

Review Article

Typhoid fever: a review

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ABSTRACT

Typhoid fever is still a deadly disease in developing countries, particularly in India. Although, the paediatric population is mostly affected by this disease, yet the disease is an important cause of morbidity and mortality in adult populations also. In India, most of the cases of typhoid fever are diagnosed clinically, or at the most by the Widal test which is not fool proof. The disease typhoid fever is an orally transmitted communicable infectious disease caused by the bacteria *Salmonella typhi*. It is usually caused by consuming impure water and contaminated food. *Salmonella typhi* is serologically positive for lipopolysaccharide antigens O9 and O12, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi. *S. typhi* Vi-positive strains are more infectious and virulent than Vi-negative strains. Following the incubation period of 7 to 14 days, there is onset of fever and malaise. The fever is then accompanied by chills, headache, malaise, anorexia, nausea, vague abdominal discomfort, dry cough and myalgia. These are followed by coated tongue, tender abdomen, hepatomegaly, and splenomegaly. Azithromycin (10mg/kg) given once daily for seven days has proven effective in the treatment of typhoid fever in some adults and children. A dose of 1g per day for five days was also found to be more effective in most adults. Of the third generation cephalosporins, oral Cefixime (15-20mg per kg per day, for adults, 100-200mg twice daily) has been widely used. Intravenous third generation cephalosporins (ceftriaxone, cefotaxime) are effective. Aztreonam and imipenem are potential third line drugs.

Keywords: Typhoid fever, Review

INTRODUCTION

200 years ago, one of the major causes of morbidity and mortality in the western world was typhoid fever or for that matter enteric fever.¹ Because of improvements in sanitation and overall health situations, the conditions have greatly improved now and the deadly disease of yester years is very scarce now in the USA and the Europe. However, typhoid fever is still a deadly disease in developing countries, particularly in India².

Although, the paediatric population is mostly affected by this disease, yet the disease is an important cause of morbidity and mortality in general adult populations also.

However, because of several reasons data on typhoid are not very reliable in Indian context. Among these reasons are: most of the patients with fever are treated as outpatients; hospitals, particularly, in rural areas which comprise the major portions of the country lack facilities for blood culture; most of the health clinics even hospitals do not keep proper records; and reliable data to estimate the burden of this disease is extremely difficult to obtain. In India, most of the cases of typhoid fever are still diagnosed clinically, or at the most with Widal test which is not foolproof. Because of all these reasons a fresh review of the recent advances on the various facets of typhoid fever will not be irrelevant at least in Indian context.

EPIDEMIOLOGY

In recent years there have been some changes in the epidemiological patterns of typhoid and related diseases in the third world countries, involving basically most of the countries in Africa, Asia and Latin America.³⁻⁶ More than 20 million cases a year occur in the hygienically compromised areas of developing countries and out of them Pakistan, India, and Bangladesh together bear the brunt of the attack accounting for 85% of the cases occurring globally.⁷ Obviously, the highest age-specific rates of typhoid and allied diseases are borne by children and young adults. Studies in Pakistan and Bangladesh show the mean age of patients affected with typhoid fever is 7 years.^{8,9} Typhoid is found to be a seasonal disease; in the monsoon itself there is occurrence of 45% of the total annual reported cases. In South Asia the disease occurrence is highest during July to October because of heavy rainfall during that period.⁸ Proper standardization of the methods of epidemiological studies on typhoid is therefore deemed necessary.¹⁰

Buckle et al did an elaborate review using standardized survey methods with 24 studies that examined typhoid fever incidences and employed blood culture as the criteria for diagnosis.¹¹⁻³⁴ We also identified five advanced surveillance reports where incidences of blood-culture-confirmed typhoid fever cases were studied.³⁵⁻³⁹ Another very recent published work on the same context was also found.⁴⁰

In total, taking all these standardized studies, typhoid epidemiology data were abstracted from 47 countries across the entire global regions. Data were also obtained from population-based and prospective vaccine studies for 13 countries. The remaining incidence data were collected by typhoid fever surveillance systems in the several developed regions where regular and systematic national-level surveillance was in vogue. Paratyphoid fever incidence data were available for only 9 countries of which the USA, despite having an advanced and regular surveillance system, did not have even a single case of paratyphoid fever during the entire period of their study.

