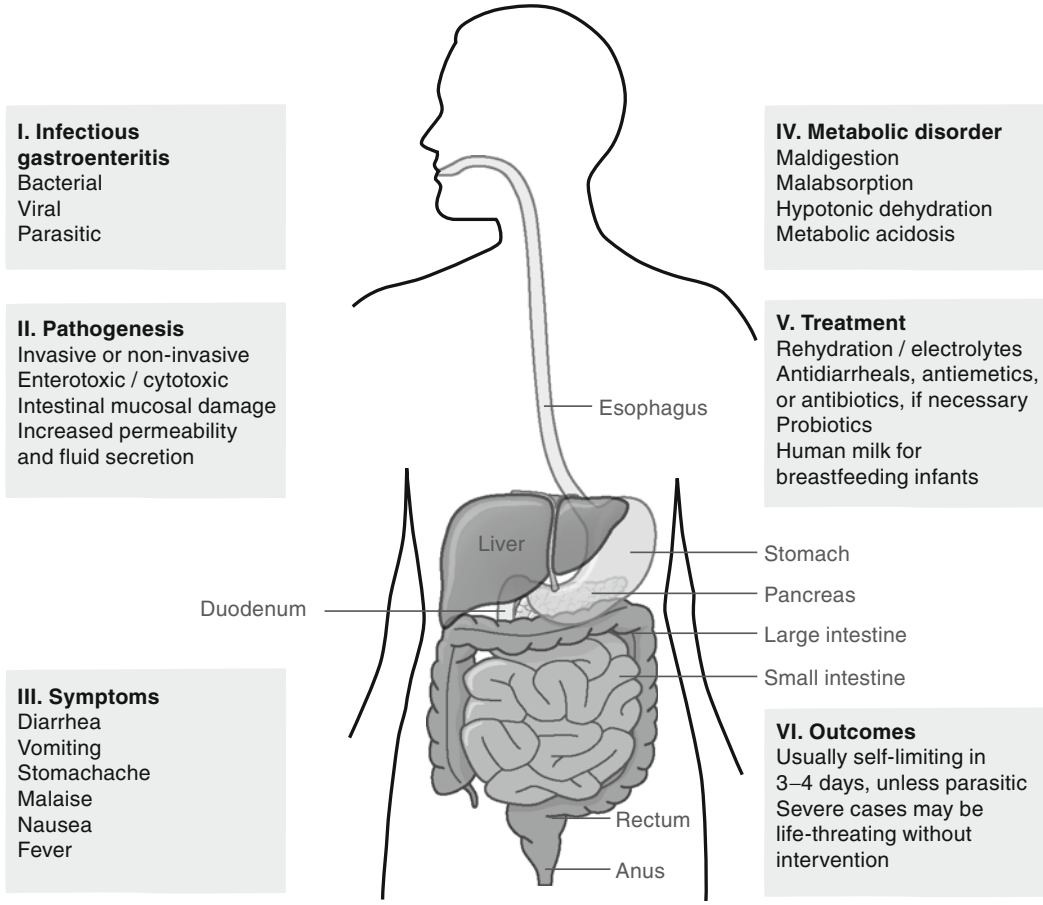

Fig. 1 Overview of acute infectious gastroenteritis. Acute gastroenteritis is a disease affecting the stomach and small and large intestine (central panel). Causes of infectious gastroenteritis include bacterial, viral, and/or parasitic pathogens (I). These pathogens can be invasive and cause cell damage and produce toxins. Alternatively, the pathogens are noninvasive and damage mainly occurs through enterotoxin production (II). The resulting mucosal damage increases permeability and peristaltic movement and impairs intestinal absorption, resulting in diarrhea and other symptoms (III). The major metabolic disorders include maldigestion and malabsorption due to impaired intestinal mucosal surfaces with consequences of hypotonic dehydration and metabolic acidosis, which can have severe complications (IV). Rehydration with proper electrolytes is critical for treatment. Antidiarrheals and antiemetics may provide relief from symptoms. Antibiotics are only used for bacterial and parasitic pathogens (V). Gastroenteritis is usually self-limiting in 3–4 days. Parasitic gastroenteritis may last longer. Life-threatening cases occur mostly in young children and the elderly (VI)

