15.18 Gastrointestinal infections 3008

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ESSENTIALS Gastrointestinal infections, especially diarrhoea and vomiting, are responsible for substantial morbidity, mortality, and socioeconomic penalties worldwide. In poor countries, the greatest burden of dis- ease is borne by infants and young children, although older people and immunocompromised patients are also at great risk of severe and complicated disease. Poor sanitation, inadequate water supplies, and globalization of food production, processing, and retailing in- crease the risk of large epidemics of food- and waterborne outbreaks of gastrointestinal disease. Clinical syndromes Acute diarrhoea can be caused by pathogens ranging from toxin-producing strains of Escherichia coli to rotavirus and Giardia spp. Gastrointestinal pathogens usually cause three principal syn- dromes: acute watery diarrhoea, acute bloody diarrhoea (inflamma- tory diarrhoea or dysentery), and persistent diarrhoea. They can also cause systemic disease. Patients who do not have high fever (>38.5°C), systemic illness, tenesmus, bloody diarrhoea, a prolonged course (>2 weeks), or de- hydration require neither investigation nor treatment. Investigation is required in patients with any of these features, with faecal spe- cimens examined by culture (bacterial pathogens and some protozoa), microscopy (ova, cysts, and parasites), immunoassays (some protozoa and viruses), and molecular methods, usually poly-merase chain reaction (PCR) or reverse transcriptase PCR (bacterial toxin genes and viruses).
A specific laboratory diagnosis is useful epidemiologically and therapeutically, especially for invasive patho- gens and diarrhoea in high-risk patients such as the very young, eld- erly, or immunocompromised. Management Oral rehydration therapy is the priority for patients with mild to moderate diarrhoea as long as vomiting is not a major feature, and it can also follow initial parenteral rehydration in severely de- hydrated patients. Antimicrobial therapy is not recommended or usually required for uncomplicated diarrhoea, but antibiotic treat- ment is beneficial for cholera, giardiasis, cyclosporiasis, shigellosis, symptomatic traveller’s diarrhoea, Clostridium difficile diarrhoea, and typhoid. Antimotility drugs are useful in controlling moderate to se- vere diarrhoea in adults but they are not generally recommended for infants and young children under the age of 4 years. Prevention Strict attention to food and water precautions and hand washing helps reduce the risk of gastrointestinal infections. Immunization has not yet proved successful for combating many gastrointestinal pathogens, with the notable exception of rotavirus.

Introduction On a global scale, diarrhoeal diseases are among the top 10 leading causes of death, killing an estimated 1.5 million people in 2012. In the infectious diseases category, which collectively cause around 23% of deaths worldwide, diarrhoeal diseases lie in second place (jointly with HIV/AIDS) behind the estimated 3.1 million deaths from lower respiratory tract infections. The impact is greatest in low- and middle-income countries. As well as killing people, gastrointestinal infections can exert a toll as major causes of chronic ill health through, for example, their contribution to malnutrition. There can also be serious systemic sequelae such as chronic kidney disease requiring long-term renal replacement therapy following haemolytic uraemic syndrome (HUS) caused by enterohaemorrhagic Escherichia coli (EHEC), and Guillain–Barré syndrome (GBS) following infection with Campylobacter spp. Aetiological agents A wide variety of bacteria, viruses, and parasites cause gastro- intestinal infections (Tables 15.18.1–15.18.3), usually by gaining entry directly via the gastrointestinal tract. Exceptions to this in- clude hookworm (Ancylostoma spp. and Necator americanus), which burrows through the skin, usually of the foot, and even- tually migrates to the intestine via the bloodstream, lymphatics, and lungs. 15.18 Gastrointestinal infections Sarah O'Brien

15.18 Gastrointestinal infections 3009 Table 15.18.1 Aetiology of gastrointestinal infection: major bacterial pathogens Organism Typical incubation period Typical symptoms Typical duration Bacillus cereus Emetic type: 30 min–6 h Nausea and vomiting 24 h Diarrhoeal type: 6–15 h Cramping abdominal pain, acute watery diarrhoea Campylobacter spp. 2–5 days Cramping abdominal pain, fever, acute watery and/or acute bloody diarrhoea 2–10 days Clostridium botulinum 12–36 h after ingesting toxin Early signs and symptoms include striking lethargy, weakness, and vertigo, normally followed by blurred or double vision and increasing problems with talking and swallowing. If untreated, symptoms may progress to descending paralysis— arms, trunk (including respiratory muscles), legs Months Clostridium difficile Unclear but could be up to 7 days Severe abdominal pain, anorexia, fever, acute watery or, rarely, bloody diarrhoea 7–10 days; around 25% of patients relapse, typically 3 days–3 weeks post cessation of treatment Clostridium perfringens 10–12 h Mild cramping abdominal pain, acute watery diarrhoea 12–24 h Diffusely adherent Escherichia coli (DAEC) 6–48 h Mild, acute watery diarrhoea Days Enteroaggregative E. coli (EAggEC) 8–18 h Acute watery diarrhoea, which turns bloody in approximately a third of cases Days Enterohaemorrhagic E. coli (EHEC) 3–4 days Range from asymptomatic to mild diarrhoea to haemorrhagic colitis, which presents as severe cramping abdominal pain, nausea or vomiting, and frequent episodes of diarrhoea that becomes obviously bloody. Fever is usually absent or low grade 2–9 days in the absence of complications Enteroinvasive E. coli (EIEC) 12–72 h Abdominal cramping pain, acute bloody diarrhoea, vomiting, fever 5–7 days Enteropathogenic E. coli (EPEC) 4–12 h Profuse acute watery diarrhoea, vomiting, low- grade fever 21–120 days Enterotoxigenic E. coli (ETEC) 8–44 h Acute watery diarrhoea, cramping abdominal pain, low-grade fever, nausea Up to 20 days Listeria monocytogenes Invasive disease: 3 days to 3 months Headache, stiff neck, photophobia, confusion, vertigo, and convulsions Days to weeks Nontyphoidal Salmonella spp. 6–72 h Headache, fever, nausea, vomiting, cramping abdominal pain, acute watery or bloody diarrhoea 4–7 days Salmonella Paratyphi 1–10 days Anorexia, headache, high fever, lassitude; abdominal pain, diarrhoea or constipation. In severe cases, signs of Gram-negative septicaemia 1–2 weeks S. Typhi 8–14 days Anorexia, headache, high fever, lassitude, abdominal pain, diarrhoea or constipation, skin rash of flat, rose-coloured spots on the trunk. In severe cases, signs of Gram-negative septicaemia 7–10 days on appropriate treatment; 3 months if untreated; 3–5% become chronic carriers Shigella spp. 8–50 h Cramping abdominal pain, fever, acute bloody diarrhoea, tenesmus 5–7 days

Staphylococcus aureus 1–7 h Acute onset of nausea, cramping abdominal pain, vomiting, and watery diarrhoea Up to 1 day Vibrio cholera Serogroups O1 and O139: 2–3 days Vomiting, mild to severe acute watery diarrhoea Days to weeks Serogroups other than O1 and O139: 12–24 h Fever, cramping abdominal pain, acute watery diarrhoea 7 days Vibrio parahaemolyticus 4–90 h Cramping abdominal pain, nausea, vomiting, fever, acute watery or bloody diarrhoea 2–6 days Yersinia enterocolitica 1–11 days Fever, abdominal pain that can be confused with appendicitis, diarrhoea and/or vomiting Up to 3 weeks

