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TYPHOID

Diagnostic & Therapeutic Update

Faculty:

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Faculty

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Editorial

Typhoid: Diagnostic & Therapeutic Update

Typhoid fever, a bacterial disease, is a common problem which is transmitted by the ingestion of food or water contaminated with the faeces of an infected person. The main burden is in the developing countries mainly due to the problem of unsafe drinking-water, inadequate sewage disposal and flooding. In developed countries, it is common in returning travellers, immigrants and refugees. The World Health Organization identifies typhoid as a serious public health problem, where its incidence is highest in children and young adults aged between 5-19 years.

In bacterial infections, antibiotics are the mainstay of treatment, which is usually prescribed for as prophylaxis, empiric therapy, or directed therapy. Improper use of antibiotics, especially the broad-spectrum antibiotics can lead to emergence of resistance. The common factors responsible for resistance to antibiotics are misuse and overuse, whereas the other indirect factors may be poverty, hygiene, inadequacy of treatment, and the compliance of the patients.

Drug resistance is a major problem in the management of typhoid fever as well. Multi-drug resistance i.e., resistance to three first-line agents (chloramphenicol, ampicillin and co-trimoxazole) were the major concerns. Also, the empirical choice of antibiotics is difficult with increasing problem of reduced sensitivity to the fluoroquinolone antibiotics. The reduced use of earlier antibiotics has lead to its increased sensitivity which is now being reconsidered for the treatment of typhoid fever.

Health education about personal hygiene, provision of a safe water supply, proper sanitation systems also help to combat typhoid fever in addition to antibiotic treatment. The typhoid vaccine does not provide full protection from infection and is not routinely recommended except for those with prolonged exposure to potentially contaminated food and water in high-risk areas.

This CME Digest mainly focuses on the diagnostic and therapeutic trends in the management of typhoid which will aid the physicians to apply this information relevantly to their practice.

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In addition to the CME, each issue would have columns on News & Notes and Medicolegal.

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News & Notes

1. *Salmonella* organism responsible for avoiding body's immune response to curb gut infections

The researchers in UC Irvine have discovered how salmonella bacterium found in contaminated raw foods causes major gastrointestinal distress in humans, and thrives in the digestive tract in spite of the immune system's best efforts to destroy it. *Salmonella* is difficult to eradicate and most people infected with salmonella suffer from diarrhoea, fever and abdominal cramps. *Salmonella* can flourish and cause disease in humans by a process by which they acquire metal ions like zinc from the body. The body's key immune response is to flood the infected area with antimicrobial proteins which includes calprotectin, which removes zinc and most pathogens eventually die with not enough of this vital element.

Salmonellae may overcome this immune response by expressing specialised transporter proteins which enables the bacteria to acquire zinc in spite of calprotectin which reduces its availability in the digestive tract, the mechanism which let the salmonella to continue to proliferate. Calprotectin inadvertently promotes the growth of salmonella by killing the microbes which normally reside in the intestines and help the immune system to battle against the pathogenic bacteria at the same time. The infection can be fought specifically with therapies that block the acquisition of zinc and other metals by salmonella. This finding may also have relevance in other illnesses like inflammatory bowel disease and colon cancer also, where high levels of calprotectin are detected.

Source: University of California - Irvine, 2012.

2. Gut microorganisms and control of obesity risk

The epidemic of obesity is widespread, nondiscriminatory, and deadly internationally. The concept of energy balance i.e., energy consumed = energy expended + energy stored is indisputable, which is driven by the first law of thermodynamics. The excessive calorie intake and reduced levels of physical activity are the main issues for the ever-expanding waistlines. However, it is not clear as why only some individuals are prone to become obese and if there is anything other than lowering the calorie consumption and increasing the level of activity to prevent and/or reverse the excessive weight gain in at-risk populations.

The intestines are filled with live bacteria, some of which are providing important substance like vitamin B12 to the host. Intestinal microbiota may also have a greater role to play.

One such possibility is that the mix of intestinal bacteria may directly influence ones risk for obesity. The microbial profile in their intestines of obese individuals may be different from that of a lean individual. The bacteria common to obesity may metabolise the food in a way which allows producing of more calories from it and depositing it as fat. The French Institute for Agricultural Research (INRA) determined whether altering one's bacterial profile can change the risk of obesity by transferring the intestinal bacteria of obesity-prone or obesity-resistant rats into the intestinal tracts of germ-free mice recipients, where there is no innate gut microbiota. Some of the animals were fed with a regular diet, and others were given unlimited high-fat diet. For 8 weeks, food intake and weight gain were monitored, and the intestinal samples were analysed for variety of physiologic markers of metabolism and normal feedback mechanisms which were known have a role in maintenance of energy balance.

The mice that received intestinal bacteria from obesity-prone animals ate more food, and gained more weight, and became more obese than those which received microbiota from obesity-resistant animals. The changes in intestinal nutrient sensors and gut peptide levels influenced how the animals responded to eating in animals with microbiota transferred from obesity-prone animals.

The conclusion was that obese individuals, when given the opportunity to overeat, may harbour specific gut microbiota profiles which promotes excess weight gain, the differences in gut microbes may be related to the behavioural changes and increased food intake and a mix of microbiota may influence the ability to properly sense and respond to a meal. Ultimately one must find ways to manipulate the profiles of intestinal microbiota, especially in at-risk individuals so that one can easily maintain a healthy body weight.

Source: Federation of American Societies for Experimental, 2012.

CME - Pre test

Typhoid: Diagnostic & Therapeutic Update

1. **Typhoid fever is a bacterial disease, caused by...**
   a. *Salmonella typhi*
   b. *Shigella* species
   c. *E. coli*
   d. None of the above

2. **The antigen in Salmonella species is...**
   a. Surface antigens Vi
   b. Somatic antigens "O"
   c. Flagellar antigens 'H'
   d. All of the above

3. **Prevention of typhoid is by...**
   a. Avoiding unhygienic food
   b. Vaccination against typhoid
   c. Taking antibiotics
   d. Both a and b

4. **The spread of typhoid can be prevented by...**
   a. Clean water
   b. Hygiene
   c. Good sanitation
   d. All of the above

5. **Worldwide, the highest incidence of typhoid fever is in...**
   a. Indian subcontinent
   b. UK
   c. USA
   d. Japan

6. **The most famous asymptomatic carrier of typhoid fever was...**
   a. Mary Mallon
   b. Mary Shallon
   c. Marlyn
   d. None of the above

7. **The WBC counts in typhoid fever may be decreased.**
   a. True
   b. False

8. **In developed countries, the commonly used antibiotics to treat typhoid fever are...**
   a. Ampicillin
   b. Chloramphenicol
   c. Ciprofloxacin
   d. All of the above

9. **Ciprofloxacin resistance is an increasing problem, especially in the Indian subcontinent and Southeast Asia.**
   a. True
   b. False

10. **In typhoid fever, the appearance of rose spots on the lower chest and abdomen is seen usually...**
    a. With onset of fever
    b. In the 1st week
    c. In the 2nd week
    d. In the 3rd week

Ans: 1-a; 2-d; 3-d; 4-d; 5-a; 6-a; 7-a; 8-d; 9-a; 10-c

Typhoid: Diagnostic & Therapeutic Update

Introduction

Typhoid fever is also known as enteric fever which is a potentially fatal multi systemic illness. It is mainly caused by *Salmonella typhi* (*S. typhi*). Because of its variable manifestations, it may be a diagnostic challenge. The classic presentation includes fever, malaise, diffuse abdominal pain and constipation and if untreated may progress to complications like delirium, obtundation, intestinal haemorrhage, bowel perforation and death, which may cause long-term or permanent neuropsychiatric complications in survivors.

S. typhi was derived from the ancient Greek word "typhos" which means an ethereal smoke or cloud which was believed to cause disease and madness. Poor sanitation, crowding and social chaos are the conditions in which the *S. typhi* usually thrives. Though the frequency of typhoid fever in the developed world has markedly reduced, in developing countries it is still endemic.

In humans, the clinical syndromes due to Salmonella infection is divided into two groups, one is enteric fever which is mainly caused by *Salmonella enterica* serovar Typhi (typhoid fever) or *Salmonella enterica* serovar Paratyphi A, B or C (paratyphoid fever) which is transmitted by contaminated water or food, and the other is a range of clinical syndromes including diarrhoeal disease which is caused by a large number of non-typhoidal Salmonella serovars (NTS).

Salmonellae are gram negative, flagellate, non-sporulating, facultative anaerobic bacilli which ferment glucose, reduce nitrate to nitrite, and when motile synthesise peritrichous flagella. It belongs to the family Enterobacteriaceae which has more than 2,300 serotypes, based on the presence of 3 main antigens:

- Somatic O antigen (lipopolysaccharide cell wall component)
- Surface Virulent (Vi) antigen (*S. Typhi* and *S. Paratyphi* C only)
- Flagellar H antigen

The only reservoirs for these organisms are humans and the main source of infection is the stool of the infected persons. Other sources of infection are contaminated water, food and possibly fly. The contamination in the resource-poor countries is due to lack of sanitation and clean running water.

The organism and its transmission

Salmonella typhi (Fig. 1) is a multiorgan pathogen and in an infected person may inhabit the lymphatic tissues of the small intestine, liver, spleen and blood stream. It was originally isolated by Karl J Erberth in 1880. It is common in developing countries, putting travellers from developed countries to these countries at high risk. It contains endotoxin as well as the Vi antigen and produces and excretes a protein called invasin which allows the non-phagocytic cells to take up the bacteria where it may live intra cellularly. It may also inhibit the oxidative burst of leukocytes which makes the innate immune response ineffective. There are various strains of the organism with varying metabolic characteristics, virulence levels and multidrug resistance genes which may complicate treatment.

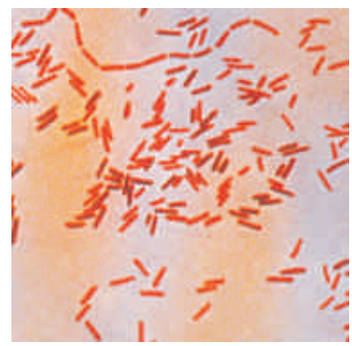


Fig. 1: *Salmonella typhi*

The only reservoirs of *S. typhi* are human beings and the transmission occurs through food and water which is contaminated by acutely ill patients or the chronic carriers of the organisms.

Modes of transmission (Fig. 2)

- Oral transmission: By food or beverages handled by an individual who chronically sheds the bacteria through stool or less commonly through urine (oral transmission via sewage-contaminated water or shellfish mostly in the developing countries)
- Hand-to-mouth transmission: Using a contaminated toilet and neglecting hand hygiene

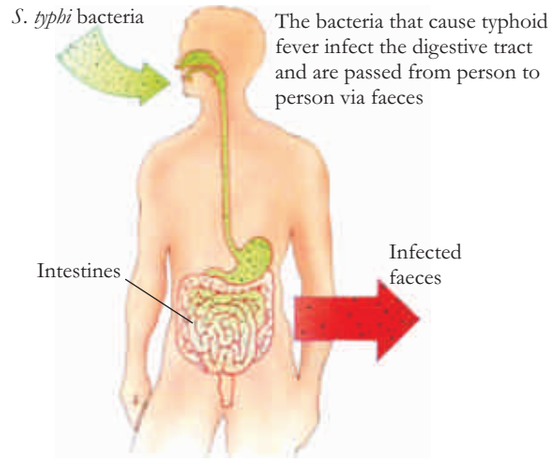


Fig. 2: Transmission of *S. typhi*

Epidemiology

Till the early 20th century, enteric fever (typhoid and paratyphoid fever) had a worldwide distribution, including the USA and Europe. The incidence of enteric fever in the developed countries has reduced significantly due to health education on personal hygiene, installation of proper sanitation systems and development of new vaccines. The two major changes in the pattern of the disease in developed countries is a marked decline in its incidence and its characterisation mainly as travel-associated disease now. The risk to travellers may vary by geographic region, where the greatest risk is travel to the Indian subcontinent. It is still common in less-industrialised countries, due to consumption of unsafe drinking water, inadequate disposal of sewage and flooding. It is still an important cause of illness and death, especially among children and adolescents in the south-central and Southeast Asia, where it is associated with poor sanitation and unsafe food and drinking water.

Among travellers though the most common cause of enteric fever is *S. typhi,* the incidence of disease caused by *S. paratyphi* may be more important as the available vaccines are protective only against *S. typhi.*

Enteric fever is an important and persistent health problem in developing nations though it is not common in the industrialised nations (Fig. 3). In Asia, the incidence of typhoid fever varies substantially, where the incidence is found to be very high in India and Pakistan. In south-central and Southeast Asia, the greatest burden of the disease is in infants, children and adolescents. In India, enteric fever is a major public health problem where the most common etiological agent is *S. typhi,* though the number of cases due to *S. paratyphi* A is increasing. *S. paratyphi* B and *S. paratyphi* C are comparatively uncommon.

Typhoid fever is more common among children and young adults than in older patients and the risk factors for the development of enteric fever due to typhoid or paratyphoid may vary.

Key Insights

- Typhoid fever is a bacterial infection of the intestinal tract and bloodstream.
- Due to the problem of unsafe drinking-water, inadequate sewage disposal and flooding, typhoid and paratyphoid fever are common in less developed countries.

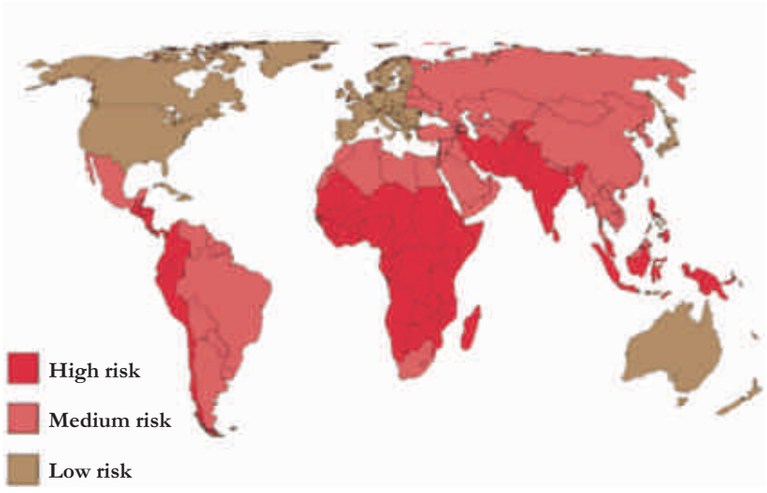


Fig. 3: Distribution of typhoid across the globe

Enteric disease is most prevalent in urban areas in India. Children < 15 years of age are usually more susceptible and may be less common in adults probably due to development of immunity either from recurrent infection or sub-clinical infection.

Typhoid fever may be seen in the population throughout the year, though there could be a peak of disease from July to September coinciding with the rainy season, when the chances of contamination water are high.

Pathophysiology of typhoid

The pathogenesis of enteric fever is dependent on number of factors and also the infecting species and the infectious dose (the greater the infectious dose, the higher the attack rate and the shorter the incubation period). The organisms that are ingested survive the exposure to gastric acid in the stomach, before they gain access to the small bowel, where they penetrate the epithelium, enter the lymphoid tissue and disseminate by the lymphatic/haematogenous route. In about 1-5% of the cases, a chronic carrier state may develop.

Among the salmonella strains, the reason for variability in enteritis is not certain and the occurrence of the frequency diarrhoea and constipation may be more or less equal.

The non-typhoidal salmonella strains that are associated with enteritis may induce IL-8-mediated neutrophil transmigration across the epithelial cell, which is not generally seen with *S. typhi* or other strains that are not associated with enteritis. With *S. typhi,* the muted IL-8 response and the relative absence of the neutrophil infiltration seen may be mediated by toll-like receptors and require the Vi capsular polysaccharide.

The *S. typhi* enters the submucosal region of the bowel by two mechanisms:

- By the M-cell, which is a specialised epithelial cell that serves as a sampling and antigen presenting cell in the mucosa (or gut) associated lymphoid system.
- By direct penetration into or around the epithelial cell.

They proliferate in the submucosa, which leads to the hypertrophy of the Peyer's patches by the mononuclear cells and lymphocytes (Fig. 4). The abdominal pain and the potentially fatal complication, ileal perforation may be due to the hypertrophy and subsequent necrosis of the submucosal tissues. In patients with typhoid fever, the microscopic or macroscopic breaches in the intestinal mucosal barrier may lead to "secondary" bacteraemia with other organisms.

S. typhi disseminates from the Peyer's patches to the reticuloendothelial system by the lymphatics and blood, where it replicates. This is basically responsible for the clinical findings of prostration, generalised sepsis and hepatosplenomegaly. The dissemination of the organisms

by blood stream usually occurs early in the course of illness and bacteraemia may be often detected and is of higher grade usually in the first week of clinical illness. In some, the organism remains within the gastrointestinal system and such patients do not become systemically ill but they become persistent carriers of *S. typhi*. The organisms ultimately, reside within monocyte derived or tissue macrophages within the liver, spleen and bone marrow (bone marrow is an important source of diagnostic culture material even after the commencement of antimicrobial therapy). The organisms that are intracellular are the likely source of relapsing infection and the late pyogenic complications like pericarditis, visceral abscesses or osteomyelitis.

The persistence of *S. typhi* intracellularly within the visceral and bone marrow macrophages is the important factor in the virulence of the organism.

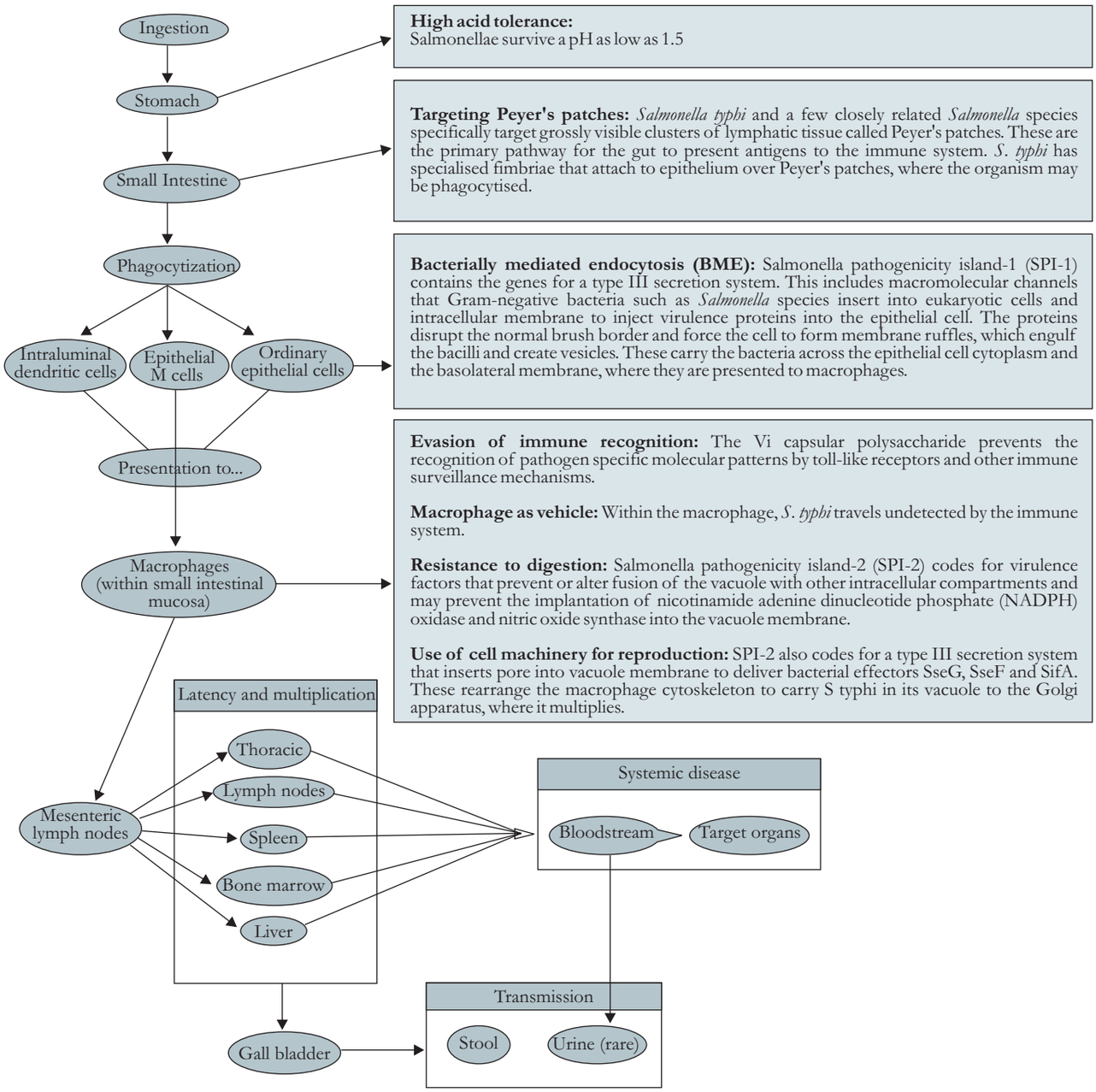


Fig. 4: Life cycle of *S. typhi*

Chronic carriage

Chronic carriage of salmonella means excretion of the organism (*S. typhi*) in stool or urine >12 months after acute infection. It is more frequent in women and in patients with cholelithiasis or other abnormalities of the biliary tract. Gallstones may be the persistent nidus of the infection. Factors other than biliary abnormalities also may contribute to the carrier state and in rare cases, where the chronic carriage may persist even after antibiotic therapy and cholecystectomy.

The chronic carriers generally do not develop recurrent symptomatic disease. They usually would have reached an immunologic equilibrium, wherein they are chronically colonised and may excrete large numbers of organisms, but have a high level of immunity and do not develop the clinical disease. The carrier state of *S. typhi* may be an independent risk factor for carcinoma of the gallbladder and also other cancers. The serum antibody titres against the Vi antigen are high in the carriers which is clinically a useful test for their rapid identification. Infection with the *S. paratyphi* strains may also cause a carrier state, though less frequently.

Enteric disease is caused by water-borne and food-borne infectious agents. Humans are the only reservoir of *S. typhi* and the main source of infection is the stool of infected persons. They are either cases or carriers. Other source of infection is contaminated water, food and probably flies. In resource-poor countries, lack of sanitation and clean running water cause contamination for long periods of time, and the contaminated surface water further contaminates the water supply. The onset of clinical symptoms depends mainly on the virulence of the organism and the infective dose.

Clinical features of typhoid

Typhoid fever is a severe, contagious and a life-threatening systemic disease caused by *S. typhi*. It may cause persistent fever with or without severe complications. It may often present with misleading symptoms, making the diagnosis difficult. The incubation period is 1-14 days. Paratyphoid fever, may present similarly as typhoid fever, where the course of the disease is more benign with lesser complications (Fig. 5).

The severity and overall clinical outcome of the infection is influenced by many factors like the duration of illness before the initiation of appropriate treatment, the choice of antimicrobial treatment, age of the patient, h/o previous exposure or vaccination, virulence of the bacterial strain, the quantity of ingested inoculums, host factors (HLA type, AIDS or other immunosuppression) and h/o intake of medications like H2 blockers or antacids which diminishes the gastric acid.

Late diagnosis or failure to respond to treatment may result in serious complications. The mortality and morbidity may be high in neonates with vertical transmission of the pathogen.

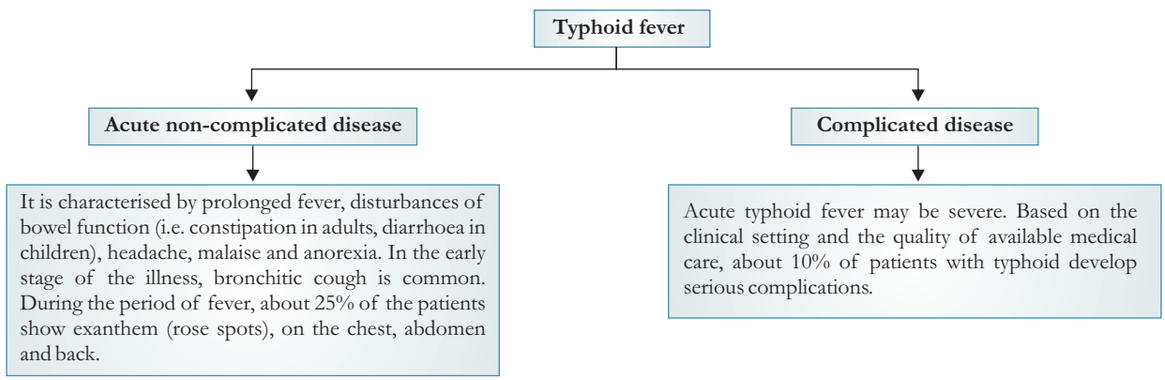


Fig. 5: Clinical presentation of typhoid fever

Classic clinical features of typhoid fever

Typhoid fever usually begins after 7-14 days of the ingestion of *S. typhi*. The pattern of fever is fever is stepladder, characterised by rising temperature over the course of each day which drops by the following morning. Over time, the peak and trough rise progressively.

The gastrointestinal manifestations of the disease: diffuse abdominal pain and tenderness and fierce colicky right upper quadrant pain (in some) develop during the 1st week of illness. Constipation is due to inflammation of the Peyer's patches by monocytic infiltration which narrows the bowel lumen that may last the duration of the illness. There may be a dry cough, dull frontal headache, delirium and an increasingly stuporous malaise in the patients. The fever plateaus at 103-104°F at the end of the first week of illness. The patient develops rose spots (salmon-coloured, blanching, truncal, maculopapules) which are usually 1-4 cm wide and may be < 5 in number, which generally resolves within 2-5 days.

The signs and symptoms progress during the 2nd week of illness. Often, there is distension of the abdomen and soft splenomegaly. There is relative bradycardia and dicrotic pulse.

The patients who are still febrile by 3rd week may become more toxic and anorexic and may have significant weight loss. The conjunctivae may become infected; the patient may become tachypneic and may also have a thready pulse and develop crackles over the lung bases. The distension of the abdomen may become severe. There may be foul, green-yellow, liquid diarrhoea (pea soup diarrhoea) in some. The patient may go into apathy, confusion and even psychosis, known as typhoid state. There may be bowel perforation and peritonitis due to necrosis of the Peyer's patches (which is often unheralded, but may be masked by corticosteroids). With this, there may be overwhelming toxemia, myocarditis, or intestinal haemorrhage that may lead to death.

If the patient is able to survive all this, then fever, mental state and abdominal distension starts improving gradually over a few days in the 4th week. In patients who survive and are untreated, the intestinal and neurologic complications may still occur. Weight loss and debilitating weakness may last for months. Some of the survivors become asymptomatic carriers of *S. typhi* and may transmit the bacteria for an indefinite period.

Various other presentations of typhoid fever

The clinical course of typhoid fever may deviate from the above description of classic disease in some individuals. The geographic region, race factors and the infecting bacterial strain may all affect the timing of the symptoms and host response. The typical stepladder fever pattern which was the hallmark of typhoid fever is not commonly seen now and in most of the cases of typhoid, the fever has a steady insidious onset.

In some regions, typhoid fever may generally cause diarrhoea rather than constipation. In young children, people with AIDS, and those who are immunocompetent may have diarrhoea rather than constipation in typhoid fever. The atypical manifestations of typhoid fever may be:

- Isolated severe headaches mimicking meningitis
- Acute lobar pneumonia
- Isolated arthralgias
- Urinary symptoms
- Severe jaundice
- Only fever

Some patients, especially in endemic areas like India and Africa may present primarily with neurologic manifestations like delirium or Parkinsonian symptoms or Guillain-Barré syndrome in rare cases. Pancreatitis, meningitis, orchitis, osteomyelitis, and abscesses anywhere on the body are unusual complications.

Delay in treatment increases the chance of complications and recovery time. With initiation of appropriate treatment within the first few days of full-blown illness, the remission may start occurring after about 2 days, and the patient's start improving within 4-5 days. Hepatomegaly, anaemia and other complications are generally more common in children < 5 years of age.

Diagnosis of typhoid

As the gut-associated lymphoid tissue reveals a prominent pathology, common finding is presence of occult blood in the stool and melena. In cases of intestinal perforation, the abdominal discomfort develops and increases and is diffuse but is often restricted to the right lower quadrant. Other symptoms and signs of intestinal perforation and peritonitis may follow at times i.e. a sudden rise in pulse rate, hypotension, marked abdominal tenderness, rebound tenderness and guarding and subsequent rigidity of the abdomen. A rising white blood cell count with a left shift and on abdominal radiographs free air is seen.

The diagnosis of typhoid fever (enteric fever) is mainly clinical.

Culture: The isolation of organism by culture is the standard criterion for diagnosis which is considered 100% specific. Bone marrow aspirate culture is 90% sensitive till at least 5 days after initiation of antibiotic treatment (Table 1). This technique is extremely painful, and is not done often. In typhoid fever, patients who present within the 1st week of onset of symptoms, the culture of blood, intestinal secretions (vomitus or duodenal aspirate), and stool may be positive for *S typhi* in about 85-90% of cases, which may decline in the later course of the disease. The stool culture may be positive for *S. typhi* several days after the ingestion of the bacteria secondary to inflammation of the intraluminal dendritic cells and later in the course of the illness, the stool culture may be positive due to shedding of bacteria through the gall bladder. The sensitivity of multiple blood cultures (> 3) is 73-97%, where a large-volume (10-30 mL) blood culture and clot culture may increase the likelihood of detection.

The sensitivity of only stool culture is < 50%, and only urine culture is even less sensitive. The sensitivity of cultures of punch-biopsy samples of rose spots is about 63% and may be positive even after antibiotic administration. A single rectal swab culture may detect *S. typhi* in about 30-40% of patients. *S. typhi* may also be isolated from the cerebrospinal fluid, peritoneal fluid, mesenteric lymph nodes, resected intestine, pharynx, tonsils, abscess and bone. The identification of the organism with the conventional culture techniques usually takes about 48-72 hours.

The isolates of *S. typhi* should be screened for resistance to nalidixic acid, or have proper sensitivity testing for clinically used fluoroquinolones (organisms with resistance to nalidixic acid should be anticipated to have reduced susceptibility to fluoroquinolones, though a fluoroquinolone sensitivity may be reported).

Table 1: Sensitivities of cultures

	Incubation	Week 1	Week 2	Week 3	Week 4
Bone marrow aspirate (0.5-1 mL)		90% (may decrease after 5 days of antibiotics)			
Blood (10-30 mL), stool or duodenal aspirate culture	40-80%		~20%	Variable (20-60%)	
Urine	40-80%		25-30%, timing unpredictable		

Polymerase chain reaction (PCR): No type of PCR is widely available for the clinical diagnosis of typhoid fever, though it has been used for the diagnosis of typhoid fever with varying success. Nested PCR, which involves two rounds of PCR using two primers with different sequences within the H1-d flagellin gene of *S. typhi*, offers the best sensitivity and specificity. This technique may have a sensitivity of 82.7% and specificity of 100%, in combining assays of blood and urine.

Specific serologic tests: Though the assays that identify Salmonella antibodies or antigens support the diagnosis of typhoid fever, they must be confirmed with cultures or DNA evidence.

For decades, widal test is the mainstay of diagnosis of typhoid fever and is used to measure agglutinating antibodies against H and O antigens of *S. typhi,* though it is neither sensitive nor specific.

In endemic areas, widal test may be of limited utility clinically because positive results may represent previous infection also. It detects the anti-S. serotype typhi antibodies, and the minimal titres defined as positive for the O (surface polysaccharide) antigens and H (flagellar) antigens must be determined for individual geographic areas (are higher in developing regions). A four-fold or greater increase is considered positive, when paired acute and convalescent samples are studied.

Indirect haemagglutination, indirect fluorescent Vi antibody, and indirect enzyme-linked immunosorbent assay (ELISA) for immunoglobulin M (IgM) and IgG antibodies to *S. typhi* polysaccharide, as well as monoclonal antibodies against *S. typhi* flagellin are also used.

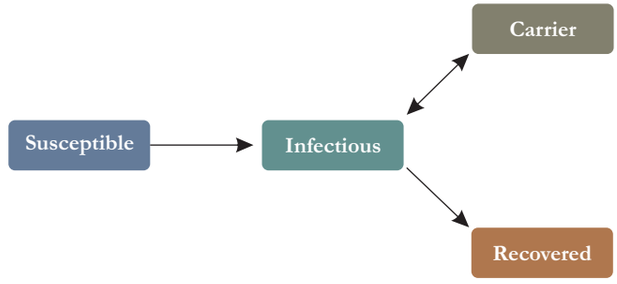
The newer serologic assays using ELISA and dipstick techniques are somewhat better than the widal test, but their sensitivity and specificity may not be adequate for routine diagnostic use. ELISA for antibodies to the capsular polysaccharide Vi antigen is useful for detection of carriers, and not for the diagnosis of acute illness.

Other non-specific laboratory parameters: There may be anaemia (moderate), elevated ESR, thrombocytopaenia, and relative lymphopaenia in most of the patients with typhoid fever. There may be also a slightly elevated prothrombin time (PT) and activated partial thromboplastin time (aPTT) and decreased fibrinogen levels. The circulating fibrin degradation products may rise to levels as seen in subclinical disseminated intravascular coagulation (DIC). The liver transaminase and serum bilirubin values may rise twice the reference range. There may be mild hyponatraemia and hypokalaemia. Typhoid may be distinguished from viral hepatitis by serum alanine amino transferase (ALT): lactate dehydrogenase (LDH) ratio of > 9:1. (ratio > 9:1 supports a diagnosis of acute viral hepatitis, and ratio < 9:1 supports typhoid hepatitis).

Cerebrospinal fluid studies are usually normal or reveal a mild pleocytosis (< 35 cells/mm^3), even in patients with neuropsychiatric symptoms.

Radiography: If bowel perforation (symptomatic or asymptomatic) is suspected, radiography of the KUB may be useful.

CT scanning and MRI: It may be necessary to investigate for abscesses in the liver or bones or other sites.



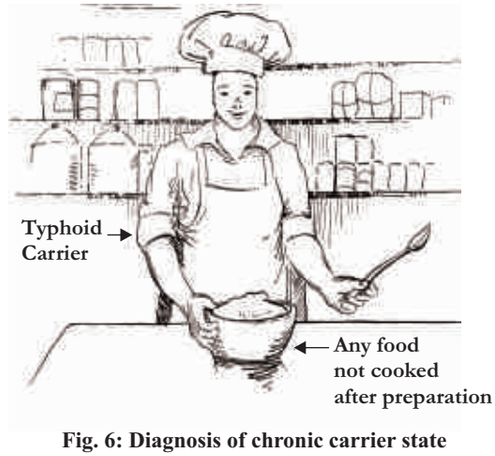


Fig. 6: Diagnosis of chronic carrier state

Depending on the age of the patient about 1-5% become chronic carriers and harbour *S. typhi* in the gall bladder (Fig. 6). After the onset of acute typhoid fever, they may excrete *S. typhi* in stools or urine for more than one year. There may be short-term carriers also. It is important to screen all patients, suspects and contacts in developed countries where adequate medical facilities are available. To prove a case of typhoid fever to be non-infectious, 3 negative stool cultures and 1 negative Vi antigen blood test is the minimum requirement. In countries where typhoid fever is endemic, the Vi test is of little use. Patients excreting *S. typhi* may not have any history of typhoid fever and the definitive diagnosis of typhoid fever depends on the isolation of *S. typhi* from blood, bone marrow or a specific anatomical lesion.

