

**Review Article**

**Current status of typhoid fever : a review**

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**Introduction**

Typhoid fever is caused by a highly specific human adapted pathogen, *Salmonella enterica* serotype typhi. This organism is an important cause of febrile illness and death in population living in crowded and poorly sanitized environment. The risk of disease has increased in population exposed to unsafe water and food and also pose a risk to, travellers visiting to endemic country.<sup>1</sup> This review addresses recent trends in global epidemiology, approaches to prevention and control, antimicrobial resistance pattern in Bangladesh and rest of the world, and treatment, conventional and newer developing diagnostic methods along with role of Widal test in diagnosing typhoid.

**The organism**

The bacterium is serological 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* sero types *hirschfeldii* (paratyphi C) and *dublin*, and *Citrobacter freundii*.<sup>2</sup> Polysaccharide capsule Vi has a protective effect against the bactericidal action of the serum of infected person.<sup>3</sup>

Epidemiology and Trends of Enteric Fever in Bangladesh  
Recent changes in trends in enteric disease epidemiology have emerged in the Africa, Asia and Latin America.<sup>1,4-6</sup> The people living in the slums of the developing world, bear 21 million cases a year. Pakistan, India, and Bangladesh together account 85% of the world cases.<sup>7</sup> Children and young adult had the highest age-specific rates of enteric infection. The mean age of those infected with typhoid fever is 7 years in Pakistan

and Bangladesh.<sup>8,9</sup> Urban areas in South Asia are rapidly growing compared to other parts of the world and the burden of the disease seems to be higher than rural part due to inadequate provision of safe water and sanitation. As *S. Typhi* bacteria can survive in water for days, contaminated surface water such as sewage, fresh water and ground water act as etiological agents of typhoid. Distinct seasonal variation is noted; 45% of reported cases found to have occurred in the monsoon. Because of heavy rainfall during the monsoon in South Asia, surface water contamination is high and disease occurrence become high in July to October.<sup>8</sup>

**Pathogenesis**

The infectious dose of *S. Enteric* serotype typhi in patients varies between 1000 and 1 million organisms. Vi-negative strains of *S. Enteric* serotype typhi are less infectious and less virulent than Vi-positive strains. *S. enteric* serotype typhi must survive the gastric acid barrier to reach the small intestine, and a low gastric pH is an important defence mechanism. Achlorhydria as a result of aging, previous gastrectomy, or treatment with proton-pump inhibitors or large amounts of antacids lowers the infective doses.<sup>1,10</sup>

In the small intestine, the bacteria adhere to mucosal cells and then invade the mucosa. 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.<sup>2,3</sup>

As a result of the silent primary bacteraemia the pathogens reaches an intracellular haven within 24 hours after ingestion. *Salmonella* organisms are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver, and spleen and bone marrow. The incubation period is usually 7 to 14 days. The incubation period in a particular individual depends on the number of bacteria, their virulence, and the host response. Clinical illness is accompanied by a fairly sustained but low level of secondary bacteraemia, usually one bacterium per millilitre of blood and about 10 bacteria per millilitre of bone marrow.<sup>1-3</sup>

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Typhoid induces systemic and local humoral and cellular immune responses, but these confer incomplete protection against relapse and reinfection. The interaction of host immunologic mediators and bacterial factors in infected tissue may contribute to the necrosis of Peyer's patches in severe disease.<sup>2,11,12</sup>

In contrast to the Asian situation, the HIV and AIDS epidemic in Africa has been associated with a concomitant increase in community bacteraemia due to non-typhoidal salmonellae such as *S.typhimurium*; it is clinically indistinguishable from typhoid.<sup>13</sup>

### Clinical Features : Importance of diagnosis in typhoid fever

Typhoid fever is among the most common febrile illness encountered by physicians in developing countries. After an incubation period of 7 to 14 days, the onset of bacteremia is marked by fever and malaise. Patients typically present toward the end of the first week after the onset of symptoms with fever, influenza-like symptom with chills, headache, malaise, anorexia, nausea, poorly localized abdominal discomfort, dry cough and myalgia. Coated tongue, tender abdomen, hepatomegaly, and splenomegaly are common.<sup>2,14</sup> The advent of antibiotic treatment has led to a change in the classic mode of presentation, a slow and step-ladder rise in fever and toxicity is rarely seen now-a-days. In areas where malaria is endemic and where Schistosomiasis common, the presentation of typhoid may be atypical.<sup>13</sup> Even polyarthritis and monoarthritis are reported presentation.<sup>14</sup> Adults often have constipation, but in young children and in adults with HIV infection, diarrhoea is more common. The presentation of typhoid is more dramatic in children younger than 5 years with higher rates of complications and hospitalization. Diarrhoea, toxicity and complications such as disseminated intravascular coagulation are also more common in infancy.<sup>2</sup>

Typhoid fever during pregnancy complicated by miscarriage, antimicrobial treatment has made this outcome less common. Vertical intrauterine transmission from an infected mother may lead to neonatal typhoid, a rare but severe and life threatening condition.<sup>2</sup>