section 15 Gastroenterological disorders 3010 Table 15.18.2 Aetiology of gastrointestinal infection: major viral pathogens Organism Typical incubation period Typical symptoms Typical duration Adenovirus 40/41 3–10 days Abdominal pain, fever, vomiting and acute watery diarrhoea Up to 10 days Astrovirus 3–4 days Anorexia, abdominal pain, fever, acute watery diarrhoea 2–3 days Hepatitis A 15–50 days Anorexia, nausea, vomiting, fever, diarrhoea, myalgia, jaundice. Jaundice occurs 5–7 days after onset of gastrointestinal symptoms 1–2 weeks Hepatitis E 3–8 weeks Anorexia, abdominal pain, arthralgia, fever, malaise, jaundice, vomiting 2 weeks Norovirus 12–24 h Explosive, projectile vomiting, acute watery diarrhoea, headache, low-grade fever, myalgia 24–48 h Rotavirus 24–72 h High fever, vomiting, acute watery diarrhoea 3–7 days Sapovirus 1–3 days Nausea, vomiting, acute watery diarrhoea, myalgia 2–3 days Table 15.18.3 Aetiology of gastrointestinal infection: major parasites Organism Typical incubation period Typical symptoms Typical duration Protozoa Balantidium coli 3–4 days Can be asymptomatic but also causes acute bloody diarrhoea, nausea, vomiting, headache If treated 5–20 days depending upon therapy chosen Cryptosporidium hominis 7–10 days Cramping abdominal pain, nausea and vomiting copious acute watery diarrhoea 2–14 days in immunocompetent people but may become chronic in the immunocompromised Cryptosporidium parvum 7–10 days Cramping abdominal pain, nausea and vomiting, copious acute watery diarrhoea 2–14 days in immunocompetent people but may become chronic in the immunocompromised Cyclospora cayetanesis 7–10 days Anorexia, weight loss, cramping abdominal pain, bloating, acute watery and explosive diarrhoea Days to months Cystoisospora belli 3–14 days Cramping abdominal pain, acute watery diarrhoea, malabsorption and weight loss Weeks to months if untreated Dientamoeba fragilis 1–2 weeks Abdominal pain and watery diarrhoea 1–2 weeks unless infection becomes chronic Entamoeba histolytica 2–4 weeks Abdominal distension, mild diarrhoea to severe acute bloody diarrhoea A few days to several weeks Giardia intestinalis 1–2 weeks Cramping abdominal pain, malaise, flatulence, foul- smelling diarrhoea, weight loss 2–6 weeks unless infections becomes chronic Toxoplasma gondii 5–23 days Acute toxoplasmosis; sore lymph nodes, myalgia, flu-like symptoms. Ocular toxoplasmosis; blurred or reduced vision, increased production of tears, eye redness and pain, photophobia Several weeks Trichinella spp. 1–4 weeks Abdominal discomfort, diarrhoea, myalgia, weakness, fever, muscle pain, facial swelling Weeks to months Helminths Ascaris lumbricoides 4–8 weeks Often asymptomatic, unless the patients spots a worm in their faeces, or, occasionally, when a worm escapes through the mouth, nose, or anus. Heavy infestations can cause abdominal pain and distension, nausea, anorexia, vomiting, self-limiting pneumonia, intestinal obstruction 1–2 years unless treated Anisakis simplex and Pseudoterranova decipiens 24 h–2 weeks Noninvasive anisakiasis; no symptoms or coughing up a nematode after a tingling sensation in the throat 3 weeks to several months Invasive anisakiasis; nausea, vomiting, severe abdominal pain, diarrhoea, mild to strong allergic response Ancylostoma duodenale 5–8 weeks Epigastric pain, abnormal peristalsis, iron-deficiency anaemia Up to 1 year if untreated Diphyllobothrium latum 15 days Abdominal discomfort, altered appetite, mild diarrhoea, vitamin B12 deficiency in prolonged or

heavy infestations, rarely intestinal obstruction Up to 25 years if left untreated Dipylidium caninum 21–28 days Mostly asymptomatic but can cause abdominal distension, restlessness, diarrhoea Following treatment: follow-up at 1 and 3 months

15.18 Gastrointestinal infections 3011 Bacteria Important bacteria causing diarrhoeal disease include the following: • Bacillus cereus—Gram-positive, spore-forming rod that produces two enterotoxins: a heat-stable emetic toxin that is formed in highly contaminated food and a heat-labile diarrhoeal toxin that forms in the small intestine. • Campylobacter spp.—Gram-negative, spiral-shaped rods, are the most frequent bacterial cause of diarrhoeal disease in high-income countries where infection is often associated with consumption of undercooked contaminated poultry. Seroepidemiological studies show that exposure to Campylobacter spp. is very common but does not necessarily lead to protective immunity. Rare but serious sequelae include GBS and reactive arthritis. It also causes mesen- teric adenitis, which can be confused with acute appendicitis. • Clostridium difficile—a Gram-positive, spore-forming drumstick (or spindle)-shaped rod, is an important healthcare-associated, or nosocomial, infection in high-income countries, although spread within the community outside healthcare settings is increasingly recognized. It colonizes the gastrointestinal tract after perturba- tions of the healthy gut microbiome, usually following treatment with broad-spectrum antibiotics. It commonly affects the elderly. • Clostridium perfringens type A strains—Gram-positive, spore- forming rods, are major causes of classical food poisoning resulting in acute watery diarrhoea following enterotoxin production. • E. coli spp.—Gram-negative rods, commonly found in diar- rhoea cases in low- and middle-income countries where they are leading cause of hospital admission for infectious diarrhoea. There are six major categories of E. coli that cause diarrhoea— enteroaggregative E. coli (EAggEC), EHEC, enteroinvasive E. coli (EIEC), enteropathogenic E. coli (EPEC), enterotoxigenic E. coli (ETEC), and diffusely adherent E. coli (DAEC). The role of DAEC as a diarrhoeal pathogen has been disputed because in many studies it has been found as frequently in asymptomatic controls as in cases. However, DAEC are gaining acceptance as a cause of diarrhoea in preschool children in low- and middle-income coun- tries and in travellers. • Salmonella spp.—Gram-negative rods, cause typhoid fever (S. Typhi), paratyphoid fever (S. Paratyphi), and foodborne dis- ease (nontyphoidal Salmonella spp.). Salmonellas are found worldwide in warm-blooded and cold-blooded animals, and in the environment. • Shigella spp.—Gram-negative rods, classically cause dysentery. HUS is an occasional, but severe, complication. • Staphylococcus aureus—a Gram-positive coccus, is another clas- sical food poisoning organism. Food handlers who are carriers of enterotoxin-producing S. aureus or who have visible purulent skin lesions, especially on their hands, can contaminate food. S. aureus produces various emetic enterotoxins, but staphylococcal entero- toxin A is most often implicated in staphylococcal food poisoning worldwide. • Vibrio spp.—Gram-negative bacilli, cause cholera (V. cholerae serogroups O1 and O139), acute gastroenteritis (V. parahaemo- lyticus and V. cholerae serogroups other than O1 and O139), and septicaemia (V. vulnificus). • Yersinia enterocolitica—a Gram-negative bacillus, is associated with eating pork meat or pig intestine (chitterlings). Pathogenic Y. enterocolitica biotype 4 (serotype 3) strains predominate in Europe and the United States of America. Extraintestinal mani- festations include mesenteric adenitis, mimicking acute appendi- citis, and erythema nodosum and reactive arthritis are recognized postinfectious complications. Viruses Important viruses, which are the commonest causes of acute watery diarrhoea globally, include the following: • Adenovirus subgroup F (types 40 and 41)—a well-known cause of acute gastroenteritis in very young children (<6 months of age). Organism Typical incubation period Typical symptoms Typical duration Enterobius vermicularis and

E. gregorii 1–2 months Intense pruritus ani and perineal pruritus 2 weeks if treated Hymenolepis nana 2–4 weeks Mainly asymptomatic but can cause abdominal pain nausea, weakness, anorexia, diarrhoea Following treatment: follow-up at 2 weeks and 3 months Necator americanicus 35–40 days (for gastrointestinal symptoms to appear) Itching and a localized rash at the entry site. Heavy infection can produce abdominal pain, anorexia, weight loss, fatigue, diarrhoea, and anaemia Up to 1 year if untreated Schistosoma spp. 6–8 weeks Abdominal pain, fatigue, fever, headache, generalized myalgia, vertigo, vomiting, bloody diarrhoea If untreated 20–30 years Strongyloides stercoralis 14–30 days Many infections are asymptomatic. When symptoms occur they include abdominal pain, heartburn, bloating, alternating diarrhoea and constipation, dry cough, rash Up to 30 years if untreated Taenia spp. 2–4 months Often asymptomatic but can lead to cause abdominal pain, nausea, anorexia, diarrhoea Years unless treated Trichiuris trichiuria Up to 3 months Light infections are mostly asymptomatic. Moderate to heavy infections produce abdominal pain, nausea, vomiting, bloody diarrhoea, anaemia, and rectal prolapse 1–2 years if left untreated Table 15.18.3 Continued

