Shigella infection: Epidemiology, microbiology, and pathogenesis

Author
Marcia B Goldberg, MD

Section Editors
Stephen B Calderwood, MD
Morven S Edwards, MD

Deputy Editor
Allyson Bloom, MD

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INTRODUCTION — Shigella species are a common cause of bacterial diarrhea worldwide, especially in developing countries. Shigella organisms can survive transit through the stomach since they are less susceptible to acid than other bacteria; for this reason, as few as 10 to 100 organisms can cause disease [1]. Ingested bacteria pass into the small intestine where they multiply; large numbers of bacteria then pass into the colon, where they enter the colonic cells. Given its relatively low infectious dose, Shigella transmission can occur via direct person-to-person spread, as well as via contaminated food and water. Humans are the only natural reservoir for disease.

The epidemiology, microbiology and pathogenesis of Shigella infections will be reviewed here. The clinical manifestations, diagnosis, and treatment are discussed separately. (See “Shigella infection: Clinical manifestations and diagnosis” and “Shigella infection: Treatment and prevention in adults”.)

EPIDEMIOLOGY — Bacterial dysentery due to Shigella species is a major cause of morbidity and mortality; 165 million cases occur annually worldwide, with 1 million associated deaths [2,3]. Shigella transmission can occur through direct person-to-person spread or from contaminated food and water. The minimal infectious dose can be transmitted directly from contaminated fingers, since intermediate bacterial replication is not required to achieve the low infectious dose.

In developed countries, most cases are transmitted by fecal-oral spread from people with symptomatic infection. Outbreaks in the United States occur predominantly in institutions such as day care centers or custodial institutions and less commonly by common source contamination of food or drinking water.

In developing countries, both fecal-oral spread and contamination of common food and water supplies are important mechanisms of transmission.

United States — In the United States, 450,000 cases are estimated to occur annually [4]. In 2008 the average incidence of confirmed shigellosis in the United States was 6.59 cases per 100,000 population; shigellosis was third in frequency after Salmonella and Campylobacter infection [5,6]. In the United States shigellosis predominantly affects children; in 2008 the incidence among children aged <4 years was 28 cases/100,000 population and the incidence among children aged 4 to 11 was 25.67 cases/100,000 population [5]. A review of FoodNet data for the period 2005 to 2006 estimates that 62,500 cases of Shigella diarrhea occur each year among children under the age of 5 years [7]. Experts estimate that the reported number of cases underestimates the true number of cases by 5- to 100-fold [7,8]. In the United States, Shigella cases occur most commonly June to October, with fewer cases occurring December to February [8].

Most cases of shigellosis in the United States are caused by Shigella sonnei (>75 percent), with Shigella flexneri the next most frequent isolate [9]. Shigella dysenteriae 1 (the Shiga bacillus) was the most common isolate both in Europe and the United States in the early 1900s but is now rare. In the United States, S. dysenteriae 1 infection is generally limited to imported cases from Mexico and Central America [10] or from laboratory contamination [11].

Transmission in institutions — Shigellosis in the United States is most common in day care centers and areas with crowded living conditions such as urban centers or residential institutions [12,13]. Day care center outbreaks can be particularly difficult to control; strict hand washing guidelines must be followed, and infected children must be excluded from the facility until they have recovered. Convalescing children should be cohorted in a separate room until stool cultures for Shigella are negative [14,15]. In addition, children who attend day care centers frequently introduce the infection to their families and serve as index cases in urban outbreaks [16]. The secondary attack rate for family members in the same household as the index case is 20 percent and is highest when the index case is between one and four years old [17].
Food borne transmission — Foodborne outbreaks are well described. Cold salads such as potato or macaroni salads have been implicated in several common source outbreaks of shigellosis [18]. In most cases, these foods were presumed to have been contaminated either by food preparers with recent illnesses or through substandard food preparation facilities [19,20]. Fecal contamination can occur during cultivation; raw vegetables including lettuce and tomatoes traced to a common supplier have also been implicated in outbreaks [21-23].

Sexual transmission in MSM — Outbreaks of shigellosis have occurred among men who have sex with men (MSM) [24,25]. In a population-based case-control study including 76 case patients and 146 controls, MSM, HIV infection, and direct oral-anal contact were each associated with an odds ratio for shigellosis of 7.5 to 8.2 [26].

Developing countries — Inadequate sewage disposal is associated with high rates of Shigella transmission. A study conducted among children in the Peruvian Amazon noted an incidence of 0.34 episodes of Shigella diarrhea per year among children <6 years of age [27]. In a report from Bangladesh including 1756 children <4 years of age in regions where a sentinel case of Shigella had been identified, 12 percent of children developed Shigella diarrhea within one month, and an additional 13 percent had culture-negative dysenteric illnesses (many of which were probably due to Shigella) [28].

The mode of transmission in high prevalence areas may be more complex than simple person-to-person fecal-oral transmission; in Bangladesh, a poor correlation was found between the Shigella serotype of the sentinel case and the serotype of the secondary cases identified [28]. In contrast, a study in the U.S. observed that all familial secondary contacts of shigellosis index cases were infected with the same organism as the index case [17].

In many developing countries, S. flexneri is the predominant species; S. sonnei is the second most prevalent [28-30]. However, S. sonnei has become the most common isolate in Vietnam [31], raising the likelihood that it will become the predominant species in parts or all of Southeast Asia. Among the cases caused by S. flexneri, serotype 2a predominates [29,32].

Breast feeding appears to confer significant protection against shigellosis and should be encouraged as a preventive measure [33].

MICROBIOLOGY — Shigella are nonmotile, facultatively anaerobic, gram-negative rods. They are members of the family Enterobacteriaceae, genus Shigella. There are four species of Shigella: S. dysenteriae (serogroup A), S. flexneri (serogroup B), Shigella boydii (serogroup C), and S. sonnei (serogroup D). Groups A, B, and C cannot be distinguished biochemically; S. sonnei can be differentiated from the other serogroups by the expression of ornithine decarboxylase.

Stool culture — Shigella is cultured by techniques that are routine for the handling of stool in most clinical microbiology laboratories. Initial inoculation should be on more than one low selectivity medium, such as MacConkey or eosin methylene blue (EMB). Colonies that appear suspicious on low selectivity media are usually subcultured onto highly selective media such as SS (Salmonella-Shigella), XLD (xylose-lysine-deoxycholate), HE (hektoen enteric), or deoxycholate citrate agar (picture 1).

All the above media contain lactose, as well as a color indicator. Shigella do not ferment lactose (they are lactose non-fermenters). At 24 hours, lactose-negative colonies are picked and inoculated onto triple sugar iron agar or lysine iron agar slants (picture 2). Shigella colonies give an alkaline slant, acid at the bottom, and no gas or hydrogen sulfide production. In the setting of possible exposure to S. dysenteriae 1 (eg, travel to an endemic area such as Southeast Asia or the Indian subcontinent), the use of more than one selective medium is warranted [34].

