56 - 173 Cholera and Other Vibrioses

173 Cholera and Other Vibrioses

Treatment for shigellosis must be adapted to the clinical context, with the recognition that the most fragile patients are children <5 years, who represent two-thirds of all cases worldwide and are the group most at risk of severe complications. There are few data on the use of quinolones in children, but Shigella dysentery is an accepted indication. The half-life of ciprofloxacin is longer in infants than in older individuals. The ciprofloxacin dose gener ally recommended for children is 30 mg/kg per day in two divided doses. Adults living in areas with high standards of hygiene are likely to develop milder, shorter-duration disease, whereas infants in endemic areas can develop severe, sometimes fatal, dysentery. In the former setting, treatment will remain minimal and bacteriologic proof of infection will often come after symptoms have resolved; in the latter setting, antibiotic treatment and more aggressive mea sures, possibly including resuscitation, are often required. REHYDRATION AND NUTRITION Shigella infection rarely causes significant dehydration, particularly in industrialized countries. It is recommended that rehydration should be oral unless the patient is comatose or in shock. Because of the improved effectiveness of reduced-osmolarity oral rehydration solutions, WHO and UNICEF now recommend a standard solu tion of 245 mOsm/L (sodium, 75 mmol/L; chloride, 65 mmol/L; glucose [anhydrous], 75 mmol/L; potassium, 20 mmol/L; citrate, 10 mmol/L). In shigellosis, the coupled transport of sodium and glucose may be variably affected, but oral rehydration therapy remains the easiest and most efficient form of rehydration, espe cially in severe cases. Nutrition should be started as soon as possible, keeping in mind that in developing countries, malnutrition remains the primary indicator of the risk of diarrhea-related death. Early refeeding is safe, well tolerated, and clinically beneficial. Because breast-feeding reduces diarrheal losses and the need for oral rehydration in infants, it should be maintained in the absence of contraindications (e.g., maternal HIV infection). NONSPECIFIC, SYMPTOM-BASED THERAPY Antimotility agents have been implicated in prolonged fever in volunteers with shigellosis. These agents are suspected of increasing the risk of toxic megacolon and are thought to have been respon sible for HUS in children infected by EHEC strains. For safety reasons, it is better to avoid antimotility agents in bloody diarrhea. TREATMENT OF COMPLICATIONS There is no consensus regarding the best treatment for toxic mega colon. The patient should be assessed frequently by both medical and surgical teams. Anemia, dehydration, and electrolyte deficits (particularly hypokalemia) may aggravate colonic atony and should be actively treated. Nasogastric aspiration helps to deflate the colon. Parenteral nutrition has not been proven to be beneficial. Fever persisting beyond 48–72 h raises the possibility of local perforation or abscess. Most studies recommend colectomy if, after 48–72 h, colonic distention persists. However, some physicians

recommend continuation of medical therapy for up to 7 days if the patient seems to be improving clinically despite persistent megacolon without perforation. Intestinal perforation, either isolated or complicating toxic megacolon, requires surgical treatment and intensive medical support. Rectal prolapse must be treated as soon as possible. With the health care provider using surgical gloves or a soft warm wet cloth and the patient in the knee-chest position, the prolapsed rectum is gently pushed back into place. If edema of the rectal mucosa is evident, making reduction difficult, it can be osmotically reduced by application of gauze impregnated with a warm solution of satu rated magnesium sulfate. Rectal prolapse often relapses but usually resolves along with the resolution of dysentery. HUS must be treated by water restriction, including discontinu ation of oral rehydration solutions and potassium-rich nutrition. Hemofiltration or peritoneal dialysis is often required.

■ ■PREVENTION Hand washing after defecation or handling of children’s feces and before handling of food is recommended. Stool decontamination (e.g., with sodium hypochlorite), together with a cleaning protocol for medi cal staff as well as for patients, has proven useful in limiting the spread of infection during Shigella outbreaks. Ideally, patients should have a negative stool culture before their infection is considered cured. Recur rences are rare if therapeutic and preventive measures are correctly implemented. Protection against fly intrusion in commonly infested sites such as kitchens and latrines is strongly advised in endemic areas.