section 15 Gastroenterological disorders 3012 • Astrovirus—accounts for between 2% and 9% of all acute child- hood nonbacterial gastroenteritis worldwide. It is a common cause of outbreaks in day-care settings and nurseries. The illness is usually self-limiting but severe, systemic infections can occur in immunocompromised and elderly patients. • Norovirus—responsible for approximately 18% of all cases of acute gastroenteritis globally and the leading cause of acute epidemic gastroenteritis. It poses a major problem in closed and semiclosed settings such as schools, hospitals, and cruise ships, where it can result in explosive outbreaks. Outbreaks are often identified using Kaplan’s criteria (Box 15.18.1) because the short-lived nature of the illness means that most infections are unconfirmed by labora- tory testing. Most of the noroviruses that infect humans belong to genogroups GI and GII. Periodically, new strains emerge and spread around the world very rapidly. Susceptibility to norovirus infection appears to be linked with the expression of human histoblood group antigens. • Rotavirus—until recently this was the leading cause of viral gastro- enteritis and diarrhoeal deaths worldwide. It led to approximately 2 million hospital admissions and around 0.5 million deaths an- nually in children less than 2 years of age. However, rotavirus vaccination appears to have reduced substantially the burden of community-acquired and hospital-acquired cases in countries with high vaccine uptake. • Sapovirus—this is from the same family of viruses as norovirus (the Calciviridae). Alongside norovirus, sapoviruses of geno groups GI, GII, GIV, and GV are the most common causes of acute viral gastroenteritis in adults. However, unlike noroviruses, sapoviruses tend to cause only mild illness in young children. In a community-based study of infectious diarrhoea in the United Kingdom, sapovirus was found to be the second most commonly identified agent after norovirus. Although many pathogens cause diarrhoea and vomiting, some agents gaining entry via the gastrointestinal tract cause extraintestinal symptoms. For example, Listeria monocytogenes rarely causes diarrhoea (<1% of reported cases) but is associated with invasive disease—meningitis and septicaemia. Similarly, V. vulnificus infection, which is associated with the consumption of raw or undercooked shellfish, results in septicaemia in immuno- compromised people or patients with liver disease. Parasites The burden of parasitic infections varies geographically. In high- income countries, protozoa are much more common causes of illness than intestinal helminths. By contrast, in low-income countries in- testinal helminths are among the most prevalent infections in hu- mans. Principal parasitic causes of gastrointestinal infection include the following: • Cryptosporidium spp.—a protozoan parasite that leads to acute watery diarrhoea in healthy people but can cause pro- longed, chronic diarrhoea in

immunocompromised people. The main pathogens for humans are C. parvum and C. homi- nis but other species can also produce disease in people. Outbreaks have been associated with contaminated drinking water and, rarely, contaminated food. The cysts are not des- troyed by the levels of chlorine used to disinfect drinking water supplies. • Cyclospora cayetanensis—a protozoan parasite causing watery diarrhoea, weight loss, anorexia, bloating, nausea, vomiting, muscle aches, and persistent fatigue. It is endemic in many low- and middle-income countries. Illness may last from a week to a month or longer if it is left untreated. It is one of the few gastro- intestinal infections for which there is specific antimicrobial therapy. • Entamoeba histolytica—a protozoan parasite affecting an esti- mated 40 to 50 million people globally, leading to approximately 40 000 deaths. Symptoms range in severity from mild diarrhoea to severe dysentery. • Giardia lamblia—a flagellate protozoan parasite resulting in both epidemic and sporadic disease. A variety of intestinal symptoms follow infection including abdominal cramps, flatulence, and chronic diarrhoea leading to weight loss and fatigue. Illness can extend to months or years if it is undiagnosed. • Soil-transmitted helminths—with the exception of Strongyloides stercoralis, these do not often cause diarrhoea. Hyperinfection with S. stercoralis can occur in immunocompromised pa- tients and the resulting heavy worm burdens can lead to se- vere complications such as intestinal obstruction. Infestations with hookworms and whipworm tend to cause extraintestinal manifestations. Certain organisms exhibit marked seasonal patterns, for ex- ample, norovirus, which is classically described as causing ‘winter vomiting,’ rotavirus, which also peaks during the cold winter months, Campylobacter spp. with a marked late spring peak in temperate climates, and nontyphoidal Salmonella spp., which tend to peak in late summer. For organisms such as nontyphoidal Salmonella spp. that can multiply outside the main reservoir (e.g. in or on food), it has been suggested that climate change might in- crease their impact in future. The time that elapses between exposure to an infectious agent and onset of symptoms or signs is called the incubation period. Each gastrointestinal infection has a typical incubation period that requires multiplication of the infectious agent to a threshold necessary to produce symptoms or laboratory evidence of infection. The incubation can vary according to the infectious dose, the replication rate of the organism and underlying host factors such as age, sex, and genetic susceptibility. The infectious dose can vary considerably from pathogen to pathogen as shown in Table 15.18.4. Box 15.18.1 Kaplan’s criteria for diagnosis of a norovirus outbreak • A mean (or median) illness duration of 12 to 60 h and • A mean (or median) incubation period of 24 to 48 h and • More than 50% of people with vomiting and • No bacterial agent found on stool examination. After Kaplan JE, et al. (1982). Epidemiology of Norwalk gastroenteritis and the role of Norwalk virus in outbreaks of acute nonbacterial gastroenteritis. Ann Intern Med, 96, 756–61.

15.18 Gastrointestinal infections 3013 Epidemiology and spread Susceptibility Susceptibility to most gastrointestinal pathogens is general, but young children, the elderly, and the immunocompromised are rec- ognized as being at higher risk of developing infection and may suffer a more severe illness. Rates of gastrointestinal infection tend to be higher in children under the age of 5 years than in any other age group. Children ex- perience higher rates of EHEC infections than adults and are also at increased risk of developing severe complications such as HUS. Indeed, in high-income countries HUS is the most common cause of acute kidney injury in young children. The elderly are at increased risk of developing another complication of EHEC infection, namely thrombotic thrombocytopenic purpura, with its associated high mortality. Listeria monocytogenes, which is ubiquitous and grows on food held at refrigerator temperature, is an important cause of fetal loss, and of invasive disease (meningitis and/or septicaemia) in the eld-

erly. Elderly men have recently been group identified as being at highest risk for hepatitis E virus infection. Underlying medical conditions and drug treatment (e.g. proton pump inhibitors to reduce stomach acid), may increase the predis- position to acquiring gastrointestinal infection. Moreover, chronic infection with certain pathogens (e.g. Cryptosporidium spp.), may herald the onset of AIDS in patients infected with HIV. Transmission The major transmission routes for gastrointestinal infection are person-to-person spread via the faecal-oral route, ingesting faecally contaminated food or drinking water, or direct spread from infected animals or the environment, which has become contaminated with pathogens. Transmission can also occur through inhalation of aero- sols containing gastrointestinal pathogens, sexual transmission, vertical transmission from mother to unborn child, and through a contaminated blood transfusion supply. Tables 15.18.5 to 15.18.7 summarize the principal reservoirs and transmission routes. Person-to-person spread Many gastrointestinal pathogens are transmitted from person to person via the faecal-oral route. The faecal–oral route (also referred to as the oral–faecal route or orofaecal route) means that patho- gens in faeces voided by one person pass to the mouth of another (Fig. 15.18.1). The so-called F-diagram was designed deliberately to be memorable, showing that faecal–oral transmission occurs via ‘fingers, flies, fields, foods, and fluids’ (i.e. polluted drinking water, surface water, or groundwater). It also illustrates where control measures can be implemented to prevent transmission. Food-borne spread The substantial impact of food-borne disease is sobering. The World Health Organization (WHO) recently produced the first es- timates of their global burden. Altogether, a total of 31 global food- borne hazards were found to cause around 600 million food-borne illnesses and 420 000 deaths in 2010. The most frequently recognized causes were diarrhoeal disease pathogens, especially norovirus and Campylobacter spp. Foodborne diarrhoeal diseases accounted for approximately 230 000 deaths. Major causes were nontyphoidal Salmonella spp., S. Typhi, Taenia solium, and hepatitis A virus. Forty per cent of the food-borne disease burden occurred in children under the age of 5 years. There was also marked regional variation, with the highest burdens witnessed in Africa, South-East Asia, and parts of the Eastern Mediterranean. Food can become contaminated at source during primary pro- duction (i.e. in the fields—crops or food-producing animals), during processing, transportation, at retail level, and/or in the hospitality sector or the domestic setting. Increasing globaliza- tion of the food supply spreads organisms rapidly worldwide. A classic example of this was the large outbreaks of Cyclospora cayetenensis in North America from contaminated raspberries imported from central America. Transporting food long distances is also a means of spreading antimicrobial resistance, such as a na- tionwide outbreak of multidrug-resistant Salmonella Heidelberg infections in the United States of America associated with con- sumption of ground turkey meat. Food handlers with poor per-sonal hygiene can also contaminate food. This is well recognized for bacterial pathogens and increasingly so for viral pathogens such as norovirus. Waterborne spread Ensuring the safety of the drinking water supply by separating sewage from it, the so-called sanitary revolution, has been described as the greatest medical advance since 1840. Yet poor water quality remains a major hazard to human health in many parts of the world. Nearly 60% of the global total of 1.5 million deaths from diarrhoeal diseases arises from unsafe water supplies, and inadequate sani- tation and hygiene. An estimated 361 000 of these 842 000 water- related deaths occur in children under 5 years of age, primarily in low- and middle-income countries. Vibrio cholerae is a classical waterborne pathogen in low-and middle-income countries, where epidemics and pandemics are strongly associated with drinking unsafe water or eating food that has been prepared using unsafe water. Mass migration following man-made or natural disasters and overcrowded refugee camps provide the perfect conditions for the rapid spread of cholera out- breaks. Case fatality rates in

these circumstances are often high. Cryptosporidium spp. are more commonly associated with water- borne outbreaks in high-income countries. Table 15.18.4 Infectious dose for selected gastrointestinal pathogens Organism Infectious dose (organisms) Escherichia coli (other than EHEC) 106–108 Vibrio cholera 104–106 Nontyphoidal salmonellas

