Salmonella infections

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Salmonella, part of the Enterobacteriaceae family, are gram-negative, nonencapsulated, flagellated, facultative anaerobic, nonlactose fermenting bacilli that infect small intestinal epithelial cells. Pediatricians need to be familiar with the clinical features, epidemiology, diagnosis, management, and prevention of 3 distinct salmonellosis syndromes: nontyphoidal Salmonella (NTS) gastroenteritis, NTS extraintestinal disease, and typhoidal Salmonella (TS) enteric fever.

NTS infections are a worldwide common cause of gastrointestinal disease in immunocompetent individuals, whereas extraintestinal disease from NTS occurs predominantly in infants and other high-risk populations. TS are the cause of enteric (typhoid and paratyphoid) fever, a systemic disease with significant mortality and morbidity in developing countries.

NTS are a common cause of bacterial gastroenteritis worldwide, with 153 million cases leading to 57,000 deaths reported annually. In the United States, NTS cause 1.2 million illnesses and 450 deaths annually, with the highest incidence in children younger than 5 years. Most human NTS infections come from 2 serotypes of Salmonella enterica: Enteritidis and Typhimurium. NTS have a wide range of reservoirs and hosts, including humans, poultry, reptiles (turtles, lizards, snakes, iguanas), and amphibians (frogs, salamanders, newts). The major mode of transmission is by ingestion of contaminated animal food products. Other modes of transmission are contact with colonized animals, consumption of contaminated water and nonanimal food products, and fecal-oral spread. The most common sources of infection in the United States are chickens and eggs. Incubation is typically 6 to 12 hours (range, 6–72 hours). Immunocompetent individuals typically experience self-limited acute gastroenteritis with nausea, emesis, abdominal pain, fever, and watery, nonbloody diarrhea lasting less than 10 days. Some infected individuals can experience bloody diarrhea, whereas some may be asymptomatic. Extraintestinal disease, including bacteremia, meningitis, osteomyelitis, septic arthritis, pneumonia, and cholangitis, can occur, especially in high-risk populations and those infected with more virulent NTS serotypes. Individuals at higher risk for extraintestinal disease include infants, the elderly, those with compromised immune systems, and those with decreased stomach acidity. Patients with sickle cell disease are at increased risk for Salmonella osteomyelitis due to impaired splenic function and areas of bone infarction. Bacterial fecal shedding can continue for up to 12 weeks, especially in children younger than 5 years and in those treated with antibiotic drugs.

Enteric fever caused by TS is a severe illness with significant rates of morbidity and mortality in many parts of the developing world, with an estimated 31 million cases leading to more than 215,000 deaths worldwide annually. In the United States, enteric fever is rare, with approximately 400 cases annually, and is typically associated with international travel. TS species known to cause enteric fever are Salmonella enterica serotypes Typhi and Paratyphi, both with exclusive human
reservoirs and fecal-oral transmission. The average incubation period is 7 to 14 days (range, 3–60 days). Symptoms include fever, chills, malaise, myalgias, headache, cough, jaundice, constipation, or diarrhea and typically last 2 to 4 weeks without treatment. The classic description of blanching, erythematous (“rose-colored”) lesions on the trunk can be seen in the second week of illness, although this clinical finding is uncommon. Complications can include intestinal perforation, splenic and brain abscesses, disseminated intravascular coagulation, rhabdomyolysis with acute renal failure, and Guillain-Barre syndrome. Stool bacterial shedding continues for more than 3 months in approximately 10% and for more than a year in 4% of infected individuals. Individuals with prolonged fecal shedding might serve as infection reservoirs.

The NTS and TS serotypes induce different inflammatory responses. NTS invasion of small intestinal epithelial cells induces a robust local inflammatory response, typically limiting infection to the gastrointestinal tract. TS infection, on the other hand, does not induce a significant inflammatory response, allowing for bacterial invasion into the mesenteric lymphatic system and transient primary bacteremia. Typically, patients with TS are initially asymptomatic, and blood cultures are negative during the incubation period, which lasts 7 to 10 days after infection. From the bloodstream, bacteria disseminate to organs with a reticuloendothelial system (liver, spleen, gallbladder, bone marrow), where they multiply in macrophages and are shed into the bloodstream, resulting in sustained secondary bacteremia and symptom onset.

Diagnosis of NTS gastroenteritis is typically made by stool culture, and cultures from other sites (blood, cerebrospinal fluid, synovial fluid) confirm extraintestinal infection. Blood culture is the primary means of diagnosing TS enteric fever, with repeated cultures often required due to low sensitivity. Stool cultures have low diagnostic yield in TS. Most patients with NTS gastroenteritis have a normal complete blood cell count. Those with extraintestinal NTS and TS can have leukocytosis, leukopenia, anemia, and transaminitis. The Widal test is a rapid, inexpensive TS antibody test of low sensitivity and specificity but is widely used in developing countries to get preliminary results before blood culture positivity. Although additional commercial assays are emerging, they are not yet widely available.

