API RECOMMENDATIONS

API Recommendations for the Management of Typhoid Fever

Rajesh Upadhyay[1], Milind Y Nadkar[2], A Muruganathan[3], Mangesh Tiwaskar[4], Deepak Amarapurkar[5], NH Banka[6], Ketan K Mehta[7], BS Sathyaprakash[8]

Introduction

Enteric fever is a condition that is taking its toll even now in India, where its prevalence doesn't seem to be decreasing in spite of the availability of antibiotics and vaccines in the market. With the emergence of antibiotic resistant strains of the pathogenic organisms, the management of this disease is becoming more challenging. Further, there are no standard India-specific guidelines to treat this scourge. In order to bridge this need gap and for the benefit of primary care doctors, the 'Enteric Conclave,' the first-of-its-kind, was conducted. This meeting was a very innovative initiative that facilitated a frank exchange of opinions between gastroenterologists, consulting physicians, and general practitioners, who had been brought together under a common roof to discuss the epidemiology, diagnosis, and management of typhoid. While gastroenterologists usually get to see only complicated forms of the disease, and consulting physicians mostly deal with cases that are severe, majority of the cases in India are taken care of by primary care doctors. Thus, the specialists barely see 15% of these cases, whereas it is the primary care doctor, who treats typhoid at the grass-root level. Many of these doctors are forced to manage their patients in the absence of diagnostic facilities such as blood culture and serological tests. Despite the advances in medicine in the developing countries, tackling a disease like typhoid may seem like a herculean task. Various important issues related to this major public health problem in India were deliberated in this focused group discussion. The practice patterns from across the country were compared, and the best clinical practices were pinpointed.

Epidemiological Concerns of Enteric Fever in the Indian Scenario

The term 'enteric fever' (EF) includes typhoid and paratyphoid fevers. Typhoid fever is caused by a Gram-negative organism, *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella typhi*), whereas paratyphoid fever is caused by any of the three serovars of *Salmonella enterica* subspecies *enterica*, namely *S. paratyphi* A, *S. schottmuelleri* (also called *S. paratyphi* B), and *S. hirschfeldii* (also called *S. paratyphi* C). Type A is the most common pathogen worldwide, whereas Type B predominates in Europe. Type C is rare, and is seen only in the Far East. The overall ratio of the disease caused by *S. typhi* to that caused by *S. paratyphi* is about 10 to 1.[1]

The panel of experts who participated in the meeting prefers to use the term 'enteric fever' instead of 'typhoid fever,' as the former covers both typhoid and paratyphoid. In adults, enteric fever tends to cause constipation. Therefore, the presence of diarrhea instead in such a case should raise suspicion of a co-infection. Long-term use of proton pump inhibitors (PPIs) increases the incidence of EF because less or no acid in the stomach facilitates the passage of bacteria without destruction by the gastric acid.[2]

Definitions[3]

Confirmed enteric fever: Fever ≥38°C for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi.*

Probable enteric fever: Fever ≥38°C for at least three days, with a positive serodiagnosis or antigen detection test but without *S. typhi* isolation.

Chronic carrier state: Excretion of *S. typhi* in stools or urine (or repeated positive bile or duodenal string cultures) for longer than one year after the onset of acute enteric fever; sometimes, *S. typhi* may be

Expert Panel

1. Director and Head, Dept. of Gastroenterology and Hepatology, Max Super-Specialty Hospital, New Delhi
2. Professor, Dept. of Medicine, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra
3. Adjunct Professor, Tamil Nadu Dr. MGR Medical University, Chennai, Tamil Nadu
4. Consultant Physician and Diabetologist, Asian Heart Institute, Mumbai, Maharashtra
5. Consultant Gastroenterologist, Bombay Hospital and Medical Research Center and Breach Candy Hospital, Mumbai, Maharashtra
6. Chief Hepato-Gastroenterologist, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra
7. Consulting Physician, Asian Heart Institute and Health Harmony, Mumbai, Maharashtra
8. Professor of Gastroenterology, MS Ramaiah Medical College, Bengaluru, Karanataka

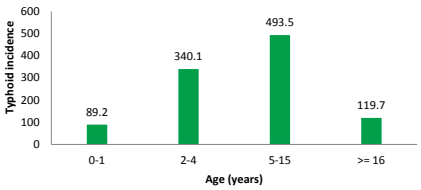

Fig. 1: Incidence of enteric fever in India per 10,0000 per year[6]

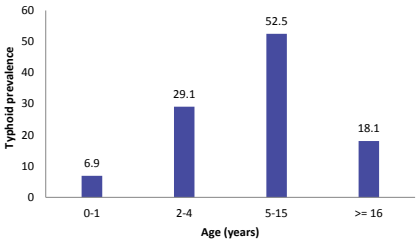

Fig. 2: Prevalence of enteric fever in India per 1,000 febrile episodes with blood culture taken[6]

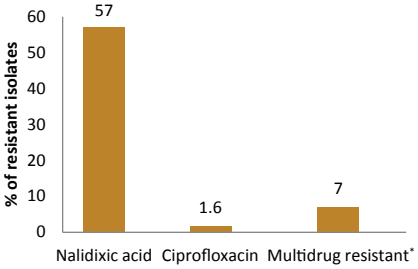

Fig. 3: Incidence of antimicrobial resistance in India[6]
***chloramphenicol, ampicillin, cotrimoxazole**

excreted without any history of enteric fever.

Contamination and Transmission

Humans are the only natural host and reservoir. The infection is transmitted by ingestion of food or water contaminated with feces. Contaminated water, and raw fruit and vegetables fertilized with sewage water, have been sources of outbreaks. The highest incidence occurs where water supplies serving large populations are contaminated with feces. Cold foods such as Ice-cream is recognized as a significant risk factor for the transmission of enteric fever.[3]

Global Prevalence of Enteric Fever

The world sees approximately 22 million new typhoid cases occur each year. The worst sufferers are young children in poor, resource-limited areas, who make up the majority of the new cases and mortality figures (215,000 deaths annually). Most of these deaths are due to *S. typhi* infection. The South-east Asian countries bear the brunt of the disease, particularly children and young adults. Other areas of prevalence include Africa and South America. Outbreaks have been reported from Zambia, Zimbabwe, Fiji and the Philippines. There is evidence that enteric fever is often under-reported, so the actual figures might be even more than those mentioned above.[4]

Prevalence of Enteric Fever in India

In disease-endemic areas, the annual incidence of enteric fever is about 1%. Peak incidence is seen in children 5–15 years of age; but in regions where the disease is highly endemic, as in India, children younger than 5 years of age may have the highest infection rates.[5]

In 2008, Ochiai et al conducted a prospective population-based survey in five Asian countries considered to be endemic for enteric, using standardized surveillance techniques, as well as standardized clinical and microbiological methods, to provide an updated assessment of the burden of enteric in Asia including India. Kolkata was chosen as the study site. Results obtained in India are depicted in Figures 1, 2 and 3.[6]

The results showed a high incidence of enteric fever in India, with the incidence in pre-school children (aged 2–5 years) being of the same order of magnitude as for school-aged children (aged 5–15 years). The high disease burden in pre-school children underscores the importance of vaccines and delivery systems in this age group, as well as older children and adolescents.[6]

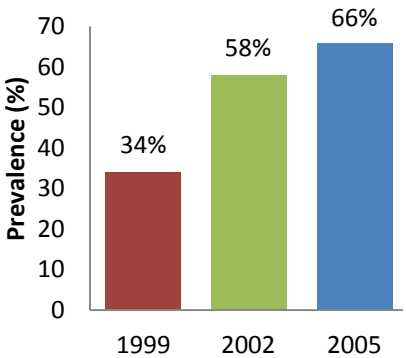

Fig. 4: Rise in the prevalence of multidrug resistance in the period 1999-2005[8]

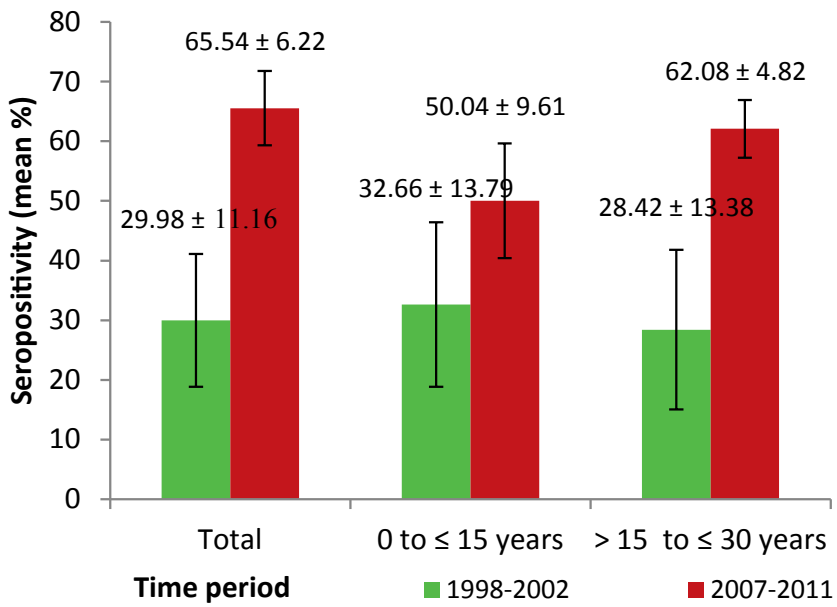

Fig. 5: Prevalence of seropositive titers in Indian patients with different age groups[9]

Table 1: Antibiotic sensitivity pattern in vivo for *Salmonella*[14]

Antibiotic	Patients (No.)	Responded (N%)	Resistant (N%)	Effervescences period*
Ampicillin	32	7 (21.8%)	25 (78.12%)	7.5
Amoxycillin	40	9 (22.5%)	31 (77.5%)	8.0
Cotrimoxazole	19	3 (15.78%)	16 (84.2%)	7.2
Ciprofloxacin	42	34 (80.5%)	8 (19.5%)	5.5
Ofloxacin	14	12 (85.71%)	2 (14.28%)	5.0
Amikacin	9	8 (88.8%)	1 (11.9%)	5.0
Cefixime	6	6 (100%)	-	6.5
Cefotaxime	5	4 (80%)	1 (20.0%)	6.5
Ceftriaxone	38	38 (100%)	-	5.0
Chloramphenicol	2	-	2 (100%)	-

*Mean in days

Fifty-seven percent of isolates were found resistant to nalidixic acid, 1.6% to ciprofloxacin, and 7% were multidrug-resistant (resistant to chloramphenicol, ampicillin and cotrimoxazole). Nalidixic acid resistance being an indirect marker of fluoroquinolone resistance; indicates high resistance to fluoroquinolone.[6] Since fluoroquinolones are empirical therapy of choice in enteric fever,[7] increasing rates of antibiotic resistance may necessitate the replacement of inexpensive antibiotics with newer, expensive agents, which may be unavailable and unaffordable to many poor patients. This also highlights the need to monitor patterns of resistance and to consider vaccines as disease control tools.[6]

A prospective study that was conducted in an Indian tertiary care hospital found that the prevalence of multidrug resistance (to chloramphenicol, ampicillin, and co-trimoxazole) in the organisms causing enteric fever had nearly doubled between 1999 and 2005 (Figure 4). While 80% of the patients were infected by *S. typhi*, *paratyphi A* was the pathogen in 9% of the cases. The remaining 11% of the patients were found to be infected by other *S. enterica* and *E. salmonella* groups, *typhimurium*, and *paratyphi C* and *senftenberg*.[8]

The social and economic impact of enteric fever is also high because patients with acute disease and complications may need to be hospitalized. This results in loss of work days and, consequently, income.[3] In the study by Ochiai *et al*,[6] 2% of Indian patients with enteric fever required hospitalization. A study analyzed the trend of antibody titers to O and H antigens of *S. typhi* over a period of ten years (1998-2002 and 2007-2011) in Indian patients of different age groups, who had been diagnosed with enteric fever. This study found that the overall seropositivity rates over the 10-year study period had increased significantly, as shown in Figure 5.[9]

Carrier State

On entering the human body, *Salmonella typhi* crosses the intestinal epithelial layer and is carried by macrophages to the liver, pancreas, and spleen. From the liver, the organisms can be shed into the gallbladder, where, being resistant to bile, they can stay for long periods and give rise to either an active infection (cholecystitis) or a chronic infection (carrier state).[10]

About 3 to 5% of infected people become carriers, particularly those with gallbladder abnormalities, such as gallstones. These people are often asymptomatic and can remain in this state for many years with little or no deleterious effect. However, they continue to excrete bacteria for prolonged periods of time, thus constituting a potential source of infection,[10] particularly in the setting of food preparation. The story of "Typhoid Mary," a cook in early 20th century New York who infected approximately 50 people (three fatally), highlights the role of asymptomatic carriers in maintaining the cycle of person-to-person spread.[11]

Besides, the chronic carrier state is the single most important risk factor for development of hepatobiliary carcinomas, as salmonella carriers with gallstones have been shown to carry an 8.47-fold higher risk of developing cancer of the gallbladder.[10]

It is for these reasons that the eradication of carriage is of prime importance.

