

TYPHOID FEVER IN CHILDREN - AN UPDATE

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Abstract:

Typhoid fever is a commonly encountered systemic disease caused by the gram negative bacteria Salmonella enterica serover typhi. For the developing countries of the tropics and subtropics, it continues to be a big public health problem as the sanitation and public health standards are poor. Multidrug resistant (MDR) typhoid fever shows up a changed clinical pattern and a higher rate of complications (20%). This review article is a discussion on epidemiology, pathogenesis, clinical features, diagnosis and modern trend of treatment of typhoid fever in children. Moreover, its complication, relapse and multidrug resistant (MDR) typhoid fever are also highlighted.

Key words: Typhoid fever, multidrug resistant (MDR) typhoid fever, children, diagnosis, treatment.

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Introduction:

Typhoid fever is a commonly encountered systemic disease caused by the gram negative bacteria Salmonella enterica serover typhi¹. For the developing countries of the tropics and subtropics, it continues to be a big public health problem as the sanitation and public health standards are poor². Typhoid fever is endemic in the south east asian countries^{3,4}. Above 22 million new cases occur each year round the world while 90% of the sufferers are from the South-east Asia. Reported deaths from typhoid fever accounts to around 2,16,000 per year^{5,6,7,8}.

Effective treatment of enteric fever dates back to 1948, when Woodward introduced chloramphenicol^{9,10}. Subsequently ampicillin and cotrimoxazole made worthwhile contribution in the field and changed the outlook as gold standards of treatment, when case fatality came down to almost one percent. However, chloramphenicol resistant strains

made their appearance and a big change in the scenario of typhoid fever was observed during the 1970s^{11,12,13,14}. Multidrug resistant strains of S. typhi with plasmid mediated gene transfer against the first line drugs is a frequent finding in these days^{12,15,16}. Fluroquinolones, the second line option are also becoming resistant through the chromosomal mutation in DNA-gyrase system of S. typhi^{17,18,19}.

In Bangladesh, typhoid fever is a round the year problem which sometimes take epidemic proportions^{6,12}. From the public health point of view the reason behind such occurrence are unsafe water supply, defective sewerage system and unhygienic food handling practice^{6,8,12,20,21}.

Antibiotics are sold over the counter causing inappropriate and indiscriminate use in febrile illnesses⁶. Drug resistance in typhoid fever is a likely outcome of such misuses⁶. A high incidence of multidrug resistant (MDR) typhoid

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fever has been reported from Bangladesh. Variation in the sensitivity pattern to the first line drugs was observed in separate studies conducted in Dhaka and Khulna^{14,15,16}. The MDR strains showed up with a changed clinical pattern and a higher rate of complications (20%)^{17,18,19}.

It has been observed that the overall scenario of the disease changes with time. The diagnostic and treatment modalities undergo revisions and changes periodically. The present approach is thus an attempt to update our knowledge about the disease, so that time required changes can be made in the diagnosis and treatment of typhoid fever.

Epidemiology:

Typhoid fever (enteric fever) is an infectious disease of the tropical world of which 80% of the cases occur in Asian countries^{2,6}. It is a water borne, food borne disorder transmitted by ingestion of contaminated food or drinks^{1,20,21}. Mode of transmission, clinical presentation & consequences vary widely among developed and developing countries^{6,22}. School age children are the commonest group of sufferers^{23,24,25}. Symptomatology greatly varies in children and in MDR cases^{1,19,22,23}. MDR typhoid is endemic in many countries and causes epidemic in many areas of Asia including India, Pakistan, Bangladesh, Vietnam, Malaysia, Indonesia, China & Tajikistan^{5,6,26}. There is also pseudo epidemic region in the Middle East and Egypt, where infection with MDR *S. typhi* is generally related to migrant workers from the endemic zone but epidemics can result. Sporadic infection occurs in Europe and north America, most often in immigrants who went to their country of origin for a holiday^{27,28,29}. However, since 1997, increasing number of MDR *S. typhi* has been reported from patients in Kenya and Ghana^{30,31,32}. Apart from a recent small outbreak in south Africa, *S. typhi*^{32,33,34} was not a problem of sub-Saharan Africa^{1,19,23}. Thus, MDR *S. typhi* does not appear to have arrived in South or Central America^{19,23}. The prevalence of MDR *S. typhi* appears to be very high in Pakistan & Vietnam. *S. typhi* occurs for the majority of positive blood culture (60-70%) and

of these, 60-80% are MDR *S. typhi*. In some countries in endemic zone like India and Bangladesh, there has been encouraging decline in MDR *S. typhi* with the recognition of sensitive strain responding to quinolones. 3.4% of blood cultures were found MDR *S. typhi* in Bangladesh in 1994. This declined to 1% in 1996^{33,34,35}. Study in Vietnam demonstrated that fluoroquinolones (ofloxacin and ciprofloxacin) are highly effective drug for the of MDR *S. typhi*. Unregulated overuse of fluoroquinolones develops resistant strains of *S. typhi* causing both sporadic and epidemic disease^{36,37}.

