Enteric Fever (Typhoid Fever)

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Enteric fever (more commonly termed typhoid fever) remains endemic in many developing countries. Given the ease of modern travel, cases are regularly reported from most developed countries, usually from returning travelers.

Etiology;

Typhoid fever is caused by Salmonella enterica serovar Typhi (S. Typhi), a gram-negative bacterium.

Epidemiology;It is currently estimated that over 21.7 million typhoid cases occur annually, with the vast majority of cases in Asia, with over 200,000 deaths. Following sporadic outbreaks of chloramphenicol-resistant typhoid, many strains of *S.* Typhi have developed plasmid-mediated multidrug resistance to all 3 of the primary antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole..

. Ingestion of foods or water contaminated with *S.* Typhi from human feces is the most common mode of transmission, although water-borne outbreaks due to poor sanitation or contamination can occur in developing countries. In other parts of the world, oysters and other shellfish cultivated in water contaminated by sewage or the use of night soil as fertilizer may also cause infection.

Pathogenesis;The disease occurs by the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs.

After ingestion, *S.* Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum *S.* Typhi crosses the intestinal mucosal barrier after attachment to the microvilli After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system, and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually symptomless, and blood cultures are frequently negative at this stage of the disease. The blood-borne bacteria are disseminated throughout the body and are thought to colonize the organs of the reticulo-endothelial system, where they may replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia, which coincides with the onset of clinical symptoms and marks the end of the incubation period

Clinical features;

The incubation period of typhoid fever is usually 7–14 days but is also dependent on the infecting dose (range 3–30 days). The clinical presentation varies from a mild illness with low-grade fever, malaise, and slight dry cough to a severe clinical picture with abdominal discomfort and multiple complications. Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

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The presentation of typhoid fever may also differ according to age, may be more dramatic in children <5 yr of age, with comparatively higher rates of complications and hospitalization. Diarrhea, toxicity, and complications such as disseminated intravascular complications are also more common in infancy, with higher case fatality rates.
Typhoid fever usually presents with high-grade fever with a wide variety of associated features such as generalized myalgia, abdominal pain, hepatosplenomegaly, abdominal pain, and anorexia. In children, diarrhea may be present in the earlier stages of the illness and may be followed by constipation. The fever may rise gradually, but the classic stepladder rise of fever is relatively rare. In about 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7th–10th day of the illness, and lesions may appear in crops of 10–15 on the lower chest and abdomen and last 2–3 days. These lesions may be difficult to see in dark-skinned children. Patients managed as outpatients will present with fever (99%) but have less emesis, diarrhea, hepatomegaly, splenomegaly, and myalgias than hospitalized patients. If no complications occur, the symptoms and physical findings gradually resolve within 2–4 wk; however, the illness may be associated with malnutrition in a number of affected children.

Complications;

Although **altered liver function** is found in many patients with enteric fever, clinically significant **hepatitis, jaundice, and cholecystitis** are relatively **rare** and may be associated with higher rates of adverse outcome. **Intestinal hemorrhage (<1%) and perforation** (0.5–1%) is infrequent among children. **Intestinal perforation** may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. A rising white blood cell count with a left shift and free air on abdominal radiographs may be seen in such cases. Rare complications include **toxic myocarditis**, which may manifest by arrhythmias, sinoatrial block, or cardiogenic shock **.Neurologic** complications are also relatively uncommon among children and may include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. **Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulation (DIC), hemolytic uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.**
The propensity to become a **carrier** follows the epidemiology of gall bladder disease, increasing with age and antibiotic resistance of the prevalent strains. In general, **rates of chronic carriage are lower in children than adults**.

Diagnosis;

The mainstay of the diagnosis of typhoid fever is a **positive culture from the blood or another anatomic site**. Results of blood cultures are positive in 40–60% of the patients seen early in the course of the disease, and **stool and urine cultures become positive after the 1st wk.** The stool culture result is also occasionally positive during the incubation period. However, the sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited as widespread antibiotic prescribing may render bacteriologic confirmation difficult. Although bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid, these are difficult to obtain and relatively invasive.Other laboratory investigations are **nonspecific**. While blood leukocyte counts are frequently low in relation to the fever and toxicity, but there is a

wide range in counts; in younger children leukocytosis is a common association and may reach 20,000–25,000/mm^3. Thrombocytopenia may be a marker of severe illness and accompany DIC. The classic **Widal test** measures antibodies against O and H antigens of *S.* Typhi but lacks sensitivity and specificity in endemic areas. Because many false-positive and false-negative results occur, **diagnosis of typhoid fever by Widal test alone is prone to error**. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect *S.* Typhi–specific antigens in the serum or *S.* Typhi Vi antigen in the urine.. **A nested PCR using *H1-d* primers has been used to amplify specific genes of *S.* Typhi in the blood of patients, and given the low level of bacteremia in enteric fever, is a promising means of making a rapid diagnosis**. Despite these new developments, in much of the developing world the mainstay of diagnosis of typhoid remains clinical.

Differential diagnosis.;

In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features, the early stages of enteric fever may be confused with alternative conditions such as acute gastroenteritis, bronchitis, or bronchopneumonia.

Treatment;.

The vast majority of children with typhoid can be managed at home with oral antibiotics and close medical follow-up for complications or failure to respond to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distension may require hospitalization and parenteral antibiotic therapy.

There are general principles of management of typhoid. Adequate rest, hydration, and attention are important to correct fluid-electrolyte imbalance. Antipyretic therapy (acetaminophen 120–750 mg every 4–6 hr PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus. Antibiotic therapy is critical to minimize complications. It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5–15% and 4–8%, respectively, whereas the quinolones and 3rd generation cephalosporins are associated with higher cure rates. The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hr for 48 hr) has been recommended among severely ill patients with shock, obtundation, stupor, or coma, this must only be done under strict controlled conditions and supervision, and signs of abdominal complications may be masked.

Prognosis;

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors include the age of the patient, general state of health and nutrition, causative *Salmonella* serotype, and appearance of complications. Infants and children with underlying malnutrition and those infected with multidrug-resistant isolates are at higher risk for adverse outcomes. Despite appropriate therapy, 2–4% of infected children may relapse after initial clinical response to treatment. **Individuals who excrete *S.* Typhi for ≥3 mo after infection are regarded as chronic carriers.** Children with schistosomiasis can develop a chronic urinary carrier state.

Prevention;.

Of the major risk factors for outbreaks of typhoid, contamination of water supplies with sewage is the most important. During outbreaks, therefore, a combination of central chlorination as well as domestic water purification are important. In endemic situations, consumption of street foods, especially ice cream and cut fruit has been recognized as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should therefore be made to target food handlers and high-risk groups for *S.* Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and given advice on handwashing and preventive strategies.

An oral, live-attenuated preparation of the Ty21a strain of *S.* Typhi has been shown to have good efficacy (67–82%) for up to 5 years. Significant adverse effects are rare. The Vi capsular polysaccharide can be used in people ≥2 yr of age. It is given as a single intramuscular dose, with a booster every 2 yr and has a protective efficacy of 70–80%. The vaccines are currently recommended for traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies.