Bacterial Enteric Infections

Updated: April 12, 2022
Reviewed: January 10, 2024

Epidemiology

Rates of Gram-negative bacterial enteric infections are at least 10 times higher among adults with HIV than in the general population, but these rates decline among people with HIV when treated with antiretroviral therapy (ART).[1-7] The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count[5] and is greatest in individuals with clinical AIDS or CD4 counts <200 cells/mm^3. The bacteria most frequently isolated by culture from adults with HIV in the United States are *Salmonella* (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter*. Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,[8] but their role is understood poorly because diagnosis remains a research-only test. *Clostridioides difficile*–associated infection (CDI) is common in people with HIV; data[9] suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to traditional risk factors, such as exposure to a health care facility or to antibiotics. Incidence of community-onset CDI is increasing, and health care providers also should consider CDI in the evaluation of outpatient diarrheal illnesses in people with HIV. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in people with HIV. Other enteric infections that may cause diarrhea—such as *Mycobacterium avium* complex (MAC) and cytomegalovirus—are discussed elsewhere in these guidelines.

As with bacterial enteric infections in HIV-uninfected persons, the probable source for most bacterial enteric infections in people with HIV is ingestion of contaminated food or water.[3] Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*[10] and *Campylobacter*.[11] HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase the risk of enteric bacterial infections.

Clinical Manifestations

Three major clinical syndromes of infection are associated with Gram-negative enteric bacteria among people with HIV:

- Self-limited gastroenteritis;
- Severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; and
- Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness.[12-15]

Severe community-associated diarrhea often is defined as six or more loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of systemic illness, such as fecal blood, orthostatic hypotension, or fever. In people with HIV, the risk of more profound illness increases with the degree of immunosuppression.[1,3,4,16] Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in people with HIV.[17-19]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (i.e., ingestion of contaminated food or water, sexual history or other fecal-oral exposures, pet exposures, travel-related exposures, exposure to antibiotics or chemotherapies, use of acid-suppressing medications, recent hospitalization); a medication review, because diarrhea is a common side effect of some ART and antibiotics; quantification of the diarrheal illness by stool frequency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever. Physical examination should include measurement of temperature and assessment of intravascular volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood or stool molecular methods (i.e., culture-independent diagnostic tests [CIDTs]). Although stool molecular methods rapidly diagnose enteric infections, stool cultures are required to obtain phenotypic antibiotic sensitivity testing for isolated enteric pathogens. Thus, the Centers for Disease Control and Prevention recommends reflex stool cultures and antibiotic sensitivity testing for specimens with positive CIDT reports given increasing resistance detected in enteric bacterial infections.[20] Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in people with HIV—particularly those with advanced disease—blood cultures should be obtained from any patient who has diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

Other infections for which people with HIV are at risk, albeit at a lower rate, are non-*jejuni*, non-*coli Campylobacter* species—such as *C. fetus, C. upsaliensis*, and *C. lari*—and the enterohepatic *Helicobacter* spp. (*H. cineadi* and *H. fennelliae)*, which were described originally as *Campylobacter* spp. Blood culture systems typically will grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

The diagnosis of CDI can be made only through careful selection of the correct population for testing and a correlation of clinical and laboratory findings. Patient populations at risk for *C. difficile* diarrhea include patients who recently received or currently are receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 weeks (or currently are hospitalized), those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medications, and those with moderate-to-severe community-acquired diarrhea.[21] Only patients with diarrhea (defined as three or more loose stools in 24 hours) should be tested for *C. difficile* to limit detection of asymptomatic colonization, and only stool samples that take the shape of the container (i.e., diarrheal) should be tested for *C. difficile* toxin B. Detection of either the *C. difficile* toxin B gene (using nucleic acid amplification testing [NAAT]) or the *C. difficile* toxin B protein (using an enzyme immunoassay [EIA]) is required for diagnosis. EIAs suffer from low sensitivity, whereas polymerase chain reaction (PCR) assays have high sensitivity and can detect asymptomatic carriers. Glutamate dehydrogenase (GDH) antigen enzyme immunoassays, which detect an antigen common to *C. difficile* strains, whether or not toxigenic, must be combined with a second confirmatory test for stool *C. difficile* toxin B.[22] Based on the criteria above (i.e., patient meets the definition of diarrhea and the stool sample is diarrhea, taking the shape of the container), Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for *C. difficile* infection support using an NAAT alone or a multiple-step algorithm (e.g., GDH plus toxin B assay) versus an EIA alone for *C. difficile* testing.[23]

Endoscopy generally should be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin B assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails. Endoscopy with biopsy may be required for diagnosing etiologies other than bacterial enteric infections—including cryptosporidiosis, microsporidiosis, cytomegalovirus, or MAC gastroenteritis—and noninfectious causes of GI symptoms.