> 105 Campylobacter spp. 100s Cryptosporidium parvum 10–30 oocysts Shigella spp. 10s Norovirus 1–10 virus particles EHEC ≤10

section 15 Gastroenterological disorders 3014 Table 15.18.5 Principal reservoirs and transmission pathways for gastrointestinal bacteria Organism Reservoirs Person-to-person Food-borne Waterborne Zoonotic Environment-to-person Bacillus cereus Soil and environment ✘ ✓✓ ✘ ✘ ✘ Campylobacter spp. Food-producing animals (including poultry) and domestic pets ✘ ✓✓ ✘ ✘ ✘ Clostridium botulinum Spores in soil, honey, animal and fish guts ✘ ✓✓ ✘ ✘ ✘ Clostridium difficile Humans ✓✓ (✓) ✘ ✘ ✓ Clostridium perfringens Humans and animals ✘ ✓✓ ✘ ✘ ✘ Diffusely adherent Escherichia coli (DAEC) Humans ✓ ✓✓ ✓✓ ✘ ✘ Enteroaggregative E. coli (EAggEC) Humans ✓ ✓✓ ✓✓ ✘ ✘ Enterohaemorrhagic E. coli (EHEC) Cattle ✓✓ ✓✓ ✓✓ ✓✓ ✓✓ Enteroinvasive E. coli (EIEC) Humans ✘ ✓✓ ✓✓ ✘ ✘ Enteropathogenic E. coli (EPEC) Humans ✓ ✓✓ ✓✓ ✘ ✓ Enterotoxigenic E. coli (ETEC) Humans (✓) ✓✓ ✓ ✘ ✘ Listeria monocytogenes Soil, water, mud, silage, domestic and wild animals, birds, humans ✓ ✓✓ ✘ (✓) (✓) Nontyphoidal Salmonella spp. Domestic and wild animals (including poultry) ✓ ✓✓ ✓ ✓ (✓) Salmonella Paratyphi Humans ✓ ✓✓ ✓✓ ✘ ✘ Salmonella Typhi Humans ✓ ✓✓ ✓✓ ✘ ✘ Shigella spp. Humans ✓✓ ✓ ✓ ✘ ✘ Staphylococcus aureus Humans, cattle, dogs, birds ✘ ✓✓ ✘ ✘ ✘ Vibrio cholera Humans ✓✓ ✓✓ ✓✓ ✘ ✘ Vibrio parahaemolyticus Marine coastal environment ✘ ✓✓ ✘ ✘ ✘ Yersinia enterocolitica Pigs, sheep, cattle, goats ✓ ✓✓ ✓✓ ✓ ✘ ✓✓, major route; ✓, minor route; (✓), rarely reported; ✘, not reported. Table 15.18.6 Principal reservoirs and transmission pathways for gastrointestinal viruses Organism Reservoirs Person-to-person Food-borne Waterborne Zoonotic Environment-to-person Adenovirus 40/41 Humans ✓✓ ✘ ✓ ✘ ✓ Astrovirus Humans ✓✓ ✘ ✘ ✘ ✘ Hepatitis A Humans ✓✓ ✓ ✓ ✘ ✘ Hepatitis E Humans, pigs ✓✓ ✓ ✓ ✘ ✘ Norovirus Humans ✓ ✓ ✓ ✘ ✓ Rotavirus Humans ✓✓ ✘ (✓) ✘ ✘ Sapovirus Humans, pigs ✓✓ (✓) (✓) ✘ (✓) ✓✓, major route; ✓, minor route; (✓), rarely reported; ✘, not reported.

15.18 Gastrointestinal infections 3015 Zoonotic spread Several bacteria, including Campylobacter spp., EHEC, nontyphoidal Salmonella spp., and Yersinia entercolitica, and protozoa, including Cryptosporidium parvum and Giardia intestinalis, are zoonotic, that is, their main reservoir is in animals, notably domestic livestock and companion animals (pets). As well as contaminating the food or water supply, these organisms can also spread to humans via direct contact with the animal source. Outbreaks of EHEC among small children visiting petting zoos, city farms, and open farms are now well documented. Environment-to-person spread Soil-transmitted helminths are classic examples of infections acquired directly from the environment. Roundworm (Ascaris lumbricoides), whipworm (Trichiuris trichiuria), and hookworms (Ancylostoma duodenale and Necator americanicus) are common in tropical and subtropical regions of low-income countries where water and sanitation facilities are inadequate. Recently it has been estimated that A. lumbricoides affects more than a billion people globally, T. trichiura around 795 million people, and hookworms approximately 740 million people. Norovirus can also be transmitted from the

environment. Virus particles aerosolized during explosive diarrhoea and vomiting can settle on hard surfaces or soft furnishings where they can survive for long periods of time before being picked up by another person who touches the contaminated surfaces days or even weeks later. In practice, many gastrointestinal pathogens can be spread via more than one route as is illustrated for Campylobacter spp. in Fig. 15.18.2. Table 15.18.7 Principal reservoirs and transmission pathways for gastrointestinal parasites Organism Reservoirs Person-to-person Food-borne Waterborne Zoonotic Environment-to-person Protozoa Balantidium coli Pigs ✓✓ ✘ ✓ ✘ ✘ Cryptosporidium hominis Humans ✘ ✘ ✓✓ ✘ ✘ Cryptosporidium parvum Livestock (cattle, sheep goats), humans ✓✓ ✓✓ ✓✓ ✓✓ ✓ Cyclospora cayetanesis Humans ✓ ✓✓ ✓ ✘ ✘ Cystoisospora belli Humans ✘ ✓✓ ✓✓ ✘ ✘ Dientamoeba fragilis Humans ✓✓ ✘ ✘ ✘ ✘ Entamoeba histolytica Humans ✘ ✓✓ ✓✓ ✘ ✘ Giardia intestinalis Humans, beavers, cats, dogs, cattle, deer ✓✓ ✓ ✓ ✘ ✓ Toxoplasma gondii Cat (✓) ✓✓ ✘ ✓✓ ✘ Trichinella spp. Pigs, dogs, cats, horses, rats, wild animals ✘ ✓✓ ✘ ✘ ✘ Helminths Ascaris lumbricoides Humans ✘ ✓✓ ✘ ✘ ✓✓ Anisakis simplex and Pseudoterranova decipiens Crustaceans, squid, octopus, fish ✘ ✓✓ ✘ ✘ ✘ Ancylostoma duodenale Humans ✘ ✓ ✘ ✘ ✓✓ Diphyllobothrium latum Fish ✘ ✓✓ ✘ ✘ ✘ Dipylidium caninum Dogs, cats ✘ ✘ ✘ ✓✓ ✘ Enterobius vermicularis and E. gregorii Humans ✓✓ ✘ ✘ ✘ ✓✓ Hymenolepis nana Humans,?mice ✓✓ ✓✓ ✓✓ ✘ ✓✓ Necator americanicus Humans ✘ ✘ ✘ ✘ ✓✓ Schistosoma spp. Humans (S. mansoni and S. haematobium); humans, dogs, cats, pigs, cattle, water buffalo, wild rodents (S. japonicum) ✘ ✘ ✓✓ ✘ ✘ Strongyloides stercoralis Humans (✓) ✘ ✘ ✘ ✓✓ Taenia spp. Cattle (T. saginata), pigs (T. solium), humans and pigs (T. asiatica) ✘ ✓✓ ✘ ✘ ✘ Trichiuris trichiuria Humans ✘ ✓✓ ✘ ✘ ✓✓ ✓✓. major route; ✓. minor route; (✓). rarely reported; ✘. not reported

section 15 Gastroenterological disorders 3016 Other transmission routes As well as the five conventional pathways described previously, gastrointestinal infections can also spread via other routes including: • sexual contact, for example, Shigella spp. and hepatitis E virus are now recognized as causing outbreaks among men who have sex with men • blood transfusion, for example, hepatitis A virus and hepatitis E virus during the viraemic phase of the illness • vertical transmission from mother to fetus, for example, listeriosis • solid organ transplant and xenotransplantation—hepatitis E Fig. 15.18.1 The ‘F-diagram’ illustrating the transmission routes for gastrointestinal infections. Source: UNICEF Philippines and Luis Gatmaitan/2014/Gilbert F. Lavides. Human infection and disease Meat Calves Weaned calves Heifers (and steers?) Milking cows Dry cows Pasture contamination Human behaviours Environmental ‘reservoirs’ Invertebrate vectors (beetles and flies) Invertebrates (beetles and flies) Human behaviours (beetles and flies) Waste Human behaviours Equipment Equipment Invertebrates Chicken Infection Human Infection and disease Likely control points Wild mammals and birds Equipment and buildings (fomites) Soil and water Protozoa and algae Pasture contamination Human behaviours Climate/ seasonal changes Pasture contamination Human behaviours Contamination of feed Contamination of feed Milk Fig. 15.18.2 The multiple transmission routes for Campylobacter infection.