Factors Affecting Epidemiology[12,13]

Age

The incidence of enteric fever in endemic areas is typically low in the first few years of life, peaking in school-aged children and young adults and then falling in middle age. Older adults are relatively resistant, probably due to frequent boosting of immunity.

Season

In endemic areas, peaks of transmission occur in dry weather or at the onset of rains. This is because warm and moist conditions favor the growth of the organism. Also, in summer, people are more likely to drink water outside their homes which may be of quality. In rainy season, the water may be contaminated.

Food habits

Eating food prepared outside the home, such as ice creams or flavored iced drinks from street vendors; drinking contaminated water; and eating vegetables and salads grown with human waste as fertilizer are major risks.

Other

A close contact or relative with recent enteric fever

Poor socioeconomic status

High population density

Poor personal hygiene

Lack of sanitation

Lack of safe water supply

Low latrine use

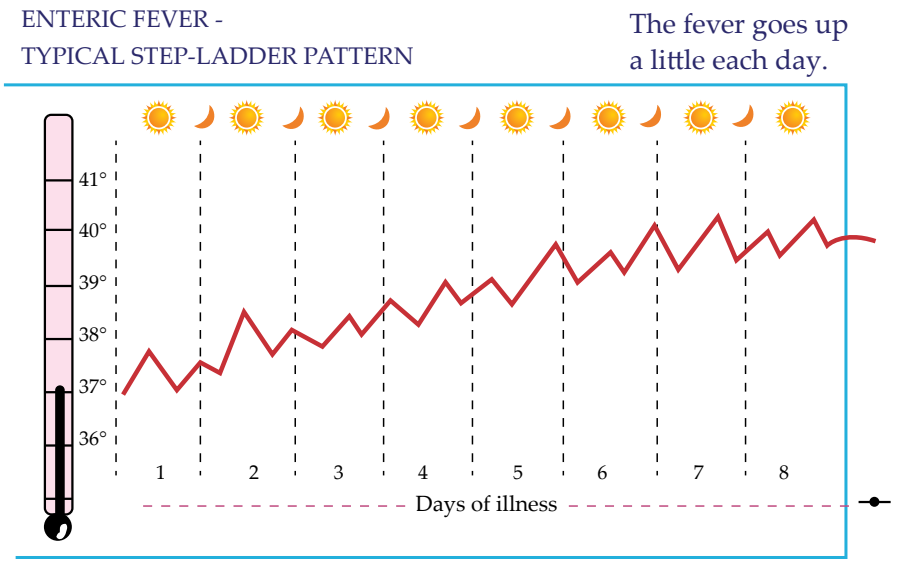

Fig. 6: Step-ladder pattern of fever

Living near an open water body

Recent consumption of antimicrobials

Transmission of enteric fever has also been attributed to flies, laboratory mishaps, unsterile instruments, and anal intercourse.

MDR Enteric Fever

In 1972, chloramphenicol-resistant *S. typhi* was first reported, and since then, chloramphenicol or multidrug-resistant enteric fever (MDREF) has been reported during outbreaks from many parts of the world. MDREF is most commonly seen in school-going children, but may affect younger children as well. MDREF is associated more commonly with hepatomegaly and splenomegaly. Resistance to ceftriaxone and cefixime has been seen in many studies, as is resistance to quinolones, indicating that Salmonella develops resistance rapidly against quinolones and hence, existing quinolones, like sparfloxacin, levofloxacin, gatifloxacin and moxifloxacin, should be used very rationally (Table 1).[14]

Economic Implications of Enteric Fever

Management of enteric fever in India is a costly affair. According to a prospective surveillance carried out in an urban slum in Delhi, the direct and indirect costs per episode of blood culture-confirmed enteric fever was INR 3,597 in an outdoor setting. This cost increased several fold (INR 18,131) in case of hospitalization. Almost similar observations have been made in other studies from other parts of the country. The costs increased several times due to increased hospitalizations and growing resistance to available antibiotics. These costs also add to the annual loss of income to the affected individuals and their families.[15]

The Diagnostic Approach in Enteric Fever

Isolation of *S. typhi* from blood, bone marrow, or a specific anatomical lesion is the only definitive way of diagnosing enteric fever.[3] The presence of characteristic clinical symptoms or the demonstration of a specific antibody response is suggestive of the disease, but not definitive.

Clinical Features

The panelists were of the opinion that a good clinical history and physical examination are very important for the diagnosis of enteric fever. In fact, the presence of fever with hepatosplenomegaly should make one think of this condition as one of the differential diagnoses. The participants were completely in agreement about this and felt that enteric fever can be diagnosed clinically by symptoms such as fever with rigors, headache, toxemia, abdominal pain (early in children), nausea, dry and coated tongue, relative bradycardia (most important clinical sign), and rose spots, which are rarely seen in clinical practice. First, the liver becomes palpable. The spleen usually becomes palpable only after a week.[2]

Typical Presentation[16]

7-14 days after ingestion of *S. typhi*

First Week

Fever

Exhibits a step-ladder pattern — i.e., the temperature rises over the course of each day and drops by the subsequent morning. The peaks and troughs rise progressively over time (Figure 6).

Gastrointestinal manifestations

Diffuse abdominal pain and tenderness; sometimes, fierce colicky pain in right upper quadrant.

Monocytic infiltration in Peyer's patches, causing inflammation and narrowing of bowel lumen, resulting in constipation.

Other symptoms

Dry cough

Dull frontal headache

Delirium

Stupor

Malaise

Second week

Progression of above signs and symptoms

Fever plateaus at 39-40°C

Rose spots

Salmon-colored, blanching, maculopapules on the chest, abdomen, and back, may not be visible in dark-skinned individuals

1-4 cm in width, less than 5 in number, present in up to 25% of patients

They resolve within 2-5 days.

Represent bacterial emboli to the dermis

Abdominal distension

Soft splenomegaly

Relative bradycardia — temperature elevations not accompanied by a physiological increase in the pulse rate

Dicrotic pulse — double beat, the second beat weaker than the first

Third week

Fever persists

Increase in toxemia

Anorexia

Weight loss

Conjunctivitis

Thready pulse

Tachypnea

Crackles over lung bases

Severe abdominal distension

Sometimes, foul, green-yellow, liquid diarrhea (pea-soup diarrhea)

Typhoid state — characterized by apathy, confusion, psychosis

Bowel perforation and peritonitis due to necrosis in Peyer's patches

Death may occur due to severe toxemia, myocarditis or intestinal hemorrhage

Fourth week

Gradual improvement in fever, mental state, and abdominal distension over a few days

Untreated patients may suffer from intestinal and neurological complications

Weight loss and debilitating weakness (may last for months)

Asymptomatic carrier state in some patients, who can transmit the bacteria indefinitely

Atypical presentation[16]

In some patients, enteric fever may not present in the typical manner described above. Presentation of the disease depends upon the host response, geographic region, race factors, and the infecting bacterial strain.

Fever: The characteristic stepladder fever pattern is seen in just about 12% of cases, and the fever has a steady insidious onset.

GI symptoms: Diarrhea, and not constipation, is common in young children in AIDS and one-third of immunocompetent adults with enteric fever

Other atypical manifestations:

Only fever

Severe headaches mimicking meningitis

Acute lobar pneumonia

Arthralgias

Urinary symptoms

Severe jaundice

Neurological symptoms in some patients, especially in India and Africa, such as delirium, Parkinsonian symptoms or Guillain-Barré syndrome

Pancreatitis

Meningitis

Orchitis

Osteomyelitis

Abscesses

Laboratory Evaluation

The expert panelists opined that a very toxic-looking patient with low counts should raise suspicion of enteric fever or a viral infection. Increased counts usually signify sepsis or perforation, with eosinopenia being an important finding. Monocytosis is also a usual finding. The presence of both eosinopenia and thrombocytopenia is strongly suggestive of enteric fever.[2]

Hematological tests[17,18]

Complete blood count

Hemoglobin: Mild anemia

Total leucocytic count (TLC): Low to normal

Eosinopenia

Platelets: Low to normal

Liver function tests:

Mildly abnormal

Serum transaminase levels 2 to 3 times the upper limit of normal

Clinical jaundice is uncommon

Significant hepatic dysfunction is rare

Cultures

Blood culture:

The specificity of a blood culture is 100%. At least 25-30 ml of blood should be collected for a good yield. The larger is the volume of blood, the better the yield. The ideal time of doing a blood culture is when the patient is having chills (and not when the fever spikes, as is commonly thought). Blood for culture should be taken before giving the first dose of antibiotics. However, in clinical practice, antibiotic therapy is initiated based on the diagnosis, and a blood culture is advised. It is always better to do an antibiotic sensitivity test along with the culture, as this will help to select the most appropriate antibiotic. Culture should be repeated after an hour and then after 24 hours. A single culture should not be encouraged. (The participants, on the other hand, revealed that they seldom did a blood culture in a primary healthcare setup, as it was expensive for the patients. They usually depended on the findings of the Widal test and the complete blood cell count, which shows eosinopenia and relative lymphocytosis). The positivity of the blood culture is as follows:

1st week – 90%

2nd week – 75%

3rd week – 60%

4th week – 25%

The positivity of blood culture decreases due to the administration of antibiotics; however, the blood culture will continue to test positive in resistant cases. Many a time, contaminants like coagulase-negative staphylococci in the blood culture may cause a false-negative report. Hence, the culture should be done with due caution. A clot culture is also being done.[2] The cost of a blood culture in India ranges from ₹600 to ₹800.