The incidence of typhoid was high (>100 cases per 100,000 population per year) in Asia (excepting Japan) and Southern Africa. It is medium (10-100 cases per 100,000 population per year) in North Africa, Latin America, Caribbean islands and Oceania. The incidence of typhoid fever was estimated to be low in Europe, North America, Australia and New Zealand (<10 cases per 100,000 population per year). Previous typhoid fever incidence rates (IR) reported in Egypt during various vaccine trials varied from 209/100,000 in 1972-73 to 48/100,000 persons in 1978-81.¹⁷

A more recent study by Crump et al, however, reported lower IR of 13/100,000 persons.¹⁶ Most cases in

developed countries arise in travellers and domestically acquired disease is very rare.

AETIOLOGY

The disease typhoid fever is an orally transmitted infectious disease caused by the bacteria *Salmonella Typhi*. It is usually caused by consuming impurified water and contaminated food. As *S. typhi* bacteria can survive in water for days, contamination of surface water such as sewage, fresh water and ground water acts as major aetiological agent of typhoid.

Defaecation in open places is another notable cause of typhoid transmission. Amidst food, cut fruits kept uncovered for some time are an important cause of contamination in most developing countries. Papaya has a neutral pH and its cut surface can support the growth of various microorganisms.

It was observed by Hosoglu et al in a Turkish study that eating cut papaya, lettuce salad and some traditional raw foods in Turkey (e.g. *cig kofte*) was an important causative factor.⁴² Inhabiting in a congested locality or household is significantly related with typhoid fever.⁴² Again, the habit of washing vegetables and compulsory use of sanitary latrine for defecation have been found to prevent typhoid.^{41,43} In a case-control study in Indonesia, paratyphoid fever was found to be associated with consumption of food from street vendors.⁴⁴

Excessive antibiotic use causes an increased risk of infection with both drug-resistant and drug-sensitive serotypes of *S. typhi*.^{43,45,46} Interestingly, two recent case-control studies in Turkey and Bangladesh failed to show such a link.^{41,42} Prolonged antimicrobial use can cause changes in gastro-intestinal flora and a decreased barrier to bacterial colonisation, facilitating *Salmonella* infection.^{47,48} Bhan et al. have found a significant association between the presence of serum anti-*Helicobacter pylori* IgG antibodies and typhoid fever.⁴⁹ In a study in Vietnam, lower risk of typhoid was found to be associated with nucleotide polymorphisms in specific HLA alleles and the TNF-alpha promoter.⁵⁰ HLA-DRB1*12 was associated with protection against complicated typhoid fever.⁵¹

BACTERIOLOGY

Salmonella enterica serovar typhi is the causative organism for typhoid fever. The bacterium is serologically positive for lipopolysaccharide antigens O9 and O12, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi. The Vi capsular antigen is largely restricted to *S. enterica* serotype *typhi*, although it is shared by some strains of *S. enterica* serotypes *Hirschfeldii* (paratyphi C) and *Dublin*, and *Citrobacterfreundii*.⁵³ Polysaccharide capsule Vi has a protective effect against the bactericidal action on the serum of infected person.⁵⁴

PATHOGENESIS

Between 1000 and 1 million organisms are required to create the disease typhoid in a human being, which therefore is said to be the infectious dose of *S. enterica* serotype *typhi*. Obviously, *S. typhi* Vi-positive strains are more infectious and more virulent than Vi-negative strains of *S. enterica* serotype *typhi*. High gastric acidity is one important barrier against invasion of *S. typhi* and a low gastric pH is therefore an important defence mechanism. Aging, gastrectomy, proton-pump inhibitors or antacids leads to achlorhydria and facilitates typhoid infection.^{52,55}

