Typhoid Fever

- Typhoid fever is a systemic infection with the bacterium *Salmonella enterica* serotype typhi.

The Bacterium

- *S. enterica* serotype typhi is a member of the family Enterobacteriaceae.
- *S. typhi* is similar to other salmonellae in that it is a gram-negative, flagellate, nonencapsulated, nonsporulating, facultative anaerobic bacillus that ferments glucose, reduces nitrate to nitrite, and synthesizes peritrichous flagella when motile.
- *S. typhi* has O and H antigens, an envelope (K) antigen, and a lipopolysaccharide macromolecular complex, called endotoxin, that forms the outer portion of the cell wall.

Epidemiology

- Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S. enterica* serotype typhi.
- It is a sporadic disease in developed countries that occurs mainly in returning travelers, with occasional point-source epidemics.
- In endemic areas, identified risk factors for disease include eating food prepared outside the home, such as ice cream or flavored iced drinks from street vendors, drinking contaminated water, having a close contact or relative with recent typhoid fever, poor housing with inadequate facilities for personal hygiene, and recent use of antimicrobial drugs.
- Today most of the burden of the disease occurs in the developing world, where sanitary conditions remain poor.

Pathogenesis

- The M cells, specialized epithelial cells overlying Peyer's patches, are probably the site of the internalization of *S. enterica* serotype typhi and its transport to the underlying lymphoid tissue.
- After penetration, the invading microorganisms translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes, and some pass on to the reticuloendothelial cells of the liver and spleen.
- Salmonella organisms are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver, and spleen.
- At a critical point that is probably determined by the number of bacteria, their virulence, and the host response, bacteria are released from this sequestered intracellular habitat into the bloodstream.

- The incubation period is usually 7 to 14 days (may last from 3-60 days)
- In the bacteremic phase, the organism is widely disseminated. The most common sites of secondary infection are the liver, spleen, bone marrow, gallbladder, and Peyer's patches of the terminal ileum.
- Gallbladder invasion occurs either directly from the blood or by retrograde spread from the bile.
- Preexisting gallbladder disease predisposes to chronic biliary infection, leading to long-term fecal carriage.
- Organisms excreted in the bile either reinvade the intestinal wall or are excreted in the feces.
- The interaction of host immunologic mediators and bacterial factors in infected tissue may contribute to the necrosis of Peyer's patches.
- The Peyer patches become hyperplastic with infiltration of chronically inflamed cells, which may lead to necrosis of the superficial layer and ulcer formation, with potential hemorrhage from blood vessel erosion or peritonitis from transmural perforation.
- Typhoid induces systemic and local humoral and cellular immune responses, but these confer incomplete protection against relapse and reinfection.

Mortality/Morbidity:

- The average case fatality rate is less than 1 percent, but the rate varies considerably among different regions of the world
- Case fatality rates of 10-50% have been reported from endemic countries when diagnosis is delayed or in cases of severe typhoid fever not treated with high-dose antibiotics.
**Clinical manifestation:**
- Initially the fever is low grade, but it rises progressively, and by the second week it is often high and sustained (39° to 40°C).
- In the first week, features are nonspecific, with headache, malaise, and a rising remittent fever as high as 103-104°F (39-40°C).
- Constipation and mild nonproductive cough are common.
- Beginning the eighth day of the disease the crops of 2-4 mm diameter pink maculopapules – roseola (rose spots) that fade with pressure develop on the upper abdomen and lower chest and more rarely on the back, arms, and legs. These lesions are easily missed in dark-skinned patients.
- Rose spots are caused by bacterial embolization, and culture results of skin snips of the spots may be positive.
- Relative bradycardia and a dicrotic pulse are also common at this time.
- During the second week of illness, the patient has a toxic appearance and seems apathetic with sustained pyrexia.
- A coated tongue, distended abdomen, hepatomegaly, and splenomegaly are common.
- It is unusual for a patient hospitalized with typhoid to have no abdominal symptoms and normal bowel movements.
- In the third week, the patient’s toxicity increases and weight loss is common.
- Pyrexia persists, and a delirious state (typhoid state) emerges.
- Pronounced abdominal distension develops, and liquid, foul, green-yellow diarrhea (pea soup diarrhea) is common.
- The patient is weak with thready pulse and tachypnea, and crackles may develop over the lung bases.
- Death may occur at this stage from overwhelming toxemia, myocarditis, intestinal hemorrhage, or perforation.
- In patients surviving into the fourth week, the fever, mental state, and abdominal distension slowly improve over a few days, but intestinal complications may still occur. Convalescence is prolonged, and most relapses occur at this stage.
- The duration of illness in an untreated individual is usually 4 weeks.
- Typhoid fever during pregnancy may be complicated by miscarriage, although antimicrobial treatment has made this outcome less common. Vertical intrauterine transmission from an infected mother may lead to neonatal typhoid, a rare but severe and life-threatening illness.