Culture involves inoculation of

the specimen (blood, bone marrow or stool) into an enrichment broth, and when a growth appears, making subcultures on solid agar. Biochemical testing is done to identify the colonies obtained. This is further confirmed by slide agglutination with appropriate antisera.[19]

Direct blood culture followed by microbiological identification remains the gold standard in the diagnosis of enteric fever.[20] Blood culture shows growth of the organism in 80% to 100% of patients,[17] particularly those with a history of fever for 7-10 days.[3] However, patients who have started antibiotics may not show any growth.[17]

The sensitivity range of blood culture is estimated to be between 40% and 80%. The sensitivity may be low in endemic areas with high rates of antibiotic use, making it difficult to estimate the true specificity.[18]

Failure to isolate the organisms can be due to delay in diagnosis, limitations of laboratory media, widespread and irrational use of antibiotics, and low volume of blood cultured, especially in children.[21] The probability of recovering the organisms is directly proportional to the volume of blood drawn; hence, it is essential to have an adequate volume of blood taken for culture.[20] Due to the higher levels of bacteremia in children compared to that in adults, at least 10-15 ml of blood from schoolchildren and adults, and 2-4 ml from toddlers and preschool children should be taken to achieve optimal isolation rates.[3]

Limitations in use

Less sensitive for diagnosis of infection among children as compared to adults[22]

Positive in only 40-60% of cases, usually early in the course of the disease[18]

Expensive and requires specialist facilities and personnel[20]

S. typhi and *S. paratyphi* A are not always culturable even if good microbiological facilities are available[20]

Bone marrow culture:

Culture of the bone marrow aspirate is the gold standard for the diagnosis of enteric fever,[3] and can yield positive results even if the patient has started antibiotics.[23]

It is of particular value in the patients who have been treated previously, have a long history of illness and had a negative blood culture with the recommended volume of blood.[3]

This test has a sensitivity of 55-67% and a specificity of 30%.[18] The positivity rate can further be increased to almost 100% if FAN culture medium is used and growth is monitored in automated culture systems.[23]

Speaking about bone marrow culture, the participants declared that this investigation is never carried out at the primary healthcare level. Even otherwise, it is avoided considering that it is costly as well as painful. The expert panelists informed that unlike blood culture, bone marrow culture remains positive even after the administration of antibiotics. Thus, it is more suitable for hospitalized and very sick patients.[2]

Limitations in use

Although the most sensitive, it is an invasive procedure, and cannot be performed outside specialist settings[20]

Has limited clinical value, especially in ambulatory management[18]

The specimen is difficult to obtain

Stool culture:

Stool culture can help in detecting typhoid carriers. Stool should be collected from acute patients in a sterile wide-mouthed plastic container and should preferably be processed within two hours of collection. The larger is the quantity of stool collected, the greater will be the likelihood of getting a positive result. Rectal swabs can be obtained instead of stool samples but they are less successful in isolating the organism.[3] A stool culture in India costs about ₹350 to ₹450.

All the panelists were in agreement about the need to do repeat stool cultures to detect carriers, as they tend to shed the bacteria sporadically. Chefs, in particular, should get their stool culture done to rule out carrier states, as they are likely to infect a large number of people when cooking.[2]

Limitations in use

Sporadic shedding of the organism in stools potentially compromises the stool culturing approach[20]

Becomes positive only after the first week of infection and has a much lower sensitivity than blood culture (30% vs. 40-90%)[18]

Sensitivity is low in developing countries[18]

Not routinely used for follow-up[18]

Urine culture:

Urine culture, according to the experts, is not usually done. Positivity of urine culture increases in carriers with urinary obstruction.[2]

Urine culture for enteric fever has variable sensitivity, the range being 0-58%.[18] In India, the cost of a urine culture varies from ₹350 to ₹450.

Rose spot culture:

Punch-biopsy samples of rose spots may be cultured to yield a sensitivity of 63% and may be positive even in patients who have reviewed antibiotics.[16]

Serum culture:

To conduct serum culture, 1-3 ml of blood is inoculated into a tube without anticoagulant. When the convalescent stage starts about 5 days later, a second sample is collected. After clotting, the

serum is separated and tested immediately or stored for a week without affecting the antibody titre.[3]

Duodenal aspirate culture:

Sharing their experiences with regard to duodenal aspirate culture, the panelists explained that this investigation may have good sensitivity because bile directly enters the duodenum. However, they added that this test is not practical and is more of academic interest. A culture of the duodenal aspirate in chefs can help to detect carriers amongst them. Other materials which can be cultured include bile, rose spot discharge, pus from a suppurative lesion, and CSF or sputum, if the patient has complications. At autopsy, culture from the liver, spleen, gall bladder, and mesenteric lymph nodes is also positive.[2]

In a study[24] of 36 patients with bacteriologically proven enteric fever, culture of duodenal contents (obtained with string capsules) was found to be as sensitive in diagnosis as bone marrow culture and more effective than blood and stool cultures in recovery of *S. typhi*. The sensitivity of duodenal content culture was not affected by the duration of illness or antibiotic therapy. Even on the seventh day of antibiotic treatment, the duodenal content culture was positive in eight of 17 patients, whereas stool culture was positive in only two of the same patients.

Apart from good sensitivity, duodenal content culture is simple, economical and can be performed with minimal facilities.[24] However, this method is not widely performed due to poor tolerance of the string device, particularly by children.[25]

According to a comparative study[25] of the various culture methods, bone marrow cultures remain the most effective method for the recovery of *S. typhi*. Stool cultures appear to be more effective in children than in adults, while duodenal content cultures offer little advantage in young (2 to 6 years old) children.

Molecular diagnostics

Polymerase chain reaction (PCR):

PCR is a promising test, which is as sensitive as blood culture, but less specific.[18] It has been found to be >90% sensitive and relatively simple to perform. Moreover, it can amplify DNA from dead or unculturable bacteria, providing an additional sensitivity benefit. However, it seems to have limited potential for the diagnosis of enteric fever. In the absence of any validated PCR test, the in-house systems currently in use are open to differing interpretation and do not meet the rigorous quality control standards for worldwide acceptance.[20] A PCR is quite expensive, costing anything between ₹3800 and ₹4000 in India.

The experts felt that PCR may not satisfy the criteria of a 'gold standard' for the diagnosis of enteric fever in terms of sensitivity and specificity, since it does not cover all the antigens of the disease. Only antigens 14, 15 and 18 are picked up by one PCR test. Moreover, this test is not available in remote and peripheral areas. The participants also echoed the same sentiments, as they added that the PCR is hardly ever used for the diagnosis of enteric fever in India.[2]

Nested polymerase chain reaction:

A nested polymerase chain reaction is more sensitive than PCR and uses H1-d primers to amplify specific genes of *S. typhi* in the blood of patients.[18] It involves two rounds of PCR using two primers with different sequences within the H1-d flagellin gene of *S. typhi*, offering the best sensitivity and specificity.[16]

It is a promising rapid diagnosis test, with potential to replace blood culture as the new gold standard.[18] It is so sensitive that it can detect even one bacterium in a given sample within a few hours.[26]

Due to its high sensitivity and specificity, nested PCR can serve as a useful tool to diagnose clinically suspected, culture negative cases of enteric fever.[27]

Benefits of nested PCR[27]

- Sensitivity of 100% and specificity of 76.9%
- Higher case detection compared to blood culture even in the later stages of the disease (53.8 vs. 46.1%)
- Can be used as a diagnostic tool in any stage of the disease
- Not affected by empirical antibiotic therapy unlike blood culture. Hence, can serve as an effective diagnostic test even after the initiation of antimicrobial therapy.

Serological tests

Serological tests are the mainstay of diagnosis of enteric fever in developing countries.[21] *S. typhi* is known to express a number of immunogenic structures on its surface. Among them, O (liposaccharide), H (flagella), and the somewhat less immunogenic Vi capsule can be identified by serological tests. *S. typhi* expressing O (O9, O12), Vi, and H:d are abundantly present in most endemic areas.[20] All the participating doctors unanimously expressed the same view that although the Typhidot, IgM Dipstick, and IDL Tubex tests are promising tests, they are still not being used routinely in India.

Widal test:

According to the World Health Organization, Widal, the most widely available test in India, should not be done before one week of the onset of fever. Even if it is positive before one week, it might be a false-positive. With the availability of other highly reliable tests, the importance of Widal has declined. A single Widal has no value. It may be obsolete; but in the absence of any other reliable modality, it may be done.[2]

Widal is the most widely used test in many regions as it is

relatively cheaper, easy to perform, and requires minimal training and equipment. The test is based on the demonstration of a rising titer of antibodies in paired samples 10 to 14 days apart. It uses O and H antigens of *S. typhi, S. paratyphi A, S. paratyphi B* and *S. paratyphi C* to detect antibodies in blood.[28] At least 1 ml of blood should be collected to obtain a sufficient amount of serum. Usually O antibodies take 6-8 days to appear and H antibodies 10-12 days after the onset of disease.[3]

In acute enteric fever, therefore, the anti-O antibody titer is the first to rise, followed by a gradual increase in anti-H antibody titer. The anti-H antibody response persists longer than the anti-O antibody.[29]

According to a study conducted in Nepal,[29] a presumptive diagnosis of enteric fever can be made if significant titers are greater than 1:80 for anti-O and greater than 1:160 for anti-H.

However, it is difficult to pinpoint a definite cut-off for a positive result since it varies between areas and between times in given areas.[3] A fourfold rise in antibody titer in a paired serum is considered more diagnostic.[21]

Widal has a sensitivity of 47-77% and specificity of 50-92%.[18] While a negative Widal test has a good predictive value for the absence of the disease, a positive result is seen to have a low predictive value for its presence.[28]

Advantages of Widal

Inexpensive[3]

Good for screening a large number of patients in endemic areas despite mixed results[18]

Use of slides instead of tubes gives results faster — in only a few minutes[19]

Limitations in use

Standardization and quality assurance of reagents may be required[18]

Moderate sensitivity and specificity[3]

The sensitivity, specificity, and predictive values differ in different geographic areas[26]

Negative in 30% of culture proven cases of enteric fever[3]

Prior antimicrobial treatment may adversely affect the antibody response[3]

False-positive results may be obtained in other clinical conditions, such as malaria, typhus, bacteremia and cirrhosis[3]

May lead to overdiagnosis if relied upon solely in endemic areas[28]

Widal need not be performed if the diagnosis has already been confirmed by the isolation of *S. typhi* from a sterile site.[3] While a tube Widal in India costs around ₹110 to ₹170, the slide Widal is priced a bit higher between ₹150 and ₹200.

Typhidot:

Typhidot is a rapid-dot enzyme immunoassay (EIA) that takes about three hours to perform.[3] It detects IgG and IgM antibodies to a specific 50 kD outer membrane protein (OMP) antigen of *S. typhi*.[21] Detection of IgM signifies acute enteric in the early phase of infection while detection of both IgG and IgM indicates acute enteric in the middle phase of infection.[3] The test becomes positive right in the first week of fever and the results are available within one hour. Thus, it is faster than blood culture and Widal, in which results take 48 and 18 hours, respectively. In addition, this test is simpler and more reliable than Widal.[21]

Its simplicity, speed, sensitivity (95%), specificity (75%), cost-effectiveness, ability to detect antigens early, and high negative and positive predictive values make Typhidot an efficient diagnostic tool in resource-poor countries.[3]

Typhidot, the experts felt, is an alternative to Widal, but is far more reliable. It is available even in tier 3 cities, so it can be easily prescribed. It becomes positive in the first week itself. Typhidot-M is done in cases of acute infection.[2] A Typhidot in India costs between ₹300 and ₹400.

Limitations in use[3]

IgG can persist for more than two years after typhoid infection. Hence, detection of only IgG cannot differentiate between acute and convalescent cases.

Previous infection may lead to false positive results.