Treatment of typhoid

Antimicrobial regimens for typhoid

Typhoid fever is generally treated with a single antibacterial drug, where the optimal choice of the drug and duration of treatment is uncertain. The selection of antibiotics depends on the local resistance pattern, the age of the patient, feasibility of oral medications, the clinical setting and the availability of resources. The results of successful treatment in uncomplicated cases are a clinical improvement usually within 3-5 days of treatment. It is rational to begin the treatment with a parenteral agent and then once symptoms improve, complete the treatment with an oral drug.

Treatment in adults

In the treatment of typhoid fever in adults, the drugs of choice are:

- Fluoroquinolone like ciprofloxacin (500 mg twice daily) or ofloxacin (400 mg twice daily), either orally or parenterally for 7-10 days. In regions with high rates of fluoroquinolone resistance, they should not be used in the first-line treatment, unless antibiotic susceptibility data is showing fluoroquinolone or nalidixic acid sensitivity.
- β-lactam like ceftriaxone (2-3 g once daily) parenterally or cefixime (20-30 mg/kg/day orally in two divided doses) for 7-14 days.
- Azithromycin (1 g orally once followed by 500 mg once daily for 5-7 days, or 1 g orally once daily for five days).
- Chloramphenicol 2-3 g/day orally in four divided doses for 14 days.

In the treatment of uncomplicated typhoid fever, fluoroquinolones are found to have therapeutic advantages over beta-lactams and is considered the drug of choice if the organisms are fully susceptible and if the patients can tolerate the drug. The quinolones may result in more rapid defervescence than β-lactam agents or chloramphenicol due to more rapid elimination of intracellular bacteria, in the treatment of fully susceptible organisms. The quinolones are bactericidal and are concentrated intracellularly and in bile. Ciprofloxacin, ofloxacin and pefloxacin are widely available and are efficacious, whereas norfloxacin is absorbed poorly and should not be used. With rising resistance to fluoroquinolones, the use of azithromycin is increasing and it is able to achieve excellent intracellular concentrations. In infections due to drug-resistant organisms, azithromycin may be superior to fluoroquinolones. In developing countries, gatifloxacin may also be given for the treatment for enteric fever due to its shorter duration of treatment and lesser adverse events.

Key Insights

- Highest incidence of typhoid fever is in the Indian subcontinent.
- Worldwide, the estimated annual incidence of typhoid is about 17 million.
- Typhoid fever is endemic in India causing significant morbidity and mortality in children as well as in adults.

Dosage of anti-microbial therapy in typhoid in adults (Table 2)

Table 2: Antimicrobial therapy in adults

Antibiotics	Route	Adult dosage/day	Dosage: mg/kg/day	Duration (in days)
First-line antibiotics				
Chloramphenicol	Oral, I.V.	500 mg qid	50 mg/kg in 4 doses*	14
Trimethoprim-Sulfamethoxazole	Oral, I.V.	160/800 mg bid	4-20 mg/kg in 2 doses	14
Ampicillin/Amoxycillin	Oral, I.M., I.V.	1000-2000 mg qid	50-100 mg/kg in 4 doses	14
Second-line antibiotics				
Fluoroquinolones				
Ciprofloxacin	Ora/ I.V.	500 mg bid/200 mg bid	NA	10-14
Norfloxacin	Oral	400 mg bid	NA	10
Perfloxacin	Oral, I.V.	400 mg bid	NA	10
Ofloxacin	Oral	400 mg bid	NA	14
Cephalosporins				
Ceftriaxone	I.M., I V.	1-2 gm bid	50-75 mg/kg in 1-2 doses	7-10
Cefptaxime	I.M., I V.	1-2 gm bid	40-80 mg/kg in 2-3 doses	14
Cefoperazone	I.M., I V.	1-2 gm bid	50-100 mg/kg in 2 doses	14
Cefixime	Oral	200-400 mg/bid	10 mg/kg in 1-2 doses	14
Other antibiotics				
Aztreonam	I.M.	1 gm/bd-qid	50-70 mg/kg : 2-4	5-7
Azithromycin	Oral	1 gm od	5-10 mg/kg: 1	5

*Dose of chloramphenicol may be reduced to 25 mg/kg after defervescence.

Treatment in children

In case of severe systemic illness, treatment must be initiated with a parenteral agent, though the drugs of choice and the dosing regimens may differ based on the preferences in developed and developing countries.

In developed countries, the treatment regimens are:

β-lactams like:

- Ceftriaxone 100 mg/kg/day i.v. once daily, maximum 4 g/day for 10-14 days.
- Cefotaxime 150-200 mg/kg/day i.v. in 3-4 equally divided doses, maximum 12 g/day for 10-14 days.
- Cefixime orally 20 mg/kg/day orally in 2 divided doses, maximum 400 mg/day for 10-14 days.

Fluoroquinolones like:

- Ciprofloxacin 30 mg/kg daily, maximum 1000 mg either orally or parenterally for 7-10 days.
- Ofloxacin 30 mg/kg daily, maximum 800 mg/day, either orally or parenterally for 7-10 days.

Azithromycin 10-20 mg/kg to 1 g maximum once daily for 5-7 days.

In infection due to a fully susceptible strain of *S. typhi,* the alternative regimens that can be used are:

- Chloramphenicol 75 mg/kg/day divided every 6 hours, maximum 3 g/day for 14-21 days
- Amoxicillin 100 mg/kg/day divided every 8 hours, maximum 4 g/day for 14 days
- Trimethoprim-sulfamethoxazole; 8-12 mg/kg of trimethoprim and 40-60 mg/kg of sulfamethoxazole/ day divided every 6 hours, a maximum 320 mg trimethoprim/1600 mg sulfamethoxazole/day for 14 days

Treatment in endemic countries

For fluoroquinolone-sensitive strains:

- Ciprofloxacin 15 mg/kg daily, maximum 1000 mg and 800 mg/day either orally or parenterally for 10-14 days
- Ofloxacin 15 mg/kg daily, maximum 800 mg/day either orally or parenterally for 10-14 days

In infection due to a fully susceptible strains of *S. typhi:*

- Chloramphenicol 100 mg/kg/day divided every 6 hours, maximum 3 g/day for 14-21 days
- Ampicillin 100 mg/kg/day divided every 8 hours, maximum 4 g/day for 10-14 days
- Trimethoprim-sulfamethoxazole 8 mg/kg trimethoprim/40 mg/kg sulfamethoxazole/day divided every 6 hours, maximum 320 mg trimethoprim/1600 mg sulfamethoxazole/ day for 10-14 days

Alternative agents in infection due to multiple drug-resistant isolates, including nalidixic acid-resistant *S. typhi* are:

- Ceftriaxone 60 mg/kg/day i.v. once daily, maximum 2 g/day
- Cefotaxime 80 mg/kg/day i.v. in 3-4 equally divided doses, maximum 12 g/ day for 10-14 days
- Ciprofloxacin or ofloxacin (20 mg/kg daily, maximum 1000 mg and 800 mg/day, respectively), either orally or parenterally for 10-14 days
- Azithromycin 10-20 mg/kg to 1 g maximum for 5-7 days

The optimal duration of third generation cephalosporin therapy in children has not been firmly established, and a 7-day course may not be sufficient. Among the 3rd generation cephalosporins, ceftriaxone may be superior to cefotaxime. Oral cefixime may be used for uncomplicated typhoid. To minimise the risk of relapse, ceftriaxone or cefixime is best given for 10-14 days.

After its introduction in the year 1948, chloramphenicol was considered to be the gold standard in the treatment of typhoid fever. Though in the late 1980s and early 1990s strains of *S. typhi* had become resistant to chloramphenicol, in recent years there have been several reports indicating the re-emergence of its susceptibility. There needs to be a reconsideration of conventionally used drugs in typhoid fever with changing trends of *S. typhi* resistance patterns.

In spite of its toxicity for bone marrow and history of plasmid-mediated resistance, chloramphenicol is making a comeback in developing countries as the *S. typhi* seems to be susceptible to it. Surveys from several South Asia countries, between 2002-04 showed variation in the prevalence of resistance (0-50%). The infection in most of the patients with typhoid fever is by strains susceptible to chloramphenicol. Hence in developing countries, the use of this inexpensive, time-honoured drug is making a comeback.

Chloramphenicol is usually bacteriostatic but in high concentrations or against more susceptible microorganisms it may be bactericidal. It has a wide spectrum of activity against Gram positive as well as Gram-negative bacteria. The antibiotic activity appears to be due to the inhibition of protein synthesis of bacterial cells, where it binds to the 50S subunit of bacterial ribosomes inhibiting the peptide bond formation. The indiscriminate and wide spread use led to development of its resistance and with reduced use there appears to be an increase in its sensitivity which may be due to loss of plasmids encoding the resistance or due to emergence of susceptible strains. It may be reconsidered for the treatment of typhoid fever as the antibiotic of choice in view of the re-emergence of sensitivity and reduced resistance to isolates of *S. typhi*.

In different regions of India, chloramphenicol sensitivity in *S. typhi* has been increasing and is > 90%. With the isolates of *S. typhi*, the re-emergence of sensitivity (94.4%) and reduced resistance (5.6%) to chloramphenicol makes it an important choice in the present treatment regimen of typhoid fever in place of ciprofloxacin or third-generation cephalosporins.

A prospective clinical and microbiological study was conducted by Verma *et al.,* over a period of 11 months (Jun 2004-Apr 2005) in 145 blood culture positive cases of enteric fever among population < 18 years of age. The aim was to study the clinical profile, the relative magnitude of enteric fever in children (especially in those < 2 years of age) and to determine the current antibiotic sensitivity pattern of *S. typhi* and *S. paratyphi*. 65% of the cases were 2- 9 years age group, 27% in 0-5 years age group, and 13% in 0-2 years age group among which 92% of the casesx were due to *S. typhi* and 8% due to *S. paratyphi*.

The *in vitro* sensitivity, using the Bauer-Kirby agar disc diffusion method was as shown below in Table 3.

Table 3: *In vitro* sensitivity by Bauer-Kirby agar disc diffusion method	
Ceftriaxone	99%
Cefixime	99%
Cefotaxime	99%
Cefpodoxime	72%
Cefoperazone	93%
Ciprofloxacin	95%
Ofloxacin	83%
Norfloxacin	79%
Ampicillin	87%
Amoxicillin	89%
Trimethoprim-sulfamethoxazole	76%
Chloramphenicol	86%
Imipenem	100%
Azithromycin	49%
Aztreonam	65%
Amikacin	98%

In adults, fluoroquinolones are in general regarded optimal for treatment of typhoid fever (Table 4). They have excellent tissue penetration, and can kill *S. typhi* in its intracellular stationary stage in monocytes/macrophages and achieve higher active drug levels in the gall bladder. They also produce a rapid therapeutic response and lower rate of post-treatment carriage. In Asian setting, fluoroquinolones may also be used in children with typhoid fever and is equally effective. Their indiscriminate use in primary care settings should be restricted, due to emergence of resistance.

Table 4: WHO recommendations for treatment of uncomplicated typhoid fever

	Optimal therapy			Alternative effective drugs		
Susceptibility	**Antibiotic**	**Daily dose mg/kg**	**Days**	**Antibiotic**	**Daily dose mg/kg**	**Days**
Fully sensitive	Fluoroquinolone e.g. ofloxacin or ciprofloxacin	15	5-7[a]	Chloramphenicol amoxicillin TMP-SMX	50-75 75-100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone or cefixime	15 15-20	5-7 7-14	Azithromycin Cefixime	8-10 15-20	7 7-14
Quinolone resistant[b]	Azithromicin or ceftriaxone	8-10 75	7 10-14	Cefixime	20	7-14

a Three day courses are also effective and are particularly so in epidemic containment.

b The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, the third-generation cephalosporins, or a 10-14 day course of high-dose fluoroquinolones is effective.
Combinations of these are now being evaluated.