Relapses occur in 5 to 10 percent patients, usually two to three weeks after resolution of fever. The relapse is usually milder than the original attack, and the *S. enterica* serotype typhi isolate from a patient in relapse usually has the same antibiotic susceptibility pattern as the isolate obtained during the original attack. Reinfection can only be distinguished from relapse by molecular typing.<sup>2,15</sup>

One to five percent of patients, become long term carrier, excreting the organism for more than one year.<sup>2,3</sup> Chronic carriage is more common among young woman and the elderly and in patient with cholelithiasis. Patient who harbours schistosomiasis, excrete organism for long time.<sup>16</sup> (Table-I)

**Table-I:** Important complications of typhoid fever

Abdominal	Gastrointestinal perforation
	Gastrointestinal hemorrhage
	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 ( <i>Salmonella enterica</i> serotype typhi, <i>Streptococcus pneumoniae</i> )
Hematologic	Anemia
	Disseminated intravascular coagulation (usually subclinical)
	Thrombocytopenia
	Haemolytic uremic syndrome
Others	Focal abscess
	Pharyngitis
	Miscarriage
	Relapse
	Chronic carriage

In the pre-antibiotic area, patient usually did not die due to intestinal haemorrhage or peritonitis. Fifteen percent patient died with prolonged persistent fever and diseases with no clear reason.

### Diagnosis

The diagnosis of typhoid can be 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. It has distinguished itself from other endemic acute and subacute febrile illness. Yet malaria, deep abscess, tuberculosis, amoebic liver abscesses, encephalitis,

influenza, dengue, leptospirosis, infectious mononucleosis, brucellosis, rickettsial diseases etc. should be considered.<sup>2,13</sup>

Fifteen to 25% patients show leucopenia and neutropenia. Leucocytosis found in intestinal perforation and secondary infection.<sup>16</sup> In younger children, leucocytosis is common association and may reach 20,000-25,000/mm<sup>3</sup>. Liver function tests may be deranged. Although significant hepatic dysfunction is rare, in some studies and case reports showed there was hepatic derangement simulating acute viral hepatitis and also present as hepatic abscesses.<sup>13,17</sup>

Blood cultures are the standard diagnostic method; they are positive in 60 to 80 percent of patients with typhoid.. Culture of the bone marrow is more sensitive, around 80 to 95 percent patient, even in patients taking antibiotic for several days, regardless of the duration of illness. Blood culture is less sensitive than bone marrow because of 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 (10-15 ml should be taken from school-children and adults, 2-4 ml are required from toddlers and preschool children). Toddlers have higher level of bacteraemia than adult. 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 percent of patients with acute typhoid fever.<sup>2,3</sup> Urine culture have got 0-58% sensitivity.<sup>13</sup>

#### **Felix-Widal test**

The classic Widal test is more than 100 years old.<sup>13</sup> 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.<sup>3</sup> Although robust and simple to perform, this test has moderate sensitivity and specificity.<sup>13</sup> Its reported sensitivity is 70 to 80 percent with specificity 80 to 95 percent. 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 mount 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. Such results may also

occur in other clinical conditions, e.g. malaria, typhus, bacteraemia caused by other organisms and cirrhosis. In areas of endemecity, there is low background level of antibodies in the normal population. It is difficult to establish an appropriate cut-off point for a positive result, since it varies between areas and between times in given areas. As because, usually a single acute serum is available, it is important to establish the antibody level in the normal population in a particular locality in order to determine a threshold above which the antibody titre is considered significant. If paired serum are available a fourfold rise in the antibody titre between convalescent and acute sera is diagnostic.<sup>2,3</sup>

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.<sup>3</sup>

#### **Evolution and usefulness of new diagnostic tools**

Tubex test detect IgMO antibodies, Typhidot detect IgM and IgG antibodies against 50 kD antigen of *S.typhi*.<sup>9</sup> 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.<sup>3</sup>In some studies, it has shown that total Ig ELISA has superior sensitivity when compared to other tests.<sup>18</sup>

Recently DNA probes and polymerase-chain-reaction (PCR) have been developed to detect *S. enteritica* serotype typhi directly in the blood.<sup>213</sup> Urine antigen detection has 65-95% sensitivity. PCR still not been used in clinical practice.

#### **Treatment: Recent trends of drug resistance and its effect in management of typhoid**

Early diagnosis and prompt institution of appropriate antimicrobial are 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.<sup>3,13</sup>

Chloramphenicol was the drug of choice for several decades after its introduction in 1948. However, the

emergence of plasmid mediate 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.<sup>19</sup>

In 1992, emergence of multidrug resistance enteric fever (resistance to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) was strongly addressed in Bangladesh; around 36.58% cases were reported in a large study.<sup>20</sup>

In the 1980s, ceftriaxone and ciprofloxacin became the drug of choice.<sup>19</sup> 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.<sup>3,19</sup> 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.<sup>3,19</sup> The available fluoroquinolones (Ofloxacin, Ciprofloxacin, Fleroxacin, perfloxacin) 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.<sup>3</sup> Culture sensitivity data of Dept. of Microbiology of BSMMU showed 8.6% sensitive to nalidixic acid, whereas ciprofloxacin is still 67% sensitive. (Table-II)