Typhidot- M:

Typhidot-M is a modified, improved version of Typhidot, obtained by inactivating total IgG in the serum sample, which removes competitive binding and allows access of the antigen to the specific IgM, thereby enhancing diagnostic accuracy. If specific IgM is detected within three hours, it points towards acute typhoid infection.[3]

Advantages

Superior to culture method in terms of sensitivity (>93%), negative predictive value, and speed[3]

Can replace Widal when used along with culture method, for rapid and accurate diagnosis of enteric fever[3]

High negative predictive value makes it useful in areas of high endemicity.[3]

Being rapid, easy to perform and reliable, it is suitable for enteric endemic countries[30]

Latex agglutination test:

Studies on the efficacy of the latex agglutination test (LAT) have shown that:

With a sensitivity of 100%, specificity of 97.6%, and positive and negative predictive values of 90.9% and 100%, respectively, LAT can be used for the presumptive diagnosis of enteric fever in remote health centers[31]

LAT could detect the antigen in 100% of the sera of patients with negative blood culture and positive Widal, indicating better sensitivity as compared to blood culture[32]

Table 2: Investigations according to week of presentation

Week of illness	Feasible tests	Non-feasible tests
1st week	Hematological tests Eosinopenia[17,18]	Bone marrow culture[3]
	Blood culture[20]	PCR[20]
	Typhidot/Typhidot-M[3]	Duodenal aspirate culture[25]
	Widal (basal)[28]	Dipstick[3]
2nd week	Hematological tests Leukocytosis[17,18]	Bone marrow culture[3]
	Blood culture[20]	Rose spot culture[16]
	Stool culture[18]	PCR[20]
	Typhidot/Typhidot-M[3]	Tubex[3]
	Widal (basal or repeat – to see rising titer)[28]	Duodenal aspirate culture[25]
		Dipstick[3]
3rd week	Hematological tests[17,18]	Bone marrow culture[3]
	USG abdomen (hepatosplenomegaly)[2]	PCR[20]
	Blood culture[20]	Tubex[3]
	Stool culture[18]	Duodenal aspirate culture[25]
	Widal (very high titer)[28]	Dipstick[3]
	Typhidot/Typhidot-M[3]	
4th week	Hematological tests[17,18]	Bone marrow culture[3]
	USG abdomen[2]	PCR[20]
	Blood culture[20]	Tubex[3]
	Stool culture[18]	Duodenal aspirate culture[25]
	Widal (very high titer)[28]	Dipstick[3]
	Typhidot/Typhidot-M[3]	

LAT can be used for rapid diagnosis of enteric fever though it cannot replace conventional blood culture required for isolation of organism to report the antibiotic sensitivity[33]

IDL Tubex test:

Tubex is an antibody-detection test that is user-friendly and can be used at the point of care.[19] This simple one-step rapid test can be performed in just two minutes.[3] The test is as simple and fast as the slide latex agglutination tests but has been modified to improve the sensitivity and specificity to 75-85% and 75-90%, respectively.[19] The O9 antigen used in the test is extremely specific, and can detect IgM O9 antibodies within minutes. A positive result is a definite indicator of a Salmonella infection.[3]

As Tubex detects only IgM antibodies and not IgG, it is highly useful for the diagnosis of current infections, and performs better than Widal, both in terms of sensitivity and specificity.[3]

Limitation in use

Negative results may be obtained in patients infected by other serotypes, such as *S. paratyphi* A[3]

IgM dipstick test:

IgM dipstick test is based on the detection of *S. typhi*-specific IgM antibodies in serum or whole blood samples. Specific antibodies appear a week after onset of symptoms and signs — this fact should be kept in mind while interpreting a negative serological test.[3]

Advantages[3]

Requires no formal training, specialized equipment, electricity or cold storage facilities

Results are available the same day, enabling prompt initiation of treatment

Fast and simple to perform

Ideal for places with no culture facilities

Table 2 gives the list of tests according to the week of presentation. The tests have been categorized as feasible and non-feasible. The non-feasible tests include those that are expensive, not easily available, require specialized equipment, or are not tolerated.

It must be borne in mind that tests are indicated after all the other febrile conditions have been ruled out.

Newer tests

Newer tests in the pipeline include salivary IgM test, molecular immunology-based tests and nanotechnology-based tests.[2]

Screening for Carriers

Enteric fever continues to have a high incidence due to the dissemination of the disease via carriers.[22] This calls for urgent measures to detect carriers as they are a silent threat to the community.[20] An ideal test for carriers should be rapid, specific, as well as sensitive.[22] One such measure is monitoring *S. typhi* in the stool. However, this may be hamstrung by low level or sporadic shedding and the fact that routine stool sampling may be expensive, time consuming and unpopular. Another option is based on the observation that enteric fever carriers may produce higher levels of Vi antibodies over extended periods compared to acutely infected patients. Hence, development of simple, cheap, and non-invasive Vi antibody assays may be of great help in identifying carriers.[20]

Current Approaches in the Treatment of Enteric Fever in India

With time, the treatment of enteric fever is not only becoming more complicated, but also costly, because of increased resistance to the commonly used antibiotics in the *Salmonella enterica* species.[34] Characterized by a lengthy incubation period, nonspecific symptoms that are diverse in nature, and complications that could threaten life, the disease only adds to the financial burden of individuals and maintains the poverty cycle. It is estimated that nearly 22 million new cases of enteric fever develop every year, the mortality rate being higher in

Table 3: Treatment of enteric fever[2]

Susceptibility	Patient	Antibiotic	Dosage
Uncomplicated enteric fever			
Quinolone sensitivity areas	Adult	**Responders**: Fluoroquinolones, namely Ciprofloxacin or Ofloxacin	15 mg/kg body weight/day × 10 days
		OR 3rd Generation Cephalosporin like Cefixime	15-20 mg/kg body weight/day × 10 days
		Nonresponders: Chloramphenicol OR	50-75 mg/kg body weight/day × 14 days
		Amoxicillin	75-100 mg/kg body weight/day × 14 days
	Child	**Responders:** 3rd Generation Cephalosporin like Cefixime	15-20 mg/kg body weight/day × 10 days
		Nonresponders: Chloramphenicol OR	50-75 mg/kg body weight × 14-21 days
		Amoxicillin	75-100 mg/kg body weight × 14 days
Quinolone resistance areas	Adult	**Responders:** Cefixime	20 mg/kg body weight/day × 14 days
		Nonresponders: Azithromycin	10-20 mg/kg body weight/day × 7 days
	Child	**Responders:** Azithromycin	10-20 mg/kg body weight/day × 7 days
		Nonresponders: Cefixime	15-20 mg/kg body weight/day × 14 days
Complicated enteric fever			
Quinolone sensitivity areas	Adult	**Responders:** 3rd and 4th Generation Cephalosporins like	
		Ceftriaxone	60 mg/kg body weight/day IV × 14 days
		Cefotaxime	80 mg/kg body weight/day IV × 14 days
		OR Fluoroquinolone like Ciprofloxacin or Ofloxacin	15 mg/kg body weight/day IV × 14 days
		Nonresponders: Chloramphenicol	100 mg/kg body weight/day IV × 14-21 days
		Ampicillin	100 mg/kg body weight/day IV × 14 days
	Child	**Responders:** Ceftriaxone or Cefotaxime	50-75 mg/kg body weight/day IV × 14 days
		Nonresponders: Chloramphenicol	100 mg/kg body weight/day IV × 14-21 days
		Amoxicillin	100 mg/kg body weight/day IV × 14 days
Quinolone resistance areas	Adult	**Responders:** Ceftriaxone or	60 mg/kg body weight/day IV × 14 days
		Cefotaxime	80 mg/kg body weight/day IV × 14 days
		Nonresponders: Fluoroquinolone	20 mg/kg body weight/day IV × 14 days
	Child	Ceftriaxone or Cefotaxime	50-75 mg/kg body weight/day IV × 14 days

bid: twice daily; qid: four times daily; tid: three times daily; IV: intravenously; PO: orally; TMP-SMX: trimethoprim-sulfamethoxazole

Adapted from

1. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ* 2006; 333:78-82.
2. World Health Organization (WHO) Department of Vaccines and Biologicals. Background document: The diagnosis, prevention and treatment of typhoid fever. Geneva: WHO; 2003:19-23. Available at: http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf; and
3. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK. IAP Task Force Report: Diagnosis of enteric fever in children. *Indian Pediatr* 2006; 43:884-7.

young children from low-resource areas.[4]

History of Antibiotic Therapy in Enteric Fever

Chloramphenicol was the drug of choice for the treatment of enteric fever since 1948, but plasmid-mediated resistance and its rare side-effect of bone marrow aplasia put it behind on the shelf. This was followed by the use of trimethoprim-sulfamethoxazole and ampicillin in the 1970s; however, their rampant use led the pathogen to get resistant to them. In the 1980s, ceftriaxone and ciprofloxacin proved to be effective against multidrug-resistant (MDR) strains of *S. typhi*, and were therefore the drugs of choice. Ciprofloxacin and ofloxacin were preferred to ceftriaxone due to their oral use and cost-effectiveness. However, decreased ciprofloxacin susceptibility (DCS) is now being seen. Since the 1990s, azithromycin has been showing good results and is a promising alternative to fluoroquinolones and cephalosporins.[35]

Drugs Recommended by the Expert Panel for the Management of Enteric Fever

After going through treatment recommendations by the World Health Organization (WHO), the Association of Physicians of India (API), and the Indian Association of Pediatrics (IAP), the expert advisory panel concluded that there was a need to simplify the choice of the drugs in the treatment of enteric fever. They unanimously declared that the fluoroquinolones (especially, ciprofloxacin and ofloxacin) and cephalosporins (specifically those of the third and fourth generation) are recommended for use as the first-line therapeutic agents.[2]

Table 3 lists the drugs recommended by the panelists for various patient populations, based on the severity of their condition, response to treatment, and possibility of antibiotic resistance in them. They emphasized on the need for doctors to titrate the dose of the antibiotics in every case, based on the patient's age and body weight. All of them agreed to the fact that it is better to slightly overdose the patient rather than underdose the patient, when trying to adjust the dose of the antibiotic for the patient, bearing in mind the strengths available in the market. Thus, if the dose requirement calculated for a patient amounts to

Table 4: List of red flag symptoms in enteric fever[36]

Involvement	Symptoms
Central nervous system	Headache, vomiting, seizures, altered states of consciousness, papilledema, and focal neurological deficits
Cardiovascular system	Chest pain, palpitations, new murmur or change in characteristics of a previous murmur, cardiac arrhythmias
Respiratory system	Chills, cough (with or without sputum), pleuritic pain, coarse crackles, and bronchial breathing
Musculoskeletal system	Local tenderness, rigidity, and pain giving rise to a loss of functionality in the affected limb; acute swelling and pain in joints with or without an effusion
Gastrointestinal system	Jaundice, nausea, vomiting, and abdominal pain
Genitourinary system	Dysuria, frequency, and suprapubic or pelvic discomfort

600 mg/day, it is advisable to give him 750 mg instead of 500 mg.[2]

When factors such as intolerance to oral drugs, dehydration, extremes of age, and associated comorbid conditions are present, parenteral treatment should be instituted. Once the condition of the patient stabilizes, s/he should gradually be de-escalated from parenteral therapy to oral drugs. With the defervescence period usually being about 5 days, any patient who is not responding adequately may be switched to a different drug after stopping the first, or the second drug may be added to the first one.[2] However, at any point during the course of the illness, patients may develop symptoms of developing complications, which should serve as red flags for the treating doctor. The important red flag symptoms have been listed in Table 4.[36]

Cephalosporins:

Cefixime, cefpodoxime proxetil, cefipime, and ceftriaxone are expanded-spectrum cephalosporins that have been very promising in the management of enteric fever. While the former two are administered orally, the latter

Table 5: Azithromycin in uncomplicated enteric fever[42]

Parameter tested	Result
Cure rate (%)	93.5
Mean day of response	3.45 ± 1.97
Blood culture positive (%)	15.5
Good global wellbeing (%)	95

two are given parenterally. The favorable pharmacokinetic profile of cefpodoxime proxetil allows for its twice daily dosing. In past studies, all the 50 strains responsible for enteric fever were found to be sensitive to ceftriaxone, cefixime, and cefpodoxime.[37] The minimum inhibitory concentration (MIC) of a drug can help to predict its efficacy. When a drug is given in an appropriate dosage on the basis of sound pharmacokinetic and pharmacodynamic principles, a clinical cure is facilitated by eradication of the pathogen's carrier status and prevention of resistance to the antimicrobial drug.[38] A study that tested the efficacy of cephalosporins in the treatment of enteric fever found that the MIC_{50} and MIC_{90} of cefotaxime, a parenteral third-generation cephalosporin, was the least in comparison to the oral third-generation cephalosporin cefixime and the parenteral fourth-generation cephalosporin cefipime.[37]