Noninvasive bacteria cause similar symptoms by adhering to the gut wall followed by production of enterotoxins, such as *Vibrio cholerae* and enterotoxigenic strains of *Escherichia coli*. Toxin production results in secretory diarrhea with a large volume of watery diarrhea characterized by excessive mucosal secretion due to adenylate cyclase induction resulting in impaired intestinal absorption [7]. In addition, cholera toxins bind to channel proteins, opening chloride channels, which results in more chloride ions in the lumen of the small intestine and causes water to move into lumen, known as osmotic diarrhea [8].

Finally, some bacterial toxins, such as enterotoxins A to E from *S. aureus*, present in contaminated food [9] may cause symptoms similar to those of noninvasive bacteria, as enterotoxins are heat resistant and thus not destroyed by cooking. Nausea and vomiting may occur more frequently with this form of gastroenteritis

due to excessive gas formation and the body's response to purge the toxins.

In all forms of bacterial gastroenteritis, inflammation as the host's immune response to toxins or pathogens combined with variable entero- and cytotoxic effects can lead to mucosal cell damage and result in overall dysfunction of the gut with maldigestion of food and malabsorption of nutrients. In addition, overgrowth of some pathogenic bacterial strains may further exacerbate these effects on metabolism [10].

On average, the symptoms of bacterial gastroenteritis infections last between 2 and 10 days. Since patients are unable to reabsorb lost fluid, dehydration is the most common severe complication of acute gastroenteritis [11]. Thus, hospitalization is sometimes required in the pediatric and geriatric populations, although generally infections are self-limiting.

Viruses

Acute viral gastroenteritis is one of the top 5 causes of death worldwide. The major viral gastroenteritis pathogens include rotavirus (RV), norovirus (NoV), astrovirus, and enteric adenovirus [12]. RV is the leading cause of severe diarrhea in children under 5 years with significant mortality in developing nations, although NoV also contributes [13]. In developed nations, NoV infections commonly occur in adults and are responsible for major outbreaks of acute gastroenteritis. These viral pathogens are typically invasive, infecting enterocytes, and cause cell death or toxic effects disturbing the normal function of the gut. Unfortunately, the precise pathogenic mechanisms of most of these viruses remain unknown [12]. RV uses sialic acid, several integrins, and heat shock cognate protein 70 as cell surface receptors, which facilitate virus penetration through the mucosal surface and infection [14]. This may cause structural changes, including villus shortening, which decreases the function of the small bowel mucosa, along with inflammation and mononuclear cell infiltration in the lamina propria (inner layer of the gut mucosa). These changes combined with cell damage lead to maldigestion and malabsorption, similar to bacterial gastroenteritis. In addition, infected epithelial cells induce villus ischemia and activation of the enteric nervous system that further exaggerate the disease [15]. Recent studies of RV showed that the viral nonstructural protein 4 (NSP4) could act as an enterotoxin, the first identified in viral infections. NSP4 binds integrins $\alpha1\beta1$ and $\alpha2\beta1$ [14] and appears to trigger epithelial cell chloride secretion by increasing intracellular Ca^{2+} through phospholipase C activation [16]. NSP4 also disrupts tight junctions, which is believed to be a new mechanism of pathogenesis leading to malabsorption and dehydration via increased permeability [17]. Symptoms related to viral gastroenteritis usually last 1–3 days and are most often self-limiting. However, severe cases can be life-threatening due to severe dehydration [12].

Parasites

The most common parasites responsible for gastroenteritis are *Giardia* and *Cryptosporidium*. Like bacteria, they can invade the intestinal mucosa or adhere to the gut wall. Subsequent inflammation and disruption of the gut mucosa lead to watery diarrhea, inadequate digestion of food, and malabsorption of nutrients [18]. The course of parasitic gastroenteritis is longer than both bacterial and viral gastroenteritis with symptoms lasting up to 4 weeks, even if the infection is cleared. It usually resolves without intervention. Due to the longer duration of symptoms, weight loss due to malabsorption, fatigue, and dehydration are commonly observed [11].

