Typhoid Fever

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by Salmonella enterica serotype typhi and, to a lesser extent, S enterica serotypes paratyphi A, B, and C. The terms typhoid and enteric fever are commonly used to describe both major serotypes.

S typhi has been a major human pathogen for thousands of years, thriving in conditions of poor sanitation, crowding, and social chaos

The name S typhi is derived from the ancient Greek typhos, an ethereal smoke or cloud that was believed to cause disease and madness. In the advanced stages of typhoid fever, the patient's level of consciousness is truly clouded

Pathophysiology

All pathogenic *Salmonella* species, when present in the gut are engulfed by phagocytic cells, which then pass them through the mucosa and present them to the macrophages in the lamina propria. Nontyphoidal salmonellae are phagocytized throughout the distal ileum and colon. With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharides. Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation and suppressing the infection.

In contrast to the nontyphoidal salmonellae, *S typhi* and paratyphi enter the host's system primarily through the distal ileum. *They* have specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. The bacteria then induce their host macrophages to attract more macrophages.

The following are **modes of transmission** of typhoidal salmonella:

- Oral transmission via food or beverages handled by an often asymptomatic individual—a carrier—who chronically sheds the bacteria through stool or, less commonly, urine
- Hand-to-mouth transmission after using a contaminated toilet and neglecting hand hygiene
- Oral transmission via sewage-contaminated water or shellfish (especially in the developing world

Classic typhoid fever syndrome

The clinical syndromes associated with *S typhi* and *paratyphi* are indistinguishable. Typhoid fever begins 7-14 days after ingestion of the organism . The fever pattern is stepwise, characterized by a rising temperature over the course of each day that drops by the subsequent morning. The peaks and troughs rise progressively over time.

Over the course of the first week of illness, the notorious gastrointestinal manifestations of the disease develop. These include diffuse abdominal pain and tenderness and, in some cases, fierce colicky right upper quadrant pain. The individual then develops a dry cough, dull frontal headache, delirium, and an increasingly stuporous malaise.

At approximately the end of the first week of illness, the fever plateaus at 103-104°F (39-40°C). The patient develops rose spots, which are salmon-colored, blanching, truncal, maculopapules usually 1-4 cm wide and fewer than 5 in number; these generally resolve within 2-5 days

During the second week of illness, the signs and symptoms listed above progress.
In the third week, the still febrile individual grows more toxic and anorexic with significant weight loss. The conjunctivae are infected, and the patient is tachypneic with a thready pulse and crackles over the lung bases. Abdominal distension is severe. Some patients experience foul, green-yellow, liquid diarrhea (pea soup diarrhea).

Diagnosis

The criterion standard for diagnosis of typhoid fever has long been culture isolation of the organism. Cultures are widely considered 100% specific.
Antibiotic treatment of typhoid fever
Severe or complicated infections
For infections that are not acquired in Pakistan, ceftriaxone should be started empirically. In this setting, resistance to ceftriaxone is unusual. In cases that do not originate in southern Asia, a fluoroquinolone should be considered because of its potential advantage of hastening defervesce then is achievable by cephalosporins.
For infections that are acquired in Pakistan, a carbapenem should be administered because of the risk of XDR strains.
Mild or uncomplicated infections
In less-severe uncomplicated infections, it is appropriate to begin oral therapy. Unless the risk of fluoroquinolone resistance is significant, ciprofloxacin or ofloxacin is preferred. Azithromycin offers dual advantages of low risk of resistance and excellent oral absorption.
Because of the risk of developing antibiotic resistance, the concept of using dual antibiotic therapy has been revived. In addition, some evidence shows that the clinical course is improved with such combinations. Specifically, the combination of cefixime-ofloxacin has been approved by the Indian Regulatory Authority for the treatment of typhoid fever.