Note: Contd. on page 25

Summary

Detach and file for future refrence

Introduction

Typhoid fever, also known as enteric fever is a potentially fatal multi systemic illness caused by *Salmonella typhi* (*S. typhi*). It may be a diagnostic challenge Because of its variable manifestations. The classic presentation in typhoid fever is fever, malaise, diffuse abdominal pain and constipation and if untreated may progress to complications like delirium, obtundation, intestinal haemorrhage, bowel perforation and death, which may cause long-term or permanent neuropsychiatric complications in survivors.

In humans, the clinical syndromes due to Salmonella infection is divided into two groups, one is enteric fever which is mainly caused by *Salmonella enterica* serovar typhi (typhoid fever) or *Salmonella enterica* serovar paratyphi A, B or C (paratyphoid fever) which is transmitted by contaminated water or food, and the other is a range of clinical syndromes including diarrhoeal disease which is caused by a large number of non-typhoidal Salmonella serovars (NTS).

Salmonellae are gram negative, flagellate, non-sporulating, facultative anaerobic bacilli which ferment glucose, reduce nitrate to nitrite and when motile synthesise peritrichous flagella. Humans are the only reservoirs for these organisms and the main source of infection is the stool of the infected persons. Other source of infection is contaminated water, food and possibly flies.

Modes of transmission of typhoid

Oral transmission: By food or beverages handled by an individual who chronically sheds the bacteria through stool or less commonly through urine (oral transmission via sewage-contaminated water or shellfish mostly in the developing countries).

Hand-to-mouth transmission: Using a contaminated toilet and neglecting hand hygiene.

Epidemiology of typhoid

Till the early 20th century, enteric fever (typhoid and paratyphoid fever) had a worldwide distribution, including the USA and Europe, where the incidence reduced considerably due to personal hygiene, installation of proper sanitation systems and vaccination. In developed countries, the incidence has decreased markedly and is now characterised mainly as a travel-associated disease and the risk to travellers may vary by geographic region, where the greatest risk is travel to the Indian subcontinent. It is still common in less-industrialised countries, due to consumption of unsafe drinking water, poor sanitation, inadequate disposal of sewage and flooding and is still an important cause of illness and death, especially among children and adolescents in the south-central and Southeast Asia.

Pathophysiology of typhoid

The pathogenesis of enteric fever is dependent on a number of factors and also the infecting species and the infectious dose (the greater the infectious dose, the higher the attack rate and the shorter the incubation period). The organisms that are ingested survive the exposure to gastric acid in the stomach, before they gain access to the small bowel, where they penetrate the epithelium, enter the lymphoid tissue and disseminate by the lymphatic/ haematogenous route. In about 1-5% of the cases, a chronic carrier state may develop.

Chronic carriage of salmonella means excretion of the organism, *S. typhi* in stool or urine >12 months after acute infection. It is more frequent in women and in patients with cholelithiasis or other abnormalities of the biliary tract. Gallstones may be the persistent nidus of the infection. The chronic carriers generally do not develop recurrent symptomatic disease. They usually would have reached an immunologic equilibrium, wherein they are chronically colonised and may excrete large numbers of organisms, but have a high level of immunity and do not develop the clinical disease. The carrier state of *S. typhi* may be an independent risk factor for carcinoma of the gallbladder and also other cancers.

Clinical features of typhoid

Typhoid fever is a severe, contagious and a life threatening systemic disease caused by *S. typhi.* It may cause persistent fever with or without severe complications. It may often present with misleading symptoms, making the diagnosis difficult. The incubation period is 1-14 days. The severity and overall clinical outcome of the infection is influenced by many factors like the duration of illness before the initiation of appropriate treatment, the choice of antimicrobial treatment, age of the patient, h/o previous exposure or vaccination, virulence of the bacterial strain, the quantity of ingested inoculums, host factors (HLA type, AIDS or other immunosuppression) and h/o intake of medications like H2 blockers or antacids which diminishes the gastric acid. Late diagnosis or failure to respond to treatment may result in serious complications.

The clinical course of typhoid fever may deviate from the above description of classic disease in some individuals. The geographic region, race factors and the infecting bacterial strain may all affect the timing of the symptoms and host response. The typical stepladder fever pattern which was the hallmark of typhoid fever is not commonly seen now and in most of the cases of typhoid, the fever has a steady insidious onset.

Classic clinical features of typhoid fever

Typhoid fever usually begins after 7-14 days of the ingestion of *S. typhi.* The pattern of fever is fever is stepladder, characterised by rising temperature over the course of each day which drops by the following morning. Over time, the peak and trough rise progressively.

Table 1: Antibiotic therapy on the basis of severity of typhoid

1st week	2nd week	3rd week	4th week
The gastrointestinal manifestations of the disease: diffuse abdominal pain and tenderness and fierce colicky right upper quadrant pain (in some) develop during the first week of illness. Constipation is due to inflammation of the Peyer's patches by monocytic infiltration which narrows the bowel	The signs and symptoms progress during the second week of illness. Often there is distension of the abdomen and soft splenomegaly. There is relative bradycardia and dicrotic pulse.	The patients who are still febrile by third week may become more toxic and anorexic and may have significant weight loss in the third week. The conjunctivae may become infected, the patient may become tachypnoeic and may also have a thready pulse and develop crackles over the lung bases. The distension of the	If the patient is able to survive all this, then fever, mental state and abdominal distension starts improving gradually over a few days in the fourth week.

Table 1: Antibiotic therapy on the basis of severity of typhoid (Table contd...)

1st week	2nd week	3rd week	4th week
lumen, that may last the duration of the illness. There may be a dry cough, dull frontal headache, delirium and an increasingly stuporous malaise in the patients. The fever plateaus at 103-104°F at the end of the first week of illness. The patient develops rose spots (salmon-coloured, blanching, truncal, maculopapules) which are usually 1-4 cm wide and may be < 5 in number, which generally resolves within 2-5 days.		abdomen may become severe. There may be foul, green-yellow, liquid diarrhoea (pea soup diarrhoea) in some. The patient may go into apathy, confusion, and even psychosis, known as typhoid state. There may be bowel perforation and peritonitis due to necrosis of the Peyer's patches (which is often unheralded, but may be masked by corticosteroids). With this, there may be overwhelming toxaemia, myocarditis, or intestinal haemorrhage that may lead to death.	

In patients who survive and are untreated, the intestinal and neurologic complications may still occur. Weight loss and debilitating weakness may last for months. Some of the survivors become asymptomatic carriers of *S. typhi* and may transmit the bacteria for an indefinite period.

The atypical manifestations of typhoid fever may be

- Isolated severe headaches mimicking meningitis
- Acute lobar pneumonia
- Isolated arthralgias
- Urinary symptoms
- Severe jaundice
- Only fever

Diagnosis and treatment of typhoid

Diagnosis

The diagnosis of typhoid fever (enteric fever) is mainly clinical. Confirmation of diagnosis is by culture and serologic tests.

Treatment

WHO recommendations for treatment of uncomplicated an severe typhoid fever is depicted below in Table 2 and 3, respectively.

Table 2: WHO recommendations for treatment of uncomplicated typhoid fever

	Optimal therapy			Alternative effective drugs		
Susceptibility	**Antibiotic**	**Daily dose mg/kg**	**Days**	**Antibiotic**	**Daily dose mg/kg**	**Days**
Fully sensitive	Fluoroquinolone e.g. otoxacin or ciprofloxacin	15	5-7[a]	Chloramphenicol Amoxicillin TMP-SMX	50-75 75-100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone or cefixime	15 15-20	5-7 7-14	Azithromycin Cefixime	8-10 15-20	7 7-14
Quinolone resistant[b]	Azithromicin or ceftriaxone	8-10 75	7 10-14	Cefixime	20	7-14

a Three day courses are also effective and are particularly so in epidemic containment

b The optimum treatment for quinolone -resistant typhoid fever has not been determined. Azithromycin, the third generation cephalosporins, or a 10-14 day course of high-dose fluoroquinolones is effective
Combinations of these are now being evaluated

Table 3: WHO recommendations for treatment of severe typhoid fever

	Optimal parenteral drug			Alternative effective parenteral drugs		
Susceptibility	**Antibiotic**	**Daily dose mg/kg**	**Days**	**Antibiotic**	**Daily dose mg/kg**	**Days**
Fully sensitive	Fluoroquinolone e.g. otoxacin	15	10-14	Chloramphenicol Amoxicillin TMP-SMX	100 100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone	15	10-14	Ceftriaxone or Cefotaxime	60 80	10-14
Quinolone resistant	Ceftriaxone or cefotaxime	60 80	10-14	Fluoroquinolone	20	7-14

MDRTF infection should be suspected when there is:

- Failure to respond (i.e., no improvement in general condition, loss of appetite, no defervescence of fever, or no reduction in toxic look) even after 5-7 days of treatment with a 1st line antibiotic (chloramphenicol or ampicillin or trimethoprim/ sulfamethoxazole)
- When there is deterioration in the clinical condition or there is a development of a complication (severe condition with shock or abnormal sensorium or other potentially life-threatening complications like intestinal haemorrhage and/or perforation, disseminated intravascular coagulation, or myocarditis) during conventional antibiotic treatment
- When there is a household contact who is a documented case of MDRTF

Contd. from page 20

Patients with typhoid fever should be closely monitored for development of complications, where timely intervention may prevent or reduce the morbidity and mortality. Fluoroquinolones are given for a minimum of 10 days in severe typhoid (Table 5). When typhoid meningitis is suspected, the patients should be immediately treated with high-dose intravenous dexamethasone in addition to antimicrobials. The dose is 3 mg/kg by slow i.v. infusion over 30 minutes and 1 mg/kg after six hours, which is repeated subsequently at six-hourly intervals. Higher dose of steroid may be given if other causes of severe disease are unlikely. In patients with intestinal haemorrhage, intensive care, monitoring and blood transfusion are necessary. Unless there is significant blood loss, intervention is generally not required. In case of intestinal perforation, surgical repair should not be delayed by more than 6 hours, as early intervention is crucial. If a fluoroquinolone is not being used to treat leakage of intestinal bacteria into the abdominal cavity, metronidazole and gentamicin or ceftriazone should be administered before and after surgery. In case of relapse, the fever may return soon after the completion of antibiotic treatment, where the clinical manifestation is often milder than that in initial illness. In such cases, cultures should be obtained. Absence of schistosomiasis must be confirmed and the standard treatment should be given in such cases.

Table 5: WHO recommendations for treatment of severe typhoid fever

	Optimal parenteral drug			Alternative effective parenteral drugs		
Susceptibility	**Antibiotic**	**Daily dose mg/kg**	**Days**	**Antibiotic**	**Daily dose mg/kg**	**Days**
Fully sensitive	Fluoroquinolone e.g. ofloxacin	15	10-14	Chloramphenicol amoxicillin TMP-SMX	100 100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone	15	10-14	Ceftriaxone or Cefotaxime	60 80	10-14
Quinolone resistant	Ceftriaxone or Cefotaxime	60 80	10-14	Fluoroquinolone	20	7-14

Other treatment considerations

- *Corticosteroids:* Severe typhoid fever is one of the few indications of acute bacterial infections for corticosteroid therapy. The dose in adults and children with severe disease (delirium, obtundation, stupor, coma, or shock) is an initial dose of 3 mg/kg followed by 1 mg/kg every 6 hours for a total of 48 hours.
- *Ileal perforation:* In typhoid, ileal perforation usually occurs in the 3rd week of febrile illness which is due to necrosis of the Peyer's patches in the antimesenteric bowel wall. Prompt surgical intervention and wider antimicrobial coverage is usually indicated. Though the extent of surgical intervention is controversial, the best surgical procedure is segmental resection of the involved intestine.
- *Relapse:* Occur in immunocompetent individuals and usually occurs 2-3 weeks after resolution of fever. When the organisms are fully sensitive, fluoroquinolones may reduce the relapse rates. For relapsing illness, an additional course of therapy with a drug which the organism is clearly sensitive is also indicated. A rational option is longer treatment with third-generation cephalosporins.