In the small intestine, the bacteria first adhere to mucosal cells and then invade the mucosa following which they rapidly penetrate the mucosal epithelium via either microfold cells or enterocytes and arrive in the lamina propria, where they rapidly elicit an influx of macrophage that ingest the bacilli but do not generally kill them. Some bacilli remain within the macrophage of the small intestinal lymphoid tissue and some microorganisms translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes and by which they enter the thoracic duct and the general circulation.^{53,54}

7 to 14 days is usually the incubation period of typhoid. After that there is an interaction between host immunologic mediators and bacterial factors leading ultimately to the necrosis of Peyer's patches.^{53,56,57} Interestingly, in Africa the disease is often due to non-typhoidal salmonellae such as Typhimurium. In contrast to the Asian situation; however, the two are clinically indistinguishable.⁵⁸

SYMPTOMATOLOGY

Typhoid fever is one of the most common febrile illnesses in developing countries. Following the incubation period of 7 to 14 days, there is onset of fever and malaise. The fever is then accompanied by chills, headache, malaise, anorexia, nausea, vague abdominal discomfort, dry cough and myalgia. These are followed by coated tongue, tender abdomen, hepatomegaly, and splenomegaly.^{53,59}

However, recent advances of antibiotic treatment have changed this classic mode of presentation, such as a slow and stepladder type of fever and features of toxicity scarcely seen these days. In areas where malaria is endemic and where Schistosomiasis is common, the presentation of typhoid may be atypical.⁵⁸ Even polyarthritis and monoarthritis are reported presentation.⁵⁹ Adults often have constipation, but diarrhoea, toxicity and complications such as disseminated intravascular coagulation are more noticeable in infants.⁵³ Vertical intrauterine transmission from an infected mother may lead to neonatal typhoid, a rare but severe and life threatening condition.⁵³ Both relapses and re-infection are common in typhoid and

occur in less than 10 per cent of cases. Reinfection can only be distinguished from relapse by molecular typing.^{53,60}

DIAGNOSIS

The diagnosis of typhoid is usually made in the developing world from clinical criteria. In areas of endemic disease, fever without evident cause that lasts for more than one week should be considered typhoid until proven otherwise. However, malaria, deep abscess, tuberculosis, amoebic liver abscess, encephalitis should also be considered for differential diagnosis. Over and above, the following complications of typhoid should be kept in mind as they are often confusing factors during diagnosis and treatment:

Abdominal

Gastrointestinal perforation, gastrointestinal haemorrhage, Hepatitis, Cholecystitis (usually subclinical).

Cardiovascular

Asymptomatic electrocardiographic changes, Myocarditis, Shock.

Neuropsychiatric

Encephalopathy, delirium, psychotic states, cranial or peripheral neuritis, Guillain-Barre syndrome, meningitis, impairment of coordination.

Respiratory

Bronchitis Pneumonia (*Salmonella enterica* serotype *typhi*, *Streptococcus pneumoniae*).

Hematologic

Anaemia, Disseminated intravascular coagulation (usually subclinical), thrombocytopenia, haemolytic uremic syndrome.

Others

Focal abscess, pharyngitis, miscarriage, relapse, chronic carrier, influenza, dengue, leptospirosis, infectious mononucleosis, brucellosis, rickettsial diseases etc. should be considered.^{53,58}

Routine blood tests

Fifteen to 25% patients show leucopenia and neutropenia. Leucocytosis found in intestinal perforation and secondary infection.⁶¹ In younger children, leucocytosis is common association and may reach 20,000-25,000/mm³.