Although several live attenuated oral and subunit parenteral vaccine candidates have been produced and are undergoing clinical trials, no vaccine against shigellosis is currently available. Especially given the rapid progression of antibiotic resistance in Shigella and its increasing recognition as a cause of child stunting, a vaccine is urgently needed. Most recent evidence indicates that synthetic polysaccharide conjugate vaccines (based on chemically synthesized, concatenated lipopolysac charide O-side chain mimics) elicit high levels of protective IgG anti bodies, hence promising protection. Protection would be particularly important for children <3 years, the population most susceptible to severe forms of shigellosis. ■ ■FURTHER READING Arena ET et al: Bioimage analysis of Shigella infection reveals targeting of colonic crypts. Proc Natl Acad Sci USA 112:E3282, 2015. Bennish ML, Wojtyniak BJ: Mortality due to shigellosis: Community and hospital data. Rev Infect Dis 13(Suppl 4):S245, 1991. Cohen D et al: Safety and immunogenicity of a synthetic carbohydrate CHAPTER 173 conjugate vaccine against Shigella flexneri 2a in healthy adult volun teers: A phase 1, dose-escalating, single-blind, randomised, placebocontrolled study. Lancet Infect Dis 21:546, 2021. Cossart P, Sansonetti PJ: Bacterial invasion: The paradigms of enteroinvasive pathogens. Science 304:242, 2004. Kotloff KL et al: The incidence, aetiology, and adverse clinical conse Cholera and Other Vibrioses quences of less severe diarrhoeal episodes among infants and children residing in low-income and middle-income countries: A 12-month case-control study as a follow-on to the Global Enteric Multicenter Study (GEMS). Lancet Glob Health 7:E568, 2019. Mani S et al: Status of vaccine research and development for Shigella. Vaccine 34:2887, 2016. Niyogi SK: Shigellosis. J Microbiol 43:133, 2005. Phalipon A, Sansonetti PJ: Shigella’s ways of manipulating the host intestinal innate and adaptive immune system: A tool box for sur vival? Immunol Cell Biol 85:119, 2007. Traa BS et al: Antibiotics for the treatment of dysentery in children. Int J Epidemiol 39:i70, 2010. World Health Organization: Guidelines for the control of shigel losis, including epidemics due to Shigella dysenteriae type 1. WHO Library Cataloguing-in-Publication Data. www.who.int/cholera/ publications/shigellosis/en/. Matthew K. Waldor, Edward T. Ryan

Cholera and Other

Vibrioses Members of the genus Vibrio cause several important infectious syndromes. Classic among them is cholera, a devastating diarrheal disease caused by Vibrio cholerae that has been responsible for seven global pandemics and much suffering over the past two centuries. Epidemic cholera remains a significant public-health concern in the

developing world today. Other vibrioses caused by other Vibrio spe cies include syndromes of diarrhea, soft tissue infection, or primary sepsis. All Vibrio species are highly motile, facultatively anaerobic, curved, gram-negative rods with one or more flagella. In nature, vib rios most commonly reside in tidal rivers and bays under conditions of moderate salinity. They proliferate in the summer months when water temperatures exceed 20°C, and the illnesses they cause also increase in frequency during the warm months.

CHOLERA ■ ■DEFINITION Cholera is an acute diarrheal disease that can, in a matter of hours, result in profound, rapidly progressive dehydration and death. Accord ingly, cholera gravis (the severe form) is a much-feared disease, par ticularly in its epidemic presentation. Fortunately, prompt aggressive fluid repletion and supportive care can obviate the high mortality that is historically associated with cholera. Although the term cholera has occasionally been applied to any severely dehydrating secretory diar rheal illness, whether infectious in etiology or not, it now refers to dis ease caused by V. cholerae serogroup O1 or O139—i.e., the serogroups with epidemic potential. ■ ■MICROBIOLOGY AND EPIDEMIOLOGY The species V. cholerae is classified into >200 serogroups based on the carbohydrate constituents of their lipopolysaccharide (LPS) O anti gens. Although some non-O1 V. cholerae serogroups (strains that do not agglutinate in antisera to the O1 group antigen) have occasionally caused sporadic outbreaks of diarrhea, serogroup O1 was, until the emergence of serogroup O139 in 1992 (see below), the exclusive cause of epidemic cholera. The O1 serogroup is further subdivided into two serotypes, termed Inaba and Ogawa. Two biotypes of V. cholerae O1, classic and El Tor, have been described, but the former is thought to be extinct. PART 5 Infectious Diseases Yearly incidence rate per 100.000 inhabitants, 2020–2022 0–0.1 No reported case 0,1–1 1–10 10–100 100–1000 FIGURE 173-1 World distribution of cholera in 2020–2022. WHO, World Health Organization. (Reproduced with permission from Dr. M. Piarroux, Université de la Méditerranée, France.)