Clinicians should remain alert to the possibility of sexually transmitted infections (STIs). Some sexually transmitted rectal infections (e.g., proctitis due to lymphogranuloma venereum, *Neisseria gonorrhoeae*, or *Treponema pallidum*) can produce symptoms similar to colitis due to *Salmonella*, *Shigella*, and *Campylobacter* spp. infection. If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, diagnostic evaluation for STIs with anoscopy, culture, and biopsy and NAATs should be considered.

Preventing Exposure

Multiple epidemiologic exposures can place people at risk of enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures. Providing advice and education about such exposures is the responsibility of the health care provider. The clinical condition and CD4 count of a person with HIV can help the provider determine what prevention recommendations are most appropriate. People with HIV with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[24] are at the greatest risk of enteric illnesses[5]; however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Individuals should be advised to wash their hands regularly with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII).** To prevent enteric infections, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are active only partially against norovirus and *Cryptosporidium* **(AIII).** People with HIV should be advised to wash their hands after potential contact with human feces (e.g., through defecation, cleaning feces from infants, contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, before preparing food and eating, and before and after sex **(AIII).** People with HIV should avoid unprotected sex practices—such as anal sex and oral-anal contact—that could result in oral exposure to feces and, in addition to handwashing, they should be advised to use barriers—such as dental dams—during sex to reduce exposures when possible **(AIII).** Avoiding sex while any partner has diarrhea may further reduce risk of transmission.

Preventing Disease

Antimicrobial prophylaxis to prevent bacterial enteric illness **is not routinely recommended,** including for travelers **(AIII).** Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase the risk of CDI. In rare cases, however, antimicrobial prophylaxis with rifaximin, azithromycin, or fluoroquinolones can be considered—such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII).**[25] Because of toxicities associated with fluoroquinolone use (e.g., *C. difficile* infection, tendinitis) and the risk for antibiotic resistance, use of fluoroquinolones for prophylaxis is discouraged.

For people with HIV already taking trimethoprim-sulfamethoxazole (TMP-SMX) (e.g., for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against traveler's diarrhea **(BIII).** For pregnant people, azithromycin would be the preferred agent for prophylaxis **(BIII).** Risk of toxicity should be considered before prophylaxis with TMP-SMX is

initiated solely because of travel. Clinicians should be aware of new concerns about fluoroquinolone safety.[26]

Treating Disease

Empiric Therapy

In most situations, treatment of diarrheal disease in people with HIV does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status. Patients should be informed of the importance of maintaining hydration and be given oral or intravenous (IV) rehydration, if indicated **(AIII).** Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates are likely to be useful **(BIII).** The effectiveness and safety of probiotics or antimotility agents have not been studied adequately in people with HIV who have diarrheal illnesses.[27] Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists **(BIII).**

After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depend on the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. For example, in patients with CD4 counts >500 cells/mm^3 who have had 1 day to 2 days of loose stools without fever or blood, no further work-up and no treatment other than oral rehydration may be required. However, a short course of antibiotics (e.g., ciprofloxacin 5 days, **[BIII]**) may be indicated in people with HIV and CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with advanced HIV disease (i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., six or more liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. Empiric therapy with ciprofloxacin is acceptable, particularly if the infection is not associated with international travel **(AIII).** In patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease, hospitalization and treatment with IV antibiotic therapy should be considered. In this scenario, IV ceftriaxone or IV cefotaxime are alternative antibiotic therapies **(BIII).**

Therapy should be adjusted based on the results of the diagnostic work-up. For diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity—such as bloody stool or dehydration—antibiotic therapy can be withheld and directed therapy initiated once a diagnosis is confirmed. Noninfectious etiologies of persistent diarrhea (e.g., inflammatory bowel disease) also can be considered in the differential diagnosis.

Diarrhea is one of the most common illnesses affecting international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is an important public health problem. For example, traveler's diarrhea caused by fluoroquinolone-resistant *C. jejuni* in South and Southeast Asia or Africa is common.[28,29] Clinicians should consider the possibility of a resistant infection when prescribing empiric therapy for travelers with HIV who experience diarrhea or a syndrome consistent with a systemic infection while traveling or upon returning to the United States, given reports of multidrug-resistant *Enterobacteriaceae* acquisition during travel.[30-34]

Pathogen-Specific Therapy

Salmonella spp.