**Table-II:** Sensitivity pattern of *S. typhi* antibiotics in Bangladeshi population. (Department of Microbiology, BSMMU)

Antimicrobial	Sensitivity to <i>S. typhi</i> (n=175)
Amoxycillin	58 (33%)
Cotrimoxazole	112(64%)
Ciprofloxacin	118(67%)
Nalidixic acid	15(8.6%)
Ceftriaxone	137(78%)
Chloramphenicol	115(65.7%)
Cefuroxime	94(53.7%)
Azithromycin	74(42.3%)
Cefepime	143(81.7%)
Cefixime	138(78.8%)

Now-a-days it is thought that Gatifloxacin is better than older fluoroquinolones. The bacteria need 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.<sup>1,21</sup> There is no reported pattern of sensitivity to Gatifloxacin in Bangladesh.

Azithromycin in a dose of 500 mg (10mg/kg) given once daily for seven days has proven effective in the treatment of typhoid fever in adults and children. A dose of 1 g per day for five days was also found effective in adult.<sup>3</sup>

Of the third generation cephalosporin, oral Cefixime (15-20 mg per kg per day, for adults, 100-200 mg 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.<sup>3,19</sup> 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 2-4 gm daily in single or two divided doses.<sup>2,3</sup> Aztreonam and imipenem are potential third line drugs.<sup>2</sup>

### Prevention of Typhoid

In Bangladesh, urban areas are rapidly growing compared to other parts of the world. In several studies, data indicate higher infection rate in this urban population.<sup>8,22</sup> 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, icecream.<sup>2,3</sup>

In Dhaka city, people living close to the rivers Buriganga, Turag, and Balu had an elevated risk of typhoid. 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.<sup>8</sup>

### Vaccination: Current status

The first parental whole-cell typhoid vaccine was introduced in 1896 and used in England and Germany but withdrawn by most of the countries because of strong side effects.<sup>2,23</sup>

The live oral vaccine Ty21a is available in enteric-coated capsule or liquid formulation. It should be taken in three doses two days apart on an empty stomach and is suitable for adult and children at least 5 years. The vaccine is well tolerated. Because it is live attenuated, it should not be given in immunocompromised and in patient who is taking antibiotic.<sup>2,3,23</sup>

The parenteral Vi-based vaccine is suitable for adults and children over the age of two years. A single dose of 0.5 ml is administered intramuscularly. In field trials conducted in Nepal and South Africa, where Typhoid is endemic, the protective efficacy of the vaccine was 72%, one and half years after vaccination. Booster dose is recommended every two years.<sup>2,3</sup>

WHO recommends vaccination for people travelling in high-risk areas where the disease is endemic, people living in such areas, people in refugee camps, microbiologists, sewage workers and children.<sup>3</sup>

#### Future vaccine

A new Vi conjugate vaccine bound to nontoxic recombinant *Pseudomonas aeruginosa* has enhanced immunogenicity in adult and children aged 5-14 years. It is recently evaluated in Vietnam and the efficacy of vaccine in children aged 2-5 years after 27 month found 91.2 percent.<sup>2,3</sup> An important advantage of this vaccine is that it has the potential to be immunogenic in infants under the age of two.<sup>2</sup> Currently DNA vaccine of typhoid fever is in phase 1 and 2 clinical trial.<sup>23</sup>

#### Conclusion

Enteric fever remains a major public health challenge. Although no exact data regarding epidemiology of typhoid fever is available in Bangladesh, study conducted in Dhaka metropolitan area found the number of cases is around 871/year.<sup>8</sup>

Cheap and available Widal test should be interpreted with caution. We should think about the higher incidence of typhoid fever in Bangladesh. Effort should be given for notify the prevalence of this disease and applicability of immunization to reduce the burden of the disease and also reduce the cost of antimicrobial treatment.

Antimicrobial resistance continues to emerge, resulting loss over time of the value of traditional first line drugs and fluoroquinolone. Decreased ciprofloxacin susceptibility and, more recently, fluoroquinolone resistance have led to greater use of third generation cephalosporines. However, recent antimicrobial sensitivity data still shows higher degree of sensitivity to Ciprofloxacin but concomitant

Nalidixic acid resistance limits its use in conventional dosage. Although in various parts of the world, azithromycin show promise for the management of fever, in Bangladesh, reports revealed relatively poor sensitivity. Till now, ceftriaxone has proven as most effect drug, precaution should be taken about serious side effect like hypersensitivity during administration. Now-a-days life threatening effect like cardiotoxicity is also reported. Historical adaptation of *Salmonella* to patterns of antimicrobial use suggests the vigilance for the emergence of ceftriaxone-resistant strains. Sensitivity pattern to Gatifloxacin should be sought. However, sensitivity to less and infrequent use of first line antibiotics (chloramphenicol, co-trimoxazole) make us rethink about reinstitution of their use. Indiscriminate and injudicious use of antibiotics rises the risk of newer strains of resistant organisms. Uses of antibiotic should be guided by culture and sensitivity report, over-the-counter sales of antibiotics must be stopped to prevent this nightmare.

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