

54 - 171 Salmonellosis

171 Salmonellosis

macrolides azithromycin and clarithromycin. *B. mallei* infection should be treated with the same drugs and for the same duration as melioidosis.

STENOTROPHOMONAS MALTOPHILIA *S. maltophilia* is the only potential human pathogen among a genus of ubiquitous organisms found in the rhizosphere (i.e., the soil that surrounds the roots of plants). The organism is an opportunist that is acquired from the environment but is even more limited than *P. aeruginosa* in its ability to colonize patients or cause infections. Immunocompromise is not sufficient to permit these events; rather, major perturbations of the human flora are usually necessary for the establishment of *S. maltophilia*. Accordingly, most cases of human infection occur in the setting of very broad-spectrum antibiotic therapy with agents such as advanced cephalosporins and carbapenems, which eradicate the normal flora and other pathogens. The remarkable ability of *S. maltophilia* to resist virtually all classes of antibiotics is attributable to the possession of antibiotic efflux pumps and of two β -lactamases (L1 and L2) that mediate β -lactam resistance, including that to carbapenems. It is fortunate that the virulence of *S. maltophilia* appears to be limited. Although a serine protease is present in some strains, virulence is probably a result of the host's inflammatory response to components of the organism such as LPS and flagellin.

S. maltophilia is most commonly found in the respiratory tract of ventilated patients, where the distinction between its roles as a colonizer and as a pathogen is often difficult to make. However, *S. maltophilia* does cause pneumonia and bacteremia in such patients, and these infections have led to septic shock. A severe form of pneumonia with significant mortality has been reported in neutropenic patients. Also common is central venous line-associated infection (with or without bacteremia), which has been reported most often in patients with cancer. *S. maltophilia* is a rare cause of ecthyma gangrenosum in neutropenic patients. It has been isolated from ~5% of CF patients but is not believed to be a significant pathogen in this setting. There are also less common sites of infection such as the endocardium, meninges, urinary tract, and skin; however, the sites of major concern remain the blood and lungs.

PART 5 Infectious Diseases TREATMENT *S. maltophilia* Infections The intrinsic resistance of *S. maltophilia* to most antibiotics renders infection difficult to treat. The antibiotics to which it is most often (although not uniformly) susceptible are TMP-SMX, ticarcillin-clavulanate, levofloxacin, minocycline, cefiderocol and tigecycline (Table 170-2). Ceftazidime is no longer recommended for treatment. A few retrospective studies show utility of minocycline, but relevant clinical outcomes have not been thoroughly evaluated. Consequently, combination therapy with TMP-SMX plus ticarcillin-clavulanate, levofloxacin, or high-dose minocycline is recommended for initial therapy pending susceptibility testing. Catheters must be removed early in the treatment of bacteremia. The treatment of proven, high-inoculum infections

due to

S. maltophilia is associated with frequent development of resistance during therapy. The newest β -lactam/ β -lactamase inhibitor combinations show mixed results against this organism probably because of the presence of two different β -lactamases, a penicillinase and a cephalosporinase, compounded by the presence of efflux pumps. Resistance to one or the other of the newer agents has already been noted, including to cefiderocol. The most controversial aspect of therapy of *S. maltophilia* is whether pulmonary cultures in a nonneutropenic patient with lung consolidation require treatment or represent colonization. Many clinicians opt not to treat such patients given the fact that the development of resistance is quite common, compromising a serious subsequent infection such as a bacteremia.

■ ■ FURTHER READING Bauer KA et al: Extended-infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infections. *Antimicrob Agents Chemother* 57:2907, 2013. Bowers DR et al: Outcomes of appropriate empiric combination versus monotherapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 157:1270, 2013. Brooke JS: *Stenotrophomonas maltophilia*: An emerging global opportunistic pathogen. *Clin Microbiol Rev* 25:2, 2012. Cattaneo C et al: *P. aeruginosa* bloodstream infections among hematological patients: An old or new question? *Ann Hematol* 91:1299, 2012. Fabre V et al: Antibiotic therapy for *Pseudomonas aeruginosa* bloodstream infections: How long is long enough? *Clin Infect Dis* 69:2011, 2019. Gupte A et al: High pyocyanin production and non-motility of *Pseudomonas aeruginosa* isolates are correlated with septic shock or death in bacteremic patients. *PLoS One* 16:e0253259, 2021. Horcajada JP et al: Epidemiology and treatment of multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* infections. *Clin Microbiol Rev* 32:e00031, 2019. Kalil AC et al: Executive summary: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 63:575, 2016. Peña C et al: Influence of virulence genotype and resistance profile in the mortality of *Pseudomonas aeruginosa* bloodstream infections. *Clin Infect Dis* 60:539, 2015. Wunderlink RG et al: Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): A randomized, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 21:213, 2021. David A. Pegues, Samuel I. Miller

Salmonellosis Bacteria of the genus *Salmonella* are highly adapted for growth in both humans and animals and cause a wide spectrum of disease. The growth of serotypes *Salmonella* Typhi and *Salmonella* Paratyphi is restricted to human hosts, in whom these organisms cause enteric (typhoid) fever. The remaining serotypes (nontyphoidal *Salmonella*, or NTS) can colonize the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. More than 200 serotypes of *Salmonella* are pathogenic to humans, in whom they often cause gastroenteritis and can be associated with localized infections and/or bacteremia. ■ ■ ETIOLOGY This large genus of gram-negative bacilli within the family Enterobacteriaceae consists of two species: *Salmonella enterica*, which contains six subspecies, and *Salmonella bongori*. *S. enterica* subspecies I includes almost all the serotypes pathogenic for humans. Members of the seven *Salmonella* subspecies are classified into >2600 serotypes (serovars); for simplicity, *Salmonella* serotypes (most of which are named for the city where they were identified) are often used as the species designation. For example, the full taxonomic designation *S. enterica* subspecies *enterica*

serotype Typhimurium can be shortened to *Salmonella* serotype Typhimurium or simply *S. Typhimurium*. Serotyping is based on antigenically diverse surface structures: the somatic O antigen (lipopolysaccharide cell-wall components), the surface Vi antigen (restricted to *S. Typhi* and *S. Paratyphi C*), and the flagellar H antigen. *Salmonellae* are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 μm by 0.4–0.6 μm . The initial