Suspicious colonies can be further tested for motility and certain biochemical characteristics. Shigella are nonflagellated and are therefore non-motile. In addition, Shigella are indole positive, urea and oxidase negative, and ferment glucose (picture 3A-B).

Further classification can be pursued including identification of serogroup and serotype, although these are rarely important to clinical management, and these studies are not performed in most clinical laboratories (picture 4). Serotype is determined by the structure of the repeating oligosaccharide that constitutes the O-antigen of the lipopolysaccharide (LPS) layer of the bacterial envelope. In addition, a variety of DNA probes of plasmid-encoded virulence determinants and ELISA of virulence proteins are available for use in the detection of Shigella.
**Polymerase chain reaction** — Polymerase chain reaction (PCR) has been used to detect *Shigella*-specific DNA sequences in stool. Using primers to the invasion associated locus (ial or ipa), as few as 10 to 100 *S. flexneri* organisms can be detected by PCR (as compared with 10^6^ organisms detected by routine culture) [35, 36]. Given the cost and labor required, PCR assays are unlikely to become generally available in clinical laboratories but are useful tools for the investigation of *Shigella* transmission and epidemiology [37].

**PATHOGENESIS** — The inoculum required for the development of clinical disease is quite low. Clinical disease was observed in 39 percent of volunteer subjects who received an inoculum of 100 *S. flexneri* organisms or 200 *S. dysenteriae* 1 organisms [38]. The minimum infectious inoculum for *Salmonella* in normal subjects is at least two orders of magnitude higher than for *Shigella* [39].

**Colonic entry** — The pathogenesis of *Shigella* involves invasion of colonic mucosal cells and induction of an intense inflammatory response, leading to the death of epithelial and immune cells and the formation of colonic mucosal ulcerations and abscesses. *Shigella* infection of mammalian cells involves entry of bacteria by induced macropinocytosis, escape from the macropinocytic vacuole, multiplication and spread within the cytoplasm, and direct passage into adjacent cells by way of finger-like protrusions of the cell membrane. *Shigella* is among the few pathogens capable of penetrating mammalian cells yet evading the phagocytic vacuole; other such organisms include enteroinvasive *Escherichia coli* and *Listeria monocytogenes*. *Shigella* infection is generally limited to the intestinal mucosa; bacteremia due to *Shigella* is rare [40, 41].

In the colonic mucosa, *Shigella* is able to enter both colonic enterocytes and specialized epithelial cells (M cells) that overlie mucosal lymphoid follicles. Entry via the M cells is thought to be an important route of entry in clinical infection as suggested by examination of rectal biopsies from humans infected with *Shigella*, in which lesions were frequently located over lymphoid follicles [42].

**Macropinocytosis** — Colonic enterocytes do not normally take up microorganisms; in vitro, *Shigella* entry occurs by a process involving bacterium-induced macropinocytosis [43]. *Shigella* enter enterocytes most efficiently via the cell's basolateral surfaces [44] and can gain access to these surfaces either from the tissue underlying the M cell or directly from the intestinal lumen following disruption of enterocyte cell-cell junctions, induced by either the transmigration of polymorphonuclear leukocytes across the epithelium [45] or by *Shigella*-induced redistribution of cell junction proteins [46]. Transmigration of polymorphonuclear leukocytes across the epithelium enhances *Shigella* invasion in vitro two- to sixfold [45].

*Shigella*-induced macropinocytosis occurs through extensive rearrangements of the host cell cytoskeleton that cause formation of large extensions of the host cell membrane, in which the bacteria become engulfed [43]. *Shigella* induces this process by injecting bacterial proteins into the host cell that activate host cytoskeletal signaling pathways.

**Cytoskeletal signaling** — The *Shigella* proteins that activate host cytoskeletal signaling pathways are secreted from the bacterium via a type III secretion apparatus. Both the proteins that are secreted and the proteins that constitute the secretion apparatus are encoded on a large virulence plasmid carried by all virulent strains of *Shigella*. Homologs of these proteins exist in several other enteric gram-negative pathogens, including *Salmonella typhimurium*, *Yersinia pestis*, and enteropathogenic *E. coli* [47, 48]. In *Shigella*, the genes that encode the effector proteins and the secretion apparatus are expressed at 37°C (normal body temperature), but not at 30°C when the bacterium is outside the human host [49], and are induced by oxygen at the surface of colonic cells [50].

Soon after uptake by induced phagocytosis, the bacterium lyases the phagocytic vacuole, releasing it into the host cell cytosol [51]. Short filaments of host cell actin then organize into a tight bundle that forms a tail several microns in length behind the bacterial body (picture 5) [52]. The bacterium uses this tail for movement through the cytosol and for passage into protrusions of the cell membrane (figure 1 and movie 1). The actin-based mechanisms usurped by *Shigella* are processes normally used by the eukaryotic cell for other purposes.

The *Shigella* surface protein IcsA (VirG) mediates the process of bacterial actin-based motility [52-55]. IcsA is unusual in that it is located on a single pole of the bacillus, the pole at which the actin tail forms [56]. IcsA binds the cellular protein neural Wiskott-Aldrich syndrome protein (N-WASP), after which N-WASP is activated at the bacterial surface by the cellular protein Toca-1 [57]. Active N-WASP in turn binds and activates the cellular complex known as Arp2/3. Arp2/3induces both actin polymerization and cross-linking of actin filaments, thereby leading to tail formation (picture 5). As the bacterium moves forward, the tail itself remains stationary in the host cytoplasm, and disassembly of the tail occurs at its distal end [58].
Spread to adjacent cells — *Shigella* spreads into adjacent cells via bacterium-induced, membrane-bound protrusions from the surface of the host cell [figure 1] and [movie 2] [59]. Bacterium-containing protrusions can extend several bacterial lengths away from the cell surface, with the bacterium at the tip. The tips are engulfed and taken up by adjacent cells, thereby transferring the bacterium into the adjacent cell. The formation of these protrusions depends at least in part on cellular actin polymerization proteins called formins [60]. Thereafter, the bacterium lyses the membranes that surround it, freeing itself into the cytoplasm of the new cell [61].

This mechanism of cell-to-cell passage enables the bacteria to spread from host cell to host cell without being enclosed within a true macropinocytic vacuole or having contact with the contents of the intestinal lumen. By remaining within the cytoplasm, the microorganism evades the toxic consequences of phagolysosomal fusion as well as other elements of the host defense system.

Eukaryotic cells are able to degrade abnormal cytosolic molecules and particles, including infecting bacteria, by a process known as autophagy [62]. *Shigella* proteins that are secreted into the host cell cytoplasm via the type III secretion apparatus inhibit autophagy, thereby enhancing the ability of *Shigella* to survive within the cell [63].