15.18 Gastrointestinal infections 3017 Pathogenesis/pathology The complex interplay between agent and host is involved in de- velopment of disease. Features of organisms that assist in causing disease are toxin production, adherence to the gut mucosa, and invasion. Features of the host that help to repel gastrointes- tinal infections include physical barriers, immunity, and the gut microbiome. Organism factors Toxin production Many gastrointestinal bacteria produce enterotoxins. These toxins can be preformed on contaminated food, for example, Bacillus ce- reus and S. aureus emetic toxins, or, like cholera toxin, they can exert their action directly on intestinal

epithelial cells. C. difficile produces two toxins. Toxin A is generally termed the enterotoxin although it also has some cytotoxic activity, and toxin B, which is a potent cytotoxin. Both are important in causing symptoms of antibiotic-associated diarrhoea and a significant complica- tion, namely pseudomembranous colitis. Shigella spp. produce two enterotoxins. These are shigella enterotoxin 1 (ShET-1) and shigella enterotoxin 2 (ShET-2), which occurs in many (but not all) shigellae and in EIEC. Each has a different mechanism of ac- tion on the gut. Adherence Enteropathogens can use various mechanisms to stick to the gut mucosa. V. cholerae uses a toxin-coregulated pilus, which is a fim- brial colonization factor. EPEC, EAggEC, and DAEC exhibit char- acteristic patterns of adherence to cultured epithelial cells. EPEC strains demonstrate a pattern called localized adherence. EAggEC isolates bind in an aggregative adherence pattern, which looks like stacked bricks on the surfaces of the cells. DAEC strains exhibit dif- fuse adherence, where the bacteria uniformly cover the entire cell surface. Giardia lamblia adheres to the gut lining using a ventral disc, also known as a sucking or adhesive disc. Invasion Invasive enteropathogens such as Campylobacter spp., Shigella spp., nontyphoidal Salmonella spp., and Yersinia spp. invade the mucosal surface of the large bowel, particularly the distal ileum and colon. They infect epithelial cells, or translocate into mesenteric lymph nodes and the bloodstream. Histological examination shows mu- cosal ulceration with acute inflammation in the lamina propria. Shigella dysenteriae produces Shiga toxin, which causes cell damage in a manner similar to ricin, and EHEC strains produce similar Shiga-like toxins, which act on the vascular endothelium of small blood vessels, particularly in the colon and renal glomeruli. The ensuing kidney destruction leads to HUS, which is a leading cause of acute kidney injury in children in high-income countries. Host factors Physical barriers The gastrointestinal tract has a series of physical barriers to repel or remove harmful pathogens. These include stomach acid, pan- creatic enzymes, bile, and intestinal secretions. Peristalsis and the normal process of shedding epithelial cells that line the gut are also important natural barriers to infection. The pH of gastric acid in the human stomach is around 1.5 to 3.5. Its main function is to kill off ingested microbes so that they never reach the small intestine. The proton pump H+/K+-ATPase maintains stomach acidity, and diseases such as atrophic gastritis, or drugs such as proton pump inhibitors that suppress gastric acid secretion, increase the risk of gastrointestinal infection. Epithelial cells in the small intestine are covered in a glycocalyx of mucins and other glycoproteins that can entrap bacteria. Defensins, which are secreted by Paneth cells localized at the bottom of the in- testinal crypts, also possess antimicrobial properties. Immune system The gastrointestinal immune system is challenged constantly through a combination of its resident microbiome, the antigen load in food, and the presence of potential pathogens. Immune mechan- isms to protect against disease are found in lymphoid tissue and in intraepithelial and lamina propria lymphocytes. Gut-associated lymphoid tissue Peyer’s patches and mesenteric lymph nodes comprise major com- ponents of the lymphoid tissues in the gut. The mucosal epithelium and underlying lamina propria are the effector sites. They contain various types of immune cells such as activated T cells, plasma cells, mast cells, dendritic cells, and macrophages. These cells are pre- sent in normal circumstances and are kept under control by various powerful regulatory mechanisms. Immune response Epithelial cells act as microbial sensors. Responding to bacterial in- cursion, they secrete several factors including IL-6, IL-8, RANTES, TNFα, and MCP-1. In turn, neutrophils, eosinophils, monocytes, phagocytic macrophages, and T cells are used to stimulate protective immunity. The inflamed intestine contains various specific immune cells such as CD4+ and CD8+ T cells, γδT cells, regulatory T cells, and IgA-secreting plasma cells. Microbiome Host–microbe interactions appear to influence immune functions at all levels from the initial innate defences to complex acquired responses. The

microflora of the small intestine is relatively scant, but the large intestine has a richly diverse microflora amounting to around 1012 bacteria per gram of luminal contents. Under normal circumstances, conditions in the large bowel are largely anaerobic and favour the Bacteroidetes and Firmicutes phyla. Regardless of causative organism, during an episode of acute diarrhoea the rapid passage of intestinal contents means that the environment in the colon becomes less anaerobic; hence, strict anaerobes reduce in number while coliforms increase. The pathogen itself dominates and is, therefore, detected on microbiological testing. The immune system must learn to cope with the commensal microflora while mounting an appropriate response to pathogens. Commensal bacteria and pathogens share many factors, which can be detected by pathogen recognition receptors such as toll-like re- ceptors. It seems that commensals fail to trigger inflammatory re- sponses through a number of different mechanisms:

section 15 Gastroenterological disorders 3018 • Modulation of gut macrophage innate activating receptors such as CD89 and CD14 • Training of local cells by immunomodulatory factors (retinoic acid, TGFβ, IL-10, thymic stromal lymphopoietin), which are pro- duced in large quantities • Decreased function of toll-like receptors in intestinal dendritic cells • The noninvasive nature of commensal organisms. Commensal bacteria only breach the epithelium after being taken up by local dendritic cells from whence they are transported to the mesen- teric lymph nodes and stopped in their tracks. Secretory IgA is produced in the gut, which restricts the number of commensals, and regulatory T cells reduce inflammatory responses. On the rare occasion that commensals breach all these barriers then they are engulfed and killed by local, noninflammatory macrophages Clinical features Most gastrointestinal infections cause symptoms of diarrhoea and vomiting but some present with extraintestinal manifestations such as meningitis, septicaemia, or jaundice. Diarrhoea The WHO defines diarrhoea as three or more loose or liquid stools in a day. For people who typically open their bowels less than once a day, diarrhoea is defined as the more frequent passage of loose or liquid stools than is normal for the individual. There are three main clinical presentations for diarrhoeal diseases. These are acute watery diarrhoea, acute bloody diarrhoea (inflammatory diarrhoea or dys- entery), and persistent diarrhoea, but it should be noted that these categories are not mutually exclusive. For example, a patient with Campylobacter spp. might complain initially of acute watery diar- rhoea but develop acute bloody diarrhoea as the illness progresses. The main clinical features produced by different pathogens are sum- marized in Tables 15.18.1 to 15.18.3. Acute watery diarrhoea Acute watery diarrhoea is characterized by passing large-volume, watery stools very frequently. This can happen as many as 10 to 20 times in a 24-h period. Patients can become dehydrated very rap- idly because of the high rate and volume of bowel movements. Acute watery diarrhoea is further split into two groups. Secretory diarrhoea In secretory diarrhoea, ion transport across the gut mucosa is al- tered. This leads to increased secretion and decreased absorption of fluids and electrolytes from the gut, particularly in the small bowel. Classically, organisms that produce enterotoxins cause secretory diarrhoea. These include V. cholerae, S. aureus, Clostridium per- fringens, and ETEC. Secretory diarrhoea tends to be unaffected by withholding food. Osmotic diarrhoea Osmotic diarrhoea happens when unabsorbed or poorly absorbed solute in the small bowel promotes fluid secretion into the gut lumen. The volume of stools is fairly small compared with secretory diarrhoea and symptoms tend to improve or subside with fasting. There are two types of osmotic diarrhoea. These are malabsorption, which happens when bacterial overgrowth occurs in the small bowel, and maldigestion, for example, lactose intolerance following acute diarrhoea. Acute watery diarrhoea is a common clinical feature of infection with viruses such as rotavirus and norovirus, V. cholera, and travel- lers' diarrhoea-