identification of *salmonellae* in the clinical microbiology laboratory is based on growth characteristics. *Salmonellae*, like other *Enterobacteriaceae*, produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase. In addition, all *salmonellae* except *Salmonella Gallinarum-Pullorum* are motile by means of peritrichous flagella, and all but *S. Typhi* produce gas (H_2S) on sugar fermentation. Notably, only 1% of clinical isolates ferment lactose; a high level of suspicion must be maintained to detect these rare clinical lactosefermenting isolates. Although serotyping of all surface antigens can be used for formal identification, most laboratories perform a few simple agglutination reactions that define specific O-antigen serogroups, designated A, B, C1, C2, D, and E. Strains in these six serogroups cause ~99% of *Salmonella* infections in humans and other warm-blooded animals. Wholegenome sequencing is used in epidemiologic investigations to identify the source of foodborne outbreaks and to explore the international transmission of multidrug-resistant *Salmonella* strains. ■ ■ **PATHOGENESIS** All *Salmonella* infections begin with ingestion of organisms, most commonly in contaminated food or water. The infectious dose ranges from 200 colony-forming units (CFU) to 10^6 CFU, and the ingested dose is an important determinant of incubation period and disease severity. Conditions that decrease either stomach acidity (an age of <1 year, acid suppression therapy, or achlorhydric disease) or intestinal integrity (inflammatory bowel disease, cytotoxic chemotherapy, prior gastrointestinal surgery, or alteration of the intestinal microbiome by antibiotic administration) increase susceptibility to *Salmonella* infection. Once *S. Typhi* and *S. Paratyphi* reach the small intestine, they penetrate the mucus layer of the gut and traverse the intestinal layer through phagocytic microfold (M) cells that reside within Peyer's patches. *Salmonellae* can trigger the formation of membrane ruffles in normally nonphagocytic epithelial cells. These ruffles reach out and enclose adherent bacteria within large vesicles by bacterium-mediated endocytosis. This process is dependent on the direct delivery of

Salmonella proteins into the cytoplasm of epithelial cells by the specialized bacterial type III secretion system. These bacterial proteins mediate alterations in the actin cytoskeleton that are required for *Salmonella* uptake. After crossing the epithelial layer of the small intestine, *S. Typhi* and *S. Paratyphi*, which cause enteric (typhoid) fever, are phagocytosed by macrophages. These *salmonellae* survive the antimicrobial environment of the macrophage by sensing environmental signals that trigger alterations in regulatory systems of the phagocytosed bacteria. For example, PhoP/PhoQ (the best-characterized regulatory system) triggers the alteration of the outer membrane by increasing the synthesis and transport of different outer-membrane proteins, lipopolysaccharides, and glycerophospholipids, so that the altered bacterial surface can resist microbicidal activities and potentially alter host cell signaling. In addition, *salmonellae* encode a second type III secretion system that directly delivers bacterial proteins across the phagosome membrane into the macrophage cytoplasm. This secretion system functions to remodel the *Salmonella*-containing vacuole, promoting bacterial survival and replication. Once phagocytosed, typhoidal *salmonellae* disseminate throughout the body in macrophages via the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow). Patients have

relatively few or no signs and symptoms during this initial incubation stage. Signs and symptoms, including fever and abdominal pain, probably result from secretion of cytokines by macrophages and epithelial cells in response to bacterial products that are recognized by innate immune receptors when a critical number of organisms have replicated. Over time, the development of hepatosplenomegaly is likely to be related to the recruitment of mononuclear cells and the development of a specific acquired cell-mediated immune response to *S. Typhi* colonization. The recruitment of additional mononuclear cells and lymphocytes to Peyer's patches during the several weeks after initial colonization/infection can result in marked enlargement and necrosis of the Peyer's patches, which may be mediated by bacterial products

that promote cell death as well as the inflammatory response. In the case of *S. Typhi* and *S. Paratyphi A*, many strains produce a toxin when localized within host cells. This toxin is then transported extracellularly and probably contributes to systemic symptoms as well as the unusual neuropsychiatric states that can be seen in severe typhoidal illness.

In contrast to enteric fever, which is characterized by an infiltration of mononuclear cells into the small-bowel mucosa, NTS gastroenteritis is characterized by massive polymorphonuclear leukocyte infiltration into both the large- and small-bowel mucosa. This response appears to depend on the induction of interleukin 8, a strong neutrophil chemotactic factor, which is secreted by intestinal cells because of nontyphoidal *Salmonella* colonization and translocation of bacterial proteins and LPS into host cell cytoplasm with subsequent activation of inflammasomes. The degranulation and release of toxic substances by neutrophils may result in damage to the intestinal mucosa, causing the inflammatory diarrhea observed with nontyphoidal gastroenteritis. An additional important factor in the persistence of NTS in the intestinal tract and the organism's capacity to compete with endogenous flora is the ability to utilize the sulfur-containing compound tetrathionate for metabolism in a microaerophilic environment. In the presence of intestinal inflammation, tetrathionate is generated from thiosulfate produced by epithelial cells through inflammatory cell production of reactive oxygen species. In contrast to nontyphoidal *Salmonellae*, typhoidal *Salmonellae* do not effectively colonize the intestinal tract but have evolved as systemic pathogens, largely through gene loss and perhaps by the loss of the ability to utilize butyrate within the human intestine.

CHAPTER 171 ENTERIC (TYPHOID) FEVER Enteric (typhoid) fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. Typhi* or *S. Paratyphi*. The disease was initially called typhoid fever because of its clinical similarity to typhus. In the early 1800s, typhoid fever was clearly defined pathologically as a unique illness based on its association with enlarged Peyer's patches and mesenteric lymph nodes. In 1869, given the anatomic site of infection, the term enteric fever was proposed as an alternative designation to distinguish typhoid fever from typhus. However, to this day, the two designations are used interchangeably.

Salmonellosis ■ ■ EPIDEMIOLOGY In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever—*S. Typhi* and *S. Paratyphi* serotypes A, B, and C—have no known hosts other than humans. Most commonly, food-borne or waterborne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures. With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. An estimated 9.2–21 million cases of typhoid fever, 5 million cases of paratyphoid fever, and 110,000–280,000 deaths occur each year. The highest estimated annual incidence rates of typhoid

fever are in the Indian subcontinent, including Pakistan, Bangladesh, Nepal, India, and Eastern Mediterranean and African regions, and exceed 1000 cases per 100,000 children in some urban areas (Fig. 171-1). A high incidence of enteric fever correlates with mixing of drinking water with human sewage. In endemic regions, enteric fever is more common in poor neighborhoods in large cities than rural areas and among young children and adolescents than among other age groups. Risk factors include fecally contaminated drinking water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced gastric acidity). Multidrug-resistant (MDR) strains of *S. Typhi* emerged in the 1980s in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol,