In patients with unexplained symptoms within 60 days of returning from a typhoid endemic area or following the consumption of food prepared by an individual who is known carrier of the infection, broad-spectrum empiric antibiotics must be started immediately and the treatment should not be delayed for confirmatory tests as prompt treatment may reduce the risk of complications and fatalities considerably. Once more information is available, antibiotic treatment must be narrowed.

Patients with uncomplicated disease may be treated on an outpatient basis. Patients who are hospitalised with more severe disease must be placed in contact isolation during the acute phase of the infection and their faeces and urine must be disposed of safely.

Multidrug-resistance is *S. typhi* resistant to the original first-line agents like ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole. The rate of fluoroquinolone resistance is generally high and rising in south and Southeast Asia and to some extent in East Asia and susceptibility to chloramphenicol, TMP-SMZ and ampicillin in these areas is rebounding.

The most recent guideline for the treatment of typhoid fever in South Asia was issued by the Indian Association of Pediatrics (IAP) (October 2006) and though these guidelines were published for paediatric typhoid fever, they may be also applicable to adults and may have more validity than the WHO recommendations for empiric treatments of typhoid fever in both adults and children (Table 6). It recommends cefixime and azithromycin for empiric treatment of uncomplicated typhoid fever and ceftriaxone. Aztreonam and imipenem are recommended second-line agents for complicated cases.

Table 6: Antibiotic therapy on the basis of severity of typhoid

	Severity	1st line antibiotics	2nd line antibiotics
South Asia, East Asia	Uncomplicated cases	Cefixime PO	Azithromycin PO
	Complicated case	Ceftriaxone IV or Cefotaxime IV	Aztreonam IV or Imipenem IV
Southeast Asia	Uncomplicated	Cefixime PO plus Ciprofloxacin PO or Ofloxacin PO	Azithromycin PO*
	Complicated	Ceftriaxone IV or Cefotaxime IV, plus Ciprofloxacin IV or Ofloxacin IV	Aztreonam IV or Imipenem IV, plus Ciprofloxacin IV or Ofloxacin IV

*Note that the combination of azithromycin and fluoroquinolones is not recommended because it may cause QT prolongation and is relatively contraindicated

Drug resistance in typhoid (Fig. 7)

One of the important factors in the morbidity and mortality in typhoid fever is drug resistance. Chloramphenicol was the drug of choice in the treatment of typhoid fever in most parts since its introduction in 1948. But, it has developed resistance to *S. typhi* due to its indiscriminate use and acquisition of plasmid mediated R factor. The distribution of chloramphenicol resistant strains of *S. typhi* is widespread and its incidence varies from 38.6-83% as per the reports from various parts of India and other tropical countries. Then the alternative drugs like co-trimoxazole, ampicillin and amoxicillin were used and resistance to these drugs was also seen in significant number of patients. Then for the treatment of multiple drug resistant cases of *S. typhi,* the quinolone group of drugs emerged as useful drugs. But, again its indiscriminate use and cross resistance within the antibiotic group led to its resistance. The resistance to quinolone is not plasmid coded and is due to an altered DNA gyrase subunit. Hence as per the sensitivity tests, appropriate antibiotics indicated should be given to the patients to prevent the development of resistant strains, and indiscriminate use of antibiotics should be avoided.

Key Insights

- Control measures to combat typhoid is health education and antibiotic treatment.
- MDRTF is a major public health problem, mainly in developing countries.

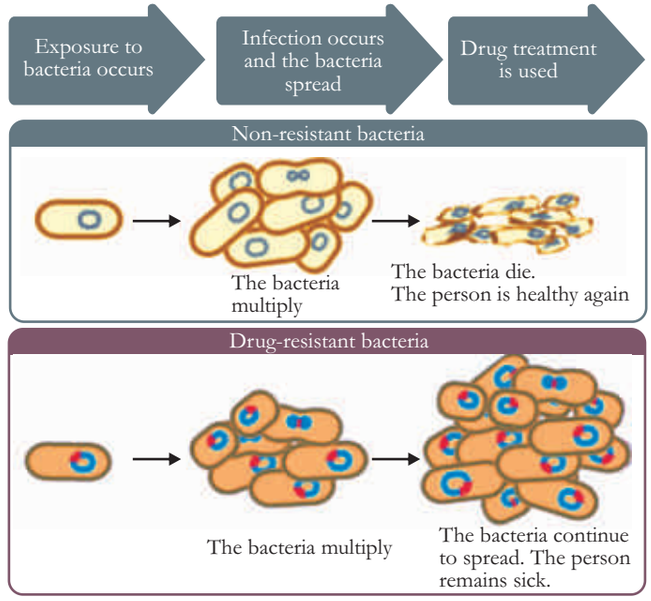


Fig. 7: Drug resistance in typhoid

Distribution of MDR Typhoid

The multidrug resistant (MDR) strains have caused several outbreaks in the Indian subcontinent, Southeast Asia, Mexico, the Arabian Gulf and Africa and these patterns of resistance is revealed in travellers returning to the United Kingdom and the United States. The pattern of resistance has led to the use of 3rd generation cephalosporins, azithromycin and fluoroquinolones in the empiric therapy of typhoid fever till the results of antimicrobial susceptibilities is awaited.

In some parts of Asia, nalidixic acid-resistant organisms with decreased susceptibility to fluoroquinolones have become a major problem. Nalidixic acid-resistant strains have been found in about 70-90% of the isolates in parts of Nepal, India and Vietnam. The nalidixic acid-resistant *S. typhi* (NARST or NAR) may be an indication of fully quinolone-resistant *S. typhi* and what is of importance clinically is the phenotype and the organisms are less effective when treated with fluoroquinolones (especially short course of 3-5 days) (Fig. 8).

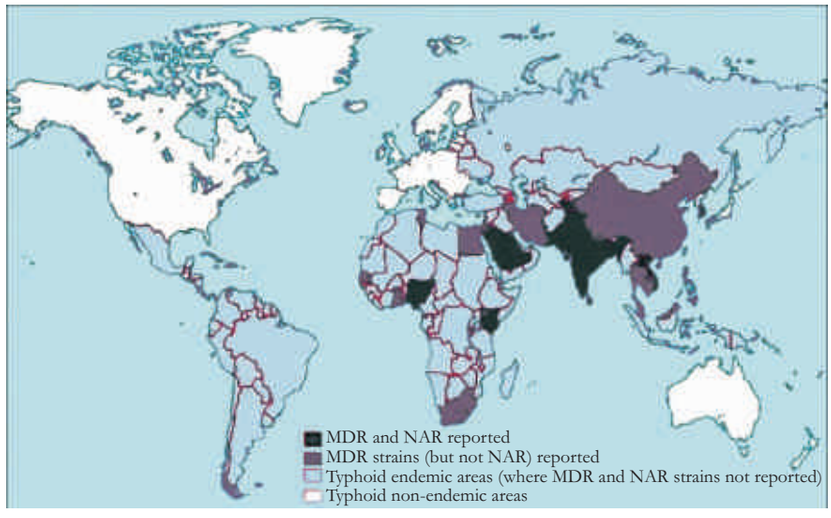


Fig. 8: Distribution of MDR Typhoid

Enteric fever caused by NAR organisms should ideally be treated with a non-quinolone drug, whenever possible, though the alternatives may be expensive, not available at times and may require parenteral administration. The alternative treatment may be with azithromycin, imipenem, the newer fluoroquinolones, fluoroquinolones in higher doses and combination therapies.

The main risk factors for the development of resistance in *S. typhi* are overuse, misuse, and inappropriate antibiotic prescribing practices. The two main mechanisms of development of drug resistance in *S. typhi*:

- Plasmid-mediated mechanism
- Chromosomal DNA-mediated mechanism

The extra-chromosomal, self-replicating circular pieces of DNA i.e., the plasmids can carry and transfer multiple resistance genes between it and the bacteria causing antibiotic resistance in *S. typhi*. Whereas the chromosomal-mediated drug resistance phenomenon against fluoroquinolones is due to selective pressure on the bacteria due to its uncontrolled use, though it may be also due to decreased permeability and active efflux of the antimicrobials.

MDRTF infection should be suspected when there is:

- Failure to respond (i.e., no improvement in general condition, loss of appetite, no defervescence of fever, or no reduction in toxic look) even after 5-7 days of treatment with a 1st line antibiotic (chloramphenicol or ampicillin or trimethoprim/sulfamethoxazole)
- When there is deterioration in the clinical condition or there is a development of a complication (severe condition with shock or abnormal sensorium or other potentially life-threatening complications like intestinal haemorrhage and/or perforation, disseminated intravascular coagulation, or myocarditis) during conventional antibiotic treatment
- When there is a household contact who is a documented case of MDRTF

As per the WHO guidelines, either fluoroquinolones or 3rd generation cephalosporins may be used in MDRTF, depending upon the sensitivity. Fluoroquinolones are recommended in quinolone-sensitive MDR strains, as they have many advantages over 3rd generation cephalosporins.

The treatment of typhoid fever especially in the developing world is a serious and growing problem. There may be increase in the morbidity and mortality rates with resistance of bacteria to the standard antibiotics. Infection not treated properly may lead to prolonged illness and also increases the chance of developing a carrier state where the person is contagious and may spread the resistant strain to others. Among circulating strains, the plasmid-mediated mutagenesis occurs much more rapidly than the development of new drugs and a highly lethal strains of resistant bacteria may evolve which may leave us with no effective way to combat this danger. Hence, vaccination may be effective in controlling typhoid especially in the resource-poor countries, especially in children < 15 years of age, who are mostly vulnerable.

Treatment of the chronic carriers (Table 7)

The treatment of the chronic carrier may be difficult. Ampicillin use may have some success, though in the convalescent stage prolonged ampicillin administration may not prevent the carrier state. Prophylaxis is the best method for preventing the spread of typhoid fever by chronic carriers who have not responded to treatment, where ciprofloxacin and norfloxacin are found to be very effective than the prolonged courses of ampicillin or co-trimoxazole.

The patient may require cholecystectomy or anti-parasitic medication in addition to antibiotics in order to achieve bacteriological cure in case cholelithiasis or schistosomiasis is present.

S. typhi carriage can be eradicated with amoxicillin or ampicillin (100 mg/kg/day) plus probenecid (1 g orally or 23 mg/kg for children) or TMP-SMZ (160-800 mg twice daily) for 6 weeks.

In chronic carriers, clearance of up to 80% can be achieved with the administration of ciprofloxacin (750 mg of twice daily) for 28 days or 400 mg of norfloxacin. All carriers, convalescent patients and any persons with possible symptoms of typhoid fever should be excluded from activities involving food preparation and serving.

For eradication of chronic carriage, high dose of ampicillin i.e., 4-6 g/day at times in combination with cholecystectomy was frequently employed in the past, though it was not always successful. For eradication of chronic carriage, fluoroquinolones are much more effective and is better tolerated than ampicillin. Ciprofloxacin 500-750 mg orally twice daily or ofloxacin 400 mg orally twice daily for 4 weeks is a reasonable approach and subsequently cholecystectomy may be considered if needed.

Table 7: Pharmacotherapy in the treatment of carriers

Antibiotics	Daily dose	Route	Dose	Duration (days)
Ampicillin or Amoxycillin + Probenicid	100 mg/kg 30 mg/kg	Oral	tid/qid	6-12 weeks
Co-trimoxazole	4-20 mg/kg	Oral	bid	6-12 weeks
Ciprofloxacin	1500 mg	Oral	bid	4 weeks
Norfloxacin	800 mg	Oral	bid	4 weeks

Prevention of typhoid

Typhoid fever is mainly by the ingestion of contaminated food or water and ingestion of the local cuisine in areas where sanitation and personal hygiene may be poor is the main mechanism of transmission in travellers (Fig. 9). The inoculum in food is likely to be more than in the contaminated water.

The natural infection does not provide complete protection against recurrent illness, which may not be the same as in relapsed infection. Vaccination may be considered even after clinical illness, especially in those not living in endemic areas, if re-exposure is expected. The best timing for vaccination following clinical illness is not known.