Cefpodoxime and cefixime have been used extensively in enteric fever. Although cefpodoxime has wide applications in pediatric infectious diseases, it hasn't been used much in enteric fever; though it is similar pharmacologically to cefixime and cheaper than cefixime. In 140 children assessed for suspected enteric fever, a comparative study showed that cefpodoxime reduced treatment cost by 33% in comparison to cefixime, and is also a safer oral option in children. The two groups showed a similar clinical response with comparable periods to defervescence in days and clinical cure rates. The MIC for cefpodoxime against all *Salmonella typhi* isolated (n = 40) was <4 μg/mL (range 2-8 μg/mL); and for cefixime was 0.5 μg/mL (range 0.25-1.0 μg/mL).[39]

Fluoroquinolones:

The World Health Organization (WHO) recommends fluoroquinolones in areas with known resistance to the older first-line antibiotics. A Cochrane study revealed that fluoroquinolones have fewer clinical failures in comparison with ampicillin, amoxicillin, chloramphenicol, and co-trimoxazole; with no clinical or microbiological failures having been seen with seven-day courses of ciprofloxacin or ofloxacin, which have been found to be superior to older antibiotics.[40] In uncomplicated enteric fever caused by nalidixic acid-resistant *Salmonella enterica* serovars *typhi* and *paratyphi* A, giving ofloxacin (20 mg/kg/day) in two divided doses for 7 days led to prompt fever clearance within 4.7 hours, on an average.[41] The panelists reminded that the use of quinolones should be avoided in children, elderly, pregnant women, and those who cannot tolerate this class of antibiotics. In such patients, alternative treatment regimens should be followed. Also, if culture and antibiotic sensitivity shows the presence of nalidixic acid-resistant *Salmonella typhi* (NARST), the use of quinolones must be avoided, as there is a great probability of the pathogen being resistant to this antibiotic class.[2]

Azithromycin:

Azithromycin is safe and efficacious for the management of uncomplicated enteric fever. An open-label, non-comparative study, which evaluated the efficacy and safety of azithromycin for the treatment of uncomplicated enteric fever, found that azithromycin (20 mg/kg/day for 6 days) cured 93% of the subjects, with a mean day of response of 3.5 as seen in Table 5. No serious adverse event was observed.[42] The panelists recommended a course of not more

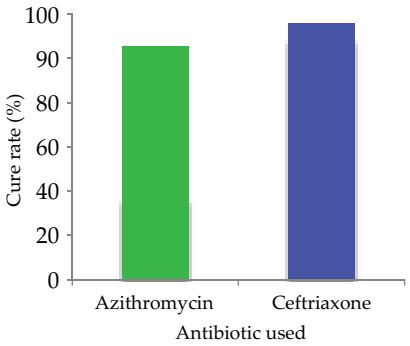

Fig. 7: Azithromycin vs. ceftriaxone in enteric fever[43]

than 7 days with azithromycin, because this drug has stronger tissue penetration and accumulates in the gall bladder. Thus, while a 5-day course of azithromycin may be considered to be an equivalent to a 10-day course of any other antibiotic, a 7-day course of the same is as good as another drug given for 14 days.[2]

When compared to intravenous ceftriaxone (75 mg/day; maximum 2.5 g/day) daily for 5 days, oral azithromycin (20 mg/kg/day; maximum 1000 mg/day) achieved an almost similar cure rat (97% vs. 94%) (Figure 7). No patient on azithromycin had a relapse, whereas few relapses were seen with ceftriaxone.[43]

Azithromycin and ofloxacin were compared for safety and efficacy in 40 patients with uncomplicated enteric fever.

Group I: Patients received ofloxacin 200 mg orally twice daily for 7 days. Nineteen out of 20 patients from group I were cured with a mean fever clearance time of 3.68 days

Group II: Patients received azithromycin orally 1 g on day 1 and then 500 mg daily from day 2 to day 6. All 20 patients from group II were cured with a mean fever clearance time of 3.65 days.

Ofloxacin and azithromycin are almost equally efficacious and safe in enteric fever, and azithromycin could be used as an alternative when ofloxacin is contraindicated, as in children, pregnant women, and quinolone-resistant cases of enteric fever.[44]

Single vs. Multiple Drug Regimens

The expert panelists declared that there are no clear-cut guidelines for the employment of monotherapy and combination therapy. Since it is not possible to tell whether a patient is going to respond to the treatment or not on the very first day, it is advisable for the clinician to use his experiences with other patients in and around the area to presume resistance or sensitivity to a particular drug. Although culture and antibiotic sensitivity would be desirable in all cases, most doctors depend on the clinical signs and symptoms when treating patients of enteric fever and refer them to a tertiary care center, whenever the development of complications is suspected. If a patient does not seem to be responding to the first-line drugs by day 5 of treatment, an alternative treatment option should be considered. Combination therapy may be considered when monotherapy fails. Usually, a fluoroquinolone is the first drug of choice. If the response is found to be inadequate, the oral cephalosporin, cefixime, is added. If the improvement in the patient is still not satisfactory, the former drug is withdrawn and azithromycin is added. A number of doctors use fixed-dose combinations these days; however, the panel of experts did not encourage their use, as these lack flexibility in dosing.[2] The emergence of MDR *S. typhi* and concerns about a delayed response to quinolones has resulted in a lot of anxiety among treating physicians. There have been several takes on the usage of single versus multiple therapies. While some advocate it, others recommend their usage only in unresponsive cases. A comparative Indian analysis was done in 62 cases of enteric fever proven by blood culture, out of which 59% received a single drug (either a quinolone or cephalosporin); and 40.3% cases received 2 drugs simultaneously. The duration of fever from the beginning of the illness to the time of defervescence was 13.54 days and 13.84 days in the single-drug and multiple-drug groups, respectively. The mean duration for defervescence after initiation of antimicrobial therapy in the single-drug group was 5.24 days; and in the multidrug group, it was 4.32 days. There was no significant difference in the total duration of fever or the time taken for defervescence after initiation of therapy in the single-drug and multidrug groups. This reinforces the traditional recommendation of treatment of enteric fever with one drug at a time. Treatment with a single drug is sufficient in enteric fever, and administration of multiple drugs should be restricted to unresponsive cases.[45]

Role of Surgery

Enteric fever perforation is a common surgical emergency in developing countries, but optimal operative management is debatable.[46] Primary ileostomy has been shown to be a better surgical option in comparison with others and can be a life-saver, particularly in patients who present late in the course of illness with rapidly deteriorating health.[47] Enteric perforation should always be treated surgically, and timely surgery within 24 hours, with adequate and aggressive resuscitation, decreases morbidity and mortality.[48] The panelists also addressed the issue of the type of surgery that should ideally be adopted to operate on such a perforation. They concluded that if CT imaging has helped to detect the exact site of perforation, laparoscopic surgery can be performed; however, if the site has not been identified, then an open surgery is advisable.[2]

Antibiotic Resistance

As seen earlier, the mainstay of enteric fever management is the use of antibiotics for empiric or

Table 6: Relapse rate categorized by bacterial drug resistance and antimicrobials used[52]

	Initial therapy of exclusively ampicillin, chloramphenicol, or TMP-SMX	Partial or full initial therapy with cephalosporins or quinolones	
Resistance profile	**Cases of relapse/total number of cases (%)**		**p value**
Pan-sensitive	47/559 (8.4)	25/377 (6.6)	0.32
Partial drug resistance	3/71 (4.2)	4/86 (4.7)	1[a]
Multidrug resistance	5/31 (16.1)	23/506 (4.5)	0.018[a]
All patients	55/661 (8.3)	52/969 (5.4)	0.018

[a]Fisher's exact

directed therapy. Improper use of antibiotics, especially broad-spectrum antibiotics can lead to emergence of resistance. The commonest factors that lead to antibiotic resistance are the misuse and overuse of these drugs.[49] A re-emergence of chloramphenicol susceptibility in *S. enterica* serovar typhi isolates has been witnessed in some regions of India, where the susceptibility has been found to be as high as 95%. Investigators have suggested using chloramphenicol, along with the third-generation cephalosporins in enteric fever due to ciprofloxacin-resistant *S. enterica* serovar typhi infection.[50] Resistance to fluoroquinolones has led to an increased use of azithromycin and third-generation cephalosporins. There are worldwide reports of high level resistance to expanded-spectrum cephalosporins (e.g. ceftriaxone). Spread of such resistance would further greatly limit the available therapeutic options, with only reserve antimicrobials like carbapenem and tigecycline being left as possible treatment options.[50] It is suggested that quinolones and third-generation cephalosporins should be used as first-line antimicrobials in enteric fever. The use of fourth-generation cephalosporins should be restricted to complicated or resistant cases.[51]

Relapse of Enteric Fever

There are several factors, which are associated with relapse of culture-proven enteric fever as seen over 15 years in 1,650 children in MDR strains in South Asia. Despite the drop in the morbidity and mortality associated with enteric fever due to the advent of antibiotics, relapses continue to occur in up to 10% of the patients, even though they are immunocompetent. Patients with drug-resistant enteric fever who received ineffective therapy have a relapse rate, which is almost twice that of those infected with pan-sensitive strains (Table 6). Diarrhea is associated with lower relapse rates in children infected with pan-sensitive enteric fever. Those infected with MDR strains have a higher relapse rate when presenting with constipation or starting specific therapy within 14 days of fever onset. The use of quinolones or cephalosporins as part of the treatment course protects against subsequent relapse. In those areas where MDR enteric fever caused by *S. typhi* is prevalent, empirical treatment of patients with a cephalosporin or quinolone should be considered, until infection is caused by a drug-sensitive strain.[52]

Role of Corticosteroids

The expert panelists emphatically stated that steroids should be used strictly under supervision by qualified physician.[2]

When to Refer

Patients with fever that lasts for more than 7 days should be investigated for enteric fever, and their blood counts and renal function should be evaluated. Referral to a tertiary care center must be done when there is any evidence of complications such as encephalopathy, gastrointestinal hemorrhage, glomerulonephritis, myocarditis, perforation, peritonitis, pneumonitis, severe dehydration, and shock. Other rare complications that serve as red flags include apathy, presence of basal crepitations, coma, endocarditis, Guillian-Barré syndrome, neuritis, meningitis, osteomyelitis, pancreatitis, pericarditis, psychosis, pyelonephritis, and unexplained tachypnea. It is also advisable to refer the patient in case of any diagnostic confusion or when s/he fails to respond to the primary or secondary line of treatment with antibiotics.[55]

Treatment of Carriers

A person is said to be a chronic carrier if s/he is asymptomatic, but his or her stool or rectal swab cultures test positive for the presence of *S. typhi*, a year after recovery.[22] There are basically three types of carriers, namely convalescent carriers, who continue to shed bacilli in their feces for 3 weeks to 3 months; temporary carriers, who sheds bacilli for more than 3 months up to a year; and chronic carriers, who shed bacilli for more than a year.[56] The Vi (virulence) antibody test is of value when screening for carriers. The WHO recommends the use of ciprofloxacin 750 mg twice daily for 4 months or 52 weeks. It is not recommended for use in pregnant women. It may be used in children only if the benefits outweigh the risks. If there is cholelithiasis, cholecystectomy is indicated. Schistosomiasis, if present, should be treated.[54]

Management Guidelines

The IAP task force has made the following statements:[53]

The timely and appropriate management of enteric fever reduces morbidity and mortality.

General supportive measures such as the use of antipyretics, maintenance of hydration, appropriate nutrition, and prompt recognition and treatment of complications ensure a favorable outcome.