FIGURE 171-1 Estimated national typhoid fever incidence and worldwide typhoid conjugate vaccine introduction, 2019–2022. (Reproduced from M Hancuh et al: Typhoid fever surveillance incidence estimates, and progress toward typhoid conjugate vaccine introduction – Worldwide, 2018–2022. *MMWR Morb Mortal Wkly Rep* 72:171, 2023.) ampicillin, and trimethoprim—antibiotics long used to treat enteric fever. With the increased use of fluoroquinolones to treat MDR enteric fever in the 1990s, MDR strains of *S. Typhi* and *S. Paratyphi* with decreased susceptibility to ciprofloxacin (DSC; minimal inhibitory concentration [MIC], ≥ 0.125 $\mu\text{g/mL}$) or ciprofloxacin resistance (MIC, ≥ 1 $\mu\text{g/mL}$) emerged on the Indian subcontinent and have spread with human migration first to Southern Asia and more recently to Eastern and Southern Africa. These strains represent clone H58, which is increasingly associated with clinical treatment failure of fluoroquinolones. Since emerging in 2016 in urban slums of Sindh province in Southeastern Pakistan, an extensively drug-resistant (XDR) *S. Typhi* H58 clone with plasmid-mediated extended-spectrum beta-lactamase (ESBL) resistance has now become the dominant cause of typhoid fever in Pakistan. Air travel from Pakistan has facilitated the international spread of this XDR strain. Azithromycin resistance has emerged in multiple countries where azithromycin is used for first-line treatment of enteric fever and for mass administration for trachoma. PART 5 Infectious Diseases In the United States, the Centers for Disease Control and Prevention (CDC) estimates that typhoid fever affects 5700 persons each year, a number far in excess of the ~ 350 cases of typhoid fever and ~ 90 cases of paratyphoid fever reported annually. In 2015, the median age of patients with typhoid fever was 23 years, and it was 29 years for paratyphoid fever. Most cases of enteric fever were associated with international travel (78%), predominantly to Indian, Pakistan, and Bangladesh, and visiting friends and family. Only 3% of travelers diagnosed with typhoid fever had received *S. Typhi* vaccine within the previous 5 years. In 2015, 66% of *S. Typhi* in the United States were DSC, and $\sim 10\%$ were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX). Infection with DSC

S. Typhi was associated with travel to the Indian subcontinent. In the United States, domestically acquired cases of enteric fever are less often DSC or MDR compared with travel-associated cases and are most often sporadic, although outbreaks linked to contaminated food products and previously unrecognized chronic carriers continue to occur. ■ ■CLINICAL COURSE Enteric fever is a misnomer, in that the hallmark features of this disease— fever and abdominal pain—are variable. While fever is documented at presentation in $>75\%$ of cases, abdominal pain is reported in only 30–40%. Thus, a high index of suspicion for this potentially fatal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

<10 10–<100 100–<500 ≥500 Not available Not applicable Introduced TCV The mean incubation period for *S. Typhi* is 10–14 days but ranges from 5 to 21 days, depending on the inoculum size and the host's health and vaccination status. The most prominent symptom is prolonged fever (38.8°–40.5°C [101.8°–104.9°F]), which can continue for up to 4 weeks if untreated. *S. Paratyphi A* is thought to cause milder disease than *S. Typhi*, with predominantly gastrointestinal symptoms. However, a prospective study of 669 consecutive cases of enteric fever in Kathmandu, Nepal, found that the infections caused by these organisms were clinically indistinguishable. In this series, symptoms reported on initial medical evaluation included headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise (10%), and arthralgia (2–4%). Gastrointestinal manifestations included anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), and diarrhea (22–28%) more commonly than constipation (13–16%). Physical findings included coated tongue (51–56%), splenomegaly (5–6%), and abdominal tenderness (4–5%). Early physical findings of enteric fever include rash ("rose spots"; 30%), hepatosplenomegaly (3–6%), epistaxis, and relative bradycardia at the peak of high fever (<50%). Rose spots (Fig. 171-2; see also Fig. A1-9) make up a faint, salmon-colored, blanching, maculopapular rash located FIGURE 171-2 "Rose spots," the rash of enteric fever due to *Salmonella Typhi* or *Salmonella Paratyphi*.

primarily on the trunk and chest. The rash is evident in ~30% of patients at the end of the first week and resolves without a trace after 2–5 days. Patients can have two or three crops of lesions, and *Salmonella* can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in highly pigmented patients. Complications of typhoid fever are estimated to occur in ~27% of hospitalized patients and correlate with a longer duration of symptoms before hospitalization, host factors (host genetics, immunosuppression, acid suppression therapy, previous exposure, and vaccination status), strain virulence and inoculum, and choice of antibiotic therapy. Gastrointestinal bleeding (6%) and intestinal perforation (1%) most commonly occur in the third and fourth weeks of illness and result from hyperplasia, ulceration, and necrosis of the ileocecal Peyer's patches at the initial site of *Salmonella* infiltration (Fig. 171-3). Both complications are life-threatening and require immediate fluid resuscitation and surgical intervention, with broadened antibiotic coverage for polymicrobial peritonitis (Chap. 137) and treatment of gastrointestinal hemorrhages, including bowel resection. Neurologic manifestations occur in 2–40% of patients and include meningitis, Guillain-Barré syndrome, neuritis, and neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects. Uncommon complications whose incidences are reduced by prompt antibiotic treatment include disseminated intravascular coagulation, hemophagocytic syndrome, pancreatitis, hepatitis, hepatic and splenic abscesses and granulomas, endocarditis, pericarditis, myocarditis, orchitis, glomerulonephritis, pyelonephritis and hemolytic-uremic syndrome, severe pneumonia, arthritis, osteomyelitis, endophthalmitis, and parotitis. Up to 10% of patients develop mild relapse, usually within 2–3 weeks of fever resolution and associated with the same strain and susceptibility profile. Up to 10% of untreated patients with typhoid fever excrete *S. Typhi* in the feces for up to 3 months, and 2–5% develop chronic asymptomatic carriage, shedding *S. Typhi* in either urine or stool for >1 year. Chronic carriage is more common among women, infants, and persons who have biliary abnormalities or concurrent bladder infection with *Schistosoma haematobium*. *S. Typhi* and other salmonellae are adapted to survive in the gallbladder environment by forming biofilms on gallstones and invading gallbladder epithelial cells. Chronic carriage is associated with an increased risk of gallbladder cancer, which is much more common in locales where *S. Typhi* is common, such as the Indian subcontinent. ■ ■ **DIAGNOSIS**

Because the clinical presentation of enteric fever is relatively non specific, the diagnosis needs to be considered in any febrile traveler FIGURE 171-3 Typical ileal perforation associated with Salmonella Typhi infection. (From JM Saxe, R Cropsey: Is operative management effective in treatment of perforated typhoid? Am J Surg 189:342, 2005.)

returning from a developing region, especially the Indian subcontinent, and the Southeast Asian or African region. Other diagnoses that should be considered in these travelers include malaria, viral hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amebic liver abscesses, and acute HIV infection (Chap. 130). Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. In 15–25% of cases, leukopenia and neutropenia are detectable. Leukocytosis is more common among children, during the first 10 days of illness, and in cases complicated by intestinal perforation or secondary infection. Other nonspecific laboratory findings include moderately elevated values in liver function tests and muscle enzyme levels.