The natural habitat of V. cholerae is coastal salt water and brack ish estuaries, where the organism lives in close relation to plankton. V. cholerae can also exist in freshwater in the presence of adequate nutrients and warmth. Humans become infected incidentally but, once infected, can act as vehicles for spread. Ingestion of water contaminated by human feces is thought to be the most common means of acquisi tion of V. cholerae. However, consumption of contaminated food and human-to-human transmission also contribute to spread. There is no known animal reservoir. Although the infectious dose is relatively high, it is markedly reduced in hypochlorhydric persons, in those using antacids, and when gastric acidity is buffered by a meal. Cholera is predominantly a pediatric disease in endemic areas, but it affects adults and children equally when newly introduced into a population. In endemic areas, the burden of disease is often greatest during “cholera seasons” associated with high temperatures, heavy rainfall, and flood ing, but cholera can occur year-round. Cholera is native to the Ganges delta on the Indian subcontinent. Since 1817, seven global pandemics have occurred. The current (seventh) pandemic—the first due to the El Tor

biotype—began in Indonesia in 1961 and spread in serial waves throughout Asia as V. cholerae El Tor displaced the endemic classic biotype, which is thought to have caused the previous six pandemics. In the early 1970s, El Tor cholera erupted in Africa, causing major epidemics before becoming a persistent endemic problem. Currently, >95% of cholera cases reported annually to the World Health Organization (WHO) are from Africa and Asia (Fig. 173-1), but the true burden and distribution of cholera are unknown because the diagnosis is often syndromic and many countries with endemic cholera do not report cholera to the WHO. In 2022 and 2023, large outbreaks involving more than 10,000 cases per country were being reported every few weeks to the World Health Organization. It is possible that >1–4 million cases of cholera occur yearly (of which only ~400,000 are reported to the WHO) and that these cases result in >20,000–140,000 deaths annually (of which <2000 are reported to the WHO). Imported cases only

After a century without cholera in Latin America, the current cholera pandemic reached Central and South America in 1991. Fol lowing an initial explosive spread that affected millions, the burden of disease has markedly decreased in Latin America. In 2010, a severe cholera outbreak began in Haiti, a country with no recorded history of this disease. Several lines of evidence indicate that cholera was likely introduced into Haiti by United Nations security forces from Asia, raising the possibility that asymptomatic carriers of V. cholerae play an important role in transmitting cholera over long distances. In 2016, an outbreak of cholera began in Yemen in the setting of a civil war and population displacement and the breakdown of health infrastructure. The recent history of cholera has been punctuated by such severe outbreaks, especially among impoverished or displaced persons. These outbreaks are often precipitated by war or other circumstances that lead to the breakdown of public-health measures. Such was the case in the camps for Rwandan refugees set up in 1994 around Goma, Zaire; in 2008–2009 in Zimbabwe; in 2015 in South Sudan and the Democratic Republic of the Congo; and in 2022 in Lebanon and the Syrian Arab Republic. Sporadic endemic infections due to V. cholerae O1 strains related to the seventh-pandemic strain have been recognized along the U.S. Gulf Coast of Louisiana and Texas. These infections are typically associated with the consumption of contaminated, locally harvested shellfish. Occasionally, cases in U.S. locations remote from the Gulf Coast have been linked to shipped-in Gulf Coast seafood. In October 1992, a large-scale outbreak of clinical cholera caused by a new serogroup, O139, occurred in southeastern India. The organ ism appears to be a derivative of El Tor O1 but has a distinct LPS and an immunologically related O-antigen polysaccharide capsule. (O1 organisms are not encapsulated.) After an initial spread across 11 Asian countries, V. cholerae O139 has once again been almost entirely replaced by O1 strains. The clinical manifestations of disease caused by V. cholerae O139 are indistinguishable from those of O1 cholera. Immunity to one, however, is not protective against the other. ■ ■PATHOGENESIS In the final analysis, cholera is a toxin-mediated disease. The watery diarrhea characteristic of cholera is due to the action of cholera toxin, a potent protein enterotoxin elaborated by the organism in the small intestine. The toxin-coregulated pilus (TCP), so named because its synthesis is regulated in parallel with that of cholera toxin, is essential for V. cholerae to survive and multiply in (colonize) the small intestine. Production of cholera toxin, TCP, and several other virulence factors are coordinately regulated by ToxR. This protein modulates the expres sion of genes coding for virulence factors in response to environmental signals via a cascade of regulatory proteins. Additional regulatory processes, including bacterial responses to the density of the bacterial population (in a phenomenon known as quorum sensing), modulate the virulence of V. cholerae. Once established in the human small bowel, the organism produces cholera toxin, which consists of a monomeric enzymatic moiety (the

A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to GM1 ganglioside, a glycolipid on the surface of epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit (A1) irreversibly transfers ADP-ribose from nicotinamide adenine dinucleotide to its specific target protein, the GTP-binding regulatory component of adenylate cyclase. The ADP-ribosylated G protein upregulates the activity of adenylate cyclase; the result is the intracellular accumulation of high levels of cyclic adenosine mono phosphate (AMP). In intestinal epithelial cells, cyclic AMP inhibits the absorptive sodium-transport system in villus cells and activates the secretory chloride-transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Because water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate)

follow. Although perturbation of the adenylate cyclase pathway is the primary mechanism by which cholera toxin causes excess fluid secre tion, cholera toxin also enhances intestinal secretion via prostaglandins and/or neural histamine receptors.