In areas of endemic disease, 90%

Table 7: Five key steps to safer food[54]

Key step	Explanation	
Keep clean	*Why?*	Dangerous microorganisms are widely found in soil, water, animals, and people. These are carried on the hands, cloth used for wiping, utensils, and cutting boards; and the slightest contact can transfer them to food and cause foodborne diseases.
	How?	Hands should be washed before handling food, during food preparation, and after using the toilet. All surfaces and equipment used for food preparation should be washed and sanitized. Kitchen areas and food should be protected from insects, pests, and other animals.
Separate raw and cooked food	*Why?*	Raw food, especially meat, poultry, and seafood, and their juices, can contain dangerous microorganisms that might be transferred onto other foods during food preparation and storage.
	How?	Raw meat, poultry, and seafood should be separated from other foods. Equipment and utensils such as knives and cutting boards should be kept separate for handling raw foods. Food should be stored in containers to avoid contact between raw and prepared foods.
Cook thoroughly	*Why?*	Cooking food to a temperature of 70°C kills almost all dangerous microorganisms and ensures that it is safe for consumption. Foods that require special attention include minced meats, rolled roasts, large joints of meat, and whole poultry.
	How?	Food should be cooked thoroughly, especially meat, poultry, eggs, and seafood. Soups and stews should be boiled till 70°C. Meat and poultry should not be pink. Ideally, the use of a thermometer is advocated.
Keep at safe temperatures	*Why?*	Microorganisms can multiply very quickly if food is stored at room temperature. By keeping the temperature below 5°C or above 60°C, the growth of microorganisms is slowed down or stopped. Some dangerous microorganisms still grow below 5°C.
	How?	Cooked food should not be kept at room temperature for more than 2 hours, and should be refrigerated promptly. Cooked and perishable food should be preserved preferably below 5°C. Cooked food should be kept piping hot (more than 60°C) prior to serving. Food should not be refrigerated for too long and frozen food should not be thawed at room temperature.
Safe water and raw materials	*Why?*	Safe water should be used or it should be treated to make it safe. Fresh and wholesome foods and pasteurized milk should be consumed. Fruits and vegetables should be washed properly, especially if eaten raw. Do not use food beyond its expiry date.
	How?	Raw materials, including water and ice, may be contaminated with dangerous microorganisms and chemicals. Toxic chemicals may be formed in damaged and moldy foods. Care in the selection of raw materials and simple measures such as washing and peeling may reduce the risk.

or more of enteric fever cases can be managed at home with proper oral antibiotics and good care.

Close follow-up is necessary to detect complications or failure to therapy.

Nalidixic acid-resistant *S. typhi* (NARST) species usually demonstrate reduced susceptibility to fluoroquinolones.

Third-generation cephalosporins are recommended for first-line treatment. While cefixime and cefpodoxime proxetil are administered orally, ceftriaxone, cefotaxime, and cefoperazone are given parenterally. Of these, ceftriaxone is the most convenient to use. Oral third-generation cephalosporins need to be given in higher doses to treat enteric fever.

Azithromycin is a preferred alternative agent in uncomplicated enteric fever.

Aztreonam and imepenem are potential second-line drugs.

For life-threatening infections resistant to all other recommended antibiotics, fluoroquinolones may be used.

Following are recommendations by the WHO:[54]

Culture and sensitivity tests should be used to guide the choice of antibiotics.

Fluoroquinolones are the optimal choice for the treatment of enteric fever in all age groups.

In areas where the bacterial species is still sensitive to traditional first-line drugs (chloramphenicol, ampicillin, amoxicillin, or trimethoprim-sulfamethoxazole), and fluoroquinolones are not available or affordable, these drugs remain appropriate for treating enteric fever.

Supportive measures like oral or intravenous hydration, antipyretics, appropriate nutrition, and blood transfusions are also important. Electrolyte imbalances, anemia, and thrombocytopenia also need to be corrected.

People infected with enteric fever, or exposed to someone infected with enteric fever, MUST NOT be permitted to work if their work involves food handling or caring for children, patients or the elderly, and should not prepare food for others.

As enteric fever can be carried on the hands it is very important to wash hands thoroughly after using the toilet and before handling food. Hands should be washed with soap and water for at least 15 seconds, rinsed and dried well.

Prevention of Enteric Fever

Primary as well as secondary strategies need to be adopted in the prevention of enteric fever and its complications. While secondary prevention stratagems attempt to reduce the morbidity and mortality associated with the disease, the primary prevention approaches entail measures that help to avoid getting infected completely or at least prevent overt clinical manifestations of the disease.[57]

Secondary Prevention

The aim of secondary prevention is to decrease the clinical severity of enteric fever and its complications, so that it doesn't prove to be fatal.

Table 8: Comparison of the Vi-PS and Ty21a vaccines[59]

Parameter	Vi-PS	Ty21a
Type of vaccine	Polysaccharide	Live attenuated
Route of administration	Parenteral	Oral
Formulations	Liquid for injection	Enteric-coated tablets and suspension
Content per dose	25 µg of the antigen	2×10^9 bacteria
Number of doses	Single dose	3 doses every other day
Protective efficacy	60% to 70% within 3 years and around 50% after 3 years of vaccination	62% and 70% after 7 years of vaccination with the enteric-coated tablets and liquid suspension, respectively
Storage	2-8°C	2-8°C
Thermostability	6 months at 37°C 2 years at 22°C	14 days at 25°C
Clinical tolerability	Well tolerated; other than local swelling, no major side-effects such as fever and erythema	Side-effects include fever, rash, headache, abdominal pain, nausea, diarrhea, vomiting, myalgia, sepsis, pain, urticaria, anaphylactic reaction, weakness, and demyelinating disease
Safety	Safe even in HIV patients	Best avoided in HIV patients
Contraindications	Children under 2 years of age	Children under 6 years of age, pregnant women, and immunocompromised state.
Cost	Cheaper	Costlier
Interactions	None reported	Reduced efficacy on concurrent use with antibiotics or IgG and increased efficacy when given to a patient being treated with mefloquine; interferes with the diagnostic effect of tuberculin test; alcohol consumption to be avoided within 2 hours of taking the vaccine.
Booster dose	Every 2 years for people who remain at risk	Every 3 years for people living in endemic areas; yearly for people traveling to endemic regions

The judicious use of efficacious antimicrobials early in the disease is the most important component of secondary prevention. When prescribing antibiotics for patients who have acquired the infection from regions where *S. typhi* species are multidrug resistant, it is advisable to select the drug, based on the most current reviews.[57]

Primary Prevention

Environmental measures to ensure the supply of treated water along with proper sanitation, identification of chronic carriers of enteric fever to break the chain of transmission of the disease, and vaccination of susceptible hosts in order to make them immune to the organism, constitute the three main approaches for primary prevention. Unfortunately, owing to cost implications, many parts of developing countries continue to have poor sanitation facilities and drink water that is not potable.[57]

Need for adequate sanitation and uncontaminated consumables:

Chlorination of drinking water at home should be advocated. The treated water should preferably be stored in a narrow-mouthed vessel and drawn out by tilting the container or using a tap to avoid contamination. People should be encouraged to use latrines at home and the disposal of wastes must be done in closed sewerage systems. Raw fruits and vegetables should be washed thoroughly, and the latter should preferably be cooked before consumption. Hygienic practices should be adopted in the storage of milk and the preparation of milk products. Studies should be done by the public health department to ascertain the quality of drinking water being supplied to the community. Surveillance by hospitals can help to evaluate the effectiveness of such interventions.[58]

The World Health Organization (WHO) has suggested some tips for safer food, which have been listed in Table 7.[54]

Identifying and treating chronic carriers:

Chronic carriers of the pathogen responsible for the development of enteric fever can cause localized or sporadic cases of the disease, particularly if they handle food that is consumed by others. Once identified, they should be taken away from these situations. Since nearly 90% of chronic carriers demonstrate high titers of serum Vi antibodies, serological tests to detect the same can be useful for screening. Doing stool cultures repeatedly after inducing strong purgation can also serve this purpose. Several weeks of oral ciprofloxacin or norfloxacin therapy has been shown to eradicate the carrier state in up to 90% of the cases, without the need for cholecystectomy, which used to be advocated in the past.[57]

Vaccination:

The use of affordable vaccines seems to be the most lucrative prophylactic intervention. In spite of the fact that the first vaccine for typhoid was introduced by Wright way back in 1896, its effectiveness was established through controlled field trials nearly seven decades later. Vaccination against typhoid as a routine is not required in countries where high sanitation standards are in place. However, its administration is recommended for individuals travelling to areas of the world where typhoid is endemic, people who are in close contact with a chronic carrier of typhoid, and laboratory staff that handle samples containing *S. typhi* bacteria. The standard old typhoid vaccines included a monovalent vaccine (containing only *S. typhi*), a bivalent vaccine (containing *S. typhi* and *S. paratyphi A*) and the traditional typhoid paratyphoid A and B (TAB) vaccine (containing *S. typhi*, *S. paratyphi A*, and *S. paratyphi B*). As of now, only two types of typhoid vaccines are available in

the Indian market for use clinically, namely the Vi polysaccharide (Vi-PS) vaccine and the Ty21a oral vaccine. A comparison of the two vaccines has been done in Table 8.[59]

Since both these vaccines are safe and do not produce major side-effects, they are good for public health and school-based immunization programs. The employment of these vaccines has been recommended by the WHO for children residing in areas where typhoid is endemic and antibiotic-resistant strains of *S. typhi* are present. In 2013, the Vi-PS vaccine was licensed for clinical use in lndia by the Drug Controller General of India (DCGI). The seroconversion rate reported with this vaccine has been 98.05%, but a significant fall in the antibody titers has been observed after 18 months, indicating the need for a booster dose. The exact time frame for administration of the booster dose can be established only on following-up for a long period.[59]

Although enteric fever is common in lndia, and there are concerns about the prevalence of multidrug resistant strains, the typhoid vaccine is being grossly underutilized. The use of vaccines appears to be very cost-effective, considering the financial implications of diagnosing typhoid by blood culture, the expenditures on hospitalization and medicines, and the loss of daily productive working hours, as a result of the illness. Therefore, the expert group recommends the use of these two typhoid vaccines routinely in unvaccinated adults, especially those who are at high risk.[59]

The Vi-TT conjugate vaccine is a fourth generation typhoid vaccine that has been indigenously developed by an Indian biotechnological company. After being tested and analyzed for efficacy and safety in more than a thousand individuals belonging to different age groups, this vaccine was launched in Hyderabad in 2013. As evident from the fourfold increase in the serum IgA responses of patients, the vaccine evoked a seroconversion of 98% in infants between 6 and 24 months of age, 99% in children aged 2 to 15 years, and 92% in individuals belonging to the 15-45 year age group. It has been shown to be superior to the Vi-PS typhoid vaccines and also has a good safety profile, being tolerated by people of all the tested age groups.[59]

Complications of Enteric Fever

When patients of enteric fever are left untreated, its complications mostly tend to occur in the third and fourth weeks of infection, the complication rate being as high as 15%. The most important complications met with in clinical practice include gastrointestinal bleeding, intestinal perforation, bronchitis, encephalopathy with confusion as a result of toxemia, and toxic myocarditis.[60] The panelists felt that it is important for the treating physician to recognize the various complications of enteric fever early and plan his or her line of management accordingly, because a number of complications need to be managed in a tertiary medical care center and hence call for timely referral followed by the medical management with appropriate antibiotics along with any surgical interventions, if found to be necessary.[2]

They were of the opinion that the complications of enteric fever are not very commonly seen in primary care setups and at the family physician level. Some doctors see only one or two complicated cases in a year at times, with children and elderly patients being the ones who are more likely to develop complications in comparison with individuals from other age groups. They felt that there is a need for doctors to identify red flag symptoms like dehydration, toxemia, altered sensorium, and abdominal rigidity and guarding in these patients early, so that the development of major complications can be averted, and the associated mortality can be decreased. Physicians also need to look for certain age or gender specific complications; for example, bronchitis is seen more often in children, whereas intestinal perforations are more common in males.[2]