The definitive diagnosis of enteric fever requires the isolation of *S. Typhi* or *S. Paratyphi* from blood, bone marrow, other sterile sites, rose spots, stool, or intestinal secretions. The diagnostic sensitivity of blood culture is only ~40–60% and is lower with low blood sample volume and among patients with prior antimicrobial use or in the first week of illness, reflecting the small number of *S. Typhi* organisms (i.e., <15/mL) typically present in the blood. Because almost all *S. Typhi* organisms in blood are associated with the mononuclear cell/platelet fraction, centrifugation of blood and culture of the buffy coat can substantially reduce the time to isolation of the organism but do not increase sensitivity. Bone marrow culture is ~80% sensitive for detection of *S. Typhi* or

S. Paratyphi, and, unlike that of blood culture, its yield is not reduced by up to 5 days of prior antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield is >90%. Stool cultures, although negative in 60–70% of cases during the first week, can become positive during the third week of infection in untreated patients. CHAPTER 171 Rapid immunodiagnostic commercial tests, including Tubex and Typhidot, mainly focus on detection of IgM and IgG antibodies to O and H antigens and are widely used at point of care to diagnose typhoid and paratyphoid fever because they are simple and low cost. In a 2017 systematic review, these rapid diagnostic tests had sensitivities ranging from ~70% to 80% and specificities ranging from ~80% to 90% and thus are not sufficiently accurate to replace blood cultures as the main approach to diagnose enteric fever. PCR detection of

S. Typhi and *S. Paratyphi* in the blood have sensitivities of ~40–100%, depending on the gene targets. Molecular-based test platforms were scarce in resource-limited settings, but advancements and investments in molecular diagnostics arising from the SARS-CoV-2 pandemic have made feasible the widespread use of molecular tests for diagnosis of enteric fever. Salmonellosis TREATMENT Enteric (Typhoid) Fever Enteric fever is associated with an overall case-fatality rate of 2.5%, but mortality rates rise to 4.5% among hospitalized patients and to 10–30% if untreated. Prompt administration of appropriate antibiotic therapy prevents severe complications of enteric fever and reduces mortality to <1%. The initial choice of antibiotics depends on the susceptibility of the *S. Typhi* and *S. Paratyphi* strains in the area of residence or travel (Table 171-1). A 2022 systematic review of 27 randomized clinical trials for the treatment of enteric fever found no difference between ceftriaxone, fluoroquinolone, or azithromycin in comparative risk of treatment

failure, microbiologic failure, relapse, convalescent carriage, or adverse events. Oral cefixime also can be used to treat enteric fever but may increase the risk of clinical failure and time to defervescence compared with fluoroquinolones. Of note, most of the trials included in this review were small and conducted >20 years ago, and data on antimicrobial resistance could not be analyzed. Because of the high prevalence of strains of *S. Typhi* and *S. Paratyphi* with decreased susceptibility to ciprofloxacin (MIC >0.125 µg/mL) on the Indian subcontinent and in some locales in Africa, fluoroquinolones should no longer

TABLE 171-1 Antibiotic Therapy for Enteric Fever in Adults INDICATION AGENT DOSAGE (ROUTE) DURATION, DAYS Empirical Treatment Ceftriaxonea 2 g/d (IV) 10–14 Ciprofloxacinb 500 mg bid (PO) or 400 mg q12h (IV) 5–7 Azithromycin 1 g/d (PO)

Fully Susceptible Optimal treatment Ceftriaxone 2 g/d (IV) 10–14 Ciprofloxacin 500 mg bid (PO) or 400 mg q12h (IV) 5–7 Azithromycin 1 g/d (PO)

Alternative treatment Amoxicillin 1 g tid (PO) or 2 g q6h (IV)

Chloramphenicol 25 mg/kg tid (PO or IV) 14–21 Trimethoprim-sulfamethoxazole 160/800 mg bid (PO) 7–14 Multidrug-Resistant, Depending on the Susceptibility Pattern Optimal treatment Ceftriaxone 2 g/d (IV) 10–14 Ciprofloxacin 500 mg bid (PO) or 400 mg q12h (IV) 5–7 Azithromycin 1 g/d (PO)

Ceftriaxone-Resistant Optimal treatment Meropenemd 1 g q8h (IV) 1 g/d (PO) 10–14

Azithromycin PART 5 Infectious Diseases Eradication of Carriage Optimal treatment Ciprofloxacin 500–750 mg bid (PO)

Alternative treatment Azithromycin 500 mg (PO)

aOr another third-generation cephalosporin (e.g., cefotaxime, 2 g q8h IV; or cefixime, 400 mg bid PO). bOr 1 g on day 1 followed by 500 mg/d PO for 6 days. cOr ofloxacin, 400 mg bid PO for 2–5 days. dOr imipenem 500 mg q6h IV. be used for empirical treatment of enteric fever in these regions. Patients with concern for ceftriaxone-resistant *S. Typhi* infection based on a history of travel to Pakistan should be treated empirically with a carbapenem or azithromycin. Ceftriaxone, cefotaxime, and (oral) cefixime are effective for treatment of MDR enteric fever in adults and children, including that caused by DSC and fluoroquinolone-resistant strains. These agents clear fever in ~1 week, with failure rates of ~5–10%, fecal carriage rates of <3%, and relapse rates of 3–6%. Fluoroquinolones are effective against susceptible strains, with cure rates of ~98% and relapse and fecal carriage rates of <2%. Oral azithromycin is recommended for the treatment of uncomplicated enteric fever, including ESBL, DSC, and fluoroquinolone-resistant strains, and results in defervescence in 4–6 days, with rates of relapse and convalescent stool carriage of <3%. Against DSC strains, azithromycin is associated with lower rates of treatment failure and shorter durations of hospitalization than are fluoroquinolones. Carbapenems are increasingly being used to treat complicated XDR *S. Typhi* infections, but cost and IV route of administration are significant barriers. Most patients with uncomplicated enteric fever can be managed at home with oral antibiotics and antipyretics. Patients with persistent vomiting, diarrhea, and/or abdominal distension should be hospitalized and given supportive therapy as well as a parenteral third-