The V. cholerae genome is composed of two circular chromo somes. Lateral gene transfer has played a key role in the evolution of epidemic V. cholerae. The genes encoding cholera toxin (ctxAB) are part of the genome of a bacteriophage, CTXΦ. The recep tor for this phage on the V. cholerae surface is the intestinal coloniza tion factor TCP. Because ctxAB is part of a mobile genetic element (CTXΦ), horizontal transfer of this bacteriophage may account for the emergence of new toxigenic V. cholerae strains. Many of the other genes important for V. cholerae pathogenicity, including the genes encoding the biosynthesis of TCP, accessory colonization factors, and virulence regulators, are clustered together in the V. cholerae pathogenicity island. Similar clustering of virulence genes is found in other bacterial pathogens. It is believed that pathogenicity islands are acquired by horizontal gene transfer. V. cholerae O139 is probably derived from an El Tor O1 strain that acquired the genes for O139 O-antigen synthesis by horizontal gene transfer. ■ ■CLINICAL MANIFESTATIONS Individuals infected with V. cholerae O1 or O139 exhibit a range of clinical manifestations. Some individuals are asymptomatic or have only mild diarrhea; others present with the sudden onset of explosive and life-threatening diarrhea (cholera gravis). The reasons for the range in signs and symptoms of disease are incompletely understood but include the level of preexisting immunity, blood type (persons with type O blood are at greatest risk of severe disease if infected, whereas those with type AB are at least risk), and nutritional status. In a nonimmune individual, after a 24- to 48-h incubation period, chol era characteristically begins with the sudden onset of painless watery diarrhea that may quickly become voluminous. Patients often vomit. In severe cases, volume loss can exceed 250 mL/kg in the first 24 h. If fluids and electrolytes are not replaced, hypovolemic shock and death may ensue. Fever is usually absent. Muscle cramps due to electrolyte disturbances are common. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat fishy, inoffensive odor. It has been called “rice-water” stool because of its resemblance to the water in which rice has been washed (Fig. 173-2). Clinical symptoms parallel volume contraction: CHAPTER 173 Cholera and Other Vibrioses FIGURE 173-2 Rice-water cholera stool. Note floating mucus and gray watery appearance. (Courtesy of Dr. A. S. G. Faruque, International Centre for Diarrhoeal Disease Research, Dhaka; with permission.)

at losses of <5% of normal body weight, thirst develops; at 5–10%, pos tural hypotension, weakness, tachycardia, and decreased skin turgor are documented; and at >10%, oliguria, weak or absent pulses, sunken eyes (and, in infants, sunken fontanelles), wrinkled (“washerwoman”) skin, somnolence, and coma are characteristic. Complications derive exclusively from the effects of volume and electrolyte depletion and include renal failure due to acute tubular necrosis. Thus, if the patient is adequately treated with fluid and electrolytes, complications are averted and the process is self-limited, resolving in a few days.

Laboratory data usually reveal an elevated hematocrit (due to hemo concentration) in nonanemic patients; mild neutrophilic leukocytosis; elevated levels of blood urea nitrogen and creatinine consistent with prerenal azotemia; normal sodium, potassium, and chloride levels; a markedly reduced bicarbonate level (<15 mmol/L); and an elevated anion gap (due to increases in serum lactate, protein, and phosphate). Arterial pH is usually low (~7.2). ■ ■DIAGNOSIS Cholera should be suspected when a patient ≥5 years of age develops acute watery diarrhea in an area known to have cholera or develops severe dehydration or dies from acute watery diarrhea, even in an area where cholera is not known to be present. The clinical suspicion of cholera can be confirmed by the identification of V. cholerae in stool; however, the organism must be specifically sought. With experience, it can be detected directly by dark-field microscopy on a wet mount of fresh stool, and its serotype can be discerned by immobilization with specific antisera. Laboratory isolation of the organism requires the use of a selective medium such as taurocholate–tellurite–gelatin (TTG) agar or thiosulfate–citrate–bile salts–sucrose (TCBS) agar. If a delay in sample processing is expected, Cary-Blair transport medium and/ or alkaline-peptone water-enrichment medium may be used as well. In endemic areas, there is little need for biochemical confirmation and characterization, although these tasks may be worthwhile in places where V. cholerae is an uncommon isolate. Standard microbiologic bio chemical testing for Enterobacteriaceae will suffice for identification of V. cholerae. All vibrios are oxidase-positive. Point-of-care antigendetection cholera dipstick assays are commercially available for use in the field or where laboratory facilities are lacking. PART 5 Infectious Diseases TREATMENT Cholera Death from cholera is due to hypovolemic shock; thus, treat ment of individuals with cholera first and foremost requires fluid resuscitation and management. In light of the level of dehydration (Table 173-1) and the patient’s age and weight, euvolemia should first be rapidly restored, and adequate hydration should then be maintained to replace ongoing fluid losses (Table 173-2). Admin istration of oral rehydration solution (ORS) takes advantage of the hexose-Na+ co-transport mechanism to move Na+ across the gut mucosa together with an actively transported molecule such as glu cose (or galactose); Cl– and water follow. This transport mechanism remains intact even when cholera toxin is active. ORS may be made by adding safe water to prepackaged sachets containing salts and sugar or by adding 0.5 teaspoon (i.e., half a small spoonful) of table TABLE 173-1 Assessing the Degree of Dehydration in Patients with Cholera DEGREE OF DEHYDRATION CLINICAL FINDINGS None or mild, but diarrhea Thirst in some cases; <5% loss of total body weight Moderate Thirst, postural hypotension, weakness, tachycardia, decreased skin turgor, dry mouth/ tongue, no tears; 5–10% loss of total body weight Severe Unconsciousness, lethargy, or “floppiness”; weak or absent pulse; inability to drink; sunken eyes (and, in infants, sunken fontanelles); >10% loss of total body weight