Liver function tests

These may be deranged. Although significant hepatic dysfunction is rare, some studies and case reports showed there was hepatic derangement simulating acute viral hepatitis and also present as hepatic abscess.^{58,62}

Blood culture

This is the standard diagnostic method; it is positive in 60 to 80 per cent of patients with typhoid. Culture of the bone marrow is more sensitive, around 80 to 95 per cent patients, even in patients taking antibiotic for several days, regardless of the duration of illness. Blood culture is less sensitive than bone marrow because there is lower number of organism in blood than bone marrow. The sensitivity of blood culture is higher in the first week of illness, increases with the volume of blood cultured (10-15ml should be taken from school-children and adults, 2-4ml are required from toddlers and preschool children). Toddlers have higher level of bacteraemia than adult.

Other cultures

Cultures have also been made from the buffy coat of blood, streptokinase treated blood clot, intestinal secretion (with the use of duodenal string capsule), and skin snips of rose spots. The sensitivity of stool culture depends on the amount of faeces cultured, and the positivity rate increased with the duration of illness. Stool cultures are positive in 30 per cent of patients with acute typhoid fever.^{53,54} Urine culture have got 0-58% sensitivity.⁵⁸

Felix-Widal test

The classic Widal test is more than 100 years old.⁵⁸ It detects agglutinating antibodies to the O and H antigens of *S. enterica* serotype *typhi*. The levels are measured by using doubling dilutions of sera in large test tube.⁵⁴ Although easy to perform, this test has moderate sensitivity and specificity.⁵⁸ Its reported sensitivity is 70 to 80 per cent with specificity 80 to 95 per cent. It can be negative in up to 30% of culture proven typhoid fever, because of blunted antibody response by prior use of antibiotic. Moreover, patients with typhoid may show no detectable antibody response or have no demonstrable rise in antibody titre. Unfortunately, *S. enterica* serotype *typhi* shares these antigens with other salmonella serotypes and shares these cross-reacting epitopes with other *Enterobacteriaceae*. This can lead to false positive results. If paired serums are available a fourfold rise in the antibody titre between convalescent and acute sera is diagnostic.^{53,54}

Considering the low cost of Widal test, it is likely to be the test of choice in many developing countries. This is acceptable, as long as the results of the test are interpreted with care, on the background of prior history

of typhoid, and in accordance to appropriate local cut-off values for the determination of positivity.⁵⁴

New diagnostic tools

Tubex test detect IgM antibodies, Typhidot detect IgM and IgG antibodies against 50 kD antigen of *S. typhi*.⁶³ Tubex has not been evaluated extensively but in preliminary studies, this test performed better than Widal test in both sensitivity and specificity. Although culture remains gold standard, Typhidot-M is superior to culture method in sensitivity (93%) and has high negative predictive value. In some studies, it has shown that for total Ig estimation ELISA has superior sensitivity when compared to other tests.⁶⁴

Recently DNA probes and polymerase-chain-reaction (PCR) have been developed to detect *S. enterica* serotype *typhi* directly in the blood.^{53,58} Urine antigen detection has 65-95% sensitivity. PCR has still not been used in clinical practice.

TREATMENT

Prompt institution of appropriate antibiotics following early diagnosis is essential for optimal management. Knowledge of the antibiotic susceptibility is crucial in determining which drug to use. More than 90% of patients can be managed at home with oral antibiotic and regular follow-up. However, patients with severe illness, persistent vomiting, severe diarrhoea, and abdominal distension, require hospitalisation and parenteral antibiotic treatment. Chloramphenicol was the drug of choice for several decades after its introduction in 1948. However, the emergence of plasmid mediated resistance and development of serious side effect like bone marrow aplasia had pushed this drug aside. Trimethoprim-sulfamethoxazole and ampicillin were employed to counter chloramphenicol resistance in 1970, but it was also discarded because of development of plasmid mediated resistance.

In 1992, emergence of multidrug resistance enteric fever (resistant to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) was strongly addressed in Bangladesh; around 36.58% cases were reported in a large study.