Treatment of Gastroenteritis

In most cases of acute gastroenteritis, the infections resolve on their own. However, severe cases with serious dehydration such as those caused by RV infection can be life-threatening. Thus, the most important aspects of symptom management are rehydration and prevention of electrolyte loss. In developing countries where intravenous

Table 1 Antibiotic treatment guidelines for bacterial and parasitic gastrointestinal infections

Pathogen	Treatment
Bacterial	
Campylobacter sp.	Erythromycin, if administered <4 day after symptom onset
Clostridium difficile	Avoid antibiotic (may prolong infection) Oral Metronidazole may be administered
Escherichia coli	Avoid antibiotic (may prolong infection or cause hemolytic-uremic syndrome)
Salmonella sp.	Antibiotic treatment not recommended for non-typhoid strains, except for immunocompromised patients Ampicillin may be used, but for resistant strains, third-generation Cephalosporins, Fluoroquinolones (not in children), or Trimethoprim-Sulfamethoxazole may be effective
Shigella sp.	Antibiotics not recommended for mild cases Ampicillin may be used for moderate to severe cases Trimethoprim-Sulfamethoxazole for resistant strains Fluoroquinolones for highly resistant strains
Staphylococcus aureus	Antibiotics ineffective (toxin present in contaminated food)
Vibrio cholera	Antibiotic selection is based on resistance
Parasitic	
Cryptosporidium parvum	Antibiotic dependent on age and general immune status
Giardia intestinalis	Commonly: Metronidazole, Paromomycin

rehydration is difficult to access, oral rehydration is strongly recommended [19]. The World Health Organization (WHO) recommendations include glucose electrolyte solutions or rice-based solutions, since they are easily accessible [20]. Other treatments to prevent dehydration include antidiarrheal over-the-counter medications or prescription antiemetics if vomiting is severe [3]. Antidiarrheal medications, such as loperamide (Imodium), bind opiate receptors in the gut, inhibiting release of acetylcholine and prostaglandins, thereby reducing peristalsis and increasing intestinal transit time [21]. Although this may allow increased water and electrolyte absorption, dehydration is still a risk and fluids should continue to be administered. The antiemetic ondansetron (Zofran) appears to decrease vomiting during acute gastroenteritis by inhibiting serotonin binding to 5-hydroxytryptamine (5-HT) receptors in the small intestine [22]. Probiotics, which consist of nonpathogenic strains of bacteria, are considered during acute gastroenteritis to help rebuild normal bacterial flora in the gut [23].

To combat the infection, feeding of human milk is recommended for breastfeeding infants [24], as it may contain antibodies against many bacterial and viral pathogens, which may reduce the infection [25]. In addition, human milk contains many carbohydrate glycans that may serve as decoy receptors for bacterial and viral pathogens that require a carbohydrate receptor to initiate infection [26].

Some bacterial and parasitic infections may require antibiotic intervention by ciprofloxacin or metronidazole, respectively, for clearance (Table 1). The WHO also recommends antibiotics for young children with bloody diarrhea and fever [27]. It is not generally recommended, however, as viruses remain unaffected.

Bismuth subsalicylate is used to treat diarrhea, since it may reduce secretions [28], bind free bacterial toxins [29], and exert topical effects on gut mucosa [4].

Finally, vaccination is a potential key to prevention. Two vaccines are available to prevent RV, which are highly recommended for children, while vaccines for NoV and others are under development.