Elaboration of toxins — *Shigella* strains elaborate three distinct enterotoxins: the virulence plasmid-encoded ShET2 (produced by all four species) [64], chromosomally-encoded ShET1 (produced by *S. flexneri* 2a) [65-67], and *Shiga* toxin (Stx) (produced by *S. dysenteriae* 1) [68]. Each of these enterotoxins induces intestinal secretion of solutes and water. The contribution of each of these toxins to the disease process is probably minor, since non-toxigenic strains cause significant disease.

Eight percent of children infected with *S. dysenteriae* 1 develop the hemolytic-uremic syndrome, which is mediated by Stx [69]. Stx is genetically and structurally similar to the Stx1 and Stx2 toxins produced by certain *E. coli* strains, such as enterohemorrhagic *E. coli* O157:H7, and the incidence of hemolytic uremic syndrome among infected children is similar to for the two pathogens. In the United States, these Stx-producing *E. coli* are the major cause of post-diarrheal hemolytic-uremic syndrome. The prominent renal involvement suggests that *Shiga* toxins may have a predilection for the renal circulation. (See "Causes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults".)

Immune response — The pocket formed within M cells and the underlying tissue is rich in macrophages, B and T lymphocytes, and dendritic cells [70]. Within the macrophages, *Shigella* are able to induce apoptosis [71] with the release of proinflammatory cytokines, including interleukin (IL)-1 (but not IL-6 or TNF-alpha) [72].

Rectal biopsies from patients with acute *Shigella* diarrhea demonstrate intense acute inflammatory infiltrates with neutrophils and plasma cells in almost all samples [42]. Immunohistochemical studies demonstrate greater numbers of cells producing IL-1a, IL-1b, IL-1ra, IL-4, IL-6, IL-10, interferon gamma (IFNg), TNF-alpha, TNF-beta, and transforming growth factor beta compared with uninfected controls [73]. The acute inflammatory response to *Shigella* invasion is clearly a major contributor to symptoms and the disease process.

*Shigella* modulates the innate immune response by secreting bacteriologic proteins capable of altering immune signaling pathways in host cells. These effector proteins variably block induction of NFkB signaling [74], alter signaling via the MAPK kinase pathway [74-77], and alter transcription of immunomodulatory proteins [78]. In addition, *Shigella* inhibits both T cell migration and the development of antigen-specific T cell responses [79,80].

Immunity following natural infection appears to occur, as evidenced by the observation that disease due to endemic *Shigella* species occurs primarily in children, while disease due to epidemic species occurs in all age groups [81]. Immune protection appears to be serotype-specific [81-85]. Serotype is determined by the O polysaccharide composition, and multiple serotypes have been described [86]. A significant component of naturally-acquired protection may be mediated by a specific response to the polysaccharide component of bacterial lipopolysaccharide. The significance of antibody responses to antigens other than lipopolysaccharide (eg, IpaBCD, IcsA, or ShETs) is not known.

No safe and effective *Shigella* vaccine is commercially available, although several are in advanced stages of human trials. However, those that are most promising appear to generate immunity only to the serotype contained in the vaccine.

SUMMARY
● Bacterial dysentery due to Shigella species is a major cause of morbidity and mortality; 165 million cases occur annually worldwide, with 1 million associated deaths. (See Epidemiology above.)

● Shigella organisms can survive transit through the stomach since they are less susceptible to acid than many other bacteria. For this reason, the inoculum required for the development of clinical disease is quite low; as few as 10 to 100 organisms can cause disease. (See ‘Introduction’ above.)

● In developed countries, most cases of Shigella are transmitted by fecal-oral spread from people with symptomatic infection. In developing countries, both fecal-oral spread and contamination of common food and water supplies are important mechanisms of transmission. (See ‘Epidemiology’ above.)

● Shigella are nonmotile, facultatively anaerobic, gram-negative rods. There are four species of Shigella: Shigella dysenteriae, Shigella flexneri, Shigella boydii, and Shigella sonnei. In developing countries, S. flexneri is the predominant species; S. sonnei is the second most prevalent. Most cases of shigellosis in the United States are caused by S. sonnei; S. flexneri is the next most frequent isolate. S. dysenteriae 1 (the Shiga bacillus) was the most common isolate both in Europe and the United States in the early 1900s but is now rare. In the United States S. dysenteriae 1 infection is generally limited to imported cases from Mexico and Central America. (See Microbiology above.)

● The pathogenesis of Shigella infection involves invasion of colonic mucosal cells and induction of an intense inflammatory response, leading to the death of epithelial and immune cells and the formation of colonic mucosal ulcerations and abscesses. Shigella-induced macropinocytosis occurs through extensive rearrangements of the host cell cytoskeleton that cause formation of large extensions of the host cell membrane, in which the bacteria become engulfed. Thereafter, the bacteria spreads from host cell to host cell without having contact with the contents of the intestinal lumen. (See Colonic entry above and ‘Macropinocytosis’ above and ‘Cytoskeletal signaling’ above and ‘Spread to adjacent cells’ above.)

● S. dysenteriae 1 can cause the hemolytic-uremic syndrome, mediated by Shiga toxin (Stx). Stx is genetically and structurally similar to the Stx1 and Stx2 toxins produced by certain Escherichia coli strains, such as enterohemorrhagic E. coli O157:H7. (See ‘Elaboration of toxins’ above.)

● Immunity following natural infection appears to occur, as evidenced by the observation that disease due to endemic Shigella species occurs primarily in children, while disease due to epidemic species occurs in all age groups. (See ‘Immune response’ above.)

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REFERENCES

i regulates tight junction type III secretion effectors: how, where, when, for what purposes?

Shigella virulence.


Isolation of enteric pathogens from stool using selective media

Selective media used in the isolation of enteric pathogens from stool. On each plate, Shigella is indicated by the arrowhead and Escherichia coli by the arrow; all three media differentiate lactose fermenting from nonlactose fermenting organisms by pH sensitive dyes. Panel A: MacConkey agar; panel B: Hektoen enteric agar; and panel C: Xylose lysine deoxycholate agar. Courtesy of Michael S Glickman, MD.