In the 1980s, ceftriaxone and ciprofloxacin became the drug of choice. Although Fluoroquinolones attain excellent tissue penetration, rapid therapeutic response and very low rate of post treatment carriage, strains of bacteria have emerged in Asia that show resistance to them in the past decade. Resistance to the fluoroquinolone may be total or partial. The nalidixic-acid-resistant strain has reduced susceptibility to fluoroquinolone drug compared to nalidixic-acid-sensitive strain. Although isolates are nalidixic acid resistant but these can be susceptible to fluoroquinolones in disc sensitivity testing. Disc sensitivity testing is

defined as a ciprofloxacin MIC of 0.12-1 mg/L, and is not always detected by testing of nalidixic acid resistance. The available fluoroquinolones (ofloxacin, ciprofloxacin, perfloracin) are highly active and equivalent in efficacy. For nalidixic-acid-resistant infections, a minimum of seven days of treatment at the maximum permitted dosage is necessary and 10-14 days are usually required. Culture sensitivity data of Department of Microbiology of BSMMU showed 8.6% sensitive to nalidixic acid, whereas ciprofloxacin is still 67% sensitive. Even a few days earlier it was thought that gatifloxacin is better than older fluoroquinolones. The bacteria needed dual point mutations (in the DNA-gyrase and Topoisomerase-4 genes) to become resistant to gatifloxacin. Most studies in endemic countries have identified gyrA mutation in *S. enterica* as a mechanism of resistance. Because there is no reported pattern of sensitivity to gatifloxacin in India or Bangladesh or most of the western countries for that matter and of its recent reports of some toxicities it has been withdrawn and no longer used for any systemic illness.

Azithromycin in a dose of 500mg (10mg/kg) given once daily for seven days has proven effective in the treatment of typhoid fever in some adults and children. A dose of 1g per day for five days was also found to be more effective in most adults. Of the third generation cephalosporins, oral Cefixime (15-20mg per kg per day, for adults, 100-200mg twice daily) has been widely used in children in a variety of geographical settings and found to be satisfactory. However, in some trials Cefixime showed higher rates of failure and relapse than fluoroquinolones. But antibiotic sensitivity pattern in BSMMU showed higher sensitivity around 78.8%.

Intravenous third generation cephalosporins (ceftriaxone, cefixime, cefotaxime) are effective with low relapse (3 to 6%) and fecal carriage (<3%) rates. Ceftriaxone is effective at a dose of 2-4gm daily in single or two divided doses.^{2,3} Aztreonam and imipenem are potential third line drugs. Prevention of Typhoid: In urban areas, these measures are rapidly growing. In India, Bangladesh and some other developing countries compared to other parts of the world. In several studies, data indicate higher infection rate in the urban population. Lack of safe water and inadequate sanitation is responsible for this increased incidence. In developing countries, reducing the number of cases in general population requires the provision of safe drinking water and effective sewage disposal. Food safety can be ensured by washing hand with soap before preparing food, water for drinking should be boiled, avoiding raw food shellfish, ice cream.

In one study from Dhaka city, people living close to the rivers Buriganga, Turag, and Balu had an elevated risk of typhoid.⁸ There are several factors responsible. Low income inhabitants of this area frequently use surface water for drinking. As *S. typhi* bacteria can survive in water for days, contaminated surface water act as etiological agents of typhoid.

CONCLUSION

Even today, enteric fever is a global public health problem, particularly in developing countries. Studies show the number of urban cases of typhoid is around 800-900/year. Widal test, though cheap and available should be interpreted with caution. We should be aware about the higher incidence of typhoid fever in India and other developing countries. Massive campaigns should be initiated to make people understand the preventive measures, role of vaccines, importance of visiting doctors and the like.

Doctors should be conscious about the gradually developing antibiotic resistance and the emerging safe and effective newer antibacterial agents. The latter includes newer fluoroquinolones and macrolides in large doses, and lastly third generation cephalosporins both in oral and injectable forms. Over and above, the profession should look forward to newer curative and preventive measures.

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