generation cephalosporin, a fluoroquinolone, or carbapenem, depending on the susceptibility profile. Therapy should be administered for at least 10 days or for 5 days after fever resolution. In a randomized, prospective, double-blind study of critically ill patients with enteric fever (i.e., those with shock and obtundation) in Indonesia in the early 1980s, the administration of

dexamethasone (an initial dose of 3 mg/kg followed by eight doses of 1 mg/kg every 6 h) with chloramphenicol was associated with a substantially lower mortality rate than was treatment with chloramphenicol alone (10% vs 55%). Although this study has not been repeated in the “post-chloramphenicol era,” severe enteric fever remains one of the few indications for glucocorticoid treatment of an acute bacterial infection. Steroid treatment beyond 48 hours may increase the relapse rate. The 2–5% of patients who develop chronic carriage of fluoroquinolone-susceptible *S. Typhi* can be treated for 4 weeks with oral ciprofloxacin or other fluoroquinolones, with an eradication rate of ~80%. A 4-week course of oral azithromycin can potentially be used to treat carriers with fluoroquinolone-resistant strains, but clinical experience is limited. Oral amoxicillin is associated with lower eradication rates than fluoroquinolones but can be considered in persons with fluoroquinolone-resistant strains that are susceptible to ampicillin. In cases of anatomic abnormality (e.g., biliary, kidney, or bladder stones), eradication often requires both antibiotic therapy and surgical correction. ■ ■

PREVENTION AND CONTROL Theoretically, it is possible to eliminate the salmonellae that cause enteric fever because they survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack adequate sewage disposal and water treatment, this goal is currently unrealistic. Thus, travelers to developing countries should be advised to monitor their food and water intake carefully and to strongly consider immunization against *S. Typhi*. Two unconjugated typhoid vaccines are commercially available in the United States: (1) Ty21a, an oral live attenuated *S. Typhi* vaccine (given on days 1, 3, 5, and 7, with revaccination with a full four-dose series every 5 years); and (2) Vi CPS, a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in a single dose, with a booster every 2 years). The minimal age for vaccination is 6 years for Ty21a and 2 years for Vi CPS. In a 2018 meta-analysis of 18 randomized clinical trials of vaccines for preventing typhoid fever in populations in endemic areas, the cumulative efficacy was 50% for Ty21a at 2.5 to 3 years and 55% for Vi CPS at 3 years. Although data on typhoid vaccines in travelers are limited, recent evidence suggests that typhoid vaccines are moderately effective (80%) in U.S. travelers. Currently, there is no licensed vaccine for paratyphoid fever. Unconjugated typhoid vaccines are poorly immunogenic in children <5 years of age because of limited ability to elicit T cell-dependent immune responses and immunologic memory. Compared with unconjugated vaccines, typhoid Vi polysaccharide conjugated vaccines are effective in children <2 years of age and elicit substantially longer duration of protection. The World Health Organization has recommended two typhoid conjugate vaccines (TCV) prioritized to prevent typhoid fever in countries with high incidence rates—Typbar TCV (manufactured by Bharat Biotech) in 2018 and TYPHIBEV (manufactured by Biological E) in 2020. A single intramuscular 0.5-mL dose of either TCV is safe and 79–95% effective, with antibody response persisting up to 7 years. As of 2023, TCV has been routinely introduced in national immunization programs in Pakistan, Nepal, Liberia, Zimbabwe, Malawi, and Samoa (Fig. 171-1). Typhoid vaccine is not required for international travel, but it is recommended for travelers to areas where there is a moderate to high risk of exposure to *S. Typhi*, especially those who are traveling to southern Asia and other developing regions of Asia, Africa, the Caribbean, and Central and South America and who will be exposed to potentially contaminated food and drink. Typhoid

vaccine should be considered even for persons planning <2 weeks of travel to high-risk areas. In addition, clinical microbiology or research laboratory staff at risk of occupational exposure to *S. Typhi* and household contacts of known *S. Typhi* carriers should be vaccinated. Because the protective efficacy of vaccine can be overcome by the high inocula that are commonly encountered in food-borne exposures, immunization is an adjunct and

not a substitute for the avoidance of high-risk foods and beverages. Immunization is not recommended for the management of persons who may have been exposed in a common-source outbreak. Enteric fever is a notifiable disease in the United States. Individual health departments have their own guidelines for allowing ill or colonized food handlers or health care workers to return to their jobs. The reporting system enables public health departments to identify potential source patients and to treat chronic carriers in order to prevent further outbreaks. In addition, because 1–4% of patients with *S. Typhi* infection become chronic carriers, it is important to monitor patients (especially child-care providers and food handlers) for chronic carriage and to treat this condition if indicated. **NON-TYPHOIDAL SALMONELLOSIS ■ ■ EPIDEMIOLOGY** Worldwide, NTS causes ~93–150 million enteric infections and ~60,000–155,000 deaths annually. In the United States, the CDC estimates that NTS causes ~1.35 million illnesses, 26,500 hospitalizations, and 420 deaths each year. In 2022, the incidence of NTS infection in the United States was 14.5 cases per 100,000 persons—the second highest rate after *Campylobacter* (17.4 cases per 100,000 persons) among the 8 food-borne enteric pathogens under active surveillance. Although declining modestly since 2017, the incidence rate remains above the U.S. Healthy People 2030 goal of 11.5 cases per 100,000 persons. Globally, *S. Typhimurium* and *S. Enteritidis* are the most common serotypes causing human disease, with large differences in serotype distributions between regions but lesser differences between countries within the same region. The incidence of NTS infection is highest during the rainy season in tropical climates and during the warmer months in temperate climates—a pattern coinciding with the peak in food-borne outbreaks. Rates of morbidity and mortality associated with NTS are highest among the elderly, infants, and immunocompromised individuals, including those with hemoglobinopathies, HIV infection, or infections that cause blockade of the reticuloendothelial system (e.g., bartonellosis, malaria, schistosomiasis, histoplasmosis). Over the past three decades, bloodstream infection caused by invasive NTS, predominantly associated with closely related lineages of