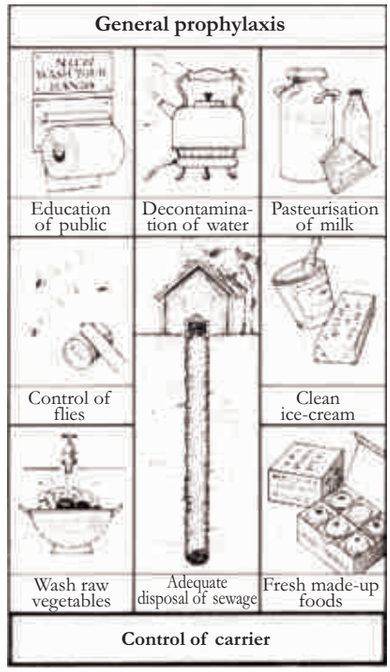
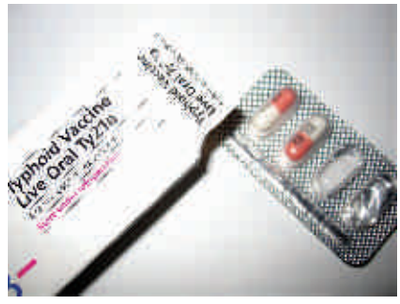


Fig. 9: Prevention of typhoid fever

- The main preventive measure is to ensure access to safe water as it is a waterborne disease.
- Appropriate food handling and processing. During epidemics, basic hygiene measures must be implemented or reinforced:
  - Washing hands with soap before preparing or eating food
  - Avoiding raw food, shellfish, ice
  - Eating only cooked and hot food or re-heating the food
- Carriers of typhoid must be excluded from any activities involving preparation and serving of food, until they have had 3 negative stool cultures at least one month apart.
- Proper sanitation like appropriate facilities for disposal of human waste in the community (pit latrines may be quickly built in emergency), proper collection and treatment of sewage, especially in the rainy season, discouraging use of human excreta as fertilisers in areas where typhoid fever is known to be present.
- The public awareness of preventive measures should be raised by health education by all possible means of communication (media, schools, women's groups, religious groups).
- Education of healthcare staff with regards to:
  - Personal hygiene at work
  - Isolation measures for the patient
  - Disinfection measures
- Vaccination

Typhoid vaccines: The two vaccines available for protection against *S. typhi* is the live oral *S. typhi* vaccine strain Ty21a and parenteral Vi polysaccharide vaccine (Fig. 10; Table 8 and 9). Neither of them may provide protection at very little risk for travelers to high-risk areas. In endemic areas, prevention of enteric fever is by implementing immunisation for young children.



A: Oral

B: Parenteral

Fig. 10: Typhoid vaccines

Table 8: Dose and administration and adverse reactions of typhoid vaccine

Vaccination	Age (Years)	Dose/mode of administration	No. of doses dosing	Dosing interval	Boosting interval
Oral, five, attenuated Ty21a vaccine (Vivotif)					
Primary series	≥6	1 capsule 1 oral	4	48 hrs	Not applicable
Booster	≥6	1 capsule 1 oral	4	48 hrs	Every 5 years
Vi Capsular polysaccharide vaccine (Typhim VI)					
Primary series	≥2	0.50 ml, intramuscular	1	Not applicable	Not applicable
Booster	≥2	0.50 ml, intramuscular	1	Not applicable	Every 2 years
Administer with cool liquid no warmer than 98.6°F (37°C).					

Table 9: Common adverse reactions to typhoid fever vaccines

Vaccine	Reactions		
	Fever	Headache	Local reactions
Ty21a1	0%-5%	0%-5%	Not applicable
Vi Capsular polysaccharide	0%-1%	16%-20%	7% erythema or induration 1 cm

Conclusion

Typhoid fever is a severe, contagious and a life-threatening systemic disease caused by *S. typhi* which may cause persistent fever with or without severe complications. Though the incidence of the disease has decreased markedly in the developed countries, where it is now characterised mainly as a travel-associated disease, it is still common in less-industrialised countries, due to consumption of unsafe drinking water, poor sanitation and inadequate disposal of sewage. Because of its variable manifestations, its diagnosis may be a challenge. The classic presentation may be fever, malaise, diffuse abdominal pain and constipation. If untreated, a case of typhoid fever may progress to complications like delirium, obtundation, intestinal haemorrhage, bowel perforation and death, causing long-term or permanent neuropsychiatric complications in survivors. As it is a waterborne/foodborne disease, the main preventive measure is to ensure access to safe water, appropriate food handling and processing and proper sanitation.

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Case study 1

Case presentation

A 40-year-old male patient came with complaints of fever since 1 week. He also gave h/o headache and generalised weakness. H/o pain in the abdomen since 2-3 days.

No other significant history in the past and there was no h/o major illness in the past.

On examination

- Temp - 103^{O}F
- Pulse - 64/min
- BP - 100/70 mmHg
- RS, CVS and CNS - NAD
- Per abdomen - Mild tenderness + in the hypochondrium, Spleen +

Investigations

- Hb - 11g/dL
- WBC - 2,500 cells/mm^3
- Platelets - 1,00,000 cells/mm^3
- LFT - Normal
- Dengue IgG, IgM - Negative
- Leptospira - Negative
- PS for MP - Negative
- Widal test - Titre O antigen - 1:160; H antigen - 1: 260

Diagnosis: Enteric fever

Treatment

Patient was given paracetamol S.O.S for his fever. He was put on T. chloramphenicol 500 mg QID for 2 weeks. The recovery was uneventful.

Take home message

- Relative bradycardia and leucopaenia is diagnostic of typhoid fever
- A titre of > 100 for O antigen and > 200 for H antigen is considered significant
- Compliant patients with uncomplicated disease may be treated on an outpatient basis

Case study 2

Case presentation

A 25-year-old female patient came with c/o fever since 6-8 days. Patient had self medicated herself with paracetamol, but since the fever was not subsiding, she came for a check-up to her family physician. The fever was intermittent and high grade. Patient also complains of headache and generalised weakness. Since the last 3-4 days, she gives h/o passing loose stools. Patient gives h/o frequent eating out. There was no other significant history in the past.

On examination

- Temp - 102^{O} F
- Pulse - 60/min
- BP - 100/60 mmHg
- RS, CVS and CNS - NAD
- Per abdomen - Liver just palpable; Spleen: palpable, mild tenderness + in the right and left hypochondrium

Investigations:

- Hb - 11 g/dL
- WBC - 3,500 cells/mm^3
- Platelets - 1,75,000 cells/mm^3
- LFT - Normal
- Widal test - Positive
- Blood culture - *S. typhi* + sensitive to ofloxacin

Diagnosis: Enteric fever

Treatment

Patient was initially treated with cefixime 200 mg b.d., but as the culture was sensitive to ofloxacin 400 mg b.d. for 7 days.

Patient started improving and the recovery was uneventful. Patient was asked to avoid outside food and asked to eat cooked food always.

Take home message

- Poor food hygiene poses a greatest risk of typhoid
- The best method of prevention of typhoid is good attention to food and water hygiene

Definitive treatment of enteric fever is based on susceptibility and antibiotic therapy should be narrowed once more information is available.

Case study 3

Case presentation

A previously healthy 15 year old boy was admitted with history of fever since 7 days. He also gives h/o vomiting and generalised weakness. No other significant history in the past.

On examination

- Temp - 103^{O}F
- Pulse - 80/min
- BP - 100/60 mmHg
- RS, CVS and CNS - NAD
- Per abdomen - Spleen palpable, soft

Investigations

- Hb - 12g/dL
- WBC - 3, 000 cells/mm^{3}
- Peripheral smear for malarial parasites - Negative
- Urinalysis - Normal
- Chest radiographs - Normal
- Widal test - A titre of 1: 320 against "O" (somatic) antigen of *S. typhi.*
- Blood culture: Growth of *Salmonella typhi,* isolates susceptible to ciprofloxacin and ceftriaxone

Diagnosis: Typhoid fever

Treatment

He was put on oral ciprofloxacin (500 mg) b.d., but patient was febrile even after 3 days of treatment. Patient was admitted and the blood culture report was received and in view of the susceptibility pattern, patient was put on intravenous ciprofloxacin b.d. He was also given symptomatic treatment. In spite of this, the fever was not subsiding. In view of patient not responding to treatment with ciprofloxacin, he was put on ceftriaxone, 1 g b.d., and patient started responding well.

Take home messages

- The most effective antimicrobial agents for treating enteric fevers are fluoroquinolones
- There is an increasing incidence of reduced susceptibility and resistance of *S. typhi* against fluoroquinolones
- Fluoroquinolones must be used with caution and their resistance must be identified early

CME-Post Test

1. **The only reservoirs of *S. typhi* are…**
   a. Humans
   b. Monkeys
   c. Pigs
   d. None of the above

2. ***S. typhi* was originally isolated by Karl J. Erberth in…**
   a. 1990
   b. 1880
   c. 1870
   d. 1860

3. **Patients who have typhoid fever, chronic carrier state may develop in…**
   a. 10%
   b. 40%
   c. 20%
   d. 1-5%

4. **The incubation period in typhoid fever is…**
   a. 1-14 days
   b. 20 days
   c. 3 weeks
   d. None of the above

5. **The salmon-coloured, blanching, truncal, maculopapular lesions which are usually 1-4 cm wide seen in typhoid are known as…**
   a. Gold spots
   b. Rose spots
   c. Jose spots
   d. None of the above

6. **The standard criterion for diagnosis of typhoid which is considered 100% specific is…**
   a. Widal test
   b. CBC
   c. Culture
   d. None of the above

7. **The serum ALT: LDH ratio which is suggestive of a diagnosis of acute viral hepatitis is…**
   a. < 9:1
   b. > 9:1
   c. >1:9
   d. <1:9

8. **In typhoid, ileal perforation usually occurs in the…**
   a. 3rd week
   b. 1st week
   c. 2nd week
   d. None of the above

9. **Multidrug-resistant typhoid fever is resistant to…**
   a. Chloramphenicol
   b. Ampicillin
   c. TMP-SMX
   d. All of the above

10. **The dose of typhoid vaccine is…**
    a. 1 ml
    b. 2 ml
    c. 1.5 ml
    d. 0.5 ml

Ans: 1-a; 2-b; 3-d; 4-a; 5-b; 6-c; 7-b; 8-a; 9-d; 10-d

Clinical challenges: Typhoid: Diagnostic & Therapeutic Update

Case 1: A case of complicated typhoid fever

Case presentation

A 33-year-old male patient came with h/o anorexia and fever for 10 days. He also complains of vague pain/discomfort in the right upper abdomen which is associated with vomiting and h/o passing high coloured urine since 3-4 days. He also gives h/o slight decrease in urine output. No h/o diarrhoea or any alteration in the colour of the stools. There is no other significant history.

Personal history

H/o alcohol plus, only social drinking, no h/o intake of any medications.

On examination

A moderately built patient who is ill looking with mild dehydration.

- Temp - Febrile
- Icterus ++
- No lymphadenopathy
- No evidence of chronic liver disease or encephalopathy
- RS, CVS - NAD
- Per abdomen - Liver: Tender firm hepatomegaly +; Spleen: soft, moderately enlarged.

Investigations

- Urine routine - Bile salts +; Urobilinogen: normal
- CBC - WBC: 4.8 × 103/μL; N: 51%; L: 44%
- Platelet count - 175 × 103/μL
- ESR - 35 mm/h
- CRP - Elevated (96 mg/L).
- LFT - Albumin: Normal; AST: 120 units/L; ALT: 240 units/L; Alkaline phosphatase: 1500 units/L; Bilirubin. Indirect: 1 mg/dL; Direct: 10 mg/dL
- S. electrolytes - normal
- BUN - Normal
- S. creatinine - Normal
- PS for malarial parasites - Negative
- USG abdomen - Hepatomegaly with a coarse echo pattern and a markedly dilated gall bladder. GB wall thickness was reported to be normal. The intra and extra-hepatic bile ducts were not dilated nor were any calculi visualized. Splenomegaly. Rest NAD

Treatment

Patient was admitted and empirically treated with IV crystalline penicillin considering a diagnosis of leptospirosis. In the meantime blood culture, urine culture, serology studies for viral hepatitis, leptospirosis and dengue were sent for. In spite of treatment for suspected leptospirosis, his fever continued and icterus progressively worsened.