Intestinal Complications

The gastrointestinal complications of enteric fever can range from something as benign as glossitis or an esophageal ulcer to a problem that can prove fatal such as intestinal perforation or bleeding. Gastrointestinal bleeding, seen in 10% of the patients, is the commonest complication; and in 2% of these cases, there may be a need for blood transfusions.[60] Severe untreated cases of enteric fever are associated with the development of intestinal as well as extraintestinal complications. Surgical interventions may be required to manage certain complications involving the small gut, acalculous cholecystitis, perforation of the gall bladder, or gangrene.[61] Salmonella cholecystitis, a rare complication of *Salmonella typhi* infection, presents with high-grade fever, jaundice and right-sided abdominal pain (Charcot's triad). Tender hepatomegaly and a distended gallbladder are the usual examination findings.[62]

Intestinal Perforation

The most serious complication of enteric fever is intestinal perforation, as the morbidity and mortality rates associated with it are high. An indicator of the endemicity of enteric fever, the incidence of intestinal perforation varies geographically, the perforation rate ranging between 0.6% and 4.9% worldwide. The rate of enteric perforation in India is higher, owing to factors such as drought, illiteracy, poverty, and proliferation of bacterial strains that are multidrug resistant. Youngsters in their second or third

Table 9: Clinical features of enteric perforation[63]

Symptom	Frequency
Fever	100%
Abdominal pain	100%
Distention	78.06%
Dehydration	76.12%
Constipation	73.54%
Vomiting	30.96%
Shock	28.38%
Chest infection	22.58%

decade of life are more likely to develop this complication, as they tend to eat street food more often, practice poor hand hygiene, and neglect their health.[63]

Ileal perforation is witnessed more frequently in remote areas due to a lack of good medical facilities. Factors associated with an increased risk of perforation include male gender, leukopenia, short disease duration, presence of bacterial strains that are multidrug resistant, and incomplete antibiotic therapy. The treating surgeon usually finds it difficult to manage such cases, as the patients present themselves or are diagnosed late after being initially treated by quacks.[63]

The indiscriminate use of glucocorticoids, lack of awareness, poverty, and poor medical and transportation facilities complicate matters further. While the mortality associated with enteric fever-related perforation ranges from 0 to 2% in the developed nations, it is much higher (9 to 22%) in the developing countries, due to reasons such as the want of intensive care, poor resuscitation facilities, antibiotic resistance, regional taboos, delay in surgery, more perforations, fecal peritonitis, and increased disease duration.[63]

The clinical features of enteric perforation and their incidence rates, as was reported by a retrospective study of 155 patients who were operated for intestinal perforation due to enteric fever in a Central Indian district hospital, have been listed in Table 9. It is advisable to manage such cases with timely and appropriate surgical interventions, safe anesthesia, proper operative care, and the use of wide-spectrum antibiotics with low resistance.[63]

Table 10: Extraintestinal complications of enteric fever[36]

Organ system	Prevalence	Complications
CNS	3-35%	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia seizures, Guillain–Barré syndrome, psychosis
Cardiovascular	1-5%	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary	1-6%	Pneumonia, empyema, bronchopleural fistula
Bone and joint	< 1%	Osteomyelitis, septic arthritis
Hepatobiliary	1-26%	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary	< 1%	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue	17 reported*	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematological	5 reported*	Hemophagocytosis syndrome

*Minimum number of cases reported in English literature

Gastrointestinal Bleeding

Gastrointestinal bleeding generally occurs in the third week as a result of ulceration, which occurs due to necrosis in the small bowels. About 20% of the patients with enteric fever test positive for the presence of occult blood in their stool. Massive bleeding is very rarely seen, although gross bleeding may be observed in 10% of the patients. The first signs of bleeding are a sudden decrease in the blood pressure and body temperature, the former dropping to 80-90 mmHg or even lower and the patient going into a state of shock. Before chloramphenicol was discovered and used for the treatment of enteric fever, the incidence rate of perforations was higher. While perforations usually occur in the third week of infection, with the distal part of the ileum being involved most of the times, they can occur even in the first 2 weeks in fulminant cases.[60]

Bleeding in the gastrointestinal tract can occur in the form of either occult blood in stool or melena. In enteric fever, this happens due to erosion of Peyer's patches into an intestinal vessel. On colonoscopy, it is seen that the terminal ileum is the most commonly involved site, followed by the ileocecal valve, the ascending colon, and the transverse colon. The ulcers seen in such cases are usually multiple and punched out in appearance, and their margins are slightly elevated.[64]

Extraintestinal Complications

S. typhi infection may at times manifest with extraintestinal infectious complications, which can involve various systems and organs of the body, as shown in Table 10. It is important to recognize these complications, specifically in patients who have just been to an endemic region and are returning home. This can help to prevent a delay in the diagnosis of enteric fever.[36]

Hematological Complications

Various hematological complications have been witnessed in patients suffering from enteric fever, such as hemolytic anemia, hemolytic uremic syndrome, and disseminated intravascular coagulation (DIC). In these patients, the hemoglobin level and platelet count may be normal or low, but their leukocytic count can be low, normal, or high. Generally, there is evidence of eosinopenia, and prolongation of the prothrombin time is also detected.[60]

Neurological Complications

The neurological complication rates in enteric fever vary (5-35%) in accordance with the extent of

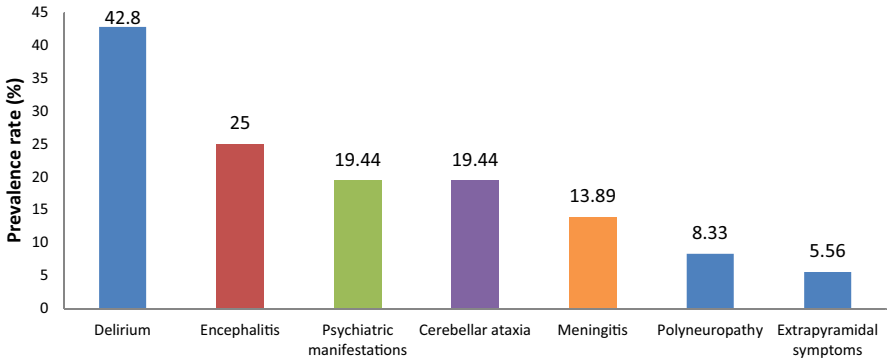

Fig. 8: Prevalence rates of various neurological manifestations in patients with neurological complications in enteric fever[65]

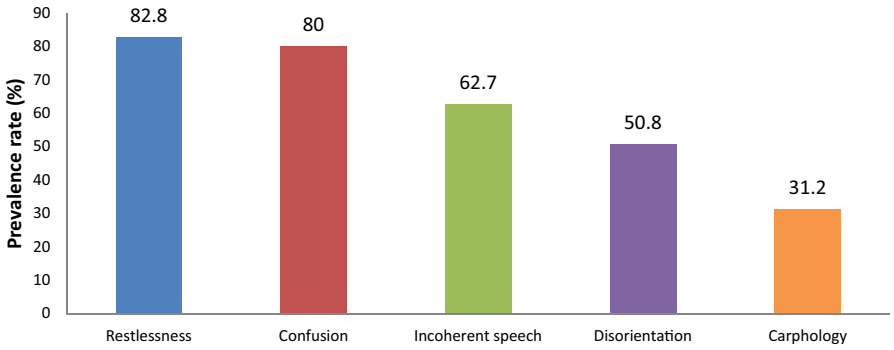

Fig. 9: Prevalence rates of the clinical features of delirium associated with enteric fever

drug resistance. Meningismus and acute confusion are the most frequent manifestations. Confusion may have an intermittent character and appears as apathy in many patients.[60] An Indian study found that 27.1% of the patients suffering from enteric fever had neurological manifestations, and the mortality rate was 6.35%. This only goes to show how important the early detection of such complications is during the course of enteric fever. Figure 8 graphically shows the common neurological complications of enteric fever, which were also observed in this study population.[65]

In this study, delirium was found to be the earliest neurological symptom and occurred 2-18 days (mean 5.9 days) after the onset of fever. The mean duration was 7.3 days (3-14 days); and following the initiation of appropriate therapeutic measures, the mean time of resolution was 3.3 days (1-7 days). The clinical features of the delirium state associated with enteric fever and their prevalence rates in the delirious patients among the study population have been shown in Figure 9.[65]

Conclusion

Enteric fever is very common in the Asian countries, especially in India; and it progresses quite rapidly to present with complications that can be both intestinal and extraintestinal. Delirium and neurological complications may also be encountered in some patients. Hence, there is a need for the treating doctors to stay alert when managing such cases. The early identification of red flag symptoms, which herald the development of complications and impending danger, can go a long way in ensuring that the patient is treated appropriately and at the right time, thereby reducing the morbidity and mortality associated with the disease. The condition can be very effectively treated with the appropriate use of drugs such as fluoroquinolones, cephalosporins, and azithromycin; however, the indiscriminate use of antibiotics has led to an increase in the incidence of drug-resistant enteric fever. While the condition is usually treated medically, surgical interventions may be required at times to manage certain complications. Strategies to reduce the disease burden include supply of purified water, thoughtful disposal of sewage and other wastes, practice of hygienic food habits, identification and treatment of chronic carriers of enteric fever, and vaccination of susceptible hosts. The Vi-PS and Ty21a vaccines are available for typhoid prophylaxis in India; however, a comparison of the two types of vaccines shows that the former is safer and more cost-effective, as compared to the latter. The indigenously developed Vi-TT conjugate vaccine seems to be showing much promise and may be the vaccine of choice in the days ahead.

Acknowledgement

Dr. M.A. Kharadi, *Ahmedabad;* **Dr. Rashmin Prajapati,** *Ahmedabad;* **Dr. Vijay Sharma,** *Amritsar;* **Dr. Ajit Kumar,** *Bangalore;* **Dr. Bharath Kumar,** *Bangalore;* **Dr. Sanjeev Murthy,** *Bangalore;* **Dr. M.B. Seshachandra,** *Bangalore;* **Dr. Ramesh S. Chaksota,** *Bhiwandi;* **Dr. Ruby Bansal,** *Delhi;* **Dr. R.K. Lutharia,** *Delhi;* **Dr. I.K. Kasturia,** *Delhi;* **Dr. Rajesh Kumar,** *Delhi;* **Dr. Vinod Kumar,** *Delhi;* **Dr. Hardeep Singh Ruproi,** *Delhi;* **Dr. Venkata Arella,** *Hyderabad;* **Dr. Vijay Gopal,** *Hyderabad;* **Dr. Kodali Vijay Kumar,** *Hyderabad;* **Dr. K.K. Reddy,** *Hyderabad;* **Dr. Bahubali Jain,** *Indore;* **Dr. Prabhat Jain,** *Indore;* **Dr. K.S. Sabharwal,** *Indore;* **Dr. Prabhat Jain,** *Indore;* **Dr. R.N. Tripathy,** *Kanpur;* **Dr. Abhay kumar,** *Kolkata;* **Dr. Nirmal Mukherjee,** *Kolkata;* **Dr. S.K. Nasirudin,** *Kolkata;*

Dr. I.M. Sorathia, *Mumbai;* **Dr. T.N. Shetty,** *Mumbai;* **Dr. Siddarth Chandra,** *Patna;* **Dr. Ravi Kumar Keshav,** *Patna;* **Dr. Awadhesh Kumar Singh,** *Patna;* **Dr. N. Gidwani,** *Pune;* **Dr. R.U. Motwani,** *Rajkot;* **Dr. Milind Kadam,** *Thane;* **Dr. Punit Kumar,** *Varanasi*