The pathogen:

Salmonella typhi is a gram negative, non-spore bearing bacterium, that is motile by means of flagellae^{22,38}. They can survive long periods in water, sewerage, dried food stuffs and withstand freezing^{1,19,22}. Infective dose is about 10⁵-10⁹ organism, with an incubation period ranging from 4-14 days^{22,38}. The complete 4.8 Mbp genome sequence of Vietnamese strain of *S. typhi* is now available^{22,38}. It contains the five known salmonella pathogenicity islands (SPI 1-5), plus another five genomic islands that have characteristics of Pathogenicity islands. Pathogenicity islands are genomic regions encoding for, among other things, type III secretion systems^{22,38,39} that deliver effector molecules from the bacterial cytoplasm, across its two membranes and inject them into the host cell, thereby modulating the ability of macrophage to kill the bacteria. Humans are the only reservoir of the *S. typhi*²². However it can survive in food and water, and cause large epidemics when human excreta contaminate water supply^{1,19,22}.

Pathogenesis:

The infectious dose of *S. enterica* Serotype typhi in volunteers varies between 1,000 to one million organisms^{22,38}. The large numbers of organisms are to be swallowed with contaminated food or drinks^{1,19,22}. Escaping acid barrier of the stomach the organisms reach the upper small intestine where they survive in alkaline media^{40,41}. Subsequently they attach to the microvilli of the ileal brush border, attack (invade) the Peyer's patches,

lymph follicles, mesenteric lymphnodes and gradually multiply within unsensitized mononuclear cells to liberate endotoxins^{1,41}. After attacking the Peyer's patches, they start traveling via local lymphatics, thoracic duct and reach the blood (primary bacteremic phase)^{1,19,41}. From the blood they are taken up by the reticulo-endothelial system, where they multiply further. Finally, they reinvade blood and small intestine via gall bladder, also bone marrow, lymphoid tissue, liver and spleen (secondary bacteremic phase)^{1,19,40,41}. This makes the end of the incubation period which takes 7-14 days with the beginning of the clinical stages of the disease^{1,19,22}.

Critical point after invasion varies which is probably determined by number of bacteria, their virulence, host response, general condition, age, genetic makeup and immune status of the individual. But in MDR *S.typhi* cases all of these factors behave differently^{1,19}. In children- incubation period may be shorter, presentation may be atypical, induced local and systemic humoral and cellular immune response behave abnormally and confer incomplete protection against relapse and re-infection.^{19,22,40} Life threatening complication is 20% higher in MDR cases in children^{1,19,22,23}.

Clinical features:

The onset of bacteraemia is marked by fever and malaise^{1,19,22}. The classic three stages of disease i.e. prodrome, toxic, defervescence stage are shorter in children⁴⁰. Patients typically present to hospital towards the end of first week with the symptoms of fever, influenza like symptoms with chills, a dull frontal headache, malaise, anorexia, nausea, poorly localized abdominal discomfort, a dry cough and myalgia with few physical signs²². Initially the fever is low grade but it rises progressively and by the second week it is often high (39⁰-40⁰C) and sustained^{1,22,41}.

Along with fever gastrointestinal symptoms like vomiting, abdominal pain, loose motion are common presentations in children with typhoid fever^{1,12,22,40}. Convulsions may occur in children under five years of age^{22,41}. Patients may present with the features of pneumonia or meningitis^{42,43,44}. Occasionally, they may

present with frank neuropsychiatric symptoms resembling catatonic schizophrenia which is more frequent in Africa and Indian subcontinent^{45,46}. Patients may be severely agitated, delirious or obtunded but complete stupor or coma is infrequent. These neuropsychiatric presentations range from 10-40% among hospitalized patients with typhoid in Indonesia and Papua New Guinea but less than 2% in Pakistan and Vietnam^{45,46}.