Investigations

- Repeat LFT showed further derangement, and the direct bilirubin was now 16 mg/dL and alkaline phosphatase - 1600 Units/L; AST - 125 Units/L; ALT - 255 units/L.
- Leptospira microscopic agglutination test - Equivocal
- Hepatitis A, B and C serology - Negative
- Dengue IgG - Positive in low titres; IgM - negative
- Blood culture - Growth of *Salmonella typhi,* sensitive to ciprofloxacin and cefotaxime, and resistant to ampicillin and chloramphenicol.

Diagnosis: Complicated typhoid fever

Patient was started on I.V. Cefotaxime, 2 g three times a day for 3 days and then switched to oral Cefixime with Tab. Azithromycin, 1g daily for 7 days. The patient started showing improvement in 48 hrs after starting treatment and over the next few days there was resolution of jaundice and constitutional symptoms. The LFT started improving. Patient was discharged and asked to follow-up after a week later, where there was substantial improvement in his condition and the lab parameters.

Questions

1. What are the systemic complications of typhoid?

2. How common is jaundice in patients with typhoid?

Case 2: A case of relapsed typhoid fever

Case presentation

A female patient aged about 40 years came with h/o fever since about 1 week. Fever is intermittent associated with chills at times. She complained of generalised weakness with headache. No other significant history.

Past history: No history of diabetes mellitus and hypertension. H/o typhoid fever in the past, 5-6 years back. She was treated for the same and had recovered completely. No other illness in the past.

Examination

- Temp - 102^{O}F
- Pulse - 70/min
- BP - 120/70 mmHg
- No pallor, icterus, lymphadenopathy
- RS, CVS, CNS - NAD

Investigations

- Hb - 11g/dL
- WBC - 4,000 cells/mm^{3}
- PS for MP - Negative
- LFT - Normal
- Widal test - Postive Titre: O antigen titre: 1: 160, H antigen titre: 1: 260
- Blood culture - No growth

Diagnosis - Relapsed typhoid fever

Treatment

Patient was diagnosed as a relapsed case of typhoid fever and was treated with a combination of cefixime 200 mg b.d. and ofloxacin 400 mg b.d. for 7 days. Patient recovered well.

Questions

1. What is the differential diagnosis of typhoid?
2. What are the risk factors for typhoid infection?
3. What are the aetiologic agents to be considered in various manifestation of foodborne illness?

Case 3: A case of typhoid fever with ileal perforation

Case presentation

A 38-years-old male patient came with complaints of fever since 3 weeks. Initially the temperature was high grade for which patient was investigated, which were suggestive of typhoid fever and was treated for the same, though he was better, he did not feel alright totally. He had came with sudden onset of pain in the abdomen which is associated with nausea and vomiting. He had h/o passing blood in stools since 2-3 days. The pain was mild initially, but it was severe now. He c/o generalised weakness and giddiness.

On examination

- Temp - 101^{O}F
- A weak low volume pulse, rate - 60/min
- BP - 90/60 mmHg
- Per abdomen - Rigidity ++, Guarding +++

Investigations were sent on urgent basis. X-ray abdomen erect showed gas under the diaphragm and multiple air fluid levels which was suggestive of intestinal perforation.

Diagnosis: Typhoid fever with ileal perforation

Treatment

Patient was immediately referred to a surgeon for further management. Exploratory laparotomy was done with closure of perforation. The patient was clinically stable after the procedure and was treated with IV fluids, antibiotics, nasogastric aspiration and bowel rest. The recovery was uneventful.

Questions

1. What are the causes of intestinal perforation?
2. What are the findings on X-ray abdomen suggestive of perforation?

Note: Answers to the Clinical Challenges will be given in the next issue.

Answers to Clinical Challenges – Approach to mixed infections of the skin

Explanation to Clinical Challenges that have appeared in the issue dated May 16th, 2012

Case 1: Eosinophilic pustular folliculitis

Questions

1. What is eosinophilic pustular folliculitis (EPF)?

EPF is characterised by chronic and recurrent annular clusters of sterile erythematous follicular papules and pustules superimposed on plaques with central clearing and peripheral extension. Individual clusters normally last for seven to ten days and tend to relapse every three to four weeks. The disease shows affinity for males.

The distribution of classic EPF lesions is concentrated on the face (85% of cases), back and trunk (59%), and other seborrheic areas; other body areas can also be affected.

Three variants of this disorder have been described: classic eosinophilic pustular folliculitis (as originally described by Ofuji), HIV-associated eosinophilic pustular folliculitis, and infantile eosinophilic pustular folliculitis.

2. What is the management of EPF?

There are multiple treatment options for EPF namely:

- Topical corticosteroids tend to be the first choice for all three types of EPF
- UVB phototherapy
- Oral indomethacin
- Isotretinoin
- 0.1% tacrolimus

Case 2: Treatment of erysipelas

Questions

1. What is erysipelas?

Erysipelas is a superficial skin infection due to Steptococci which nowadays is localised on legs in most cases. The disease itself gives wide undermining of subcutaneous tissue which is very characteristic but even in severe cases like bullous erysipelas big ulcers are rare.

Staphylococcus aureus may play the role in bullous erysipelas with MRSA strains present.

The usual presentation is that of rash; characterised by an abrupt onset of illness with initial fever and chills followed by a painful rash occurring 1-2 days later. Myalgia and joint pain is likely to be there.

2. What is the management?

The condition needs to be differentiated form cellulitis; necrotising fasciitis may start in a similar way but the patients are sicker with generalised malaise and fever and there is often reduced sensation of overlying skin.

Group A streptococci or mixed bacterial infection often in association with an infected traumatic wound or surgical wound may cause this. Surgical exploration is mandatory as this is potentially life threatening.

- Advise rest and use cool compresses on the affected areas.
- Antipyretics and analgesics for fever and pain
- Surgical debridement done, if necessary

Case 3: Necrotising fasciitis

Questions

1. What is necrotising fasciitis?

Necrotizing fasciitis nick named as "flesh eating bacteria syndrome" is a polymicrobial in origin severe, insidiously advancing, soft-tissue infection characterised by widespread fascial necrosis. Since it has similar presentation to cellulites in early stages both the conditions are easily mistaken.

2. What is the treatment of NF?

The main features of treatment are:

- Early reconition of NF and differentiating it from cellulites
- Administer intravenous antibiotics
- Surgical debridement
- Intensive care unit support
- Hyperbaric oxygen
- Intravenous immunoglobulin
- Wound management

Medicolegal

CLINICS, LABS AND NURSING HOMES IN RESIDENTIAL PREMISES – ARE THEY PERMITTED?

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Of late, there are many queries from medical practitioners who own clinics, laboratories and nursing homes situated in residential housing premises, asking whether their nursing homes, clinics and laboratories are illegal, as made out to be by the managing committee members of their co-operative housing societies.

These hospital owners are being harassed by the managing committee of the co-operative housing society, which rakes up an unnecessary controversy that health care activities are not permissible in areas which are classified as 'PURELY RESIDENTIAL ZONE'. Under the situation nursing home owners/doctors are under immense pressure to part away with huge amounts to get their premises regularised and many have succumbed to these pressures.

What is the law that governs private clinics, laboratories and nursing homes in residential premises? Are such activities permissible in residential premises? Can a co-operative housing society object to such an activity? Are there any conditions imposed on such an activity by the Appropriate Authority (Municipal Corporation of Greater Mumbai in Mumbai), are the relevant questions that come-up for consideration.

Land Use Classification and Permitted Uses are enumerated by the Urban Development Department – Government of Maharashtra in PART IV of the DEVELOPMENT CONTROL REGULATIONS FOR GREATER MUMBAI.

In Greater Mumbai, land can be used for pure residential purpose, residential-cum-shop purpose, commercial (local and district) purpose, service industry purpose and for the purpose of general industry.

Regulation 51 deals with the permitted ancillary uses of residential premises in a purely residential zone.

Regulation 51 permits in residential zone, medical or dental practitioner's dispensary or clinic, including pathological or diagnostic clinic with a restriction of one dispensary or clinic per building on the ground floor or the first floor.

Nursing homes, polyclinics, maternity homes and consulting rooms are permissible in residential/independent buildings on the ground floor, first floor and second floor with separate means of access/staircase from within the building or outside.

If the doctor is a resident of the premises, dispensaries or clinics with only out patient treatment facilities and without any indoor work is permitted to the extent of 30 sq. m.

Research, experimental and testing laboratories, not involving any danger of fire or explosion, are also permitted in residential premises.

The Development Control Regulations also require one parking space for every 300 sq. m of total hospital floor area and an additional parking space of 10 m x 4 m for the parking of an ambulance for all hospitals with bed strength of 100 or more.

The above-mentioned activities are also legally permitted in 'RESIDENTIAL ZONE WITH SHOP LINE'.

The Municipal Corporation is vested with the authority to lay down rules and regulations to permit health-care activity in resident user premises with or without shop line and the Asstt. Health Officer (Epdt.) has laid down several requirements few of which are as follows:

1) Nursing homes can be allowed in residential/commercial/independent buildings.

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2) The nursing home should have a separate entrance leading to the nursing home.

3) All ICUs, gynaecological, obstetrical and orthopaedic hospital must have a lift even up to the first floor.

4) Minimum area allotted to one bed must be 50 sq. feet and the width between two beds should be minimum 3 feet for free trolley movements. Every bed must be 7 feet by 3 feet. Minimum size of a room must be 100 sq. feet with none of the sides less than 8 feet and minimum height of 9 feet. Size of the door should be minimum 3 feet for trolley to enter.

5) Nursing homes must have a separate water storage tank and water must be procured from the municipal mains and there must be a separate water meter.

6) WC blocks must be separate for males and females. For males there must be 1 toilet for 8 patients and for females 1 toilet for 6 patients. Each WC block should be minimum 12 sq. feet.

7) The nursing home must have 2 bathrooms (if not attached with WC), for 10 male/female beds and each should be minimum 20 sq. feet.

8) The nursing home must employ 1 sweeper per 8 beds and wards should be cleaned with broom at least 3 times a day and mopped with disinfectant at least twice a day. WC blocks must be cleaned 3 times a day.

9) All passages must be minimum 3 feet wide and clear of obstruction.

10) Generator is a must for all nursing homes having operation theatre, labour room, ICUs and ICCUs.

11) Air-conditioning is essential for all ICUs, ICCUs, burns units and cardiac surgery/neurosurgery wards. Each ICU and ICCU bed must be allotted 150 sq. feet. There must be monitors, defibrillators, ventilators and essential drugs.

12) The nursing home must have at least one doctor who is a specialist in the type of health care activity the hospital conducts i.e., a cardiologist for an ICCU. The doctor may be a residential doctor if not he should be easily available on telephone at his residence.

13) Ten different kinds of records to be maintained.

APART FROM THIS THERE ARE MANY OTHER CONDITIONS IMPOSED.

Carrying on nursing home activity in residential premises is thus not an illegal activity, and the same is permitted by law, of course, with certain pre-conditions.

Under the situation can co-operative housing societies prevent such an activity?

The Constitution of India guarantees the right of every individual to practice his profession and this is a fundamental right. Article 19(1)(g) of the Constitution of India guarantees every citizen, the freedom to practice any profession or carry on any occupation, trade or business. This right is subject to reasonable restrictions. Activities which are illegal or immoral are not protected by Article 19(1)(g). Carrying on a health care activity in residential premises is not an illegal activity.

Co-operative housing societies, under the situation, cannot deprive any doctor from carrying out his profession in residential premises, as long as he does not violate any provisions of law.

Currently the Municipal Corporation also insists on a change of user.

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