References

1. Typhoid and Paratyphoid Fever [Internet] [cited 2015 April 6]. Available from: http://www.patient.co.uk/doctor/typhoid-and-paratyphoid-fever-pro
2. Enteric Fever Conclave, 2015.
3. Background document: The diagnosis, treatment and prevention of typhoid fever. Communicable Disease Surveillance and Response Vaccines and Biologicals. World Health Organization [Internet] [cited 2015 April 6]. Available from: http://www.who.int/rpc/TFGuideWHO.pdf
4. Darton TC, Blohmke CJ, Pollard AJ. Typhoid epidemiology, diagnostics and the human challenge model. *Curr Opin Gastroenterol* 2014; 30:7-17.
5. Brooks WA, Hossain A, Goswami D, Nahar K, Alam K, Ahmed N. Bacteremic typhoid fever in children in an urban slum, Bangladesh. *Emerg Infect Dis* 2005; 11:326-9.
6. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. Typhoid Study Group. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ* 2008; 86:260-8.
7. Ray P, Sharma J, Marak RS, Garg RK. Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolone resistance in Salmonella enterica var Typhi. *Indian J Med Res* 2006; 124:105-8.
8. Kumar S, Rizvi M, Berry N. Rising prevalence of enteric fever due to multidrug resistant Salmonella: an epidemiological study. *J Med Microbiol* 2008; 57:1247-50.
9. Banerjee T, Shukla BN, Filgona J, Anupurba S, Sen MR. Trends of typhoid fever seropositivity over ten years in north India. *Indian J Med Res* 2014; 140:310-3.
10. Prouty AM, Schwesinger WH, Gunn JS. Biofilm formation and interaction with the surfaces of gallstones by Salmonella spp. *Infect Immun* 2002; 70:2640-9.
11. Brooks J. The sad and tragic life of Typhoid Mary. *CMAJ* 1996; 154:915.
12. Sur D, Ali M, von Seidlein L, Manna B, Deen JL, Acosta CJ, Clemens JD, Bhattacharya SK. Comparisons of predictors for typhoid and paratyphoid fever in Kolkata, India. *BMC Public Health*. 2007; 7:289.
13. Parry CM. Epidemiological and clinical aspects of human typhoid fever. In: Mastroeni M, Maskell D, eds. 'Salmonella' Infections: Clinical, Immunological and Molecular Aspects [Internet]. Cambridge University Press, 2005 [cited 2015 April 7]. Available from: http://www.langtoninfo.com/web_content/9780521835046_excerpt.pdf
14. Gosai MM, Hareshwaree HB, Purohit PH, Abeda MG. A study of clinical profile of multidrug resistant typhoid fever in children. *NJIRM* 2011; 2:87-90.
15. Sharma P, Taneja DK. Typhoid vaccine: a case for inclusion in national program. *Indian J Public Health* 2011; 55:267-71.
16. Brusch JL. Typhoid Fever [Internet] 2015 [cited 2015 April 7]. Available from: http://emedicine.medscape.com/article/231135-clinical#showall
17. Typhoid infection diagnosis – step-by-step. BMJ Best Practice [Internet] [cited 2015 April 7]. Available from: http://bestpractice.bmj.com/best-practice/monograph/221/diagnosis/step-by-step.html
18. Bhutta ZA, Dewraj HL. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ* 2006; 333:78–82.
19. Tam FCH, Ling TKW, Wong KT, Leung DTM, Chan RCY. The TUBEX test detects not only typhoid- specific antibodies but also soluble antigens and whole bacteria. *J Med Microbiol* 2008; 57: 316-323.
20. Baker S, Favorov M, Dougan G. Searching for the elusive typhoid diagnostic. *BMC Infectious Diseases* 2010; 10:45.
21. Sanjeev H, Nayak S, Pai AKB, Rai R, Karnaker V, Ganesh HR. A systematic evaluation of rapid dot-EIA, blood culture and Widal test in the diagnosis of typhoid fever. *NUJHS* 2013; 3:21-4.
22. Ismail A. New advances in the diagnosis of typhoid and detection of typhoid carriers. *Malays J Med Sci* 2000; 7:3-8.
23. Singh S. Pathogenesis and laboratory diagnosis. *JIACM* 2001; 2:17-20.
24. Benavente L, Gotuzzo J, Guerra O, Grados H, Bravo N. Diagnosis of typhoid fever using a string capsule device. *Trans R Soc Trop Med Hyg* 1984; 78:404-6.
25. Vallenas C, Hernandez H, Kay B, Black R, Gotuzzo E. Efficacy of bone marrow, blood, stool and duodenal contents cultures for bacteriologic confirmation of typhoid fever in children. *Pediatr Infect Dis J* 1985; 4:496-8.
26. Prakash P, Mishra OP, Singh AK, Gulati AK, Nath G. Evaluation of nested PCR in diagnosis of typhoid fever. *J Clin Microbiol* 2005; 43:431-2.
27. Khan S, Harish BN, Menezes GA, Acharya NS, Parija SC. Early diagnosis of typhoid fever by nested PCR for flagellin gene of *Salmonella enterica* serotype Typhi. *Indian J Med Res* 2012; 136:850-854.
28. Andualem G, Abebe T, Kebede N, Gebre-Selassie S, Mihret A, Alemayehu H. A comparative study of Widal test with blood culture in the diagnosis of typhoid fever in febrile patients. *BMC Research Notes* 2014; 7:653.
29. Pokhrel BM, Karmacharya R, Mishra SK, Koirala J. Distribution of antibody titer against Salmonella enterica among healthy individuals in Nepal. *Ann Clin Microbiol Antimicrob* 2009; 8:1.
30. Krishna S, Desai S, Anjana VK, Paranthaaman RG. Typhidot (IgM) as a reliable and rapid diagnostic test for typhoid fever. *Ann Trop Med Public Health* 2011; 4:42-4.
31. Tantivanich S, Chongsanguan M, Sangpetchsong V, Tharavanij S. A simple and rapid diagnostic test for typhoid fever. *Southeast Asian J Trop Med Public Health* 1984; 15:317-22.
32. Kaur I, Talwar V, Gupta H. Latex agglutination test for rapid diagnosis of typhoid fever. *Indian J Med Microbiol* 1990; 8:78¬83.
33. Sahni GS. Latex agglutination test (LAT) for the diagnosis of typhoid fever. *J Indian Med Assoc* 2013; 111:3957, 403.
34. Jog S, Soman R, Singhal T, Rodrigues C, Mehta A, Dastur FD. Enteric fever in Mumbai – clinical profile, sensitivity patterns and response to antimicrobials. *JAPI* 2008; 56:237-40.
35. Butler T. Treatment of enteric fever in the 21st century: promises and shortcomings. *Clin Microbiol Infect* 2011; 17:959-63.
36. Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection. *Lancet Infect Dis* 2005; 5:341-8.
37. Capoor MR, Nair D. Quinolone and Cephalosporin Resistance in Enteric Fever. *J Glob Infect Dis* 2010; 2:258-62.
38. Senekal M. Importance of minimum inhibitory concentration (MIC) values. *CME*. 2010; 28:276-7.
39. Shakur MS, Arzuman SA, Hossain J, Mehdi H, Ahmed M. Cefpodoxime proxetil compared with cefixime for treatment of enteric fever in children. *Indian Pediatr* 2007; 44:838-41.
40. Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, et al. Fluoroquinolones for treating enteric fever and paraenteric fever (enteric fever). *Cochrane Database Syst Rev* 2011; (10):CD004530.
41. Koirala S, Basnyat B, Arjyal A, et al. Gatifloxacin versus ofloxacin for the treatment of uncomplicated enteric fever in Nepal: an open-label, randomized, controlled trial. *PLoS Negl Trop Dis* 2013; 7:e2523.
42. Aggarwal A, Ghosh A, Gomber S, Mitra M, Parikh AO. Efficacy and safety of azithromycin for uncomplicated enteric

fever: an open label non-comparative study. *Indian Pediatr* 2011; 48:553-6.

43. Frenck RW Jr, Mansour A, Nakhla I, et al. Short-course azithromycin for the treatment of uncomplicated enteric fever in children and adolescents. *Clin Infect Dis* 2004; 38:951-7.
44. Chandey M, Multani AS. A comparative study of efficacy and safety of azithromycin and ofloxacin in uncomplicated enteric fever: a randomised, open labelled study. *J Clin Diagn Res* 2012; 6:1736-9.
45. Balasubramanian S, Rajeswari, Sailakshmi, Shivbalan S. Single vs. multidrug therapy in enteric fever. *Indian J Pediatr* 2006; 73:103.
46. Chowdhury JUA, Iftekhar MH, Shaheed N. Development of an ideal operative procedure in enteric fever perforation management. *Orion Med J* 2010; 33:716-7.
47. Malik AM. Different surgical options and ileostomy in enteric fever perforation. *World J Med Sci* 2006; 1:112-6.
48. Ansari AG, Naqvi SQH, Ghumro AH, Jamali AH, Talpur AA. Management of enteric fever ileal perforation: A surgical experience of 44 cases. *Gomal J Med Sci* 2009; 7:27-30.
49. Khandeparkar P. Re-emergence of chloramphenicol in enteric fever in the era of antibiotic resistance. *JAPI* 2010; 58(Suppl):45-6.
50. Harish BN, Menezes GA. Determination of antimicrobial resistance in Salmonella spp. *Methods Mol Biol* 2015; 1225:47-61.
51. Vala S, Shah U, Ahmad SA, Scolnik D, Glatstein M. Resistance patterns of enteric fever in children: a longitudinal community-based study. *Am J Ther* 2014 [Epub ahead of print]
52. Ahmad KA, Khan LH, Roshan B, Bhutta ZA. Factors associated with enteric fever relapse in the era of multiple drug resistant strains. *J Infect Dev Ctries* 2011; 5:727-31.
53. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK. IAP Task Force Report: Diagnosis of enteric fever in children. *Indian Pediatr* 2006; 43:884-7.
54. WHO Guidelines for the Management of Enteric fever 2011. Available at http://apps.who.int/medicinedocs/documents/s20994en/s20994en.pdf
55. Directorate of health services. Referral Guidelines for the common conditions for institutions under DME and DHS in Kerala. Available at http://dhs.kerala.gov.in/docs/pdf/reference.pdf
56. Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. *J Infect Dev Ctries* 2011; 5:324-37.
57. Levine MM, Lepage P. Prevention of Typhoid Fever. In: Pollard AJ, Finn A, editors. Hot Topics in Infection and Immunity in Children. New York: Springer. 2005 :161-73.
58. Sharma PK. Ramakrishnan R, Hutin Y, Manickam P, Gupte MD. Risk factors for typhoid in Darjeeling, West Bengal, India: evidence for practical action. *Trop Med Int Health* 2009; 14:696-702.
59. Murugunathan A, Mathai D, Sharma SK, editors. Adult Immunization 2014. 2nd Ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. for the Association of Physicians of India. 2015. p. 220-3.
60. BuzğanT, Evirgen O, Irmak H, Karsen H, Akdeniz H. A case of typhoid fever presenting with multiple complications. *Eur J Gen Med* 2007; 4:83-6.
61. Pandove PK, Moudgil A, Pandove M, Aggarwal K, Sharda D, Sharda VK. Multiple ileal perforations and concomitant cholecystitis with gall bladder gangrene as complication of typhoid fever. *J Surg Case Rep* 2014; 2014:rju070.
62. Ali R, Ahmed S, Qadir M, Atiq H, Hamid M. Salmonella cholecystitis: atypical presentation of a typical condition. *J Coll Physicians Surg Pak* 2013; 23:826-7.
63. Shrivastava D, Kumar JA, Pankaj G, Bala SD, Sewak VR. Typhoid intestinal perforation in Central India – A surgical experience of 155 cases in resource limited setting. *Int J of Biomed and Adv Res* 2014; 05:600-4.
64. Kumar S. Management of Enteric fever. Available at http://www.apiindia.org/pdf/monograph_2015_update_on_tropical_fever/013_management_of_enteric_fever.pdf
65. Lakhotia M, Gehlot RS, Jain P, Sharma S, Bhargava A. Neurological Manifestations of Enteric Fever. *JIACM* 2003; 4:196-9.

Disclaimer

"The initiative of 'Enteric Conclave' is supported by Abbott Healthcare Private Limited (through its Truecare division) in the quest of widening therapy knowledge in Enteric fever by bringing together experts and primary care physicians on one platform for the benefit of patients and medical fraternity."