Anti-microbial therapy

Antibiotic	**Route**	**Adult dosage/day**	**Dosage:mg/kg/day**	**Duration (in days)**
First-line antibiotics :				
Chloramphenicol	Oral, IV	500 mg qid	50 mg/kg in 4 doses [@]	14
Trimethoprim-	Oral, IV	160/800 mg bid	4-20 mg/kg: in 2	14

Antibiotic	**Route**	**Adult dosage/day**	**Dosage:mg/kg/day**	**Duration (in days)**
Sulfamethoxazole			doses	
Ampicillin/Amoxycillin	Oral, IM, IV	1000-2000 mg qid	50-100 mg/kg: in 4 doses	14

Second-line antibiotics:

Fluoroquinolones

Ciprofloxacin	Oral/IV	500 mg bid/200 mg bid	NA	10-14
Norfloxacin	Oral	400 mg bid	NA	10
Pefloxacin	Oral, IV	400 mg bid	NA	10
Ofloxacin	Oral	400 mg bid	NA	14

Ceph alosporins

Antibiotic	Route	Adult dosage/day	Dosage:mg/kg/day	Duration (in days)
Ceftriaxone	IM, IV	1-2 gm bid	50-75 mg/kg: in 1-2 doses	7-10
Cefotaxime	IM, IV	1-2 gm bid	40-80 mg/kg: in 2-3 doses	14
Cefoperazone	IM, IV	1-2 gm bid	50-100 mg/kg: in 2 doses	14
Cefixime	Oral	200-400 mg od/bid	10 mg/kg: in 1-2 doses	14
Other antibiotics:				
Aztreonam	IM	1 gm/bd-qid	50-70 mg/kg: 2-4	5-7
Azithromycin	Oral	1 gm od	5-10 mg/kg:1	5

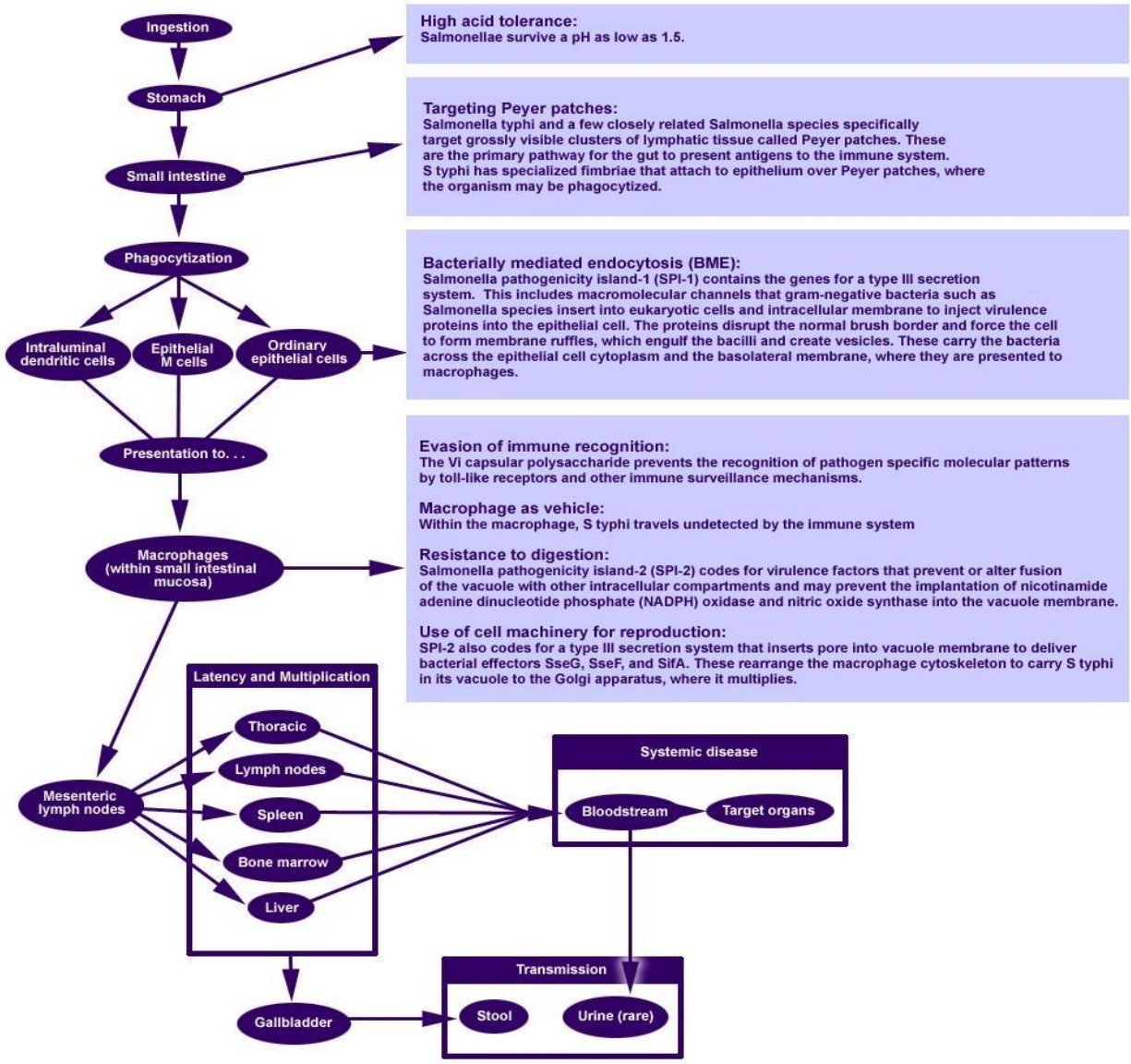
[@]Dose of chloramphenicol may be reduced to 25 mg/kg after defervescence.

