Enteric fever: A clinical review
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Introduction
Enteric fever is a systemic salmonella infections characterized by prolonged fever, abdominal pain, sustained bacteremia, bacterial invasion and multiplication within the mononuclear phagocytic cells of liver, spleen and lymphocytes and payers patches.

The term Enteric fevers encompass both typhoid fever and paratyphoid fever as their main pathological involvement affect the lower part of small intestine. Salmonella typhi produces typhoid fever and Salmonella para A, B & C produce paratyphoid fever. Typhoid fever has got longer incubation period with severe pathology and clinical manifestations but paratyphoid has got shorter incubation period with milder pathology and clinical manifestations. Due to similar pathogenesis, pathology and clinical manifestations both typhoid and paratyphoid fever will be discussed together under the term of enteric fever.

Epidemiology
Typhoid and paratyphoid fevers are endemic in the Indian subcontinent, south and central America, and Asia, and is related to rapid population growth, increased urbanization, inadequate waste treatment, limited water supply, and over burdened health care system. It occurs during all season. Adults and children of all ages and both sexes equally susceptible to infection. In developing countries, most cases occur in school aged children and young adults. Although acquired immunity provides some protection, reinfactions have been documented. Salmonella typhi only infects man and disease transmitted from fecal carriers and patients. Females and older males are prone to become chronic fecal carriers, because of underlying cholecystitis. Salmonella typhi is resistance to drying and cooling, thus allowing bacteria for prolonged survival in dried sewage, water, food and ice. The typhoid bacilli enter the host by the oral route. The major vehicles of infection are water and food, contaminated by feces or urine of infected patients or carriers. A small proportion of typhoid cases may occur by direct transmission through contaminated hands. Rarely, transmission can occur in homosexual. Enteric fever can occur by transplacental infection from a bacteremic mother to her fetus. Flies have been shown to transmit typhoid bacilli.

In endemic region 15-35 age group with HIV positive individual the rate of clinical typhoid is about 25 fold greater than HIV negative individuals. Asymptomatic HIV positive patients have a typical clinical presentation and response to therapy. In AIDS patient it is associated with fulminate diarrhoea and or colitis and are for more likely to relapse.

Etiopathogenesis
The typhoid bacillus is a motile gram negative rod in the family of enterobacteriaceae. It has flagellar H antigen, a cell wall lipopolysaccharide O-antigen and a cell wall capsule, virulence Vi antigen. The somatic antigen i.e. O antigen confers serologic specificity of the organism. The capsular Vi-antigen is one of the virulent factor. These antigens play a critical role in permitting the organisms to invade the lymphoid tissue from the gut lumen and to multiply within macrophages.

After ingestion the organisms rapidly proceeds through the pylorus into the small bowel. After attachment to the microvilli, salmonella typhi penetrate the intestinal mucosa and travel first to the mesenteric glands and then into blood stream (primary bacteremia). The organisms are taken up from blood by reticuloendothelial
tissue (including liver, spleen and bone marrow) where they multiply silently until the end of the incubation period.

After proliferation in the reticuloendothelial system, the bacteremia occurs (secondary bacteremia). The gall bladder is particularly susceptible to infection. Local multiplication in the walls of the gall bladder produces a large amount of organisms, which secondarily reach the intestine through the bile. Circulating endotoxin, a lipopoly saccharide component of the bacterial cell wall, thought to cause prolonged fever and toxic symptom of enteric fever. Payer's patches become further affected by secondary bacteremia and by infected bile. Inflamed payer's patches may later ulcerate leading to hemorrhage and intestinal perforation. In carriers, a large number of virulent bacilli pass into the intestine daily and are excreted in to the stool, without entering the epithelium of host.

**Clinical course**

The incubation period of Salmonella typhi ranges from 3-21 days. The onset of symptom is insidious and initial symptom is fever, preceded by chills, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pain. The temperature increases in a stepwise fashion over the course of 2-3 days reaching a peak of 103°-104°F. Epistaxis may occur occasionally. Early intestinal manifestations include constipation, associated with abdominal distention and slight tenderness in the right iliac fossa. Early physical examination reveals bradycardia relative to high fever.

During the 2nd week, the patient become dull and apathetic with sustained high temperature. Erythematous maculopapular rash which blanch on pressure, known as rose spot, appears chiefly on the upper abdomen and thorax, in this week and lasts for only 2-3 days. Splenomegaly (in 75% cases) and hepatomegaly (in 30% cases) with cervical lymphadenopathy may be present.

3rd week is the week of complications. If therapy is not yet started, the patient becomes toxic and ill, high fever continues and delirious, confusional state (Typhoid state) sets in. Marked abdominal distention and 'pea soup' diarrhoea are common. Intestinal hemorrhage and perforation are likely to occur. Toxemic myocarditis is another various complication of this stage.

If therapy started and no complications arise, symptoms of physical findings gradually resolve within 2-4 weeks but malaise and lethargy may persist for an additional 1-2 months. In paratyphoid fever the course tends to be shorter and milder, but the onset is often abrupt with acute enteritis. Sometimes atypical manifestations occur in typhoid fever like, fever with burning micturation with normal urine examinations, diarrhoea in first week, isolated hepatomegaly, pneumonitis and bone marrow depression. Though presentation is atypical patients respond to the conventional treatment (Internet).

**Infants and young children**

Enteric fever rare in this group. The disease surprisingly mild at presentation making diagnosis difficult, though clinical sepsis can occur. Diarrhoea is more common than adult. Others may present with signs symptoms of lower respiratory tract infection.