causing organisms such as ETEC. Acute watery diar- rhoea tends to last several hours or days and is caused by organisms that target the small intestine. Accompanying symptoms include an- orexia, nausea, vomiting, cramping abdominal pain, bloating, and a low-grade fever. If acute watery diarrhoea is left untreated, the associated fluid and electrolyte losses can lead to rapid dehydration and associated meta- bolic disturbance. Cholera, a classical cause of acute watery diar- rhoea, can produce profound dehydration leading to death as little as 3 to 4 h after symptom onset. Three levels are used to describe the extent of dehydration. There are no overt symptoms or clinical signs associated with early dehy- dration. Thirst, restlessness, and irritability, decreased skin turgor, and sunken eyes are features of moderate dehydration. Severe dehy- dration occurs when these symptoms worsen and lead to hypovol- aemic shock. If body fluids and electrolytes are not replaced urgently then the patient will die. Acute bloody diarrhoea Acute bloody diarrhoea (dysentery) is caused by invasive enteropathogens such as Campylobacter spp., C. difficile, EHEC, Entamoeba histolytica, Shigella spp., nontyphoidal Salmonella spp., V. parahaemolyticus and Yersinia entercolitica. These organisms mainly affect the colon. Acute bloody diarrhoea is often preceded by acute watery diarrhoea but, as the illness progresses, the volume of liquid stools produced might actually reduce as blood and mucus appear in the stools. Severe cramping lower abdominal pain and fever often accompany acute bloody diarrhoea. Three hypotheses have been developed to explain the mechanism of fluid production in acute bloody diarrhoea. Firstly, that an en- terotoxin stimulates fluid production. For example, the B subunit of ShET-1 is known to affect the transport of fluid and electrolytes into the small bowel. Secondly, that invading enteropathogens cause intense inflammation at the invasion site, leading to fluid secretion and diarrhoea. For example, ShET-2 is an enterotoxin haemolysin that elicits a profound inflammatory response during mucosal in- vasion. Thirdly, that physical damage to the epithelium might stop fluids from being reabsorbed so that a net build-up of fluid in the lumen of the bowel leads to diarrhoea. Persistent diarrhoea Persistent, or chronic, diarrhoea is defined by passing three or more loose stools per day for more than 4 weeks. Pathogens that affect the small intestine can cause persistent diarrhoea, with Giardia intestinalis the commonest infectious cause. Accompanying symp- toms include anorexia, bloating, weight loss, and steatorrhoea. Cryptosporidium spp. can lead to chronic diarrhoea in immunocom- promised patients, particularly those with AIDS. Up to 3% of travellers returning from low- or middle-income countries can experience persistent diarrhoea lasting for a month or more. Various pathogens, including Giardia and Cyclospora cayeten- ensis, are implicated but often the cause is not identified.

15.18 Gastrointestinal infections 3019 Other clinical manifestations Invasive disease Salmonella Typhi and Listeria monocytogenes both cause septicaemia. L. monocytogenes is also a relatively rare but important cause of meningoencephalitis. Neonates, the elderly, immunocompromised individuals, and people with alcoholic liver disease, cirrhosis and diabetes are all at increased risk of invasive listeriosis. Cronobacter sakazakii is a rare cause of bacteraemia, meningitis, and necrotizing enterocolitis. Infection happens when vulnerable people, chiefly infants and immunocompromised adults, eat con- taminated food. It has caused outbreaks in neonatal units because of its ability to survive for prolonged periods in low-moisture foods such as powdered infant formula. The case-fatality rate is very high. Occasionally, as well as causing septicaemia, nontyphoidal Salmonella spp. can present with focal infection at body sites dis- tant from the gut, such as septic arthritis, cholecystitis, endocarditis, pericarditis, or pyelonephritis. Jaundice Hepatitis A and hepatitis E both cause acute jaundice in adults not previously exposed to the viruses in childhood, when infection may be asymptomatic or very mild. Malnutrition Diarrhoeal diseases are

recognized as both causes and consequences of malnutrition, especially in young children. Similarly, the illness burden associated with intestinal helminths is mainly due to the chronic and deleterious effects on the nutritional status and health of the people afflicted. Paralysis Clostridium botulinum produces one of the most potent neurotoxins known to man. Symptoms of botulism occur following the inges- tion of preformed toxin in food. C. botulinum can produce seven different types of toxin, of which four affect humans (types A, B, E, and, rarely, F). It classically causes a descending paralysis (not to be confused with the ascending paralysis of GBS). Intestinal botulism Intestinal botulism (also known as infant botulism) is very rare, but usually occurs in infants under 2 months of age, although it may affect infants up to 12 months of age. Intestinal botulism hap- pens when they eat food, such as honey, that contains spores of C. botulinum. The spores then germinate, colonize, and produce neurotoxin in the infant's gut. This can lead to constipation and a floppy baby. Differential diagnosis Acute diarrhoea The differential diagnosis of acute diarrhoea usually includes con- sideration of the likely causative organism based on symptom- atology and incubation period. The differential diagnosis of acute diarrhoea is long and includes inflammatory bowel disease, bowel ischaemia, radiation injury, adverse drug reactions, heavy metal poisoning, toxin-mediated shellfish poisoning (ciguatera shellfish poisoning, paralytic shellfish poisoning, neurotoxic shellfish poi- soning, diarrhoetic shellfish poisoning, amnesic shellfish poisoning, puffer fish poisoning, azaspiracid poisoning), scombrotoxin (hista- mine) poisoning, mushroom poisoning, thyrotoxicosis, Addison's disease, carcinoid, medullary tumour of the thyroid and vasoactive intestinal peptide-secreting adenomas. Persistent diarrhoea The differential diagnosis of persistent diarrhoea is very long and includes bowel cancer, coeliac disease, inflammatory bowel disease, chronic pancreatitis, diverticular disease, adverse drug reactions, Whipple's disease, and short-gut syndrome. The diagnosis of irrit- able bowel syndrome should be made on positive clinical grounds, but is often a diagnosis of exclusion once other causes of persistent diarrhoea have been investigated and ruled out. Typhoid fever There is a very large differential diagnosis during the early stages of typhoid fever. Depending on the context, infectious possibil- ities include brucellosis, malaria, tuberculosis, and Gram-positive septicaemia. Clinical investigation Expert bodies such as the National Institute for Health and Care Excellence, the British Society for Gastroenterology, the American Academy of Family Physicians, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the European Society for Pediatric Infectious Diseases, and the WHO have all produced guidelines on the clinical evaluation and management of acute and persistent diarrhoea. The mainstay of clinical investigations for diarrhoea remains searching for an aetiological agent (organisms and/or toxins) using microbiological methods that involve stool examination by culture (for bacterial pathogens and some protozoa), microscopy (for ova, cysts, and parasites), immunoassays (for some protozoa and vir- uses), and molecular methods, usually polymerase chain reaction (PCR) or reverse transcriptase PCR (for bacterial toxin genes and viruses). Despite thorough examination of stool samples, the diag- nostic gap is large—more than 50% of diarrhoeal samples may not yield a pathogen. Culture usually produces a positive result in 24 to 48 h. Negative results will not usually be reported until 72 h after the plates were started to be sure that the sample really is negative. Culturing an organism is still regarded as the gold standard test, but the rapidly expanding range of nonculture-based methods, which can provide an accurate answer within the working day, is likely to change the diagnostic landscape in future. Although the physician managing a case of acute gastrointestinal infection does not necessarily need to know the precise identity of the causative pathogen because in many cases it will not alter their clinical management plan, knowing the aetiology is very important from a public health point of view. The public health investigation and management of a case of cryptosporidiosis

is quite different from that of a case of salmonellosis. For most patients, especially in high-income settings, symptoms of acute diarrhoea may resolve without clinical investigation since