Shigella on triple sugar iron agar slant

Triple sugar iron agar slant shows the reaction pattern of Shigella. This pattern is designated alkaline (red) over acid (yellow), indicating the absence of lactose fermentation by the test organism. In addition, there is no gas or the black color indicative of hydrogen sulfide visible.
Motility testing on nonlactose fermenting gram negative rods

Left tube: The nonmotile Shigella does not migrate away from the central stab line in the agar. Right tube: Motile Proteus produces visible opacification of the agar away from the central stab line. The color difference between the two samples is unrelated to the motility test. Courtesy of Michael S Glickman, MD. Graphic 60548 Version 1.0

Shigella versus urease positive gram-negative rods on urea slant

Urea slant shows the positive (pink) and negative (yellow) reactions that differentiate Proteus (left) from Shigella (right). Courtesy of Michael S Glickman, MD. Graphic 52747 Version 2.0

Serologic grouping by agglutination with antisera

Isolates of Salmonella and Shigella can be presumptively identified by agglutination with appropriate antisera. A positive agglutination is on the left, a negative agglutination on the right.
Shigella and actin filaments on electron microscopy

Scanning electron microscopy of HeLa cell infected by Shigella flexneri. The cytoskeleton has been insolubilized, and the host cell membrane has been removed. A dividing bacterium is seen with tight bundles of actin filaments at one extremity (arrow). Redrawn from Prevost MC, Lesourd M, Arpin M, et al. Infect Immun 1992; 60:4088. Graphic 56214 Version 2.0

Diagram of Shigella spread in the epithelium

Epithelial cells

Schematic representation of intracellular movement and spread of Shigella in epithelium. Step 1: Soon after uptake by induced phagocytosis, the bacterium lysed the phagocytic vacuole, thereby releasing it into the host cell cytosol. Step 2: Short filaments of host cell actin (brown thick lines) then organize into a tight bundle that forms a tail several microns in length behind the bacterial body. Step 3: The bacterium uses this tail to motor both its movement through the cytosol and its passage into protrusions from the cell surface; the bacterium-containing protrusions can extend several bacterial lengths away from the cell surface, with the bacterium at the tip. Step 4: The bacterium-containing protrusion tips are endocytosed by adjacent cells, thereby transferring the bacterium into the adjacent cell. Step 5: Once endocytosed within the adjacent cell, the bacterium lysed the membranes that surround it, freeing itself into the cytosol of that cell. Redrawn from Goldberg MB, Sansonetti PJ. Infect Immun 1993; 61:4941.
INTRODUCTION — *Shigella* species are a common cause of bacterial diarrhea worldwide, especially in developing countries. *Shigella* organisms can survive transit through the stomach since they are less susceptible to acid than other bacteria; for this reason as few as 10 to 100 organisms can cause disease [1]. Ingested bacteria pass into the small intestine where they multiply; large numbers of bacteria then pass into the colon, where they enter the colonic cells. Given its relatively low infectious dose, *Shigella* transmission can occur via contaminated food and water and via direct person-to-person spread. (See "*Shigella* infection: Epidemiology, microbiology, and pathogenesis").

The clinical manifestations, complications, and diagnosis of *Shigella* infection will be reviewed here. The treatment of this infection is discussed separately. (See "*Shigella* infection: Treatment and prevention in adults" and "*Shigella* infection: Treatment and prevention in children").

CLINICAL MANIFESTATIONS

General features — *Shigella* is an infection of the lower gastrointestinal tract. Patients with *Shigella* gastroenteritis typically present with high fever, abdominal cramps, and bloody, mucoid diarrhea [2-6]:

- Fever – 30 to 40 percent
- Abdominal pain – 70 to 93 percent
- Mucoid diarrhea – 70 to 85 percent
- Bloody diarrhea – 35 to 55 percent
- Watery diarrhea – 30 to 40 percent
- Vomiting – 35 percent

The incubation period ranges from one to seven days, with an average of three days [7]. The disease typically begins with constitutional symptoms such as fever, anorexia, and malaise. Initially diarrhea is watery, but subsequently may contain blood and mucus. Tenesmus is a common complaint.

Stool frequency is typically 8 to 10 per day, but may increase to up to 100 per day. Significant fluid loss is uncommon (average approximately 30 mL/kg per day); this is in contrast to small bowel infections, which are typified by large volumes of watery diarrhea associated with abdominal cramping, bloating, gas and weight loss [8]. (See "Approach to the adult with acute diarrhea in resource-rich countries" and "Approach to the child with acute diarrhea in resource-limited countries").

The spectrum of disease severity varies depending on the serogroup of the infecting organism. *Shigella sonnei* commonly causes mild disease, which may be limited to watery diarrhea, while *Shigella dysenteriae* 1 or *Shigella flexneri* commonly causes dysenteric symptoms (bloody diarrhea) [6,9]. In a normal host, the course of disease is generally self-limited, lasting no more than seven days when left untreated.

The typical course of disease varies with age group. In a review of 318 infants and children hospitalized with shigellosis in Bangladesh, infants had fewer days with diarrhea (four versus six) and were more likely to have watery (as opposed to bloody) stools, hyponatremia, abdominal distension, and acidosis than older children [10]. Older children were more likely to have a leukemoid reaction than infants. The mortality rate for infants was twice that of older children. In another study conducted at the same institution, infants who were breast fed were less frequently infected and had a milder illness than infants who were not breast fed [2].

Intestinal complications — Several intestinal complications can occur in the setting of *Shigella* infection; each is relatively rare (table 1).
Proctitis or rectal prolapse — In infants and young children, the severe inflammation of the rectum and distal colon that is induced by invasion of the organism into the colonic mucosa may lead to proctitis or rectal prolapse [6].

Toxic megacolon — Toxic megacolon occurs primarily in the setting of S. dysenteriae 1 infection. The pathogenesis of this complication is unclear; it occurs in the setting of pancolitis and seems to be related to the intensity of inflammation rather than being mediated by Shiga toxin. The incidence of toxic megacolon among patients admitted to the diarrhea treatment center in Bangladesh was 3 percent [11].

Intestinal obstruction — Severe colonic disease may result in intestinal obstruction. The incidence in one series of 1211 patients with shigellosis was 2.5 percent [12]. The patients with obstruction were more likely to be infected with S. dysenteriae 1 and were more severely ill, as evidenced by a significantly higher white blood cell count and lower serum sodium concentration than patients without evidence of obstruction.

Colonic perforation — Colonic perforation is an extremely rare complication of shigellosis. It occurs principally in infants or severely malnourished patients and is associated with infection due to S. dysenteriae 1 or S. flexneri. In one epidemic of S. dysenteriae 1 in Central America, colonic perforation was seen at autopsy in 1.7 percent of fatal cases [13].

Systemic complications — Shigellosis may be associated with a number of systemic complications (table 1).

Bacteremia — The incidence of bacteremia has been reported to be 0 to 7 percent [14-16]. Signs that correlate with bacteremia are leukocytosis, hypothermia, temperature above 39.5ºC, severe dehydration, and lethargy [17]. Bacteremia is more common among children than adults, occurring primarily among children younger than five years of age [14,17,18]. Among the 22 cases of bacteremia described among adults in the literature, one-third of patients were older than 65 years of age, and more than half had an underlying disease (most commonly diabetes) [19]. HIV infection does not appear to confer significant predisposition to Shigella bacteremia. Among adults in Soweto, South Africa, the rate of HIV infection nearly doubled between 1996 and 2006 although the rate of Shigella bacteremia remained stable (approximately 0.2 per 1000 adults; 0.8 per 100 children) [18].

