

# Changing Trends in Enteric Fever

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## Introduction

The enteric fever syndrome is an acute systemic illness characterized by fever, headache and abdominal discomfort. Confirmed case of typhoid fever is defined, according to the World Health Organization (WHO), as a patient with fever ( $> 38^{\circ}\text{C}$ ) that has lasted for at least three days, with a laboratory confirmed positive culture of *S. Typhi*. Probable case of typhoid fever is a patient with fever ( $> 38^{\circ}\text{C}$ ) that has lasted for  $> 3$  days, with a positive serodiagnosis or antigen detection test but without *S. Typhi* isolation. The micro-organism was first isolated by Gaffkey, a German in 1884.

The most recent classification, based on DNA sequences, has left only 2 species, *S. enteritica* and *S. bongori*, further subdivided into subspecies and serovars. To avoid confusion, *S. enteritica* serovar Typhi continues to be referred to as *S. typhi*.

Two features characterize enteric fever in industrialized countries. One is the general decline in the incidence of the disease and the second is the concomitant rise in the percentage of travel-related enteric fever.

A recent study from Indonesia identified consumption of food from street vendors and flooding as being independently associated with

paratyphoid fever. In contrast, typhoid fever was associated with household risk factors, such as presence of a household member with recent typhoid fever, lack of soap for hand washing, and sharing food from the same plate.

Evidence of *Helicobacter pylori* infection also represents an increased risk of acquiring typhoid fever. Recurrent salmonellosis (usually *S. typhimurium*) is an AIDS defining criterion in HIV positive patients, though for reasons unknown this is rarely due to *S. typhi*. HIV positive patients are more prone to develop enteric fever and its frequent relapses.

## Clinical Features

The majority of patients with typhoid seen in affluent countries present with the triad of persistent fever, headache and abdominal symptoms (mainly abdominal pain and diarrhea). Diarrhea is present in approximately 50% of patients. Constipation is equally well known. Their symptoms rarely progress beyond this stage. The absence of abdominal symptoms does not exclude typhoid and in some patients the systemic symptoms very much dominate the clinical picture. In developing countries, patients tend to present later and are more likely to be seen with the vast array of less common symptoms and complications that are associated with typhoid.

Prominent temperature-pulse dissociation is a well-known feature of typhoid but it is not invariably present, nor is it unique to typhoid.

In one of the Indian study from JIPMER, Pondicherry; atypical manifestations observed were burning micturition with normal urine examination. Patients with MDR strains had atypical manifestations. Atypical manifestations do not necessarily mean a worse prognosis.

The enteric fever can present directly with any of the complications as the initial presentation. Rarely perforation of the colon have also been reported.

Travelers usually seek advice more promptly than do local patients; thus, the complications are usually less common in the traveler population.

## Diagnosis

Laboratory diagnosis of typhoid fever is based on three principles :

- A. Isolation of organism
- B. Detection of microbial antigen
- C. Titration of antibody against causative organism

Blood cultures are the standard diagnostic method, and the results can be positive in 60 – 80% of patients, provided that a large volume of blood (typically 15 ml for adults) is cultured.

The role of the classic Widal test is controversial, with divergent views on the test's utility in various areas of endemicity. Usually, O antibodies appear on days 6-8 and H antibodies on days 10-12 after the onset of the disease.

As per the one study from southeast asia, patients tested positive for the Widal agglutination test with titers ranging from 1:80 to 1:320, no Salmonella organism was encountered in some cultures. The results suggest that serological

investigations alone may not be a reliable index for the diagnosis of Salmonella infections. Malaria can interfere with serological diagnosis of typhoid and hence can lead to over diagnosis of typhoid.

Recent advances include the IDL Tubex® test by a Swedish company, which reportedly can detect IgM O9 antibodies. The O9 antigen used in the test is extremely specific because its immunodominant epitope is a rare dideoxyhexose sugar in nature. This antigen has been found in serogroup D salmonellae but not in other microorganisms. A positive result given by Tubex® invariably suggests a Salmonella infection. Tubex® detects IgM antibodies but not IgG. This makes it invaluable as an aid in the diagnosis of current infections.

Another rapid serological test, Typhidot®, makes use of the 50 kD antigen to detect specific IgM and IgG antibodies to S. Typhi and takes three hours to perform. This dot enzyme immuno assay (EIA) test offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values. The detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection. Since IgG can persist for more than two years after typhoid infection, the detection of specific IgG cannot differentiate between acute and convalescent cases.