On examination, relative bradycardia is not common in children but paradoxical relationship of high temperature and low pulse rate may be observed²². A few rose spots are present in less than 50% cases and some reported in 5-30% cases^{1,19,22,23}. They usually occur on abdomen and chest and rarely on back, arms and legs. A coated tongue, tender abdomen and hepatosplenomegaly are common^{1,19,22,41}. Hepatosplenomegaly was the most common physical sign observed in children with typhoid fever followed by abdominal tenderness^{4,47,48}. Another study on typhoid fever in children showed hepatomegaly in 85.3% and splenomegaly in 27.5% cases⁴. In some Bangladesh studies it is shown that palpable liver was present in 58% and palpable spleen was present in 33% cases and hepatosplenomegaly was present in 44.1% cases^{24,47,48}. Abdominal distension, coated tongue are common findings in Bangladesh studies.

Complications:

Complications occur in 10-15% of patients and occur particularly in patients who have been ill for more than two weeks^{1,8,19,22}. Typhoid ileal perforation is a major problem in developing countries and causes a high mortality⁴⁹. Some studies revealed that intestinal (usually ileal) perforation is the most serious complication, occurring in 1-3% of hospitalized patients⁵⁰. A Nigerian study showed the overall perforation rate of 10.3% in children with typhoid fever⁵¹. Some authors found that gastrointestinal bleeding is the most common complication occurring in 10% of patients⁸. Another study showed 20.3% of bleeding in the form of hematochezia⁵¹. Complications of typhoid fever may involve any

system of the body⁵². Though isolated cerebellar ataxia or nephritis is rare in enteric fever, it may occur in the second week⁵³. Common complications related to urinary tract are cystitis, pyelitis and pyelonephritis, but glomerulonephritis is uncommon in enteric fever⁵³. Toxic myocarditis, endocarditis, shock and meningitis are reported in children in typhoid fever¹.

Antimicrobial resistance in typhoid fever:

Most drug resistance is the result of a genetic change in the organism caused either by a chromosomal mutation or the acquisition of a plasmid or transposon^{38,39}. Plasmid mediated resistance is more common in MDR typhoid fever and occurs with a high frequency rate³⁸. First successful therapy of typhoid fever was with chloramphenicol in 1948 by T. Woodward^{9,10}. Emergence of *S. typhi* strains resistant to chloramphenicol was reported in 1970^{13,14,54}, then subsequently resistance to ampicillin and co-trimoxazole emerged soon^{12,15,55}. MDR *S. typhi* resistant to all three first line antimicrobials emerged sporadically⁵⁶. First documented outbreak of multidrug resistance occurred in Malaysia in 1984⁵⁷. Since then MDR *S. typhi* spread throughout south-east Asia and China where they became endemic⁵⁸. In most cases resistance to chloramphenicol, ampicillin and co-trimoxazole was transferable on plasmid either individually or en bloc^{55,56,59,60,61,62}.

Plasmids are extrachromosomal supercoiled loops of DNA that were probably originally derived from bacteriophages^{38,47}. When greater than 40 kbp in size they are able to transfer the plasmid from host bacterium to others. The plasmids found in *S. typhi* are of two major types. First as pH CM2 cryptic plasmid which can carry gene encoding mechanisms of DNA metabolism and replication and virulence found in Asia and not in Africa. Second, strain approximately 140-180 kbp self transferable plasmid. Large resistant plasmids are built up by the addition of resistant gene encoded on integrons and transposons³⁸. These large plasmids can then be transferred to and from enteric gram negative bacterium such as *Escherichia coli*, *Klebsiella pneumoniae* and *S.*

enterica, especially when antimicrobials are being administered³⁸. Chromosomally acquired quinolone resistance in *S. typhi* has been found in different parts of Asia,^{1,2,13,38} which may be the consequence of wide spread indiscriminate use of these drugs.

Relapse and long term carriers:

Relapse may occur in 10-15% patients usually two to three weeks after the resolution of fever⁸. Following the acute disease, some patients continue to excrete the organism in stool and less commonly in urine^{22,52}. Up to 10% of convalescing patients with untreated typhoid excrete *S. enterica* serotype typhi in the faeces for up to three months and 1-4% become long term carriers excreting the organism for more than one year^{1,8,19,22}.