TABLE 173-2 Treatment of Cholera, Based on Degree of Dehydrationa DEGREE OF DEHYDRATION, PATIENT’S AGE (WEIGHT) TREATMENTb None or Mild, but Diarrheac <2 years 1/4–1/2 cup (50–100 mL) of ORS, to a maximum of 0.5 L/d 2–9 years 1/2–1 cup (100–200 mL) of ORS, to a maximum of 1

L/d ≥10 years As much ORS as desired, to a maximum of 2 L/d Moderatec,d <4 months (<5 kg) 200–400 mL of ORS 4–11 months (5–<8 kg) 400–600 mL of ORS 12–23 months (8–<11 kg) 600–800 mL of ORS 2–4 years (11–<16 kg) 800–1200 mL of ORS 5–14 years (16–<30 kg) 1200–2200 mL of ORS ≥15 years (≥30 kg) 2200–4000 mL of ORS Severec All ages and weights Undertake IV fluid replacement with Ringer's lactate (or, if not available, normal saline). Give 100 mL/kg in the first 3-h period (or the first 6-h period for children <12 months old); start rapidly, then slow down. Give a total of 200 mL/kg in the first 24 h. Continue until the patient is awake, can ingest ORS, and no longer has a weak pulse. aAdapted from World Health Organization: Outbreak Response Field Manual, Global Task on Cholera Control; https://www.gtfcc.org/wp-content/uploads/2020/05/gtfccholera-outbreak-response-field-manual-2024.pdf. bContinue normal feeding during treatment. cReassess regularly; monitor stool and vomit output. dVolumes of ORS listed should be given within the first 4 h. Abbreviation: ORS, oral rehydration solution. salt and 6 level teaspoons (i.e., 6 small spoonfuls) of table sugar to 1 L of safe water. Potassium intake in bananas or green coconut water should be encouraged. A number of ORS formulations are available, and the WHO now recommends "low-osmolarity" ORS for treatment of individuals with dehydrating diarrhea of any cause (Table 173-3). If available, rice-based ORS is considered superior to standard ORS in the treatment of cholera. ORS can be administered via a nasogastric tube to individuals who cannot ingest fluid; how ever, optimal management of individuals with severe dehydration includes the administration of IV fluid and electrolytes. Because profound acidosis (pH <7.2) is common in this group, Ringer's lac tate is the best choice among commercial products (Table 173-4); it must be used with additional potassium supplements, prefer ably given by mouth. The total fluid deficit in severely dehydrated patients (>10% of body weight) can be replaced safely within the first 3–4 h of therapy, half within the first hour. Transient muscle cramps and tetany are common. Thereafter, oral therapy can usually TABLE 173-3 Composition of World Health Organization ReducedOsmolarity Oral Rehydration Solution (ORS)a,b CONSTITUENT CONCENTRATION, mmol/L Na+

K+

Cl–

Citratec

Glucose

Total osmolarity

aContains (per package, to be added to 1 L of drinking water): NaCl, 2.6 g; $Na_3C_6H_5O_7 \cdot 2H_2O$, 2.9 g; KCl, 1.5 g; and glucose (anhydrous), 13.5 g. bIf prepackaged ORS is unavailable, a simple homemade alternative can be prepared by combining 3.5 g (~1/2 teaspoon) of NaCl with either 50 g of precooked rice cereal or 6 teaspoons of table sugar (sucrose) in 1 L of drinking water. In that case, potassium must be supplied separately (e.g., in orange juice or coconut water). c10 mmol of citrate per liter, which supplies 30 mmol of HCO_3/L.