Bacteremia is associated with an increased risk of death [17]. Young, malnourished children are at greatest risk. Additionally, the mortality rate associated with Shigella bacteremia may be higher in the setting of HIV infection. In a study of systemic Shigellosis in South Africa, HIV-infected patients were substantially more likely to die than HIV-uninfected individuals (29 of 78 versus 5 of 40 fatal cases, respectively) [20]. We recommend antibiotic treatment for all patients who become bacteremic with Shigella. (See “Shigella infection: Treatment and prevention in adults”, section on ‘Clinical approach to therapy’ and “Shigella infection: Treatment and prevention in children”, section on ‘Antibiotic therapy’.)

Metabolic disturbances — Substantial volume depletion is uncommon in shigellosis because the stool volume is usually low. In a review of 412 patients with shigellosis, 36 percent had mild dehydration, 12 percent had moderate dehydration, and 2 percent had severe dehydration [2]. In another series, hyponatremia (defined as serum sodium below 120 meq/L) was noted in 29 percent of patients hospitalized with diarrhea due to S. dysenteriae 1 [21]. Hyponatremia is generally due to the syndrome of inappropriate antidiuretic hormone secretion, not volume depletion [11,21].

Protein-losing enteropathy also may be observed. In one report that used the level of alpha-1 antitrypsin in stool as an indicator of protein excretion, protein loss was high during the acute phase in patients who had dysentery, remained high in patients who failed therapy, and fell to normal low values in those who were cured [22]. Increased catabolism secondary to fever, stool protein loss, decreased intake due to anorexia and malabsorption can exacerbate pre-existing malnutrition.

Leukemoid reaction — A leukemoid reaction (defined as a white blood count of 50,000/mm² or more) has been observed in Bangladesh among approximately 4 percent of patients, most commonly in children between 2 and 10 years of age (and not at all in children younger than one year of age) [23]. The white blood cell count in these patients ranged from 50,000 to 195,000/mm² and was accompanied by an increased number of immature forms. In this study, the mortality rate also was increased among patients with a leukemoid reaction (21 versus 7 percent). In contrast, a study conducted in the United States found no association between disease severity and a high white blood cell count [3].
Neurologic disease — Seizures are the most common neurologic complication associated with Shigella infection. They tend to be generalized and are not associated with specific neurologic deficits but have been associated with a higher risk of death [24,25]. Seizures occur almost exclusively among children <15 years. The occurrence of seizures is associated with fever (often greater than 39°C), increased proportion of immature leukocytes, low serum sodium, and high serum potassium. Seizures have been observed during infection with all serotypes of Shigella.

The reported prevalence of seizures among children with shigellosis has ranged from 5 to 45 percent; among patients of all ages hospitalized with shigellosis the prevalence is about 10 percent [11,24,25]. Analysis of cerebrospinal fluid obtained by lumbar puncture is typically normal, although up to 15 percent may have mild lymphocytic pleocytosis with up to 12 cells.

Neurologic complications of Shigella infection were previously thought to be induced by circulating Shiga toxin produced by S. dysenteriae 1, though this is not likely to be correct [26]. In a study of five children performed to determine whether seizures were associated with Shiga toxin, clinical specimens including stool, serum, and cell-free cerebrospinal fluid were examined in vitro for cytotoxic activity [27]. Cytotoxic activity was not detected in serum or spinal fluid, although it was present in stool, at levels 1000-fold below that of cultured S. dysenteriae 1. The stool cytotoxic activity was not neutralized by anti-Shiga toxin antibodies, no patient had neutralizing antibodies to Shiga toxin, and DNA hybridization studies of the Shigella isolates that probed for the gene encoding Shiga toxin were negative.

Thus, although this study is too small to be conclusive, it did not demonstrate a relationship between Shiga toxin and seizures. Furthermore, the majority of patients who have seizures are infected with S. flexneri or S. sonnei, which do not express Shiga toxin. Taken together, these data suggest that other Shigella enterotoxins might contribute to the induction of seizures, although this possibility requires further study. The enterotoxin ShET1 has been identified in strains of S. flexneri 2a [28,29], and the enterotoxin ShET2 has been identified in members of all four serogroups [30], but the role of these or other as yet unidentified enterotoxins in Shigella-induced seizures is unknown.

In addition to seizures, other neurologic findings have been described in up to 40 percent of children hospitalized with Shigella infection, including encephalopathy with lethargy, confusion, and headache [31]. Obtundation, coma and posturing are rare. In cases of fatal encephalopathy, cerebral edema has been observed at autopsy.

A particularly lethal form of shigellosis, known as the Ekiri syndrome, was responsible for 15,000 deaths per year in Japan during the pre-World War II era [11]. The Ekiri syndrome was associated with S. sonnei infection and was characterized by the rapid development of seizures and coma in patients with high fever and few dysenteric symptoms. The mechanism of the fulminant course remains unclear.

Reactive arthritis — Following S. flexneri infection, reactive arthritis is an uncommon complication that may be observed alone or in association with conjunctivitis and urethritis. In a study of US military personnel, reactive arthritis occurred in 0.5 percent of cases of Shigella gastroenteritis [32]. (See “Reactive arthritis”.)

The arthritis is a sterile inflammatory arthritis. Symptoms develop one to two weeks following symptoms of dysentery, regardless of whether or not the dysentery was treated with antibiotics. Approximately 70 percent of patients with arthritis are HLA-B27 positive [33]. A 5 amino acid peptide encoded on a 2 Md Shigella plasmid has been associated with reactive arthritis in two separate studies [34,35]. This peptide has sequence similarity to the HLA B2 alpha 1 domain, suggesting that molecular mimicry may play a pathogenetic role in arthritis. (See “Pathogenesis of spondyloarthritis”.)

There is one case report in which bacterial lipopolysaccharide antigen was detected in the synovial fluid of a patient with post-Shigella reactive arthritis; the significance of this finding is uncertain [36].

Sterile reactive arthritis has also been described following infection with Campylobacter jejuni, Salmonella enteritidis, Shigella typhimurium, Yersinia enterocolitica, and Yersinia pseudotuberculosis [37].