S. Typhimurium sequence type (ST) 313, as well as *S. Enteritidis* ST11, have emerged in sub-Saharan Africa and have spread to South Asia, the United Kingdom, and Brazil. These invasive NTS strains are adapted to person-to-person transmission through stepwise loss-of-function mutations and typically present with nonspecific febrile illness similar to enteric fever and uncommonly cause diarrhea. In 2017, there were ~535,000 invasive NTS cases and ~77,500 deaths, most of which (~80%) occurred in sub-Saharan Africa. Most (75%) *S. Typhimurium* ST313 isolates are MDR to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, and some are also resistant to ceftriaxone or ciprofloxacin, especially in South Asia. Recently, a sublineage of *S. Typhimurium* ST313 combining MDR with both ceftriaxone and azithromycin resistance has emerged in the Democratic Republic of the Congo. The incidence of invasive NTS infection is highest in children <5 years of age, exceeding 100 per 100,000 person-years in several West African countries, and risk is associated with malaria, HIV, malnutrition, and unclean drinking water sources. Transmission from asymptomatic stool carriers in the household and food or water sources has been proposed, but the sources of invasive NTS infection remain uncertain. Unlike *S. Typhi* and *S. Paratyphi*, whose

only reservoir is humans, NTS can be acquired from multiple animal and plant reservoirs that are part of the typical food supply. Transmission is most commonly associated with food products of animal origin (especially eggs, poultry, undercooked ground meat, and dairy products), fresh produce contaminated with animal waste, and contact with animals or their environments. In the United States, NTS are the second most common cause of food-borne outbreaks after norovirus, causing 30% of outbreaks and 35% of outbreak-associated illnesses. *S. Enteritidis* infection associated with chicken eggs emerged as a major cause of food-borne disease during the 1980s and 1990s.

S. Enteritidis infection of the ovaries and upper oviduct tissue of hens results in contamination of egg contents before shell deposition. Infection is spread to egg-laying hens from breeding flocks and through contact with rodents and manure. The number of *S. Enteritidis* outbreaks and the proportion attributable to egg-containing foods have continued to decline since the mid-1990s; these declines have coincided with interventions in the egg-producing and food service industries. Despite these control efforts, outbreaks of *S. Enteritidis* infection associated with shell eggs continue to occur. Transmission via contaminated eggs can be prevented by cooking eggs until the yolk is solidified and pasteurizing egg products. Increasingly, outbreaks of *S. Enteritidis* infection are associated with other foods, including meat, chicken, vegetables, dairy, and baked goods.

Salmonella serotype 4,[5],12:i:-, an antigenic variant of *S. Typhimurium* that lacks the second-stage flagellar antigen, has emerged since the 1990s as a foodborne pathogen primarily associated with pigs and pork products. This serotype is the second most common NTS in Europe and the fifth most common in the United States. These strains are MDR, with resistance to ampicillin, streptomycin, sulfonamides, and tetracycline. Increasing reports of plasmid-mediated colistin resistance in these strains have been linked to international travel to Thailand and swine farm isolates. Centralization of food processing and widespread food distribution have contributed to the increased incidence of NTS in developed countries. NTS accounts for a significant majority of illnesses and hospitalizations associated with multistate foodborne outbreaks and retail food establishment outbreaks in the United States. Manufactured foods to which recent multistate *Salmonella* outbreaks have been traced include peanut butter; milk products, including powdered infant formula; and various processed foods, including packaged breakfast cereal, salsa, frozen prepared meals, and snack foods. Large outbreaks have also been linked to fresh produce, including alfalfa sprouts, nuts/seeds, cantaloupe, mangoes, papayas, tomatoes, and the herbal substance kratom consumed for its stimulant effect; these items become contaminated by manure or water at a single site and then are widely distributed.

CHAPTER 171 Salmonellosis

In the United States, NTS infection associated with exotic pets is an ongoing clinical and public health problem, especially from contact with reptiles or amphibians, including iguanas, snakes, turtles, and lizards. Other pets, including hedgehogs, rodents, birds, baby chicks, ducklings, dogs, and cats, also are potential sources of NTS. Compared to foodborne outbreaks, outbreaks of NTS linked to animal contact more commonly affect young children (<1–4 years of age), result in hospitalization, and are more sustained. Increasing antibiotic resistance in NTS species is a global problem and has been linked to the widespread use of antimicrobial agents in food animals and especially in animal feed. In the United States, clinically important resistant NTS infections, defined as resistance to ampicillin or ceftriaxone or nonsusceptibility to ciprofloxacin, increased an estimated 40% during 2015–2016 (annual incidence ~220,000) compared with 2004–2008 (~159,000 infections). The incidence (51.0 per 100,000 persons per year) and proportion of invasive NTS infections that are

multidrug-resistant (75% with co-resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) is dramatically higher across all sub-Saharan African regions. In the United States, infections caused by NTS with any antimicrobial resistance compared to NTS with no resistance are less likely to be associated with an outbreak and more likely to be associated with international travel, an increased risk of hospitalization, hospital length of stay, and death. Outbreaks and sporadic cases of NTS resistant to third-generation cephalosporins have been reported, and international travel and adoption may have contributed to the global spread. Resistance is most commonly mediated by a transferable plasmid containing the *ampC* (*bla*CMY) gene and has been linked to the widespread use of the veterinary cephalosporin ceftiofur. In 2021, 3.0% of NTS isolates from humans in the United States were ceftriaxone resistant (MIC, ≥ 4 $\mu\text{g/mL}$). Ceftriaxone resistance is more common among invasive NTS isolates from sub-Saharan Africa ($>5\%$). Carbapenem-producing NTS have been reported sporadically in Europe, North Africa, and South Asia but remain extremely rare in the United States.

Since the early 2000s, strains of DSC NTS (MIC, ≥ 0.125 $\mu\text{g/mL}$) have emerged and have been associated with delayed response and treatment failure. In 2021, 10.6% of NTS isolates in the United States were DSC but only 0.5% of isolates were resistant to ciprofloxacin. These strains have diverse resistance mechanisms, including single and multiple mutations in the DNA gyrase genes *gyrA* and *gyrB*, mutations in the chromosomally encoded quinolone resistance-determining region, and plasmid-encoded quinolone resistance genes that are not reliably detected by nalidixic acid susceptibility testing or standard ciprofloxacin disk diffusion. In 2012, the U.S. Clinical Laboratory Standards Institute proposed a lower ciprofloxacin susceptibility breakpoint (≥ 0.06 $\mu\text{g/mL}$) for all *Salmonella* species to address this issue. Because some commercial test systems do not contain ciprofloxacin concentrations as low as the revised ≥ 0.06 $\mu\text{g/mL}$ susceptibility breakpoint, laboratories can also determine the ciprofloxacin MIC by Etest or another alternative method.