A newer version of the test, Typhidot-M®, was recently developed to detect specific IgM antibodies only. This test can replace the Widal test, when used in conjunction with the culture method, for the rapid and accurate diagnosis of typhoid fever. The high negative predictive value of the test suggests that Typhidot-M® would be useful in areas of high endemicity.

The typhoid IgM dipstick assay is also being designed for the serodiagnosis of typhoid fever, through the detection of S. Typhi-specific

IgM antibodies in serum or whole blood samples.

There has been study on validation of a PCR for diagnosis of typhoid fever and salmonellosis by amplification of the *hliA* gene in clinical samples from Colombian patients. But, it may not be cost-effective.

Mixed infection with multiple *Salmonella* serotypes in the same patient is an unusual finding; but there have been isolated such case reports.

## Treatment

Resistance to commonly used antibiotics such as chloramphenicol, ampicillin and cotrimoxazole has been reported from different parts of India. Quinolones are being used as a first line therapy. Levofloxacin 750 mg administered orally once daily is an effective, safe, well-tolerated and cost-effective option in the treatment of typhoid fever in adult Indian males and non-pregnant females.

Third generation cephalosporins such as cefotaxime, ceftriaxone, and cefoperazone have been used successfully to treat typhoid fever, with courses as short as 3 days showing similar efficacy to the usual 10 to 14 days regimen, but it is recommended to treat with ceftriaxone for 10-14 days. Sensitivity of *S. typhi* isolates to cephalosporins have increased from 2001 – 2004 while that of *S. paratyphi A* showed a decline. Despite demonstrating *in vitro* killing of salmonellae, first- and second-generation cephalosporins and aminoglycosides are ineffective in treating enteric fever.

Azithromycin has shown promise in a limited number of trials. The main advantage of aztreonam and azithromycin is that they can be used in children and in pregnant or nursing females.

Most laboratories use disk diffusion for evaluation, the sensitivity of which does not reflect true sensitivities. Nalidixic acid resistance

is a marker for predicting low-level resistance to ciprofloxacin among *S. typhi* and also an indicator of treatment failure of ciprofloxacin. Clinical and Laboratory Standards Institute recommends testing for nalidixic acid resistance in all extraintestinal *Salmonella* isolates. Fluoroquinolone-susceptible, nalidixic acid-resistant isolates may not be eradicated by fluoroquinolone treatment. Typhoid fever caused by nalidixic acid-resistant *S. typhi* (NARST) infection is associated with poor clinical outcomes, probably due to delay in initiating appropriate antibiotic therapy.

Quinolones and zidovudine have a synergistic antibacterial effect against *Salmonella*, administration of both drugs may dramatically decrease the risk of recurrent infection.

## Surgery

Early surgery in enteric perforation is the only accepted form of treatment in modern day medicine and gives excellent results. Exploratory laparotomy continues to be the mainstay of surgical treatment and several different procedures are recommended in literature. As per the recent studies a first line laparoscopic approach in all patients with typhoid perforation is recommended; as it is a safe and effective method of managing such cases.

## Vaccinations

The 2 most readily available vaccines are the parenteral capsular polysaccharide vaccine and the oral live, attenuated vaccine.

Circumstantial evidence indicates that typhoid vaccine does not offer protection to travelers visiting areas of endemicity. Cases of enteric fever due to vaccine failure are no milder than those in whom vaccine was not received.

Recent concerns are the increasing incidence of paratyphoid fever in Asia, which is not covered by available typhoid vaccines. Crucially paratyphoid vaccine are urgently needed, and a bivalent preparation would be ideal. Finally,

pregnant travelers to an area where enteric fever is endemic should receive the parenteral capsular polysaccharide vaccine.

Three new attenuated *S. typhi* strains that could be used as live oral vaccines are currently at an advanced clinical stage of development.

1. the Ty800 live attenuated oral one-dose vaccine
2. the CVD908-htrA live attenuated oral vaccine
3. another attenuated *S. typhi* strain, which has been developed by Microscience (UK) as a live single dose oral typhoid vaccine.

## Conclusion

The classical picture has changed over the years. Atypical presentations seen more often than not nowadays may delay the clinical suspicion of the disease. Management of typhoid fever continues to pose a challenge. The absence of a reliable rapid diagnostic test, will test the diagnostic skills of the treating physician. Therapeutic strategies will have to take into account the local antibiotic sensitivity patterns of *S. typhi* while defining treatment.

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