Influence of Treatment on Metabolism

Prompt rehydration is key to stop continued deterioration of the gut and restore normal metabolism. Without proper reabsorption of lost fluid due to mucosal damage, overall fluid deficit can rapidly lead to dehydration, which can lead

to hypovolemic shock, where the heart cannot efficiently pump blood through the body due to severe fluid deficits and even death [30]. Because dehydration is accompanied by loss of electrolytes, rehydration with proper solutions containing sufficient electrolytes is important. Insufficient electrolytes can alter neurologic and myocardial functions, while severe sodium excess (due to decreased water in dehydration) can lead to cerebrovascular damage, hemorrhage, and death [31]. Rehydration plus some antidiarrheal treatment will restore the body's normal functions allowing it to heal damaged mucosal surfaces of the gut. Proper digestion of food and absorption of nutrients also may help to restore the overall conditions of the gut, including normal bacterial flora. However, antidiarrheal treatments are contraindicated if symptoms include fever and/or bloody stool, as they can prolong or exacerbate bacterial infections [19]. Since antimotility agents increase bowel stasis, bacteria may proliferate, creating additional toxins and exacerbating gastroenteritis [32]. Antibiotic intervention also has limitations; because many prescribed antibiotics cannot distinguish between pathogenic bacteria and normal gut flora, treatment may also destroy endogenous bacteria and prolong maldigestion and malabsorption. Thus, more specific antibiotics showing a narrow spectrum (e.g., erythromycin against *Campylobacter* infections) are recommended [33].

Perspectives

Prevention and rehydration are the keys for control of pathogenic acute gastroenteritis. Oral rehydration is critical for patients with severe symptoms and a large volume of body fluid loss. Washing of hands after toilet use and before meals is the most important hygiene practice to prevent spread of these diseases. Most diarrheal pathogens are resistant to environmental conditions and are carried by food and water.

Research on the mechanisms these pathogens use to persist in the environment and the procedures to prevent contamination of food and water are important areas for disease control and prevention. Current research on NoV and RV recognition of human blood group antigens may shed new light on mechanisms of virus/host interactions, particularly for mucosal infection, potentially revealing new treatment approaches.

Further studies aim to understand the protection of some pathogens from disinfection procedures, such as UV, γ-irradiation, and high pressure. Although research of viral pathogens causing gastroenteritis remains difficult due to the inability to cultivate them *in vitro*, virus surrogates (replacements from other species closely related to human pathogens) provide an important new tool.

Most likely, cases of acute infectious gastroenteritis will continue to occur despite our best efforts to prevent them. Our hope is that increased availability to clean water sources and improved sanitary conditions in developing nations will decrease worldwide infection rates. New and improved vaccines may also decrease infection rates and/or hospitalizations, especially for viral infections. The constantly evolving knowledge and understanding of ideal treatment procedures will hopefully decrease mortality rates and frequency of complications due to acute infectious gastroenteritis.

References

1. World Health Organization (2013) Diarrhoeal disease. Available from: http://www.who.int/mediacentre/factsheets/fs330/en/index.html. Accessed 21 June 2013
2. Kosek M, Bern C, Guerrant RL (2003) The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ 81:197–204
3. Aranda-Michel J, Giannella RA (1999) Acute diarrhea: a practical review. Am J Med 106(6):670–676
4. Thielman NM, Guerrant RL (2004) Clinical practice. Acute infectious diarrhea. N Engl J Med 350(1):38–47
5. Hao W-L, Lee Y-K (2004) Microflora of the gastrointestinal tract. Methods Mol Biol 268:491–502
6. Festi D, Schiumerini R, Birtolo C, Marzi L, Montrone L, Scaioli E, Di Biase AR, Colecchia A (2011) Gut microbiota and its pathophysiology in disease paradigms. Dig Dis 29(6):518–524
7. Navaneethan U, Giannella RA (2008) Mechanisms of infectious diarrhea. Nat Clin Pract Gastroenterol Hepatol 5(11):637–647
8. Sellin JH (2001) The pathophysiology of diarrhea. Clin Transplant 15(Suppl 4):2–10

