

IN THE NAME OF GOD

ENTERIC FEVER

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- Enteric fever is characterized by severe systemic illness with fever and abdominal pain .
- The organism classically responsible for the enteric fever syndrome is *Salmonella enterica* serotype Typhi .
- Other *Salmonella* serotypes, particularly *S. enterica* serotypes Paratyphi A, B, or C, can cause a similar syndrome; however, it is usually not clinically useful or possible to reliably predict the causative organism based on clinical findings .
- Humans are the only reservoir for *S. Typhi* and *S. Paratyphi A*.

Classic presentation

- Enteric fever usually presents with abdominal pain, fever, and chills approximately 5 to 21 days after ingestion of the causative microorganism.
- Classic manifestations include relative bradycardia, pulse-temperature dissociation, and "rose spots" (faint salmon-colored macules on the trunk and abdomen).
- Hepatosplenomegaly, intestinal bleeding, and perforation may occur, leading to secondary bacteremia and peritonitis.
- Laboratory findings may include anemia, leukopenia, leukocytosis, and abnormal liver function tests.

- In the first week of illness, rising ("stepwise") fever and bacteremia develop .
- While chills are typical, frank rigors are rare . Relative bradycardia or pulse-temperature dissociation may be observed.
- In the second week of illness, abdominal pain develops and "rose spots" (faint salmon-colored macules on the trunk and abdomen) may be seen .
- During the third week of illness, hepatosplenomegaly, intestinal bleeding, and perforation due to ileocecal lymphatic hyperplasia of the Peyer's patches may occur, together with secondary bacteremia and peritonitis.
- Septic shock or an altered level of consciousness may develop; among 300 cases of typhoid fever in Indonesia, these findings were observed in approximately 15 percent of patients .
- In the absence of acute complications or death from overwhelming sepsis, symptoms gradually resolve over weeks to months.

Risk factors

- For individuals outside of endemic areas, a history of travel to settings in which sanitation is poor or contact with a known typhoid case or carrier is useful; however, a specific source or contact is identified in a minority of cases.
- Among individuals residing in endemic areas, enteric fever is more common in children and young adults than in older patients.

- **Gastrointestinal manifestations**

- Reports in the pre-antibiotic era suggested that constipation occurred more frequently than diarrhea .
- Subsequent reports suggest that these symptoms occur with approximately equal frequency or that diarrhea may be more common, particularly in young children and in adults with HIV infection .
- Specifically, the incidence of diarrhea in children with culture proven typhoid fever was 78 percent in a series from Australia and 50 percent in a report from Vietnam .
- Constipation occurs in approximately 30 percent of individuals perhaps more frequently in adults.
- Among 552 patients with culture-confirmed typhoid fever in Bangladesh, abdominal tenderness or distension (57 percent) and rectal bleeding (9 percent) were equally distributed across age groups .

- Intestinal perforation generally occurs more frequently among adults than children and is associated with high mortality rates.
- Although this complication was observed in 10 percent of 105 adults with enteric fever in a study from India this high rate from a hospital-based study is likely not representative of the general natural history of typhoid.
- Typhoid intestinal perforation usually occurs in the ileum during the third week of febrile illness and is due to necrosis of the Peyer's patches in the antimesenteric bowel wall .
- Affected patients present with increasing abdominal pain, distension, peritonitis, and sometimes secondary bacteremia with enteric aerobic and anaerobic microorganisms.

Neurologic manifestations

- Although headache is a frequent symptom reported in 44 to 94 percent of cases.
- Neurological manifestations including disordered sleep patterns, acute psychosis, myelitis, and rigidity have been observed but are uncommon, as are meningitis and focal central nervous infections with *S. Typhi* .
- Patients with severe enteric fever may develop "typhoid encephalopathy," with altered consciousness, delirium, and confusion.
- This has been observed in up to 17 percent of patients, with no clear frequency difference between children and adults .