Hemolytic-uremic syndrome — Although relatively uncommon, the hemolytic-uremic syndrome (HUS) is the most frequent cause of acute renal failure among infants and young children worldwide [38]. Ninety percent of cases of HUS in children follow a diarrheal prodrome; it is most often due to infection with enterohemorrhagic Escherichia coli (particularly type O157:H7), but may also be induced by infection with S. dysenteriae 1 [6]. The other 10 percent of cases have a variety of etiologies, including drugs, malignancy, pregnancy, and collagen vascular disease. Thrombotic thrombocytopenic purpura is a related disorder with overlapping clinical findings that occurs more
commonly in adults [39]. (See “Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children” and “Causes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults”.

Patients present at the end of the first week and during the recovery phase of diarrheal or dysenteric symptoms with the combination of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (initially oliguric and then anuric). The patient may be considered to have thrombotic thrombocytopenic purpura if fever and transient neurologic symptoms are also present. Seizures occur in approximately 10 percent and stroke or cerebral edema in 5 percent.

The pathogenesis of HUS or TTP involves cytotoxic damage to the vascular endothelium. In most studies, Shiga-toxin production by S. dysenteriae 1 is thought to be directly involved. In the setting of infection due to enteropathogenic E. coli, antibiotic treatment may increase the risk of the development of HUS [40,41]. (See “Clinical manifestations, diagnosis and treatment of enterohemorrhagic Escherichia coli (EHEC) infection”, section on 'Treatment'.)

Some retrospective clinical data suggest that antibiotic use in the setting of S. dysenteriae 1 infection does not induce development of HUS, and that treatment with antibiotics may reduce its likelihood. In a retrospective review of several studies including 128 adults and 250 children with S. dysenteriae 1 infection treated with antibiotics, only one child developed HUS [42]. This may be due to a difference in the genomes between S. dysenteriae 1 and enteropathogenic E. coli. In S. dysenteriae 1, the phage that carries the Shiga toxin genes is unable to undergo lysogenic conversion, whereas the phage that carries these genes within pathogenic E. coli is not defective [43,44].

Other manifestations — In young girls, Shigella can cause vaginitis or vulvovaginitis with or without diarrhea [45]. The vaginal discharge usually is painless and may be bloody. Untreated Shigella vaginitis can persist for several months.

Shigella is a rare cause of keratitis and should be considered as the cause of keratitis or conjunctivitis in young children who have had a recent diarrheal illness or who have a recent exposure [46].

Acute myocarditis has been associated with acute S. sonnei gastroenteritis in two children [47].

DIAGNOSIS — Shigella should be suspected in the setting of frequent, small volume, bloody stools, abdominal cramps, and tenesmus, particularly if accompanied by fever. Nausea and vomiting are notably absent in most patients, and fecal leukocytes are generally present [2].

The differential diagnosis for this constellation of symptoms and signs includes infection with Salmonella, Campylobacter, Yersinia, enteroinvasive E. coli, or Clostridium difficile, or noninfectious inflammatory bowel disease [1]. (See “Approach to the adult with acute diarrhea in resource-rich countries” and "Evaluation of diarrhea in children".)

Stool culture — Definitive determination of the infecting organism requires stool culture. Direct microscopic examination of stool specimen for the presence of white blood cells and red blood cells may facilitate early diagnosis of Shigella. Shigella is a fastidious organism; it requires prompt handling and optimally should be inoculated onto agar at the bedside. Culture from a stool sample may give a better yield than culture from a rectal swab [48]. If transport of the sample is required, the best medium is buffered glycerol saline (BGS) [49]. The best yield is from a mucoid part of stool. The methods used to culture Shigella in the laboratory and newer, more sensitive techniques, such as polymerase chain reaction, are discussed separately. (See "Shigella infection: Epidemiology, microbiology, and pathogenesis".)

SUMMARY

● Shigella is a common cause of bacterial diarrhea. It is transmitted by direct person-to-person spread and, less commonly, through contaminated food and water. (See "Shigella infection: Epidemiology, microbiology, and pathogenesis".)

● The incubation period ranges from one to seven days. Patients with Shigella gastroenteritis typically present with high fever, abdominal cramps, and bloody, mucoid diarrhea; tenesmus is common. Shigella gastroenteritis generally is self-limited, lasting no more than seven days in an untreated immunocompetent host. (See 'General features' above.)
Intestinal complications of *Shigella* infection include proctitis, rectal prolapse, toxic megacolon, intestinal obstruction, and colonic perforation. (See Intestinal complications above.)

Systemic complications of *Shigella* infection include bacteraemia, metabolic disturbances (hypovolemia, hyponatremia, protein-losing enteropathy), leukemoid reaction, neurologic disease (seizures, encephalopathy), reactive arthritis, and with *Shigella dysenteriae* 1 hemolytic uremic syndrome. (See Systemic complications above.)

*Shigella* should be suspected in patients with frequent, small volume, bloody stools, abdominal cramps, tenesmus, and fever, particularly if accompanied by fecal leukocytes. Stool culture is required for definitive diagnosis. (See Diagnosis above.)

Treatment of *Shigella* is discussed separately. (See "Shigella infection: Treatment and prevention in adults" and "Shigella infection: Treatment and prevention in children").

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REFERENCES


34. Stiegitz H, Lipsky P. Association between reactive arthritis and antecedent infection with Shigella flexneri carrying a 2-Md plasmid and encoding an HLA-B27 mimetic epitope. Arthritis Rheum 1993; 36:1387.
# Major complications of Shigella infection

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Proctitis or rectal prolapse</td>
<td>( ^* )</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>( 3^\dagger )</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>( 2.5^\dagger )</td>
</tr>
<tr>
<td>Colonic perforation</td>
<td>( 1^\dagger )</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>( 4 )</td>
</tr>
<tr>
<td>Moderate to severe hypovolemia</td>
<td>( 10-12^\dagger )</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>( 29^\dagger )</td>
</tr>
<tr>
<td>Leukemoid reaction</td>
<td>( 3^\dagger )</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>( 12-45 )</td>
</tr>
<tr>
<td>Reactive arthritis or Reiter's syndrome</td>
<td>( 1.4 )</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>(&lt;1 )</td>
</tr>
</tbody>
</table>

* Unknown. \( ^\dagger \) Prevalence rate has been reported for a subpopulation of individuals with *Shigella* enteritis, and therefore the reported prevalence probably represents an overestimation of the true prevalence in all individuals with the disease.
Shigella infection: Treatment and prevention in adults

INTRODUCTION — Shigella infections are a major cause of morbidity and mortality in developing countries. Worldwide, about 165 million cases occur annually with 1 million associated deaths [1]. In the United States, the incidence of Shigella infections is 4 to 8 per 100,000, with nearly 14,000 reported cases in 2004 [2]. The mortality in developed countries is less than 1 percent [3]. (See "Shigella infection: Epidemiology, microbiology, and pathogenesis").

Shigella gastroenteritis is typically characterized by high fever, abdominal cramps, and diarrhea. The stools are characteristically small in volume, bloody, and mucoid. Individuals with underlying immune deficiency (including HIV infection) or malnutrition are at increased risk for complications of shigellosis [4-7].