Immunocompetent hosts who do not have HIV often do not require treatment for *Salmonella* gastroenteritis (typically caused by nontyphoidal *Salmonella* spp.), because the condition is usually self-limited, and treatment may prolong the carrier state. In contrast, all people with HIV and salmonellosis should be treated **(AIII),** even though no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20 to 100 times and mortality as much as 7 times compared to people who do not have HIV.[1,35]

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone **(AIII).** Ciprofloxacin is the preferred agent[36] **(AIII).** Other fluoroquinolones—such as levofloxacin and moxifloxacin—likely would be effective in treating salmonellosis in people with HIV, but they have not been well evaluated in clinical studies **(BIII).** Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins, such as ceftriaxone or cefotaxime **(BIII).**

The optimal duration of therapy for HIV-related *Salmonella* infection has not been defined. For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable. For the same patients with bacteremia, 14 days is appropriate provided clearance of bacteremia is documented. Longer treatment is suggested if bacteremia persists or if the infection is complicated; that is, if metastatic foci are present **(BIII).** For patients with advanced HIV disease (CD4 count <200 cells/mm^3), 2 to 6 weeks of antibiotics is often recommended **(CIII).**[37]

People with HIV and *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment **(BIII).** Recurrence may present as bacteremia or as an anatomically localized infection, including intra-abdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci. Secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII),** and it also might be considered for patients with recurrent gastroenteritis (with or without bacteremia), and in those with CD4 counts <200 cells/mm^3 with severe diarrhea **(BIII).** The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness,[38] and HIV suppression with ART appears to decrease the risk of recurrent illnesses.[39]

In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis probably can be discontinued **(CII).**[7] Clinicians also should be aware that recurrence may indicate development of antimicrobial resistance during therapy.

Shigella spp.

Therapy for *Shigella* infections should be considered because it may slightly shorten the duration of illness and help prevent transmission to others **(AIII);** however, because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission, antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 whose diarrhea resolves before culture confirmation of *Shigella* infection. When treatment is offered, antibiotic selection should be guided by the results of antibiotic susceptibility testing.[36]

The recommended treatment for shigellosis is a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days **(AIII)** with levofloxacin or moxifloxacin serving as alternatives **(BIII).** Although current Clinical and Laboratory Standards Institute criteria categorize *Shigella* isolates with ciprofloxacin minimum inhibitory concentration (MIC) 0.12 to 1 ug/mL as fluoroquinolone susceptible, these isolates may harbor plasmid-mediated resistance genes. Until the clinical significance of these findings can be determined, fluoroquinolones should be used to treat only isolates with MIC <0.12 ug/mL.[40]

Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* have been reported in the United States and are associated with international travel, homelessness, and men who have sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[34] Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) **(BIII).** Azithromycin has not been evaluated in people with HIV and shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[40]

Azithromycin susceptibility testing, however, is not widely available in clinical laboratories but can be performed by many state public health laboratories. An estimated 36% of *Shigella* spp. isolated among the general U.S. population in 2018 was resistant to azithromycin, and azithromycin-resistant *Shigella* spp. infections in MSM with HIV have been reported recently.[41-44] Treatment for patients with *Shigella* bacteremia is less well defined, but extending treatment to at least 14 days is reasonable **(BIII).** Azithromycin **is not recommended** for treatment of *Shigella* spp. bacteremia **(AIII).** Chronic suppressive or maintenance therapy **is not recommended** for first-time *Shigella* infections **(BIII).** Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm^3, in which case, extending antimicrobial therapy for up to 6 weeks is reasonable **(BIII).** As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter spp.

The optimal treatment of campylobacteriosis in people with HIV is defined poorly. Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII).** Rates of resistance to antimicrobial agents differ by *Campylobacter* species. In the United States in 2018, 29% of *C. jejuni* isolates were resistant to ciprofloxacin, and 2% were resistant to azithromycin; among *C. coli* isolates, 40.5% of isolates were resistant to fluoroquinolones, and 13.3% were resistant to azithromycin.[44]

For patients with mild disease and CD4 counts >200 cells/mm^3, some clinicians opt to withhold therapy unless symptoms persist for more than several days **(CIII).** For mild-to-moderate campylobacteriosis, initiating therapy with azithromycin for 5 days or a fluoroquinolone—such as ciprofloxacin—for 7 to 10 days (if the organism is sensitive) is a reasonable approach **(BIII).** Azithromycin has not been evaluated in people with HIV and campylobacteriosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[28] Azithromycin susceptibility testing, however, is not widely available in clinical laboratories but can be performed by many state public health laboratories. *Campylobacter* bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive **(BIII).** Azithromycin **is not recommended** for treatment of *Campylobacter* bacteremia **(AIII).** Adding a second active agent—such as an aminoglycoside—may be prudent in these patients to limit the emergence of antibiotic resistance **(BIII).** Antibiotic choice should be guided by antibiotic susceptibility tests. Chronic suppressive or maintenance therapy **is not recommended** for first-time *Campylobacter* infections in people with HIV **(BIII).** However, recurrent infections can occur, particularly in patients with CD4 counts <200 cells/mm^3. In recurrent

disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII).** As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.