TABLE 173-4 Electrolyte Composition of Cholera Stool and of Intravenous Rehydration Solution CONCENTRATION, mmol/L SUBSTANCE NA+ K+ CL– BASE Stool Adult

Child

Ringer’s lactate

4a

aPotassium supplements, preferably administered by mouth, are required to replace the usual potassium losses from stool. be initiated, with the goal of maintaining fluid intake equal to fluid output. However, patients with continued large-volume diarrhea may require prolonged IV treatment to match gastrointestinal fluid losses. Severe hypokalemia can develop but will respond to potas sium given either IV or orally. In the absence of adequate staff to monitor the patient’s progress, the oral route of rehydration and potassium replacement is safer than the IV route. Although not necessary for cure, the use of an antibiotic to which the organism is susceptible diminishes the duration and volume of fluid loss and hastens clearance of the organism from the stool. Adjunctive antibiotics should therefore be administered to patients with moderate or severe dehydration due to cholera. In many areas, macrolides such as erythromycin (adults, 250 mg orally four times a day for 3 days; children, 12.5 mg/kg per dose four times a day for 3 days) or azithromycin (adults, a single 1-g dose; children, a single 20-mg/kg dose) are the agents of choice. Increasing resistance to tetracyclines is widespread; however, in areas with confirmed susceptibility, tetracycline (nonpregnant adults, 500 mg orally four times a day for 3 days; children >8 years old, 12.5 mg/kg per dose four times a day for 3 days) or doxycycline (nonpregnant adults, a 300-mg single dose; children >8 years old, a single dose of 4–6 mg/ kg) may be used. Similarly, increasing resistance to fluoroquino lones is being reported, but in areas with confirmed susceptibil ity, a fluoroquinolone such as ciprofloxacin may be used (adults, 500 mg twice a day for 3 days; children, 15 mg/kg twice a day for 3 days). Oral administration of supplemental zinc is associated with decreased volume and severity of diarrhea in young children, including in those with cholera. Children <6 months of age with cholera should be treated with 10 mg of zinc daily for 10 days; chil dren from 6 to <60 months of age should be treated with 20 mg of oral zinc daily for 10 days. ■ ■PREVENTION Provision of safe water and of facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household can significantly reduce the incidence of cholera. In addition, precautions should be taken to prevent the spread of cholera via infected and potentially asymptomatic persons from endemic to nonendemic regions of the world (as was probably the case in the out break in Haiti; see “Microbiology and Epidemiology,” above). Much effort has been devoted to the development of an effective cholera vaccine over the past few decades, with a particular focus on oral vaccine strains. In an attempt to maximize mucosal responses, two types of oral cholera vaccine have been developed: oral killed vac cines and live attenuated vaccines. Currently, three oral killed cholera vaccines have been prequalified by the WHO. BivWC (ShancholTM; Shantha Biotechnics, Hyderabad, India) contains both biotypes and serotypes of V. cholerae O1 and V. cholerae O139 without supplemen tal cholera toxin B subunit, but its manufacture is being terminated. A related vaccine is produced in South Korea (EuvicholTM, EuvicholPlusTM; Eubiologics, Seoul) and currently accounts for the vast majority of cholera vaccine available to global health control programs. WC-rBS (Dukoral®; Valneva, Sweden AB, Stockholm,) contains both biotypes and serotypes of V. cholerae O1 supplemented with 1 mg of recombi nant cholera toxin B subunit per dose. The vaccines are administered

as a two- or three-dose regimen, with doses usually separated by 14 days. They provide ~60–85% protection for the first few months. Booster immunizations of WC-rBS are recommended after 2 years for individuals ≥6 years of age and after 6 months for children 2–5 years of age. For BivWC, no formal recommendation regarding booster immu nizations exists. However, BivWC was associated with ~60% protection over 5 years among recipients of all ages in a study in Kolkata, India; the rate of protection among children ≤5 years of age approximated 40%. In outbreak situations, even a single dose of BivWC can provide some protection: 40% and 63% adjusted protection for 6 months for all and severely dehydrating cholera, respectively—although there was no evidence of protection in children younger than 5 years of age. Models predict significant herd immunity when vaccination coverage rates exceed 50%. The killed vaccines have been safely administered among populations with high rates of HIV infection.

Oral live attenuated vaccines for V. cholerae O1 also are in develop ment. These strains have in common their lack of the genes encod ing cholera toxin. One such vaccine, CVD 103-HgR (VaxchoraTM; Emergent BioSolutions, Washington, DC), is derived from a classic strain of V. cholerae and has been approved by the U.S. Food and Drug Administration for use in travelers to cholera-endemic regions but is not prequalified by the WHO. The vaccine was 90% and 80% efficacious against severe cholera after experimental infection of North American volunteers 10 days and 90 days after vaccination, respectively. Vaxchora is approved for use in individuals 2–64 years of age; no recommendations concerning the timing or need for booster vaccinations are currently available. Other live attenuated vaccine can didate strains have been prepared from El Tor and O139 V. cholerae and have been tested in studies of volunteers. An advantage of live attenuated cholera vaccines is that they may induce more potent pro tection after a single oral dose. Conjugate and subunit cholera vaccines also are being developed. CHAPTER 173 Recognizing that it may be decades before safe water and adequate sanitation become a reality for those most at risk of cholera, the WHO has recommended incorporation of cholera vaccination into compre hensive control strategies and has established an international stockpile of oral killed cholera vaccine to assist in outbreak responses. A global strategy on cholera control was launched in 2017 with the WHO hosting the secretariat of the Global Task Force on Cholera Control (GTFCC). This country-by-country approach aims to reduce cholera deaths by 90% and to eliminate cholera in as many as 20 countries by 2030. Integral components of this strategy are advancing water, sanita tion, and hygiene (WASH) programs, as well as use of cholera vaccine. From 2016 to 2023, almost 300 million doses of cholera vaccine have been requested from the Global Vaccine Stockpile, and approximately 150 million doses have been shipped to requesting countries for use in control programs. Due to vaccine shortages, cholera vaccines have most recently been almost solely used in reactive and not preventative campaigns, and are often given as single doses. Cholera and Other Vibrioses OTHER VIBRIO SPECIES The genus Vibrio includes several human pathogens that do not cause cholera. Abundant in coastal waters throughout the world, noncholera vibrios can reach high concentrations in the tissues of filter-feeding mollusks. As a result, human infection commonly follows the inges tion of seawater or of raw or undercooked shellfish (Table 173-5). Most noncholera vibrios can be cultured on blood or MacConkey agar, which contains enough salt to support the growth of these halophilic species. In the microbiology laboratory, the species of noncholera vibrios are distinguished by standard biochemical tests. The most important of these organisms are Vibrio parahaemolyticus and Vibrio vulnificus. Vibriosis causes an estimated 80,000 illnesses and 100 deaths in the United States every year. The two major types of syndromes for which these noncholera vib rios are responsible are gastrointestinal illness (due to V. parahaemo

lyticus, non-O1/O139 V. cholerae, V. mimicus, V. fluvialis, V. hollisae, and

V. furnissii) and soft tissue infections (due to V. vulnificus, V. alginolyticus, and V. damselae). V. vulnificus is also a cause of primary sepsis in some immunocompromised individuals.

TABLE 173-5 Features of Selected Noncholera Vibrioses ORGANISM VEHICLE OR ACTIVITY HOST AT RISK SYNDROME Vibrio parahaemolyticus Shellfish, seawater Normal Gastroenteritis Seawater Normal Wound infection Non-O1/O139 Vibrio cholerae Shellfish, travel Normal Gastroenteritis Seawater Normal Wound infection, otitis media Vibrio vulnificus Shellfish Immunosuppresseda Sepsis, secondary cellulitis Seawater Normal, immunosuppresseda Wound infection, cellulitis Vibrio alginolyticus Seawater Normal Wound infection, cellulitis, otitis Seawater Burned, other immunosuppressed Sepsis aEspecially with liver disease or hemochromatosis. Source: Table 161-3 in Harrison's Principles of Internal Medicine, 14th edition. ■ ■SPECIES ASSOCIATED PRIMARILY WITH GASTROINTESTINAL ILLNESS V. parahaemolyticus Widespread in marine environments, the halophilic V. parahaemolyticus is the leading seafood-borne bacterial cause of enteritis worldwide. This species was originally implicated in enteritis in Japan in 1953, accounting for 24% of reported cases in one study—a rate that presumably was due to the common practice of eating raw seafood in that country. In the United States, commonsource outbreaks of diarrhea caused by this organism have been linked to the consumption of undercooked or improperly handled seafood or of other foods contaminated by seawater. Since the mid-1990s, the incidence of V. parahaemolyticus infections has increased in several countries, including the United States. Serotypes O3:K6, O4:K68, and O1:K-untypable, which are genetically related to one another, account in part for this increase. Recent reports from China and Thailand suggest that serotype O10:K4 may be an emerging serotype. The enteropathogenicity of V. parahaemolyticus is associated with its abil ity to cause hemolysis via a thermostable direct hemolysin (Vp-TDH). Although the mechanisms by which the organism causes diarrhea are not fully defined, most V. parahaemolyticus genomes encode two type III secretion systems, which directly inject toxic bacterial proteins into host cells. The activity of one of these secretion systems is required for intestinal colonization and virulence in animal models. V. parahaemo lyticus should be considered a possible etiologic agent in all cases of diarrhea that can be linked epidemiologically to seafood consumption or to the sea itself. The incidence of V. parahaemolyticus infection in the United States has increased from 0.06 per 100,000 persons in 1996 to 0.9 cases per 100,000 in 2019. PART 5 Infectious Diseases Infections with V. parahaemolyticus can result in two distinct gas trointestinal presentations. The more common of the two presenta tions (including nearly all cases in North America) is characterized by watery diarrhea, usually occurring in conjunction with abdominal cramps, nausea, and vomiting and accompanied in ~25% of cases by fever and chills. After an incubation period of 4 h to 4 days, symptoms develop and persist for a median of 3 days. Dysentery, the less common presentation, is characterized by severe abdominal cramps, nausea, vomiting, and bloody or mucoid stools. V. parahaemolyticus also causes rare cases of wound infection and otitis and very rare cases of sepsis. Most cases of V. parahaemolyticus–associated gastrointestinal ill ness, regardless of the presentation, are self-limited. Fluid replacement should be stressed. Antimicrobial agents may be of benefit in moderate or severe disease. Doxycycline, fluoroquinolones, macrolides, or thirdgeneration cephalosporins are usually used. Deaths are extremely rare among immunocompetent individuals. Severe infections are associated with underlying diseases, including diabetes, preexisting liver disease, iron-overload states, or immunosuppression. Non-O1/O139 (Noncholera) V. cholerae The heterogeneous non-O1/O139 V. cholerae organisms cannot be