In the United States, azithromycin-resistant NTS strains (MIC, ≥ 32 $\mu\text{g/mL}$) remain uncommon (1.1% in 2021), but most such isolates were also MDR. Azithromycin resistance is conferred by plasmid-encoded macrolide resistance genes, and their emergence may be related to international travel, especially to Thailand, and azithromycin overuse. Sporadic cases of carbapenemase-resistant NTS have been reported in Europe, North Africa, and southern Asia. ■ ■ CLINICAL MANIFESTATIONS

Gastroenteritis Infection with NTS most often results in gastroenteritis indistinguishable from that caused by other enteric pathogens. Nausea, vomiting, and diarrhea occur 6–48 h after the ingestion of contaminated food or water. Patients often experience abdominal cramping and fever (38–39°C [100.5–102.2°F]). Diarrheal stools are usually loose, nonbloody, and of moderate volume. However, large-volume watery stools, bloody stools, or symptoms of dysentery may occur. Rarely, NTS causes pseudoappendicitis or an illness that mimics inflammatory bowel disease. PART 5 Infectious Diseases Gastroenteritis caused by NTS is usually self-limited. Diarrhea resolves within 3–7 days and fever within 72 h. Stool cultures remain positive for 4–5 weeks after infection—and in rare cases of chronic carriage ($<1\%$) for >1 year. Persistent NTS infection and relapsing diarrhea have been described in a small fraction of Israeli patients and were associated with in-host single-nucleotide mutations in key virulence regulators. For acute NTS gastroenteritis, antibiotic treatment usually is not recommended and may prolong fecal carriage. Neonates, the elderly, and immunosuppressed patients (e.g., transplant recipients, HIV-infected persons) with NTS gastroenteritis are especially susceptible to dehydration and invasive infection and may require

hospitalization and antibiotic therapy. Acute NTS gastroenteritis was associated with a threefold increased risk of dyspepsia and irritable bowel syndrome at 1 year in a study from Spain. Bacteremia and Endovascular Infections Up to 8% of patients with NTS gastroenteritis develop bacteremia; of these, 5–10% develop localized infections. Bacteremia and metastatic infection are most common with *Salmonella Choleraesuis* and *Salmonella Dublin* and among infants, the elderly, and immunocompromised patients, especially those with HIV infection. NTS endovascular infection should be suspected in high-grade or persistent bacteremia, especially with preexisting valvular heart disease, atherosclerotic vascular disease, prosthetic vascular graft, or aortic aneurysm. Arteritis should be suspected in elderly patients with prolonged fever and back, chest, or abdominal pain developing after an episode of gastroenteritis. Endocarditis and arteritis are rare (<1% of cases) but are associated with serious and potentially fatal complications, including valve perforation, endomyocardial abscess, infected mural thrombus, pericarditis, mycotic aneurysms, aneurysm rupture, aortoenteric fistula, and vertebral osteomyelitis. Invasive NTS disease is among the most common causes of bacteremia in children and in HIV-infected adults in sub-Saharan Africa and Southeast Asia, causing 39% of community-acquired bloodstream infection in one study. NTS bacteremia among these children is not

associated with diarrhea and has been associated with poor nutritional status, malaria, sickle cell disease, and HIV infection. *S. Typhimurium* ST 131, the most common cause of invasive NTS disease in sub-Saharan Africa, forms a specific clade that is associated with genome reduction and loss of traits required for environmental stress resistance, likely contributing to making this strain more human adapted. Localized Infections • INTRAABDOMINAL INFECTIONS

Intraabdominal infections due to NTS are rare and usually manifest as hepatic or splenic abscesses or as cholecystitis. Risk factors include hepatobiliary anatomic abnormalities (e.g., gallstones), abdominal malignancy, and sickle cell disease (especially with splenic abscesses). Eradication of the infection often requires surgical correction of abnormalities and percutaneous drainage of abscesses. CENTRAL NERVOUS SYSTEM INFECTIONS NTS meningitis most commonly develops in infants 1–4 months of age and in adults with HIV infection. It often results in severe sequelae (including seizures, hydrocephalus, brain infarction, and mental retardation), with death in up to 60% of cases. Other rare central nervous system infections include ventriculitis, subdural empyema, and brain abscesses. PULMONARY INFECTIONS NTS pulmonary infections usually present as lobar pneumonia, and complications include lung abscess, empyema, and bronchopleural fistula formation. The majority of cases occur in patients with lung cancer, structural lung disease, sickle cell disease, or glucocorticoid use. URINARY AND GENITAL TRACT INFECTIONS Urinary tract infections caused by NTS present as either cystitis or pyelonephritis. Risk factors include malignancy, urolithiasis, structural abnormalities, HIV infection, and renal transplantation. NTS genital infections are rare and include ovarian and testicular abscesses, prostatitis, and epididymitis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation. BONE, JOINT, AND SOFT TISSUE INFECTIONS *Salmonella* osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Prolonged antibiotic treatment is recommended to decrease the risk of relapse and chronic osteomyelitis. Septic arthritis occurs in the same patient population as osteomyelitis and usually involves the knee, hip, or shoulder joints. Reactive arthritis can follow NTS gastroenteritis and is seen most frequently in persons with the HLA-B27 histocompatibility antigen.

NTS rarely can cause soft tissue infections, usually at sites of local trauma in immunosuppressed patients. ■ ■DIAGNOSIS The diagnosis of NTS infection is based on isolation of the organism from freshly passed stool or from blood or another ordinarily sterile body fluid. Salmonella is increasingly identified by culture-independent molecular diagnostic tests due to increased sensitivity, rapid turnaround, and ability to detect multiple enteric pathogens in one test. Culture-independent positive specimens should have primary isolation performed to replicate results and recover NTS isolates. All NTS isolates should be referred to local public health departments for serotyping. Blood cultures should be obtained whenever a patient has prolonged or recurrent fever. Endovascular infection should be suspected if there is high-grade bacteremia (>50% of three or more sets of blood cultures positive). Echocardiography, CT, and indium-labeled white cell scanning are used to identify localized infection. When a localized infection is suspected, joint fluid aspiration, bone biopsy, abscess drainage, or cerebrospinal fluid should be cultured, as clinically indicated.