**Complications**
Complications occur in 10 to 15 percent of patients and are particularly likely in patients who have been ill for more than two weeks.
- Gastrointestinal bleeding is the most common, occurring in up to 10 percent of patients. It results from erosion of a necrotic Peyer’s patch through the wall of an enteric vessel.
- In 2 percent of cases, bleeding is clinically significant and can be rapidly fatal if a large vessel is involved.
- Intestinal (usually ileal) perforation is the most serious complication, occurring in 1 to 3 percent of hospitalized patients.
- Perforation may be manifested by an acute abdomen or, more covertly, by simple worsening of abdominal pain, rising pulse, and falling blood pressure in an already sick patient.
- A reduced level of consciousness or encephalopathy, often accompanied by shock, is associated with high mortality.
- The patient is commonly apathetic although rousable. Patients can be severely agitated, delirious, or obtunded, but complete stupor or coma is infrequent. The incidence of these neuropsychiatric presentations varies among countries 2-40%.

**Relapse**
- Occurs in 5 to 10 percent of patients, usually two to three weeks after the resolution of fever.
- The relapse is usually milder than the original attack.
The *S. enterica* serotype typhi isolate from a patient in relapse usually has the same antibiotic-susceptibility pattern as the isolate obtained from the patient during the original episode.

- Up to 10 percent of convalescing patients with untreated typhoid excrete *S. enterica* serotype typhi in the feces for up to three months; 1 to 4 percent become long-term carriers, excreting the organism for more than one year.
- Up to 25 percent of long-term carriers have no history of typhoid. Chronic carriage is more common among women and the elderly and in patients with cholelithiasis.
- Most carriers are asymptomatic. Patients with an abnormal urinary tract, such as those who have schistosomiasis, may excrete the organism in the urine for long periods.

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**TABLE 1. IMPORTANT COMPLICATIONS OF TI PHOID FEVER.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Complications</th>
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</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Gastrointestinal perforation, Gastrointestinal hemorrhage, Hepatitis, Cholecystitis (usually subclinical)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Asymptomatic electrocardiographic changes, Myocarditis, Shock</td>
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<tr>
<td>Neuropsychiatric</td>
<td>Encephalopathy, Delirium, Psychotic states, Meningitis, Impairment of coordination</td>
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<tr>
<td>Respiratory</td>
<td>Bronchitis, Pneumonia (<em>Salmonella enterica</em> serotype typhi, <em>S. pneumoniae</em>, <em>S. pseudintermedius</em>)</td>
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<tr>
<td>Hematologic</td>
<td>Anemia, Disseminated intravascular coagulation (usually subclinical)</td>
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<tr>
<td>Other</td>
<td>Focal abscess, Pharyngitis, Miscarriage, Relapse, Chronic carriage</td>
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**Histologic Findings:**