distinguished from V. cholerae O1 or O139 by routine biochemical tests but do not agglu tinate in O1 or O139 antiserum. Non-O1/O139 strains have caused several well-studied food-borne outbreaks of gastroenteritis and have also been responsible for sporadic cases of otitis media, wound

infection, and bacteremia. Generally, non-O1/O139 V. cholerae strains do not produce cholera toxin and do not cause large epidemics of diar rheal disease. Like other vibrios, non-O1/O139 V. cholerae organisms are widely distributed in marine environments. In most instances, recognized cases in the United States have been associated with the consumption of raw oysters or with recent travel. The broad clinical spectrum of diarrheal illness caused by these organisms is probably due to the group's heterogeneous virulence attributes. The typical incubation period for gastroenteritis due to these organ isms is <2 days, and the illness lasts for ~2–7 days. Patients' stools may be copious and watery or may be partly formed, less voluminous, and bloody or mucoid. Diarrhea can result in severe dehydration. Many cases include abdominal cramps, nausea, vomiting, and fever. Like those with cholera, patients who are seriously dehydrated should receive oral or IV fluids; the value of antibiotics is not clear. Extraintestinal infections due to non-O1/O139 V. cholerae com monly follow occupational or recreational exposure to seawater. Around 10% of non-O1/O139 V. cholerae isolates come from cases of wound infection, 10% from cases of otitis media, 20% from cases of bacteremia (which is particularly likely to develop in patients with liver disease), and approximately 40% from stool. Extraintestinal infec tions should be treated with antibiotics. Information to guide antibiotic selection and dosing is limited, but most strains are sensitive in vitro to tetracycline, ciprofloxacin, and third-generation cephalosporins. ■ ■SPECIES ASSOCIATED PRIMARILY WITH SOFT TISSUE INFECTION OR BACTEREMIA (See also Chap. 134) V. vulnificus Infection with V. vulnificus is rare, but this organism is the most common cause of severe Vibrio infections in the United States. Like most vibrios, V. vulnificus proliferates in the warm summer months and requires a saline environment for growth. In the United States, infections in humans typically occur in coastal states between May and October and most commonly affect men >40 years of age. V. vulnifi cus has been linked to two distinct syndromes: primary sepsis, which usually occurs in patients with underlying liver disease, and primary wound infection, which generally affects people without underlying disease. (Vulnificus is Latin for "wound maker.") Some authors have suggested that V. vulnificus also causes gastroenteritis independent of other clinical manifestations. V. vulnificus is endowed with a number of virulence attributes, including a capsule that confers resistance to phagocytosis and to the bactericidal activity of human serum as well as a cytolysin. Measured as the 50% lethal dose in mice, the organism's virulence is considerably increased under conditions of iron overload; this observation is consistent with the propensity of V. vulnificus to infect patients who have hemochromatosis. Primary sepsis most often develops in patients who have cirrho sis or hemochromatosis. However, V. vulnificus bacteremia can also affect individuals who have hematopoietic disorders or chronic renal insufficiency, those who are using immunosuppressive medications or alcohol, or (in rare instances) those who have no known underly ing disease. After a median incubation period of 16 h, the patient develops malaise, chills, fever, and prostration. One-third of patients

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