TREATMENT Nontyphoidal Salmonellosis Antibiotics should not be used routinely to treat uncomplicated NTS gastroenteritis. The symptoms are usually self-limited, and the duration of fever and diarrhea is not significantly decreased by

TABLE 171-2 Antibiotic Therapy for Nontyphoidal Salmonella Infection in Adults INDICATION AGENT
 DOSAGE (ROUTE) DURATION, DAYS Preemptive Treatmenta Ciprofloxacinb 500 mg bid (PO) 2–3
 Severe Gastroenteritisc Ciprofloxacin 500 mg bid (PO) or

400 mg q12h (IV) 500 mg once daily

Azithromycin

Trimethoprim-sulfamethoxazole 160/800 mg bid (PO)

Amoxicillin 1 g tid (PO)

Ceftriaxone 1–2 g/d (IV)

Bacteremia Ceftriaxoned 2 g/d (IV) 7–14 Ciprofloxacin 400 mg q12h (IV), then 500 mg bid (PO)
 Endocarditis or Arteritis Ceftriaxone 2 g/d (IV)

Ciprofloxacin 400 mg q8h (IV), then 750 mg bid (PO) Ampicillin 2 g q4h (IV) Meningitis
 Ceftriaxone 2 g q12h (IV) 14–21 Ampicillin 2 g q4h (IV) Other Localized Infection Ceftriaxone 2
 g/d (IV) 14–28 Ciprofloxacin 500 mg bid (PO) or

400 mg q12h (IV) Ampicillin 2 g q6h (IV) aConsider for neonates; persons >50 years of age with possible atherosclerotic vascular disease; and patients with immunosuppression, endovascular graft, or joint prosthesis. bOr ofloxacin, 400 mg bid (PO). cConsider on an individualized basis for patients with severe diarrhea and high fever who require hospitalization.

dOr cefotaxime, 2 g q8h (IV). antibiotic therapy. In addition, antibiotic treatment has been associated with increased rates of relapse, prolonged gastrointestinal carriage, and adverse drug reactions. Dehydration secondary to diarrhea should be treated with fluid and electrolyte replacement. Preemptive antibiotic treatment (Table 171-2) should be considered for patients at increased risk for invasive NTS infection, including neonates (probably up to 3 months of age);

■ 50 years of age with known or suspected atherosclerosis; and patients with immunosuppression, cardiac valvular or endovascular abnormalities, or significant joint disease. Treatment should consist of an oral or IV antibiotic administered for 48–72 h or until the patient becomes afebrile.

Immunocompromised persons may require up to 7–14 days of therapy. The <1% of persons who develop chronic carriage of NTS should receive a prolonged antibiotic course, as described above for chronic carriage of *S. Typhi*. Because of the increasing prevalence of antibiotic resistance, empirical therapy for life-threatening NTS bacteremia or focal NTS infection should include a third-generation cephalosporin or a fluoroquinolone (Table 171-2). If the bacteremia is low-grade (<50% of blood cultures positive), the patient should be treated for 7–14 days. Patients with HIV/AIDS and NTS bacteremia should receive 1–2 weeks of IV antibiotic therapy followed by 4 weeks of oral therapy with a fluoroquinolone. Patients whose infections relapse after this regimen should receive long-term suppressive therapy with a fluoroquinolone, azithromycin, or TMP-SMX, as indicated by bacterial sensitivities. If the patient has endocarditis or arteritis, treatment for 6 weeks with an IV β -lactam antibiotic (such as ceftriaxone or ampicillin)

is indicated. IV ciprofloxacin followed by prolonged oral therapy is an option. Early surgical resection of infected aneurysms or other infected endovascular sites is recommended. Patients with infected prosthetic vascular grafts that cannot be resected have been maintained successfully on chronic suppressive oral therapy. For extraintestinal nonvascular infections, a 2- to 4-week course of antibiotic therapy (depending on the infection site) is usually recommended. In chronic osteomyelitis, abscess, or urinary or hepatobiliary infection associated with anatomic abnormalities, surgical resection or drainage may be required in addition to prolonged antibiotic therapy for eradication of infection.

■ ■ **PREVENTION AND CONTROL** Immunization against Invasive NTS Despite an urgent need for safe and effective vaccines, there is no available vaccine to protect against invasive NTS disease, and few candidate vaccines have progressed into early clinical trials. Candidate human NTS vaccines are O-antigen based and contain *S. Typhimurium* and *S. Enteritidis* bivalent components. NTS vaccines will need to target young children and protect those in at-risk groups, including persons with HIV infection and with malaria and those with sickle cell disease. In addition, rapid, point-of-care diagnostics are critically needed to reduce the morbidity and mortality associated with invasive NTS infection. Despite widespread efforts to prevent or reduce bacterial contamination of animal-derived food products and to improve food-safety education and training, recent declines in the incidence of NTS in the United States have been modest compared with those of other food-borne pathogens. This observation probably reflects the complex epidemiology of NTS. Identifying effective risk-reduction strategies requires monitoring of every step of the food supply chain, including farm sources, slaughter and processing of raw animal or plant products, storage and transport, and preparation of finished foods. Contaminated food can be made safe for consumption by pasteurization, irradiation, or proper cooking. All cases of NTS infection should be

reported to local public health departments because tracking and monitoring of these cases can identify the source(s) of infection and help authorities anticipate large outbreaks. Prudent use of antimicrobial agents in both humans and animals is needed to limit the emergence of MDR and XDR Salmonella. CHAPTER 171 Salmonellosis ■ ■ FURTHER READING Cruz Espinoza LM et al: Occurrence of typhoid fever complications and their relation to duration of illness preceding hospitalization: A systematic literature review and meta-analysis. Clin Infect Dis 69:S435, 2019. Kuehn R et al: Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins. Cochrane Database Syst Rev 11:CD010452, 2022. Marchello CS et al: Complications and mortality of non-typhoidal salmonella invasive disease: A global systematic review and metaanalysis. Lancet Infect Dis 22:692, 2022. Medalla F et al: Increased Incidence of Antimicrobial-Resistant Non typhoidal Salmonella Infections, United States, 2004-2016. Emerg Infect Dis 27:1662-1672, 2021. Milligan R et al: Vaccines for preventing typhoid fever. Cochrane Database Syst Rev 5:CD001261, 2018. Onwuezobe IA et al: Antimicrobials for treating symptomatic non-typhoidal Salmonella infection. Cochrane Database Syst Rev 11:CD001167, 2012. Pulford CV et al: Stepwise evolution of Salmonella Typhimurium ST313 causing bloodstream infection in Africa. Nat Microbiol 6:327, 2021. Watkins LKF et al: Clinical outcomes of patients with nontyphoidal Salmonella infections by isolate resistance—foodborne diseases active surveillance network, 10 US sites, 2004 – 2018. Clin Infect Dis 78:535, 2024.

Revision #1

Created 2026-01-06 16:33:11 UTC by Omar Ayman

Updated 2026-01-06 16:33:11 UTC by Omar Ayman