Clostridioides difficile

No randomized controlled trials have been conducted for CDI therapy in people with HIV. Available data suggest that people with HIV respond to treatment of CDI similarly to people without HIV. Thus, treatment of CDI in people with HIV is the same as in people without HIV. Guidelines and subsequent updates for treatment of CDI have been published[23,45] and should be consulted for further information.

Treatment of an Initial Episode of CDI

Four randomized clinical trials all conducted in the general population (two identical studies with ~60% hospitalized patients; two studies restricted to hospitalized patients)[46-49] have revealed that, when compared to oral vancomycin, fidaxomicin increased the likelihood of a sustained clinical response of CDI (at 28 days) in the initial therapy of CDI (relative risk [RR] 1.16; 95% confidence interval [CI], 1.09–1.24).[45] Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events and all-cause mortality. Given these data, the 2021 IDSA CDI guidelines update[45] for adults suggests treatment with fidaxomicin **(AI),** rather than oral vancomycin, for initial CDI (see the table below) whether CDI is severe or nonsevere. Fidaxomicin remains very expensive but should be considered in people with HIV and CDI, if available. Oral vancomycin is also an acceptable option for initial CDI **(AI).** Earlier multicenter, randomized, double-blind studies identified that oral vancomycin is superior to metronidazole for treatment of CDI.[50,51] Thus, metronidazole is to be considered as an alternative drug for CDI therapy only if access to either fidaxomicin or vancomycin is limited (see the table below) and CDI is nonsevere (white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL) **(CI).**[23]

Treatment of Recurrent CDI

Treatment of recurrent CDI is complex and, in part, defined by the specific circumstances of the patient with recurrent CDI and the number of prior CDI episodes. Brief guidance is provided here; the 2017 and 2021 IDSA CDI guidelines should be consulted for a full discussion of this topic.[23,45] Risk factors for CDI recurrence are age ≥65 years, history of CDI, compromised immunity, severe CDI, and certain virulent strains (ribotypes 027/078/244). Similar to an initial episode of CDI and also based on the randomized clinical trials cited above,[46-49] the 2021 IDSA CDI guidelines update[45] suggests treatment of adults with recurrent CDI with fidaxomicin **(AI),** rather than oral vancomycin (see the table below). Fidaxomicin therapy increased the likelihood of a sustained clinical response for recurrent CDI at 30 days (RR 1.27; 95% CI, 1.05–1.54). For treatment of an initial CDI episode, fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events, and all-cause mortality. Vancomycin is also an acceptable option for recurrent CDI **(AI).**

Bezlotoxumab (FDA approved in 2016) is a humanized monoclonal antibody against *C. difficile* toxin B approved for prevention of recurrent CDI in high-risk adults when used in conjunction with standard-of-care (SOC) antibiotic therapy. The 2021 IDSA CDI guidelines update suggests use of bezlotoxumab as a co-intervention along with vancomycin as the SOC antibiotic in patients with a history of CDI in the last 6 months and/or other risk factors for recurrence **(CI).**[45] However, data on the benefit of bezlotoxumab therapy when fidaxomicin is used as the SOC antibiotic are limited **(CIII).** Limited case reports suggest that fecal microbiota therapy (FMT) (i.e., fecal transplant) may be successful and safe to treat recurrent CDI in people with HIV **(CIII).**[52] However, it is important to

note that complications of FMT, including transmission of enteric pathogens and antibiotic-resistant bacteria with deaths, have been reported.[53] FMT for treatment of recurrent CDI may be considered after three total CDI episodes (initial and two recurrent CDI episodes) **(CIII).**[23,45] The effect of ART on recurrence of CDI is unknown but, similar to other enteric infections, ART initiation should follow standard guidelines (see the Special Considerations with Regard to Starting ART section below).

Special Considerations with Regard to Starting ART

ART initiation should follow standard guidelines. The presence of an enteric infection should not delay ART initiation **(BIII).** The presence of a diarrheal illness is relevant only in terms of a patient's ability to ingest and absorb ART. If recurrent enteric infections are documented or *Salmonella* bacteremia occurs, prompt initiation of ART should be considered regardless of CD4 count.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored closely for response to treatment, defined clinically by improvement in systemic signs and symptoms, resolution of diarrhea, and sterilization of infected tissues or body fluids, such as blood. Follow-up stool testing may be required when public health considerations and state policies dictate the need to ensure microbiologic cure, such as in health care or food service workers. Follow-up stool culture and antibiotic susceptibility testing should be considered for patients with incomplete clinical response to appropriate antimicrobial therapy. In patients with persistent or recurrent diarrhea despite therapy, clinicians should consider other enteric infections in the context of the patient's immune status and exposures, as well as the possibility of *C. difficile* or the development of antimicrobial resistance.