The diagnosis of Shigella infection should be considered in a toxic-appearing patient with the sudden onset of bloody diarrhea, cramping, and tenesmus, and with polymorphonuclear leukocytes on a methylene blue stain of the stool. Shigella is isolated by culture of a stool specimen or rectal swab using techniques that are routine in most microbiology laboratories. Isolation of the organism from blood is uncommon.

The treatment and prevention Shigella infection in adults will be reviewed here. The clinical manifestations and diagnosis of Shigella and the management of Shigellainfection in children are discussed separately. (See "Shigella infection: Clinical manifestations and diagnosis" and "Shigella infection: Treatment and prevention in children").

NATURAL HISTORY OF INFECTION — Infection with Shigella is generally self-limited; the average duration of untreated Shigella gastroenteritis is seven days [8]. Antibiotic therapy is not essential, since infection clears spontaneously in most individuals; however, because of the severity of the disease and for public health reasons, most favor antibiotic therapy for patients with positive stool culture [9]. Antibiotics have been shown to decrease the duration of fever and diarrhea by about two days [10,11]. Shortening the duration of shedding with the administration of antibiotics can also reduce the risk of person-to-person spread.

In the absence of specific antibiotic treatment, patients with Shigella gastroenteritis may shed the organism for up to six weeks in the absence of symptoms; risk factors for asymptomatic shedding are not known. It is uncertain whether antibiotics reduce the incidence of reactive arthritis (formerly Reiter syndrome), a rare complication of shigellosis.

The Shiga toxin produced by Shigella dysenteriae type 1 is structurally identical to one of the Shiga toxins produced by enterohemorrhagic Escherichia coli (EHEC) and is associated with hemolytic uremic syndrome (HUS), although the mechanism that controls Shiga toxin production in S. dysenteriae is distinct from that in EHEC. Therefore, although antibiotic treatment of EHEC infection has been associated with an increased relative risk of developing HUS [12], antibiotic treatment ofS. dysenteriae infection has not been observed to increase the incidence of HUS [13]. (See "Microbiology, pathogenesis, epidemiology, and prevention of enterohemorrhagic Escherichia coli (EHEC)").

ANTIMICROBIAL RESISTANCE — The increasing antimicrobial resistance of Shigella species is a major problem in the treatment of shigellosis. Thus, antibiotic susceptibility testing is essential for management of all patients with suspected Shigella infection. This is particularly important in patients who are at risk of infection with a resistant isolate, including patients with infections in Asia and Africa, those who report international travel, HIV-infected individuals, and men who have sex with men (MSM).

The major route for dissemination of resistance to multiple agents is horizontal transfer of plasmids carrying antibiotic resistance genes (R-plasmids). A commonly isolated plasmid carries resistance against ampicillin, chloramphenicol, tetracycline, sulfonamides, streptomycin, and trimethoprim [14]. Macrolide resistance genes are also commonly plasmid-encoded [15]. Ampicillin resistance is mediated by beta-lactamases, most frequently OXA-1 and TEM-1.
High rates of antimicrobial resistance were first reported in Asia, Africa, and South America, and antimicrobial resistance has spread rapidly to developed countries [16-18]. In Asia and Africa, 65 to 85 percent of isolates are resistant to nalidixic acid and trimethoprim-sulfamethoxazole and 20 to 30 percent are resistant to fluoroquinolones [19,20]. Resistance to nalidixic acid has also been reported in England [21]. Increasing levels of resistance to ceftriaxone and azithromycin have been reported in Asia [22,23] and France [24]. A clone that has spread through parts of Vietnam displays resistance to third-generation cephalosporins and fluoroquinolones [25].

Antimicrobial resistance is an increasing problem in the United States, with some reports of strains resistant to ceftriaxone, ciprofloxacin, and nalidixic acid [18,26-28]. Clusters of ciprofloxacin-resistant S. sonnei have been reported throughout the United States, likely introduced by international travelers with subsequent domestic spread [29]. Decreased susceptibility to azithromycin (minimum inhibitory concentration [MIC] >16 mcg/mL) has also been detected, including, but not limited to, a 2012 S. sonnei outbreak in California [15,30].

Since 1999, the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria has tested every 10th (through 2002) or 20th (since 2003) Shigella isolate submitted from public health laboratories across the United States for antimicrobial susceptibility [31]. Among the 353 isolates tested during 2012, the following results were reported (figure 1):

- Most isolates were susceptible to ceftriaxone and ciprofloxacin. Only 1.1 and 2.0 percent of isolates were resistant to these agents, respectively, but these proportions are higher than those prior to 2010.
- Most isolates were susceptible to azithromycin (4.2 percent with MIC >16 mcg/mL).
- Forty-three percent of isolates were resistant to trimethoprim-sulfamethoxazole (TMP-SMX).
- Twenty-six percent of isolates were resistant to ampicillin, which reflects a continued decrease over time from 80 percent in 2001.
- Thirty-seven percent of isolates were resistant to ≥3 antimicrobial classes.

Some cases of drug resistant Shigella have been associated with international travel or adoption. As an example, in an analysis of data on 1118 Shigella isolates reported to the Foodborne Diseases Active Surveillance Network (FoodNet) of the Centers for Disease Control and Prevention, and tested through NARMS between 2000 and 2010, strains isolated from individuals with a history of international travel within the preceding week were more likely to be resistant to TMP-SMX (75 versus 39 percent of isolates from those without such travel) or resistant to at least five antibiotic classes (13 versus 4 percent) [32]. However, decreased susceptibility to azithromycin appears to have other demographic associations in the United States. In an analysis of cases of Shigella infection with decreased susceptibility to azithromycin identified through NARMS or public health reporting, none of the 29 adults for whom information was available had reported international travel [15]. Instead, a majority of the patients for whom such information was available were HIV-infected (13 of 16 men) or men who have sex with men (MSM, 11 of 14 men).

**CLINICAL APPROACH TO THERAPY** — Given the low inoculum required for transmission of disease and the efficacy of antibiotic therapy in reducing the duration of diarrhea, antibiotic therapy is warranted for individuals with positive stool culture for Shigella [9]. Because of the increasing antimicrobial resistance of Shigella species, antibiotic susceptibility testing is essential for management to optimally guide antibiotic choice. Unfortunately, standardized testing for susceptibility to azithromycin does not currently exist; consequently, clinical laboratories typically do not test isolates for azithromycin susceptibility. Therefore, clinicians should monitor patients receiving azithromycin for clinical response to therapy.