section 15 Gastroenterological disorders 3020 many illnesses tend to be short lived. Indeed, patients might never contact the healthcare system. In the United Kingdom, for example, only a few people with acute diarrhoea ever present to their primary care physician. When they do it is often because of the presence of blood in the stools or because of persistent diarrhoea. Both these symptoms require further investigation. If symptoms persist after an infectious diagnosis has been ruled out then further, more in- vasive investigations might be required, for example, colonoscopy. Investigations for suspected typhoid fever must include drawing blood for blood films, a malaria rapid diagnostic test, and blood cultures. Investigation of suspected botulism may involve ruling out other potential causes of muscle weakness such as myasthenia gravis. Management Supportive care Oral rehydration salts The mainstay of treatment for acute gastroenteritis is restoring and maintaining adequate fluid and electrolyte balance. In children, in the main this will be achieved using oral rehydration salts. The WHO and UNICEF published a joint statement on the clinical management of acute diarrhoea (http://www.unicef.org/publica- tions/files/ENAcute_Diarrhoea_reprint.pdf), which describes the recommended composition of reduced osmolarity oral rehydra- tion salts (Table 15.18.8). It needs to be administered frequently, in small amounts, and on a continuous basis until symptoms have subsided. Adults with mild diarrhoea do not often need to use formal pre- parations of oral rehydration salts. Instead, they can be encouraged to increase their fluid intake using products that contain sodium (e.g. soups), potassium (e.g. fruit juice), and glucose. As soon as the patient can eat and drink properly they can start eating food again. Some patients may experience secondary lactose intolerance, which initiates diarrhoea again, so temporarily changing to a diet excluding milk or dairy products, or using lactose-free milk, deals with the symptoms. Zinc supplements There is good evidence that using zinc supplements reduces both the duration and severity of diarrhoea. Zinc supplementation also lessens the odds of subsequent gastrointestinal infections for 2 to 3 months. The WHO therefore recommends their use in conjunc- tion with oral rehydration salts: 20 mg zinc supplements daily for 10 to 14 days in children with acute diarrhoea (10 mg daily for infants <6 months old). Dietary zinc deficiency is particularly common in low-income countries. Intravenous rehydration Where diarrhoea and vomiting are severe, or where a patient shows clinical evidence of severe dehydration, then intravenous rehydra- tion must be used. Early intravenous hydration with isotonic saline also appears to decrease the risk of oligoanuric acute kidney injury in children with diarrhoea who are at risk of developing HUS. Antidiarrhoeal medication Antimotility agents, which bind to opioid receptors in the gastro- intestinal tract, delay intestinal transit. Loperamide does not cross the blood–brain barrier readily. They are most useful for adult trav- ellers who have no alternative but to continue their journey while they are symptomatic. They are not recommended for use in infants and young children under the age of 4 years where they can mask the severity of diarrhoea and thus the extent of dehydration. Specific treatments Antimicrobials Antimicrobial therapy is not recommended or usually required for uncomplicated diarrhoea. The decision to treat should ideally be made after the results of a stool examination are available and in discussion with a microbiologist. Growing levels of antimicrobial resistance among gastrointestinal pathogens means that, should therapy be required, it needs to be administered taking into account the context of local antimicrobial resistance patterns. Antimicrobials are used to treat pseudomembranous colitis asso- ciated with C. difficile and may also be indicated in persistent diar- rhoea. They are required to treat typhoid fever and other

invasive gastrointestinal infections. They are not generally recommended to treat EHEC infection because there is some, albeit mixed, evidence that using antibiotics may precipitate HUS. Patients with underlying medical conditions, especially con- ditions that lead to immune compromise, require treatment with antimicrobials, with the treatment plan guided by the causative or- ganism and local antibiotic sensitivity patterns. Faecal microbiota transplant Faecal microbiota transplantation, also known as faecal transplant, is quickly gaining acceptance as a safe, viable, and effective treatment for recurrent C. difficile infection. It can be administered in several different ways—into the proximal colon using a colonoscope, into the distal colon via an enema/rectal tube, or into the upper gastro- intestinal tract by means of a nasogastric tube. Cure rates of 90% and greater are reported. Table 15.18.8 The reduced osmolality oral rehydration solution recommended by WHO and UNICEF Reduced osmolarity ORS g/litres Sodium chloride 2.6 Glucose, anhydrous 13.5 Potassium chloride 1.5 Trisodium citrate, dihydrate 2.9 Total weight 20.5 Reduced osmolarity ORS mmol/litre Sodium 75 Chloride 65 Glucose, anhydrous 75 Potassium 20 Citrate 10 Total osmolarity 245 ORS, oral rehydration solution.

15.18 Gastrointestinal infections 3021 Mass drug administration for soil-transmitted helminths The WHO's strategy for controlling soil-transmitted helminth in- fections is to prevent and control morbidity by periodic treatment of at-risk populations who live in endemic areas. The intention of treating the whole of the at-risk population is to diminish the worm burden and reduce morbidity. The WHO defines people at risk as being preschool-aged children, school-aged children, and women of childbearing age. The treatment regimen is based on the preva- lence of soil-transmitted helminths in the community and is as fol- lows: once per annum when the prevalence exceeds 20%; twice per annum when the prevalence exceeds 50%. Botulinum antitoxin Suspected botulism is a clinical and public health emergency. Early diagnosis and treatment are absolutely critical. Botulinum antitoxin should be given as soon as possible. Although it does not reverse paralysis, botulinum antitoxin does stop its progression. The patient will almost certainly require intensive care with close observation of respiratory function. Severe cases may need 2 to 8 weeks of mech- anical ventilation. Patients eventually recover when new neuromus- cular connections have been generated. Prognosis Most cases of uncomplicated diarrhoea in high-income countries recover completely with no lasting after-effects. In low-income and middle-income settings, the picture is very different, and it is sobering to think that in the 21st century diarrhoeal diseases still kill 1.5 million people each year, exacting a particular toll on children. Listeriosis is a potentially lethal infection with a case-fatality rate of around 30% in neonates and over 60% in the elderly. The case fatality rate of botulism in high-income countries is between 5 and 10%, and around 1% of children affected by intestinal botulism die from it. Typhoid fever is estimated to cause around 600 000 deaths annually in low- and middle-income countries. Special circumstances/complications HUS and thrombotic thrombocytopenic purpura Approximately 10% of children with EHEC infection develop HUS, which has a case-fatality rate ranging from 3 to 5%. Neurological complications (e.g. seizure, stroke, and coma) occur in up to 25% of HUS patients, and chronic renal sequelae, which are often mild, affect around 50% of survivors. In the elderly, the case-fatality rate for thrombotic thrombocytopenic purpura, another complication of EHEC infection, is at least 50%. Guillain–Barré syndrome GBS is a recognized late complication of Campylobacter infection. This ascending paralysis (not to be confused with the descending paralysis of botulism) is estimated to occur in around 1 in 2000 cases of Campylobacter infection. The mechanism appears to be molecular mimicry. In these patients, the immune system produces IgG anti- bodies to lipo-oligosaccharides in the bacterial cell wall that cross- react with human nerve cell gangliosides. A quarter of people

with GBS develop weakness of the respira- tory muscles leading to respiratory failure and requiring mechanical ventilation. Despite the best care, approximately 5% of GBS cases will die. For people who recover, the extent to which they get better is variable. GBS prognosis hinges on age (worse in those >40 years of age) and symptom severity after 2 weeks. Campylobacter-associated GBS can leave people severely disabled 1 year post onset. Irritable bowel syndrome Postinfectious irritable bowel syndrome develops in up to a third of people with recent gastrointestinal infection. It has been described following infection with Campylobacter spp., Salmonella spp., diarrhoeagenic strains of Escherichia coli, Shigella spp., and, more recently, norovirus. Typically patients complain of recurrent diar- rhoea. Management is as for other causes of the condition. Joint complications Two types of joint complications are recognized after gastrointes- tinal infection: reactive arthritis and septic arthritis. Reactive arthritis characteristically starts 2 to 4 weeks after in- fection with a triggering organism such as Campylobacter spp., nontyphoidal Salmonella spp., Shigella spp., and Yersinia spp. People who express HLA B27 are at increased risk of developing reactive arthritis. Most people make a full recovery and can resume normal activities a few months after the initial presentation, although their symptoms may last up to a year. Between 15 and 50% of patients experience symptoms again after the initial flare has abated and it is postulated that these relapses occur as a result of reinfection. Septic arthritis is a rare complication of infection with Salmonella spp. that usually affects the large joints. The onset of septic arthritis typically occurs 2 to 7 weeks after acute gastroenteritis in 0.2 to 2.5% of patients with nontyphoidal Salmonella spp. Prevention Important and effective ways of preventing gastrointestinal infec- tion are sanitation, hygiene, vaccination, prevention of secondary spread, and ensuring food safety. Sanitation Separating sewage from drinking water to maintain a safe supply of drinking water is critical for good health and well-being, yet 1.1 billion people worldwide still defecate in the open. Open defeca- tion happens most often in low-income countries where childhood mortality from diarrhoeal disease is very high. Added to this, an estimated 90% of wastewater in developing countries is discharged either untreated or partially treated. The WHO has declared that eliminating open defecation by increasing levels of access to ad- equate sanitation would reduce cases of diarrhoea in children under the age of 5 years by a third. Hygiene Where access to a safe supply of potable water has been secured, the next similarly effective measure in reducing the spread of diarrhoeal disease is washing hands with soap and water. There is good evi- dence from randomized controlled trials and from a Cochrane sys- tematic review that washing hands properly reduces the incidence of diarrhoea by around a third. What is much less clear is how to help people to maintain good hand washing habits lifelong.