- In one study of 38 patients in Indonesia with typhoid fever, delirium, obtundation, and stupor were grave prognostic signs, with a mortality rate as high as 55 percent .
- In this study, intravenous [dexamethasone](#) was administered in a randomized placebo-controlled fashion as an adjunctive to antibiotic therapy; a reduction in mortality from 55 to 10 percent was observed.
- In another series of 23 cases of typhoid encephalopathy from Bangladesh, the mortality rate was 13 percent; in a retrospective analysis of this series, survivors were more likely to have received intravenous dexamethasone .
- Cough is not rare and has been observed in approximately 20 to 45 percent; arthralgias and myalgias occur in about 20 percent.
- Focal extraintestinal manifestations, including involvement of the hepatobiliary, cardiovascular, respiratory, genitourinary, musculoskeletal, and central nervous systems, have been described as a result of bacteremic seeding, but are observed infrequently.

Laboratory abnormalities

- Patients with enteric fever frequently have anemia and either leukopenia or leukocytosis; leukopenia with left shift is typically seen in adults, while leukocytosis is more common in children.
- If observed in the third week of illness, leukocytosis should prompt suspicion of intestinal perforation.
- Abnormal liver function tests are frequently observed .In an outbreak in 34 patients, abnormal liver function tests were observed in all .
- In some patients, the clinical and laboratory picture may be suggestive of acute viral hepatitis .
- In one study comparing 27 patients with *Salmonella* hepatitis to 27 cases of viral hepatitis, *Salmonella* hepatitis was more frequently associated with **bradycardia** (42 versus 4 percent) and **fever >40°C** (44 versus 4 percent); serum aminotransferases also tended to be lower (peak serum ALT 296 versus 3234 international units/L).
- A potential diagnostic challenge in patients presenting with abnormal liver function tests is that the two infections may be present at once.
- Although nonspecific, serum C-reactive protein (CRP) is often elevated in patients with enteric fever .
- Cerebrospinal fluid studies are usually normal or reveal a mild pleocytosis (<35 cells/mm³), even in patients with neuropsychiatric symptoms .

DIFFERENTIAL DIAGNOSIS

- Evaluation of suspected enteric fever also includes consideration of other potential causes of fever, in particular :
- Malaria
- Amebiasis
- Rickettsial infections
- Leptospirosis
- Dengue fever
- other causes of bacteremia (including typhoidal tularemia)
- Bacterial gastroenteritis
- less common causes include leishmaniasis, Q fever.

- The possibility of enteric fever should be considered in a febrile patient living in, traveling from, or visiting from an endemic area.
- Duration of fever for more than three days or accompanying gastrointestinal symptoms (abdominal pain, diarrhea, or constipation) should heighten the suspicion.
- When enteric fever is suspected, blood and stool culture should be performed.
- Other specimens can be cultured, including bone marrow, which yields the most sensitive culture but is invasive and usually not warranted.
- The diagnosis of enteric fever is made by isolating *S. Typhi* or *Paratyphi* from a culture specimen in the setting of a compatible clinical illness.
- However, culture of most specimens is not highly sensitive, and other diagnostic tests (such as culture-independent methods and serology) are of limited clinical utility. Furthermore, even positive cultures usually require several days to incubate.

- It is important to recognize that the clinical syndrome of enteric fever is nonspecific, and the positive predictive value of a clinical diagnosis even in high-burden settings is typically less than 50 percent.
- Blood cultures are positive in 50 to 70 percent of patients with typhoid, depending upon the series and culture techniques used .Blood cultures may require several days of incubation.
- The diagnosis can also be made by culture of stool, urine, rose spots, or duodenal contents (via string capsule) .
- Stool culture is positive in up to 30 to 40 percent of cases, but is often negative by the time that systemic symptoms bring patients to medical attention .
- Polymerase chain reaction-based diagnostics have had limited sensitivity in most studies given the low concentration of bacteria during bacteremia .
- Bone marrow culture is the most sensitive diagnostic modality but is rarely indicated in routine clinical practice It may be reserved for complicated cases, including suspected treatment nonresponse due to antimicrobial resistance.
- Bone marrow cultures are positive in >90 percent of patients and may remain positive in as many as 50 percent of patients after as many as five days of antibiotics .
- In a systematic review of 10 studies in which 635 individuals were tested by both blood and bone marrow cultures, the sensitivity of blood culture was 66 percent when bone marrow culture results were used as the reference.