- The hallmark histologic finding in typhoid fever is infiltration of tissues by macrophages (typhoid cells) containing bacteria, erythrocytes, and degenerated lymphocytes.
- Aggregates of these macrophages are called typhoid nodules, which are found most commonly in the intestine, mesenteric lymph nodes, spleen, liver, and bone marrow but may be found in the kidneys, testes, and parotid glands.
• In the intestines, 4 classic pathologic stages occur in the course of infection:
  o (1) hyperplastic changes,
  o (2) necrosis of the intestinal mucosa,
  o (3) sloughing of the mucosa, and the development of ulcers. The ulcers may perforate into the peritoneal cavity.
  o (4) epithelization

Management
• The absence of specific symptoms or signs makes the clinical diagnosis of typhoid difficult. In areas of endemic disease, a fever without evident cause that lasts more than one week should be considered typhoid until proved otherwise.
• Blood cultures are the standard diagnostic method; provided a large volume of blood is cultured (15 ml in adults), they are positive in 60 to 80 percent of patients with typhoid.
• Culture of bone marrow is more sensitive. The result is positive in 80 to 95 percent of patients with typhoid, even patients who have been taking antibiotics for several days, regardless of the duration of illness.
• The sensitivity of blood culture is higher in the first week of the illness, is reduced by prior use of antibiotics, and increases with the volume of blood cultured and the ratio of blood to broth.
• Cultures have also been made from skin snips of rose spots.
• The sensitivity of stool culture depends on the amount of feces cultured, and the positivity rate increases with the duration of the illness. Stool cultures are positive in 30 percent of patients with acute typhoid fever.
• For the detection of carriers, several samples should be examined because of the irregular nature of shedding.

Serology is as follows:
  o The Widal test is the traditional serologic test used for the diagnosis of typhoid fever. The test measures agglutinating antibodies against flagellar (H) and somatic (O) antigens of *S. typhi*.
  o The Widal reaction is indicative of typhoid fever in only 40-60% of patients at the time of admission.
  o In acute infection, O antibody appears first, rising progressively, later falling, and often disappearing within a few months. H antibody appears slightly later but persists longer.
  o Rising or high O antibody titers generally indicate acute infection, whereas elevations of H antibody help to identify the type of enteric fever.
  o Numerous studies have shown that the sensitivity, specificity, and predictive values of this test vary dramatically among laboratories. This wide variation is caused by differences in patient population, antigens, and techniques. The Widal reaction is indicative of typhoid fever in only 40-60% of patients at the time of admission.
  o Indirect hemagglutination, indirect fluorescent *Vi* antibody, and indirect enzyme-linked immunosorbent assay for immunoglobulin M (IgM) and immunoglobulin G antibodies to *S. typhi* polysaccharide are available.

Treatment
  ➢ Chloramphenicol, amoxicillin, and trimethoprim–sulfamethoxazole remain appropriate for the treatment of typhoid fever in areas of the world where the bacterium is still fully susceptible to these drugs and where the fluoroquinolones are not available or affordable.
  ➢ There are few data on the treatment of pregnant women with typhoid. The beta-lactam antibiotics are considered safe.
  ➢ Adults and children with severe typhoid characterized by delirium, obtundation, stupor, coma, or shock benefit from the prompt administration of dexamethasone.
  ➢ The mortality rate was reduced from over 50 percent to 10 percent in Indonesian adults and children who were given dexamethasone at an initial dose of 3 mg per kilogram by slow intravenous infusion over a period of 30 minutes, followed by 1 mg of dexamethasone per kilogram given at the same rate every 6 hours for eight additional doses. Hydrocortisone at a lower dose was not effective.
Further Outpatient Care:

- Management of long-term carriers is as follows:
  - Prolonged courses of amoxicillin or co-trimoxazole may be effective, but the failure rate is high if the patient has chronic gallbladder disease. Ciprofloxacin (750 mg bid) and norfloxacine (400 mg bid) have been much more effective, with cure rates of 78% and 83%, respectively.
  - In nonendemic countries, patients should be kept under bacteriological surveillance after clinical recovery until 6 consecutive negative results are obtained on fecal and urine cultures. Long-term urinary carriers should be assessed for urinary tract abnormalities, including schistosomiasis.