Diagnosis:

The absence of specific symptoms or signs makes the clinical diagnosis of typhoid fever in children difficult²². A fever without evident causes lasting more than 1 week should be considered typhoid until proved otherwise. A number of rapid relatively newer diagnostic tests are being evaluated¹⁹. These include tests to detect IgM antibodies against specific *Salmonella typhi* antigen eg. typhidot M, tubex, dipstick test and nested PCR¹⁹. In a patient with suspected enteric fever, multiple sites should be sampled for culture, because no single specimen culture has a yield of 100%²². Cultures should be performed on blood (70 to 80% in 1st week and 40% to 54% in 2nd week positive in patients with the disease), urine (approximately 7% positive), stool (35% to 37% positive), rose spots (approximately 63% positive), duodenal string capsule (38% positive), and bone marrow specimens (30% to 90% positive after the first week of illness)^{1,22,40}. Nearly all cases of enteric fever can be identified if adequate culture specimens are obtained. Result of bone marrow culture can be positive even if the patient has been treated with antibiotics^{1,19,22}. Antimicrobial susceptibility testing must be routinely performed to guide therapy.) *Salmonella* serum agglutinin testing generally is not considered helpful in the diagnosis of such infections^{1,19,22}.

Though the blood culture is considered as standard diagnostic method, bone marrow⁶² is more sensitive than blood culture because of lower numbers of micro organism in blood as compared to bone marrow. Bacteria in the bone marrow of typhoid fever patients are less affected by antibiotic treatment than bacteria in the blood¹⁹. Enteric fever is the only bacterial infection of human for which bone marrow examination is routinely recommended by some authors²².

The ELISA-Ty test has a high reliability for the detection of typhoid fever in children based on the finding of a degree of diagnostic sensitivity as high as 94.45% and 90.91% for IgM and IgG respectively and a diagnostic specificity as high as 93.33% for both IgM and IgG⁶³.

Application of a dipstick assay for the detection of *S. typhi* specific IgM antibodies on samples collected from *S. Typhi* and samples collected from *S. typhi* and *S. paratyphi* culture positive patients revealed the presence of specific IgM antibodies in 43.5%, 92.9% and 100% for samples collected 4-6 days and 6-9 days and >9 days after the onset of fever respectively⁶⁴. The result can be obtained on the same day allowing a prompt treatment and no special laboratory equipment is needed to perform the study.

Currently, the laboratory diagnosis of typhoid fever is dependant upon either the isolation of *Salmonella entereca* serotype typhi from a clinical sample or the detection of raised titre of agglutinating serum antibodies against the lipopolysaccharide (LPS) (O) or flagellum (H) antigens of serotype typhi (the Widal test). The serological assays based on the detection of IgM antibodies against either serotype typhi LPS (ELISA) or whole bacteria (dipstick) had a significantly higher sensitivity than the Widal TO test when used with a single acute phase serum sample (Pe^{0.007})⁶⁵. These tests could be of use for the diagnosis of typhoid fever in patients who have clinical typhoid fever but are culture negative or in the region where bacterial culturing facilities are not available⁶⁵. Though the gold standard for the diagnosis of typhoid fever is isolation of *S. typhi* from blood, bone marrow, stool, urine or any other body fluid, in resource limited countries like

Bangladesh isolation of organism is often jeopardized due to lack of facilities or improper antibiotic use prior to culture. For this reason, laboratory diagnosis of *S. typhi* infection relies heavily on serological test, Widal test⁶⁵. On the basis of cut off value for TO (1:80) and TH (1:160) and considering both the agglutinin equally important, sensitivity and specificity of the test were 89% and 97% respectively. Moreover, it lacks sensitivity and specificity in endemic area⁶⁶.

Newer modern approach for rapid diagnosis by application of immunologic method and DNA technology include:

1. By using a 50 Kd protein isolated from surface membrane of *S. typhi* by Dot FIA antibody measurement has come up with promising result with 80% sensitivity and 96% predicitive value.
2. Direct detection of *S. typhi* specific antigen in the serum or *S. typhi* Vi antigen in the urine by using monoclonal antibody.
3. A nested PCR using HI-d primers has been used to amplify specific gene of *S. typhi* in the blood within few hours. This method is more specific and more sensitive than blood culture^{1,19,22,40}.