Observational studies suggest that plasma drug concentrations in people with HIV may be decreased as a result of diarrhea or malabsorption.[54] Coadministration of fluoroquinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these agents interfere with fluoroquinolone absorption. Although larger prospective studies are needed to determine the impact of severe diarrhea on antibiotic absorption, it is prudent to use IV antibiotics in clinically unstable patients **(AIII).**

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with treatment for bacterial enteric pathogens.

Preventing Recurrence

The pharmacologic approach to recurrent enteric infections is covered in the section on directed therapy for each bacterial species. As noted above, secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and, in some circumstances, for those with recurrent shigellosis **(BIII)** or campylobacteriosis **(BIII).**

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infection in pregnant people with HIV is the same as in people who are not pregnant and should be managed the same, with several considerations. Based on their safety profile, expanded-spectrum cephalosporins or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing **(BIII).**[55] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating

quinolone use in pregnant people did not find an increased risk of birth defects or musculoskeletal abnormalities.[56-58] Thus, quinolones can be used for bacterial enteric infections in pregnant people with HIV if indicated by susceptibility testing or failure of first-line therapy, as listed above **(BIII).** TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII).**[59-61] However, a recent review of potential risks related to TMP-SMX use cites the low quality of current data and supports the use of TMP-SMX in pregnant people with HIV as clinically indicated.[62] Neonatal care providers should be informed if maternal sulfa therapy was used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus in the newborn. Because oral rifaximin and fidaxomicin are not absorbed systemically, these can be used in pregnancy as in nonpregnant individuals. Limited data are available on the risks of vancomycin use during pregnancy; however, minimal absorption is expected with oral therapy. Although vancomycin for enteric disease is recommended for use only in its oral formulation, which is not absorbed in meaningful concentrations from the gastrointestinal tract,[63] it should be noted that with intravenous use, vancomycin readily crosses the placenta.[64] A study of 10 infants evaluated after the second or third trimester for *in utero* exposure of maternal intravenous vancomycin therapy for serious staphylococcal infections found no hearing loss or renal toxicity attributed to vancomycin.[64] A recent review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.[65] Studies on the use of metronidazole for CDI in pregnancy were not found.

Recommendations for Preventing and Treating Bacterial Enteric Infections
Preventing Bacterial Enteric Illness
• Antimicrobial prophylaxis to prevent bacterial enteric illness is not routinely recommended, including for travelers (AIII). • In rare cases—such as for immunosuppressed travelers (depending on their level of immunosuppression, the region of travel, and the trip's duration)—antimicrobial prophylaxis with rifaximin, azithromycin, or fluoroquinolones can be considered (CIII). Because of toxicity associated with fluoroquinolone use (e.g., bacterial resistance, CDI, tendinitis), use of fluoroquinolones for prophylaxis is discouraged. • For patients already on TMP-SMX for prophylaxis against *Pneumocystis* pneumonia, TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to rifaximin, azithromycin, or fluoroquinolones (BIII). • For pregnant people, azithromycin is the preferred agent for prophylaxis (BIII).
General Considerations When Managing Patients with Bacterial Enteric Infections
• Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea (AIII). • Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists (BIII). • Diagnostic fecal specimens should be obtained before initiation of empiric antimicrobial therapy. • If a pathogen is identified in stool, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance. Reflexively culturing the stool of patients diagnosed using PCR-based methods will facilitate antibiotic susceptibility testing among these patients. • Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/mm^3. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response occurs after 3 to 4 days of therapy, consider follow-up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug–drug interactions. • Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Empiric Treatment of Bacterial Enteric Infections (Pending Diagnostic Studies and Antimicrobial Resistance Testing)
For people with HIV and CD4 count 200–500 cells/mm^3, with diarrhea severe enough to compromise quality of life or ability to work *Preferred Therapy* • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (BIII) *For people with advanced HIV (CD4 count <200 cells/mm^3 or concomitant AIDS-defining illnesses) and clinically severe diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills)* *Preferred Therapy* • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (AIII) *Alternative Therapy* • Ceftriaxone IV 1 g every 24 hours (BIII), or • Cefotaxime IV 1 g every 8 hours (BIII) Note: Therapy and its duration should be adjusted depending on stool microbiology results and antibiotic sensitivity testing. See recommendations for specific bacteria below. If no pathogen is identified and the patient recovers quickly, 5 days of therapy is reasonable. IV antibiotic therapy with hospitalization should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease. For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed. Diarrhea is a common illness of international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is common. Clinicians should consider the possibility of resistant infections when prescribing empiric antibiotic therapy for travelers with HIV while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia or Africa.
Treating Nontyphoidal Salmonellosis
All people with HIV and salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20- to 100-fold) and mortality (by as much as 7-fold) compared with people without HIV (AIII). *Preferred Therapy for Salmonella Gastroenteritis with or Without Bacteremia* • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (AIII) *Alternative Therapy* • Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), or • Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII) Alternatives to fluoroquinolone may include one of the following: • Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) every 12 hours (BIII), or • Ceftriaxone IV 1 g every 24 hours (BIII), or • Cefotaxime IV 1 g every 8 hours (BIII)

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count >200 cells/mm^3: 7–14 days (BIII)
- If CD4 count <200 cells/mm^3, particularly if the primary illness was severe: 2–6 weeks (BIII)

Duration of Therapy for Gastroenteritis with Bacteremia

- If CD4 count >200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present) (BIII)
- If CD4 count <200 cells/mm^3: 2–6 weeks (BIII)

Secondary Prophylaxis

The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure (BIII). Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.