Widal test

- The Widal test detects anti-*S. Typhi* antibodies; this assay is of limited clinical utility in endemic areas because positive results may represent previous infection.
- The minimum titers defined as positive for the O (surface polysaccharide) antigens and H (flagellar) antigens must be determined for individual geographic areas; they are higher in developing regions than in the United States .
- When paired acute and convalescent samples are studied, a fourfold or greater increase is considered positive. Positive results have been reported in 46 to 94 percent of cases .
- In a study of healthy blood donors performed in central India, seropositivity for typhoid fever using the *S. Typhi* O antigen or *S. Typhi* H antigen was observed in 8 and 14 percent, respectively .In many other settings, specificity of Widal testing has been lower.
- Rapid antibody-based diagnostic tests have only moderate diagnostic accuracy in field testing .A 2017 Cochrane review and meta-analysis concluded that rapid diagnostic tests are not sufficiently accurate to replace blood culture .
- **Tubex**, which measures, had sensitivity and specificity of 78 and 87 percent, respectively **immunoglobulin (Ig)M antibodies to *S. Typhi* lipopolysaccharide.**
- **Typhidot**, which measures **IgM or IgG responses to an outer membrane protein**, had overall average sensitivity and specificity of 84 and 79 percent, respectively.
- **Newer approaches** are in development; antibody tests to **detect serum IgA against hemolysin E are promising.**

- Thus, when cultures are negative or not available, as in some resource-limited settings, the diagnosis of enteric fever is often made presumptively on the basis of a protracted febrile illness without other explanation.
- Empiric therapy is often appropriate in the absence of an alternative diagnosis because of the risk for severe sequelae with untreated enteric fever.

ANTIMICROBIAL THERAPY

- Enteric fever is usually treated with a single antibacterial drug.
- Antibiotic selection depends upon the severity of illness, local resistance patterns, whether oral medications are feasible, the clinical setting, and available resources.
- The optimal choice of drug and duration of therapy are uncertain .
- The main options are fluoroquinolones, third-generation cephalosporins, and [azithromycin](#).
- Extensively drug-resistant (XDR) strains (those resistant to five antibiotics: [ampicillin](#), [trimethoprim-sulfamethoxazole](#), [chloramphenicol](#), fluoroquinolones, and third-generation cephalosporins .
- **Carbapenems** are reserved for suspected infection with extensively drug-resistant (XDR) strains.
- In some circumstances, older agents such as [chloramphenicol](#), [ampicillin](#), or [trimethoprim-sulfamethoxazole](#) may be appropriate, but these drugs are generally not used widely because of the prevalence of resistance.

Empiric therapy

- When treating presumptively for enteric fever or before results of susceptibility testing are available, appropriate options for empiric therapy depend, in part, on the severity of disease and the risk of infection with an antibiotic-resistant isolate.

Severe or complicated disease

- For patients who have severe disease (eg, systemic toxicity, depressed consciousness, prolonged fever, organ system dysfunction, or other feature that prompts hospitalization), initial therapy with a parenteral agent is appropriate.
- The geographic region where infection was likely acquired helps inform the choice of parenteral agent because of the risk of resistance in certain locations.
- For most patients with severe or complicated enteric fever without recent travel to Pakistan or Iraq, we suggest empiric therapy with [ceftriaxone](#).
- If ceftriaxone is not available, [cefotaxime](#) is a reasonable alternative.