section 15 Gastroenterological disorders 3022 In healthcare settings in high-income countries, alcohol-based hand gels have been introduced to help reduce the incidence of healthcare-associated infections such as meticillin-resistant S. aureus. However, these gels are ineffective against norovirus, Cryptosporidium spp., and C. difficile so that, for preventing the spread of gastrointestinal infection, washing hands with soap and water still remains the best advice. Vaccination There are relatively few vaccines directed towards gastrointestinal pathogens. Typhoid There are two widely used typhoid vaccines. The Ty21a vaccine is a live, orally administered vaccine, a three-dose schedule of which prevents 35 to 58% of cases of typhoid fever in the first 2 years after vaccination. The Vi capsular polysaccharide vaccine, which is sub- unit vaccine administered by a single injection, prevents around 69% of cases in the first year after administration. A new conjugate form of the Vi capsular polysaccharide vaccine, called Vi-rEPA, ap- pears to have similar or even superior efficacy and might induce longer-term immunity. Cholera

There are two types of oral cholera vaccine, both preventing over 50% of cholera cases for up to 2 years in vaccinated endemic popula- tions. The monovalent vaccine is based on formalin and heat-killed whole cells of V. cholerae serogroup O1 (classical and El Tor, Inaba, and Ogawa strains) coupled with a recombinant cholera toxin B subunit. Since cholera toxin B resembles the heat-labile toxin of ETEC functionally and structurally, and the two toxins cross-react, Dukoral also helps to prevent ETEC infection. The bivalent cholera vaccine provides protection against V. cholerae serogroups O1 and O139 but does not prevent infection with ETEC since it does not contain the cholera toxin B subunit. Rotavirus Mass vaccination with rotavirus vaccine has been hugely successful in countries around the globe following its implementation in na- tional vaccination programmes. There are two live, attenuated rota- virus vaccines that can be administered orally, and they are highly effective (>85%) at preventing severe rotavirus gastroenteritis in children under 2 years of age in high-income countries. In low- income countries, vaccine efficacy in children under 2 years is lower (>40%). Nevertheless, because the overall burden of rotavirus dis- ease is much higher in low-income countries, the absolute benefit of vaccination is actually greater than in high-income countries. Hepatitis A There are three highly effective vaccines that can be used to prevent hepatitis A infections. Indications for vaccination include inter- national travel to an endemic country and occupational exposure to hepatitis A. Vaccination of food-producing animals As well as vaccinating the population there are examples of vaccinating food-producing animals that yield benefits for public health. A potent illustration of this occurred in the United Kingdom. Following a prolonged epidemic of nontyphoidal Salmonella spp. due to S. Enteritidis phage type 4, which was linked to the consump- tion of contaminated, undercooked poultry and hens' eggs, a vac- cine was developed and administered to broiler-breeder and laying poultry flocks. It has produced a dramatic and sustained reduction in nontyphoidal Salmonella spp. in people in the United Kingdom. Preventing secondary spread Many public health departments produce guidelines for reducing the secondary spread of gastrointestinal infections. There are spe- cial considerations for people working in the food and hospitality industries (food handlers), healthcare workers, children aged less than 5 years, and people who find it difficult to practise good hy- giene. Stipulations may include exclusion from nursery, school, or work until symptom free for at least 48 h when, in general, the risk of onward transmission lessens. Depending on the causative organism and the occupation, some groups may also need to provide consecu- tive negative stool samples before they can return to work. Various pathogens or clinical syndromes, like food poisoning, are statutorily notifiable. This means that the clinician who suspects that a patient is suffering a notifiable disease is obliged, by law, to report it to the competent public health authority. The purpose of notifi- cation is to allow public health agencies to investigate and control the spread of infection. For example, a single case of botulism con- stitutes both a medical and public health emergency. Swift action is required to trace a contaminated food and prevent anyone else from eating it. If a diagnosis of food-borne botulism is suspected it is imperative that public health authorities trace people who might have shared the same meal as the index case as quickly as possible to ascertain their welfare. The list of notifiable diseases can vary by country so clinicians should familiarize themselves with the locally relevant list and make sure that they comply with the law on notification. Food safety Delivering a safe and secure supply of food is very important for good health and well-being. This means either keeping patho- gens out of food, or controlling their growth, right along the chain from 'farm to fork'. Food safety is everybody's responsibility from primary production, through processing and retail, to the com- mercial or domestic kitchen. Safe handling of food in the kitchen is often summarized as the so-called four Cs. These are adequate Cooking; proper Cleaning of food preparation utensils, surfaces and hands;

correct use of Cooling (refrigeration); and avoiding Cross- contamination (i.e. transferring pathogens from raw to cooked or ready-to-eat foods). Intestinal botulism can be avoided by not giving honey to children less than 1 year of age and by washing fruit and vegetables with pot- able water before feeding them to infants. Uncertainty, controversy,
and future developments Uncertainty There are a great many organisms that are shed in faeces but, given the current state of knowledge, their relevance as causes of human illness is still doubtful.

15.18 Gastrointestinal infections 3023 Several viruses falling into this category of doubtful pathogenicity include aichi virus, bocavirus, cardiovirus, cosavirus, klassevirus, picobirnavirus, and torovirus. Controversy More than half of all antibiotics used worldwide are delivered to live- stock to treat or prevent infections and as growth promoters, hence a very real threat to human health arises from antimicrobial resistant organisms that are transmitted through the food chain. Indeed, it has been suggested that over 1500 deaths each year in the European Union are directly associated with antibiotic use in poultry. The emergence of colistin resistance in E. coli in China, thought to be associated with intensive pig production, is very bad news in- deed. This is the antibiotic of last resort for treatment of severe in- fections in humans. Even worse is the news that colistin resistance is plasmid mediated. This mechanism has previously spread resistance determinants around the globe very rapidly. There is every reason to think that this will also happen with colistin resistance. The burden of antimicrobial resistance in animals is compounded by the fact that only around 50% of the antibiotics prescribed in hu- mans are for bacterial infections. They are used too frequently for patients who turn out to have viral or parasitic infections against which they are ineffective. There is good evidence that antimicrobial resistance can be curtailed or even reversed. In Australia, where the use of fluoro quinolones was banned in animal husbandry, resistance in food- borne pathogens and in people is very low. Similarly, in northern Europe there have been steep and swift drops in the levels of resistant bacteria in livestock in countries where antibiotic use in animal husbandry has been reduced. Ever since the 1960s, medical and veterinary practitioners have argued about who is to blame for antimicrobial resistant infections in humans. In the absence of new classes of antimicrobials (and even if they are developed), the only solution to this apocalyptic threat is responsible prescribing by both professions. Future developments Nonculture diagnostics, next-generation sequencing,
and metagenomics New methods for diagnosing and characterizing microorganisms are set to revolutionize our understanding of gastrointestinal in- fections. These methods are sensitive, quick, can detect multiple pathogens at once and, increasingly, can be performed at the point of care. The challenge will be to interpret the results in a situation when mixed infections may appear to occur much more often. In conjunction with metagenomics our understanding of the com- plex interplay between pathogens and the microbiome should increase, hence it is likely that these technological advances will unlock much more information about the ecology of the gut in health and disease. Vaccines in development There are several vaccine candidates against pathogens that cause acute gastroenteritis, including norovirus, Campylobacter jejuni, EHEC, ETEC, nontyphoidal Salmonella spp., and Shigella spp. Some of these are at a very early stage of development and it remains to be seen whether or not they make it all the way to market.
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