9. Le Loir Y, Baron F, Gautier M (2003) Staphylococcus aureus and food poisoning. Genet Mol Res 2(1):63–76
10. Schiller LR (2007) Evaluation of small bowel bacterial overgrowth. Curr Gastroenterol Rep 9(5):373–377
11. McClarren RL, Lynch B, Nyayapati N (2011) Acute infectious diarrhea. Prim Care 38(3):539–564
12. Clark B, McKendrick M (2004) A review of viral gastroenteritis. Curr Opin Infect Dis 17(5):461–469
13. Ramani S, Kang G (2009) Viruses causing childhood diarrhoea in the developing world. Curr Opin Infect Dis 22(5):477–482
14. López S, Arias CF (2004) Multistep entry of rotavirus into cells: a Versaillesque dance. Trends Microbiol 12(6):271–278
15. Ciarlet M, Gilger MA, Barone C, McArthur M, Estes MK, Conner ME (1998) Rotavirus disease, but not infection and development of intestinal histopathological lesions, is age restricted in rabbits. Virology 251(2):343–360
16. Dong Y, Zeng CQ-Y, Ball JM, Estes MK, Morris AP (1997) The rotavirus enterotoxin NSP4 mobilizes intracellular calcium in human intestinal cells by stimulating phospholipase C-mediated inositol 1,4,5-trisphosphate production. Proc Natl Acad Sci 94(8):3960–3965
17. Lorrot M, Vasseur M (2007) How do the rotavirus NSP4 and bacterial enterotoxins lead differently to diarrhea? Virol J 4(1):31
18. Huston CD (2004) Parasite and host contributions to the pathogenesis of amebic colitis. Trends Parasitol 20(1):23–26
19. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, Hennessy T, Griffin PM, DuPont H, Sack RB, Tarr P, Neill M, Nachamkin I, Reller LB, Osterholm MT, Bennish ML, Pickering LK (2001) Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 32(3):331–351
20. Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis (1996) Pediatrics 97(3):424–435
21. Sandhu BK, Tripp JH, Candy DC, Harries JT (1981) Loperamide: studies on its mechanism of action. Gut 22(8):658–662
22. Cubeddu LX, Trujillo LM, Talmaciu I, Gonzalez V, Guariguata J, Seijas J, Miller IA, Paska W (1997) Antiemetic activity of ondansetron in acute gastroenteritis. Aliment Pharmacol Ther 11(1):185–191
23. Preidis GA, Hill C, Guerrant RL, Ramakrishna BS, Tannock GW, Versalovic J (2011) Probiotics, enteric and diarrheal diseases, and global health. Gastroenterology 140(1):8–14
24. King CK, Glass R, Bresee JS, Duggan C, Centers for Disease Control and Prevention (2003) Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52(RR-16):1–16
25. Hayani KC, Guerrero ML, Morrow AL, Gomez HF, Winsor DK, Ruiz-Palacios GM, Cleary TG (1992) Concentration of milk secretory immunoglobulin A against Shigella virulence plasmid-associated antigens as a predictor of symptom status in Shigella-infected breast-fed infants. J Pediatr 121(6):852–856
26. Morrow AL, Ruiz-Palacios GM, Altaye M, Jiang X, Guerrero ML, Meinzen-Derr JK, Farkas T, Chaturvedi P, Pickering LK, Newburg DS (2004) Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. J Pediatr 145(3):297–303
27. Singh A (2010) Pediatric emergency medicine practice acute gastroenteritis — an update. Emerg Med Pract 7
28. Gyles C, Zigler M (1978) The effect of adsorbant and anti-inflammatory drugs on secretion in ligated segments of pig intestine infected with Escherichia coli. Can J Comp Med 42(3):260–268
29. Ericsson CD, Evans DG, DuPont HL, Evans DJ, Pickering LK (1977) Bismuth subsalicylate inhibits activity of crude toxins of Escherichia coli and vibrio cholerae. J Infect Dis 136(5):693–696
30. Kreimeier U (2000) Pathophysiology of fluid imbalance. Crit Care 4(Suppl 2):S3–S7
31. Hirschhorn N (1980) The treatment of acute diarrhea in children. An historical and physiological perspective. Am Journal Clin Nutr 33(3):637–663
32. Church J, Fazio V (1986) A role for colonic stasis in the pathogenesis of disease related to Clostridium difficile. Dis Colon Rectum 29(12):804–809
33. Ternhag A, Asikainen T, Giesecke J, Ekdahl K (2007) A meta-analysis on the effects of antibiotic treatment on duration of symptoms caused by infection with campylobacter species. Clin Infect Dis 44(5):696–700