**Neonates**

The neonatal disease usually begins within 3 days of delivery. Vomiting, diarrhoea and abdominal distension are common. Temperature is variable but may be as high as 105° F. Convulsions may occur. Hepatomegaly, Jaundice, anorexia and weight loss can be marked.

Approximately 10% patients suffer a relapse 1-3 weeks after apparent clinical recovery. This usually occurs within 2 weeks of stopping therapy. The relapse in usually milder than initial illness.
Approximately 1-5% of patients become asymptomatic, long-term, chronic carriers who shed salmonella typhi in either urine or stool for >1 year. Incidence is higher among women and among persons with biliary abnormalities like gall stone, carcinoma of gall bladder, and gastrointestinal malignancy. (Harrison)

Complications
Without treatment the disease may become serious and complications develop about 30% of cases and account for 75% of all deaths. Complications include:-
1. Intestinal hemorrhage,
2. Intestinal perforation,
3. Others are - anicteric hepatitis - bone marrow suppression - paralytic ileus - myocarditis - psychosis - cholecystitis - syndrome of inappropriate release of antidiuretic hormone (SIADH).

Diagnosis
The preferred method of diagnosis is isolation of salmonella typhi by culture of blood, stool and urine and bone marrow from iliac crest. Serological tests like WIDAL test maybe helpful. Blood culture is usually positive during the first 2 weeks of illness. Stool and urine culture are positive in 3rd weeks onward. When culture of the above mentioned materials are negative, bone marrow culture is done and it is positive nearly 90% cases. In WIDAL test the Oagglutinin titer of >1:80 or 4 fold rise support a diagnosis of typhoid fever. Whereas the Hagglutinin are more often nonspecifically elevated by immunization or previous infections with other bacteria. Serodiagnosis has limited value, false positive and false negative result may arises. Newer serodiagnostic test such as Vi indirect immunofluorescent antibody test and detection of IgM antibody to salmonella typhi lipopolysaccharide antigen by enzyme-linked immunosorbent assay (ELISA) are under investigation.

Other laboratory findings include
- Transient leukocytosis during the first 7-10 days of illness, but leucopenia (predominantly neutropenia) subsequently develops and is most severe during he 3rd week disease.
- Anaemia of variable severity with diminished platelet count.
- Liver function tests frequently show elevated aminotransferase and bilirubin concentration.
- In patients with diarrhoea stool shows fecal leukocytosis.

Differential diagnosis
1. Malaria, in particular falciparum malaria which does not have the characteristic periodicity of vivax malaria.
2. Brucellosis.
3. Acute liver abscess.
4. Infectious mononucleosis.
5. Typhus fever.

Management
General measure
It is very much important and includes sufficient bed rest, good nutrition, proper nursing care and careful observation for evidence of intestinal bleeding or perforation. Fluid replacement is very much essential and sometimes blood transfusion may be needed. Supportive treatment with antipyretics and vitamins is often helpful.

Specific treatment
The emergence of multi drugs resistant salmonella typhi (MDRST) has made the treatment limited and ciprofloxacin, a quinolone derivative, become the drug of choice as it found to be most effective drugs against enteric fever. The dose of ciprofloxacin is 750mg orally twice daily or 200mg intravenously twice daily for 2 weeks, but 5-10 days maybe sufficient.

Alternative drugs include co-trimoxazole with standard adult dose 640mg, trimethoprim and 320mg sulphamethxazole are given orally in two divided dose for 14 days. For children the
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dose is 185mg/m² of body surface area per day of the trimethoprim component for 14 days. Amoxicillin (750mg 6 hourly) and chloramphenicol (500mg 6 hourly) for 14 days. Ceftriaxone is effective against salmonella infection and the dose is 2gm I/V once daily for 7 days.

In case of children treatment with fluoroquinolones to MDRST maybe used with a dose of ciprofloxacin 15-25mg/kg body weight for 9-16 days with monitoring for possible damage of cartilage and arthropathy. In that case ceftriaxone can be given with a dose of 50-80mg/kg body weight for 5 days.

In carriers treatment should be continued at least 4 weeks. Cholecystectomy may also achieve this goal.

**Prognosis**
The mortality rate of typhoid fever is about 2% in treated case, with complications the prognosis is poor. Relapses occur in upto 15% of case.

**Prevention**

*General measure :
1. Cases and potentially exposed contacts should be instructed about hand washing after defecation and diaper changing and before food preparation or meals.  
2. Patient should be isolated and guidelines for the safe handling of fecal and other contaminated materials should be provided.  
3. All individuals who have Salmonella infection should be excluded from work, school or day nurseries until they are free of symptoms.  
4. Food of animal origin should be thoroughly cooked. Eggs should be boiled for at least 5 minutes.

**Immunization**

Immunization is generally recommended for household contacts of chronic carriers, for travelers of endemic areas, and during outbreaks. Two subcutaneous injections of heat-killed phenol-extracted whole typhoid vaccine at a dose of 0.5ml at intervals of 4 weeks, with booster dose given every 3 years if needed. Or first-generation live oral vaccine given as 1 capsule every other day for a total of 4 capsules. These vaccines give only partial protection and thus vaccinated persons should be still exercise dietary precaution.

**Conclusions**

There is rapid emergence of multi drug resistant typhoid fever. There are only a few drugs left to fight the infection. Appropriate health education, early diagnosis, and eradication of carrier stage can probably improve this situation.

**References**

5. Therapeutic re-appraisal of multiple drug resistant Salmonella typhi (MDRST) in Pakistani children, Hazir,-T ; Qazi,-S-A ; Abbas,-K-A; et-al, J-Pak-Med-Assoc, 2002 Mar: 52(3) : 123-7