Treatment:

For hospitalized patients, effective antibiotics, good nursing care, adequate nutrition, careful attention to fluid and electrolyte balance and prompt recognition and treatment of complication are necessary to avert death⁸. Ampicillin, chloramphenicol and co-trimoxazole as the first line of drugs for the treatment of typhoid fever are loosing their efficacy and most of the organisms have resistance against these drugs^{55,60,61,62,67}.

Emergence of drug resistance for treating typhoid fever in children is a major challenge for paediatricians^{1,22}. As regards the MDR cases it is recognized that MDR *S. typhi* infection is a more severe clinical illness with a higher rate of toxicity, complications and case fatality along with atypical presentation^{17,18,19,22}. There is evidence that fluroquinolones e.g. ciprofloxacin or ofloxacin are the most effective

drugs for the treatment of typhoid fever and these drugs have been proved in all age groups and are rapidly effective even with short course (3-7 days)^{37,68}. The fluoroquinolones are associated with lower rate of stool carriage than the traditional first line drugs. The use of fluoroquinolones is warranted in the treatment of typhoid fever in some study^{21,69,70}. Unfortunately quinolone resistant strains are often multidrug resistant and the choice of drug moves to azithromycin and cephalosporines^{71,72,73}. The third generation cephalosporines (cefotaxime, ceftriaxone, cefixime, cefoperazone) and azithromycin are effective for typhoid^{1,19,22,23}. Due to unavailability of culture reports in time, knowledge of the likely sensitivity from the available global and country data as well as local experience may be useful in the treatment of MDR typhoid fever⁷⁴. In MDR cases, fluoroquinolones like ciprofloxacin 25 mg per kg IV, followed by 30 mg per kg orally for 7-14 days is the treatment regimen. Ofloxacin 15-20 mg per kg per day orally for 10-14 days is also effective. Alternative options include azithromycin and cephalosporins such as ceftriaxone or cefixime. Azithromycin 10-20 mg per kg per day for 10 days, and ceftriaxone 60-80mg per kg IV once daily for 7-14 days or until 3 days after defervescence is effective. Cefixime 20 mg per kg per day is an alternative for uncomplicated cases^{1,19,22,23}.

Azithromycin is a macrolide, azolide antibiotic with relatively poor in vitro activity against *S. typhi* (MIC 4-16 mg/l). However it is concentrated 50-100 fold inside cells such as macrophages, where *S. typhi* reside. It also has a long half life (68 hours) and is thus given as a once-daily regimen⁷¹. In a study in India, 88% of 42 patients with *S. typhi* had a clinical cure after receiving once daily dose of azithromycin for 7 days and after 14 days of treatment all were cured^{71,72}. In a Vietnam study, azithromycin for 5 days was effective as ofloxacin in MDR typhoid fever, rather was significantly better than ofloxacin in patients infected with quinolone-resistant *S. typhi*⁶⁹. In both studies azithromycin was well tolerated but was expensive, and resistant strains have already been detected.

Children with severe typhoid fever characterized by delirium, obtundation, stupor, coma or shock get benefit from the prompt administration of dexamethasone along with fluoroquinolone. The dexamethasone should be given at an initial dose of 3 mg/kg by slow intravenous infusion over a period of 30 minutes followed by 1 mg per kg at the same rate every six hours for eight additional doses. High index of suspicion and prompt treatment is highly critical in the treatment of septicemia in young children^{1,19,22,40}.

Case fatality:

The average case fatality rate is less than 1% but it varies considerably among different regions of the world^{1,19,22,23}. Among hospitalized patients the fatality rate varies from less than 2% in Pakistan, 36 % Vietnam, to 30-50% in some areas of Papua New Guinea and Indonesia^{42,43,44}. Case fatality rate is highest among children under one year of age²². Poor outcome is usually related to delay in instituting effective antibiotic treatment^{22,41}.

Prevention:

A combination of mass vaccination and improvement of water supplies has been suggested as a method to control epidemics in typhoid fever^{3,4,5,6}. A number of different vaccines are available for the prevention of typhoid fever. However recently developed Vi-conjugate vaccine has shown to have a greater than 90% protective efficacy in children of 2-5 years in Vietnam over a period of at least 27 months post immunization²¹. So, recommendation is mass vaccination in endemic areas, travelers, antimicrobial resistant areas along with creation of public awareness, improvement of sanitation and planned water with improvement of personal hygiene. In our country medical practitioners should be aware regarding the overuse and misuse of fluoroquinolones and cephalosporin group of drugs in the treatment of typhoid fever to overcome the burden of drug resistance.

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