Treatment of immunocompetent individuals with NTS gastroenteritis is supportive. Antibiotic drugs are not recommended because they do not shorten the illness and may cause prolonged fecal bacterial shedding. Hospitalization, blood cultures, and antibiotic drug therapy are indicated for NTS gastroenteritis in infants younger than 3 months and should be considered in other individuals at high risk for extraintestinal disease. Hospitalization and antibiotics (typically third-generation cephalosporins [ceftriaxone or cefotaxime]) are indicated for all individuals with NTS extraintestinal disease and those with TS. Because increasing Salmonella antibiotic drug resistance is a global public health concern, local susceptibility patterns should be taken into account in starting empirical treatment and therapy adjusted once sensitivities are available. Typical antibiotic drug therapy duration is 5 to 7 days for isolated gastroenteritis, 2 weeks for isolated bacteremia, and 4 to 6 weeks for extraintestinal infections. Those with severe enteric fever who present with shock, obtundation, or coma may benefit from systemic corticosteroids. Chronic TS carriers should be treated with 4 weeks of an oral fluoroquinolone after initial treatment and might require a cholecystectomy because carriage is thought to result from gallbladder biofilm formation.

There are currently no vaccines for either NTS or paratyphoid enteric fever. Two vaccines are available for Salmonella Typhi enteric fever. Vivotif® (Crucell Switzerland Ltd, Bern) is an oral live-attenuated vaccine approved for immunocompetent individuals 6 years and older. The vaccine requires 4 doses administered every other day. Typhim Vi® (Sanofi Pasteur Inc, Swiftwater, PA) is an intramuscular purified capsular antigen vaccine approved for individuals 2 years and older and requires a single dose. Neither vaccine provides complete protection. In enteric fever endemic areas, vaccination is recommended for all school-aged children. In the United States, vaccination is indicated for people traveling to endemic areas, those exposed to typhoid fever carriers, and laboratory workers in frequent contact with Salmonella Typhi.

Primary methods for Salmonella prevention include handwashing, proper disposal of human waste, and water treatment. In addition, avoiding contact with high-risk animals and thoroughly cooking food can prevent NTS. Families should be counseled about the potential risk of Salmonella carriage in high-risk pets and advised to keep pets and cages away from the kitchen or food preparation area and to wash hands after handling pets. High-risk pets...
should be avoided in child care centers, households with children younger than 5 years (especially infants), and other individuals at high risk for extraintestinal NTS disease. Although outbreaks in child care centers are rare; children with NTS gastroenteritis should be kept home until asymptomatic for at least 24 hours. Children with TS must not return to school or child care until they have 3 negative stool cultures obtained more than 48 hours after discontinuation of antibiotic drug therapy. All cases of *Salmonella* infection must be reported to the health department.

Although NTS *Salmonella* typically causes self-limited gastroenteritis requiring only supportive care, pediatricians need to be aware of the possibility of extraintestinal infection, especially in high-risk populations. TS enteric fever is a serious systemic illness common in areas of the developing world. Both NTS extraintestinal illness and TS require hospitalization and intravenous antibiotic drug therapy. Prevention is primarily through appropriate hygiene and avoidance of contact with high-risk pets.

**COMMENT:** *Salmonella* infections are fascinating in that more than 2,600 serotypes have been identified. The wide range of clinical presentations, from asymptomatic carriage to serious invasive disease leading to morbidity and even death, depends on the interplay between the virulence of the serotypes and the host factors. As mentioned in the *In Brief,* it is critical to not use antibiotic drugs in low-risk patients with uncomplicated *Salmonella* NTS gastroenteritis because this disease is self-limited, antibiotic drug administration can prolong the carrier stage, and the indiscriminant use of antibiotic agents contributes to the development of resistant organisms. In contrast, TS infections require treatment with antibiotic drugs due to the significant morbidity and mortality that can result. Hence, familiarity with the various presentations and access to a laboratory with the sophisticated ability for correct serotype identification is critical. I remember 2 recent patients for whom I provided care. One was a young, malnourished boy from Nigeria who presented with fever without an obvious etiology and was determined to have typhoid fever by serial blood cultures. Hence, the importance of obtaining blood cultures in febrile children without an etiology, especially when foreign travel is known. The other patient was a 7-month-old with *Salmonella* gastroenteritis. Through some detective work and good questioning on the part of an astute house of physician, it was determined that the parents had given the infant a chicken bone from dinner to chew on as a pacifier because she was teething. Determining the etiology of *Salmonella* infections is important to provide more education to families and the community.

Because positive *Salmonella* cultures should be reported to local health departments, this surveillance in collaboration with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) is incredibly helpful in identifying outbreaks, high-risk practices, or contamination of food products to inform population health.
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