- Although some studies have demonstrated **slower time to defervescence** with **cephalosporins** (compared with fluoroquinolones), resistance to the third-generation cephalosporins is uncommon in most locations.
- ceftriaxone is likely to be an effective empiric agent in individuals without a history of travel to Pakistan or Iraq.
- However, if there is suspicion for ceftriaxone resistance, a carbapenem can be used while awaiting susceptibility testing.
- For patients with severe or complicated enteric fever acquired in Pakistan or Iraq (eg, following recent travel to those countries), we suggest empiric therapy with a carbapenem (eg, [meropenem](#)). This is because of the presence of XDR *S. Typhi* in these regions.
- Extensively drug-resistant typhoid
- Extensively drug-resistant (XDR) strains (those resistant to five antibiotics: [ampicillin](#), [trimethoprim-sulfamethoxazole](#), [chloramphenicol](#), fluoroquinolones, and third-generation cephalosporins).
- For patients with suspected or known enteric fever and severe systemic illness (delirium, obtundation, stupor, coma, or shock), we suggest adjunctive [dexamethasone](#) (3 mg/kg followed by 1 mg/kg every 6 hours for a total of 48 hours).

ANTIMICROBIAL RESISTANCE

- Treatment of enteric fever has been complicated by the development and rapid global spread of typhoidal organisms resistant to [ampicillin](#), [trimethoprim-sulfamethoxazole](#), and [chloramphenicol](#).
- Additionally, development of increasing resistance to fluoroquinolones and cephalosporins is a growing challenge.
- Most *S. Typhi* and *S. Paratyphi* isolates remain susceptible to [azithromycin](#) and [ceftriaxone](#) although resistant isolates have been reported.
- Increasing rates of full resistance to fluoroquinolones have also been reported; in some cases, these resistant isolates have been classified as a subclass of the **multidrug resistant (MDR) H58 typhoid strain** that had widely disseminated throughout Asia and some African countries .

- Relapse of enteric fever after clinical cure can occur in immunocompetent individuals; in such cases, it typically occurs two to three weeks after resolution of fever.
- The risk of relapse depends on the antibiotic used to treat the initial infection.
- Relapse rates with [chloramphenicol](#), a bacteriostatic agent, were 10 to 25 percent, but subsequent studies that have included multidrug-resistant *S. Typhi* infections and newer antibiotics have noted lower relapse rates of 1 to 6 percent.
- A longer treatment course with a third-generation cephalosporin is also reasonable.
- Surveillance studies of patients with acute typhoid fever have shown that up to 10 percent of untreated individuals shed bacteria in their stool up to three months post-infection
- With antibiotic treatment, approximately 5 percent of children continue to shed *S. Typhi* 30 days after onset of fever.
- To document clearance of post-acute stool shedding, samples are typically collected at least one week after discontinuation of antibiotics and at least one month after illness onset.
- Typically, three stool (with or without urine) samples are collected at least 24 hours apart. If any cultures are positive, repeat cultures should be performed monthly until there are three consecutive negative samples.

- Chronic carriage of Salmonellae is defined as excretion of the organism in stool for more than 12 months after the acute infection.
- Chronic carriage rates after *S. Typhi* infection range from 1 to 6 percent .
- **Risk factors** include older age (>50 years), female sex, gallbladder abnormalities, and gallstones.
- Risk factors for chronic urinary carriage include kidney stones and schistosomal infection .
- Management of chronic carriage generally consists of antimicrobial therapy.
- If eradication is not achieved with antimicrobial therapy, cholecystectomy may be warranted.
- The effectiveness of cholecystectomy in eradicating carriage is around 70 to 80 percent.
- The efficacy may be better with combined antibiotic and surgical management; however, available data are decades old.

Vi polysaccharide vaccine

- This consists of the Vi polysaccharide antigen. It is administered as a single intramuscular dose.
- It can also be given subcutaneously. If continued protection is needed, revaccination is recommended every two to three years.
- In a systematic review and meta-analysis of randomized controlled trials, efficacy at one, two, and three years was 69, 59, and 55 percent .

Ty21a vaccine

- This is a live oral vaccine that consists of an attenuated *S. Typhi* strain Ty21a.
- It is administered in three to four doses taken on alternate days. If continued protection is needed, revaccination is recommended every three to five years.