Drug treatment of typhoid carriers

Antibiotic	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	1500mg	Oral	Bid	4 weeks
Norfloxacin	800 mg	Oral	Bid	4 weeks

Reference

- SP Kalra,[*] N Naithani,[+] SR Mehta,[#] and AJ Swamy , Current Trends in the Management of Typhoid Fever Med J Armed Forces India. 2003 Apr; 59(2): 130–135.
- https://emedicine.medscape.com/article/231135-medication (DOR 24-4-2020)


Ingestion
Stomach
Small intestine
Phagocytization
Intraluminal dendritic cells
Epithelial M cells
Ordinary epithelial cells
Presentation to. . .
Macrophages (within small intestinal mucosa)
Mesenteric lymph nodes
Latency and Multiplication
Thoracic
Lymph nodes
Spleen
Bone marrow
Liver
Gallbladder
Systemic disease
Bloodstream
Target organs
Transmission
Stool
Urine (rare)
High acid tolerance:
Salmonellae survive a pH as low as 1.5.
Targeting Peyer patches:
Salmonella typhi and a few closely related Salmonella species specifically target grossly visible clusters of lymphatic tissue called Peyer patches. These are the primary pathway for the gut to present antigens to the immune system. S typhi has specialized fimbriae that attach to epithelium over Peyer patches, where the organism may be phagocytized.
Bacterially mediated endocytosis (BME):
Salmonella pathogenicity island-1 (SPI-1) contains the genes for a type III secretion system. This includes macromolecular channels that gram-negative bacteria such as Salmonella species insert into eukaryotic cells and intracellular membrane to inject virulence proteins into the epithelial cell. The proteins disrupt the normal brush border and force the cell to form membrane ruffles, which engulf the bacilli and create vesicles. These carry the bacteria across the epithelial cell cytoplasm and the basolateral membrane, where they are presented to macrophages.
Evasion of immune recognition:
The Vi capsular polysaccharide prevents the recognition of pathogen specific molecular patterns by toll-like receptors and other immune surveillance mechanisms.
Macrophage as vehicle:
Within the macrophage, S typhi travels undetected by the immune system
Resistance to digestion:
Salmonella pathogenicity island-2 (SPI-2) codes for virulence factors that prevent or alter fusion of the vacuole with other intracellular compartments and may prevent the implantation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase into the vacuole membrane.
Use of cell machinery for reproduction:
SPI-2 also codes for a type III secretion system that inserts pore into vacuole membrane to deliver bacterial effectors SseG, SseF, and SifA. These rearrange the macrophage cytoskeleton to carry S typhi in its vacuole to the Golgi apparatus, where it multiplies.