**Supportive therapy** — Hydration is important to compensate for fluid loss from the gastrointestinal tract; oral rehydration is sufficient in most cases. Intestinal antimotility drugs such as paregoric, diphenoxylate (Lomotil) or loperamide (Imodium) should be avoided [33]. (See "Oral rehydration therapy" and "Maintenance and replacement fluid therapy in adults").

**Antibiotic treatment**

**Indications** — For public health reasons, most favor antibiotic therapy for patients with positive stool culture, although antibiotic therapy is not essential since infection clears spontaneously in most individuals [9]. Antibiotics have been shown to decrease the duration of fever and diarrhea by about two days [10,11]. Shortening the duration of shedding
with the administration of antibiotics may reduce the risk of person-to-person spread, although this has not been definitively demonstrated.

While culture data are pending, the choice to initiate empiric antibiotic therapy in the setting of diarrheal illness should be based on the degree of clinical suspicion for *Shigella*, the severity of illness, and the presence of host factors that predispose to severe infection. Empiric antibiotic therapy is warranted in severely ill patients with diarrhea, particularly when hospitalization is required. Other groups for whom empiric therapy is reasonable because of personal or public health concerns include elderly patients, malnourished individuals, patients with HIV infection, food handlers, health care workers, and individuals in day care centers (including children and their caretakers).

**Antibiotic selection** — In the absence of susceptibility data, the antibiotic of choice for adults with *Shigella* infection is a fluoroquinolone (table 1). Oral quinolones achieve high concentrations in serum and stool and have activity against *Shigella* as well as other bacterial causes of diarrhea including *Salmonella* and *Campylobacter* [34,35]. The duration of therapy is three days; five to seven days of therapy should be administered to patients with infection due to *S. dysenteriae* type 1 or with HIV coinfection [36-38].

Because of the increasing rates of antibiotic resistance in *Shigella* isolates, obtaining susceptibility testing is important to ensure adequate efficacy of the chosen antimicrobial. This is particularly critical for shigellosis that may have been acquired in the Asian sub-continent or Africa, since there is widespread resistance to *ciprofloxacin, trimethoprim-sulfamethoxazole*, and *azithromycin* in those regions, with a pocket of resistance to third generation cephalosporins in Vietnam [22,25]. Of note, HIV-infected individuals and men who have sex with men (MSM) may be at higher risk for infection with isolates that have reduced susceptibility to azithromycin [15].

Reasonable agents for treatment of infection due to isolates with known susceptibility include *azithromycin* (three days) or *trimethoprim-sulfamethoxazole* (five days) (table 1) [35,39]. *Ampicillin* is not an appropriate empiric agent due to high resistance rates, but it can be used if the isolate has documented susceptibility [40]. *Ampicillin* should not be used to treat *Shigella* infection. (See ‘Antimicrobial resistance’ above.)

**Counselling** — Food handlers should not be involved in food preparation as long as their stool cultures are positive; conversion to negative stool cultures generally requires at least 48 hours of antibiotic therapy.

**PREVENTION** — Control measures to prevent spread of infection are an important component of management. Hygiene measures include frequent handwashing with soap and water, particularly after using the restroom and prior to food preparation [41]. Food handlers should not be involved in food preparation as long as their stool cultures are positive; conversion to negative stool cultures generally requires at least 48 hours of antibiotic therapy. Access to safe drinking water is an important component of prevention in developing settings.

There is no effective vaccine against *Shigella*; potential vaccines are in clinical trials [42]. Use of prophylactic *rifaximin* in travelers to areas in which shigellosis is endemic has been proposed as a measure for prevention of shigellosis; further study is needed before routine use is warranted [43].

**SUMMARY AND RECOMMENDATIONS**

- Infection with *Shigella* is generally self-limited; the average duration of untreated *Shigella* gastroenteritis is seven days. Hydration is important to compensate for fluid loss from the gastrointestinal tract; oral rehydration is sufficient in most cases. (See ‘Natural history of infection’ above and ‘Supportive therapy’ above.)
- The increasing antimicrobial resistance of *Shigella* species is a major problem in the treatment of shigellosis. Antibiotic susceptibility testing is essential for management of all patients with suspected *Shigella* infection. (See ‘Antimicrobial resistance’ above.)
- Whenever possible, cultures of stool should be obtained, so that if the isolate is resistant to the prescribed empiric antibiotic, antibiotic therapy can be adjusted appropriately. (See ‘Antibiotic treatment’ above.)
- Prior to the availability of culture results, we suggest empiric antibiotic therapy for severely ill patients, elderly patients, malnourished individuals, patients with HIV infection, food handlers, health care workers and individuals in day care centers (including children and their caretakers) (Grade 2C). (See ‘Antibiotic treatment’ above.)
- We suggest antibiotic therapy for treatment of adults with diarrheal illness that is known to be due to shigellosis (Grade 2A). Antibiotics have been shown to decrease the duration of fever and diarrhea by about two days. Shortening the duration of shedding with the administration of antibiotics can also reduce the risk of person-to-person spread. (See ‘Antibiotic treatment’ above.)
Prior to the availability of susceptibility data, we suggest treatment of shigellosis in adults with a fluoroquinolone (Grade 2B). In the setting of shigellosis that may have been acquired in the Asian sub-continent, we suggest treatment of shigellosis with a third-generation cephalosporin (Grade 2B). Subsequent therapy should be guided by susceptibility data; other antibiotic agents that may be effective include azithromycin and trimethoprim-sulfamethoxazole (table 1). (See 'Antibiotic treatment' above.)

Frequent handwashing with soap and water is important for prevention, particularly after using the restroom and prior to food preparation. Food handlers should not be involved in food preparation as long as their stool cultures are positive; conversion to negative stool cultures generally requires at least 48 hours of antibiotic therapy. (See 'Prevention' above.)

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REFERENCES


Antimicrobial resistance pattern for *Shigella*, United States, 2012

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptible, intermediate, and resistant proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td></td>
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<tr>
<td>Ceftiofur*</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
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<td>Ampicillin</td>
<td></td>
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<tr>
<td>Ciprofloxacin</td>
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<td>Nalidixic acid</td>
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<td>Cefoxitin</td>
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<tr>
<td>Sulfadoxazole</td>
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</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td></td>
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<tr>
<td>Chloramphenicol</td>
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<tr>
<td>Tetracycline</td>
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</table>


### Treatment of shigellosis in adults

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>500 mg orally once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg orally twice daily or 750 mg orally once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg orally once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (co-trimoxazole)</td>
<td>160/800 mg (one double strength tablet) orally twice daily</td>
<td>5 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 to 2 g intravenously once daily</td>
<td>5 days</td>
</tr>
</tbody>
</table>

See text for approach to choice of therapy and comments regarding antimicrobial therapy. The duration of therapy is as outlined above; in addition, five to seven days of therapy should be administered to patients with infection due to *S. dysenteriae* type 1 or patients with HIV coinfection.