HIV suppression with ART is expected to decrease the risk of recurrent illnesses.

Clinicians should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Some experts recommend secondary prophylaxis for the following:

- Patients with recurrent bacteremia, or
- Patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 and severe diarrhea (BIII)

When to Stop Secondary Prophylaxis

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3 (CII)

Treating Shigellosis

Therapy should be considered because it may slightly shorten the duration of illness and help prevent spread of the infection to others (AIII); however, antibiotic selection should be guided by the results of antibiotic susceptibility testing. Because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission, antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 whose diarrhea resolves before culture confirmation of *Shigella* infection (CIII).

Preferred Therapy

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours if MIC <0.12 ug/mL (see Note) (AIII)

Alternative Therapy (Depending on Susceptibility Results)

- Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), or
- Moxifloxacin (PO or IV) 400 mg every 24 hours (BIII), or
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours (BIII), or
- Azithromycin 500 mg PO daily for 5 days (BIII) (Note: azithromycin is not recommended for *Shigella* bacteremia [AIII])

Duration of Therapy

- Gastroenteritis: 7–10 days (AIII) (except azithromycin, treat for 5 days)
- Bacteremia: ≥14 days (BIII)
- Recurrent infections: up to 6 weeks (BIII)

Chronic Maintenance or Suppressive Therapy

- Not recommended for first-time *Shigella* infections (BIII)

Note: Increased resistance of *Shigella* to fluoroquinolones is occurring globally and in the United States. Avoid treating *Shigella* with fluoroquinolones if ciprofloxacin MIC is ≥0.12 ug/mL even if the laboratory identifies the isolate as sensitive. Many *Shigella* strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of *Shigella* isolates from individuals with HIV should be performed routinely. Azithromycin susceptibility testing is not widely available in clinical laboratories but can be performed by many state public health laboratories.

Treating Campylobacteriosis

- Optimal treatment is defined poorly.
- The rate of fluoroquinolone resistance in the United States is increasing (28.5% resistance in 2018 among *C. jejuni* isolates).
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease if CD4 Count >200 cells/mm^3

- If diarrhea resolves before culture confirmation of *Campylobacter* infection, antibiotic treatment can be withheld (CIII). If symptoms persist, consider antibiotic therapy (CIII).

Mild to Moderate Disease

Preferred Therapy

- Azithromycin 500 mg PO daily for 5 days (BIII) (Not recommended for bacteremia [AIII]), or
- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (BIII) (if susceptible)

Alternative Therapy (Depending on Susceptibility Results)

- Levofloxacin 750 mg PO or IV every 24 hours (BIII), or
- Moxifloxacin 400 mg PO or IV every 24 hours (BIII)

Bacteremia

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (BIII) plus an aminoglycoside (BIII) in bacteremic patients to limit the emergence of antibiotic resistance

Duration of Therapy

- Gastroenteritis: 7–10 days, except for azithromycin, which is 5 days (BIII)
- Bacteremia: ≥14 days (BIII)
- Recurrent disease: 2–6 weeks (BIII)

Chronic Maintenance or Suppressive Therapy

- Not recommended for first-time *Campylobacter* infections (BIII)

Treating *Clostridioides difficile*–associated Infection (CDI)

Preferred Therapy (Severe or Nonsevere CDI)*

- Fidaxomicin 200 mg (PO) 2 times per day for 10 days (AI)
- Vancomycin 125 mg (PO) 4 times per day for 10 days (AI)
- For severe, life-threatening CDI, see text and references for additional information.

*Alternative Therapy for Nonsevere CDI**

- If fidaxomicin or vancomycin access is limited and if CDI is nonsevere, outpatient disease: metronidazole 500 mg PO 3 times per day for 10 days (CII).

Note: Based on clinical trials, vancomycin is superior to metronidazole for therapy of CDI (discussed in text).

Recurrent CDI

- Treatment is the same as in patients without HIV infection (see text and references). Use of bezlotoxumab (CIII) or FMT (CIII) may be successful and safe to treat recurrent CDI in people with HIV although recent concerns have been raised (discussed in text).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CDI = *Clostridioides difficile*–associated infection; FMT = fecal microbiota therapy; IV = intravenously; MIC = minimum inhibitory concentration; PCR = polymerase chain reaction; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

* Severe CDI: white blood cell count >15,000 cells/mL or serum creatinine concentrations >1.5 mg/dL; nonsevere CDI: white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

References

1. Celum CL, Chaisson RE, Rutherford GW, Barnhart JL, Echenberg DF. Incidence of salmonellosis in patients with AIDS. *J Infect Dis*. 1987;156(6):998-1002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3680999.

2. Sorvillo FJ, Lieb LE, Waterman SH. Incidence of campylobacteriosis among patients with AIDS in Los Angeles County. *J Acquir Immune Defic Syndr*. 1991;4(6):598-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2023099.

3. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21 Suppl 1:S84-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8547518.

4. Nelson MR, Shanson DC, Hawkins DA, Gazzard BG. Salmonella, Campylobacter and Shigella in HIV-seropositive patients. *AIDS*. 1992;6(12):1495-1498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1362879.

5. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. *Clin Infect Dis*. 2005;41(11):1621-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267735.

6. Wilcox CM, Saag MS. Gastrointestinal complications of HIV infection: changing priorities in the HAART era. *Gut*. 2008;57(6):861-870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18203808.

7. Hung CC, Hung MN, Hsueh PR, et al. Risk of recurrent nontyphoid Salmonella bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. *Clin Infect Dis*. 2007;45(5):e60-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17682981.

8. Huang DB, Mohanty A, DuPont HL, Okhuysen PC, Chiang T. A review of an emerging enteric pathogen: enteroaggregative Escherichia coli. *J Med Microbiol*. 2006;55(Pt 10):1303-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17005776.

9. Haines CF, Moore RD, Bartlett JG, et al. Clostridium difficile in a HIV-infected cohort: incidence, risk factors, and clinical outcomes. *AIDS*. 2013;27(17):2799-2807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23842125.

10. Aragon TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. *Clin Infect Dis*. 2007;44(3):327-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17205436.

11. Quinn TC, Goodell SE, Fennell C, et al. Infections with Campylobacter jejuni and Campylobacter-like organisms in homosexual men. *Ann Intern Med*. 1984;101(2):187-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6547580.

12. Snijders F, Kuijper EJ, de Wever B, van der Hoek L, Danner SA, Dankert J. Prevalence of Campylobacter-associated diarrhea among patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1997;24(6):1107-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9195065.

13. Tee W, Mijch A. Campylobacter jejuni bacteremia in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients: comparison of clinical features and review. *Clin Infect Dis*. 1998;26(1):91-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9455515.

14. Tee W, Mijch A, Wright E, Yung A. Emergence of multidrug resistance in Campylobacter jejuni isolates from three patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(3):634-638. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8527556.

15. Meier PA, Dooley DP, Jorgensen JH, Sanders CC, Huang WM, Patterson JE. Development of quinolone-resistant Campylobacter fetus bacteremia in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177(4):951-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9534967.

16. Casado JL, Valdezate S, Calderon C, et al. Zidovudine therapy protects against Salmonella bacteremia recurrence in human immunodeficiency virus-infected patients. *J Infect Dis*. 1999;179(6):1553-1556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10228081.

17. Kristjansson M, Viner B, Maslow JN. Polymicrobial and recurrent bacteremia with Shigella in a patient with AIDS. *Scand J Infect Dis*. 1994;26(4):411-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7984973.

18. Mayer KH, Hanson E. Recurrent salmonella infection with a single strain in the acquired immunodeficiency syndrome. confirmation by plasmid fingerprinting. *Diagn Microbiol Infect Dis*. 1986;4(1):71-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3510806.

19. Rubino S, Spanu L, Mannazzu M, et al. Molecular typing of non-typhoid Salmonella strains isolated from HIV-infected patients with recurrent salmonellosis. *AIDS*. 1999;13(1):137-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10207558.

20. Huang JY, Henao OL, Griffin PM, et al. Infection with Pathogens Transmitted Commonly Through Food and the Effect of Increasing Use of Culture-Independent Diagnostic Tests on Surveillance--Foodborne Diseases Active Surveillance Network, 10 U.S. Sites, 2012-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(14):368-371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27077946.

21. Pulvirenti JJ, Mehra T, Hafiz I, et al. Epidemiology and outcome of Clostridium difficile infection and diarrhea in HIV infected inpatients. *Diagn Microbiol Infect Dis*. 2002;44(4):325-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12543536.

22. Brecher SM, Novak-Weekley SM, Nagy E. Laboratory diagnosis of Clostridium difficile infections: there is light at the end of the colon. *Clin Infect Dis*. 2013;57(8):1175-1181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23788237.

23. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987-994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29562266.

24. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep*. 2008;57(RR-10):1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052530.

25. Advice for travelers. *Med Lett Drugs Ther*. 2019;61(1582):153-160. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31599872.

26. Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics.

27. Nwachukwu CE, Okebe JU. Antimotility agents for chronic diarrhoea in people with HIV/AIDS. *Cochrane Database Syst Rev*. 2008(4):CD005644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18843696.

28. Kuschner RA, Trofa AF, Thomas RJ, et al. Use of azithromycin for the treatment of Campylobacter enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis*. 1995;21(3):536-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8527539.

29. Tribble DR, Sanders JW, Pang LW, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis*. 2007;44(3):338-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17205438.

30. Lubbert C, Straube L, Stein C, et al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol*. 2015;305(1):148-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25547265.

31. Kantele A, Laaveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. *Clin Infect Dis*. 2015;60(6):837-846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25613287.

32. Johnning A, Kristiansson E, Angelin M, et al. Quinolone resistance mutations in the faecal microbiota of Swedish travellers to India. *BMC Microbiol*. 2015;15:235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26498929.

33. Barlow RS, Debess EE, Winthrop KL, Lapidus JA, Vega R, Cieslak PR. Travel-associated antimicrobial drug-resistant nontyphoidal Salmonellae, 2004-2009. *Emerg Infect Dis*. 2014;20(4):603-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24655581.

34. Centers for Disease Control and Prevention. Importation and Domestic Transmission of Shigella sonnei Resistant to Ciprofloxacin — United States, May 2014–February 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(12):318-320. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6412a2.htm?s_cid=mm6412a2_w.

35. Cummings PL, Sorvillo F, Kuo T. Salmonellosis-related mortality in the United States, 1990-2006. *Foodborne Pathog Dis*. 2010;7(11):1393-1399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20617938.

36. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. 2001;32(3):331-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11170940.

37. Gordon MA, Banda HT, Gondwe M, et al. Non-typhoidal salmonella bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. *AIDS*. 2002;16(12):1633-1641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12172085.

38. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(RR-17):1-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1361652.

39. Chou YJ, Lin HW, Yang CJ, et al. Risk of recurrent nontyphoid Salmonella bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy. *J Microbiol Immunol Infect*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26316009.

40. Centers for Disease Control and Prevention. CDC Recommendations for Diagnosing and Managing *Shigella* Strains with Possible Reduced Susceptibility to Ciprofloxacin. 2017. Available at: https://emergency.cdc.gov/han/han00401.asp.

41. Heiman KE, Karlsson M, Grass J, et al. Notes from the field: Shigella with decreased susceptibility to azithromycin among men who have sex with men - United States, 2002-2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(6):132-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24522098.

42. Hassing RJ, Melles DC, Goessens WH, Rijnders BJ. Case of Shigella flexneri infection with treatment failure due to azithromycin resistance in an HIV-positive patient. *Infection*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24488332.

43. Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. *Lancet Infect Dis*. 2015;15(8):913-921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25936611.

44. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System (NARMS) Now: Human Data. 2021. Available at: https://wwwn.cdc.gov/narmsnow/.

45. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. *Clin Infect Dis*. 2021;73(5):e1029-e1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34164674.

46. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21288078.

47. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22321770.

48. Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. 2018;18(3):296-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29273269.

49. Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in a randomized, double-blind, comparative Phase III study in Japan. *J Infect Chemother*. 2018;24(9):744-752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29934056.

50. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799326.

51. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17599306.

52. Di Bella S, Gouliouris T, Petrosillo N. Fecal microbiota transplantation (FMT) for Clostridium difficile infection: Focus on immunocompromised patients. *J Infect Chemother*. 2015;21(4):230-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25703532.

53. Food and Drug Administration. Fecal Microbiota for Transplantation: Safety Alert - Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms. 2020. Available at: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission.

54. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis*. 2004;38(2):280-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14699462.

55. Bérard A, Sheehy O, Zhao J, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiology and Drug Safety*. 2015;24(12):1241-1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26513406.

56. Padberg S, Wacker E, Meister R, et al. Observational cohort study of pregnancy outcome after first-trimester exposure to fluoroquinolones. *Antimicrob Agents Chemother*. 2014;58(8):4392-4398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24841264.

57. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69(2):83-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8902438.

58. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42(6):1336-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9624471.

59. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. 2001;15(6):637-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11738517.

60. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343(22):1608-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11096168.

61. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11384952.

62. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014;66(5):512-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24853309.

63. Rao S, Kupfer Y, Pagala M, Chapnick E, Tessler S. Systemic absorption of oral vancomycin in patients with Clostridium difficile infection. *Scand J Infect Dis*. 2011;43(5):386-388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21198337.

64. Bourget P, Fernandez H, Delouis C, Ribou F. Transplacental passage of vancomycin during the second trimester of pregnancy. *Obstet Gynecol*. 1991;78(5 Pt 2):908-911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1923224.

65. Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf*. 2015;10(2):170-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25986038.