

## Published on



# MANAGEMENT OF SEVERE TYPHOID FEVER

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## ABSTRACT

Typhoid fever, also called enteric fever, or simply ‘typhoid’, is a systemic illness caused by a Gram negative organism, *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella typhi*), whereas paratyphoid fever is caused by any of the three serovars of *Salmonella enterica* subspecies *enterica*, namely *S. paratyphi* A, *S. schottmuelleri* (also called *S. paratyphi* B), and *S. hirschfeldii* (also called *S. Paratyphi* C). Type A is the most common pathogen worldwide. Typhoid fever characterised by: 1) fever that is intermittent during the first week, but becomes sustained (lasting > 48 hours) thereafter; 2) headache (43-90%), 3) gastrointestinal symptoms such as abdominal pain/cramps, nausea and vomiting, constipation or diarrhoea. Other uncommon clinical signs include a relative bradycardia, a skin rash (‘rose spots’) which are faint-pink spots 2-4 cm in diameter which develop on the chest, abdomen and back, hepatosplenomegaly. Both outpatients and inpatients with typhoid fever should be closely monitored for the development of complications. Timely intervention can prevent or reduce morbidity and mortality. The parenteral fluoroquinolones are probably the antibiotics of choice for severe infections. In severe typhoid the fluoroquinolones are given for a minimum of 10 days. Patients with changes in mental status, characterized by delirium, obtundation and stupor, should be immediately evaluated for meningitis by examination of the cerebrospinal fluid. If the findings are normal and typhoid meningitis is suspected, adults and children should immediately be treated with high-dose intravenous dexamethasone in an initial dose of 3 mg/kg by slow i.v. infusion over 30 minutes and if, after six hours, 1 mg/kg is administered and subsequently repeated at six-hourly intervals for two days. In addition to antimicrobials. Patients with intestinal haemorrhage need intensive care, monitoring and blood transfusion. Intervention is not needed unless there is significant blood loss. Surgical intervention for suspected intestinal perforation is indicated. If perforation is confirmed, surgical repair should not be delayed longer than six hours. Metronidazole and gentamicin or ceftriazone should be administered before and after surgery.

**Keywords:** *Severe Typhoid - intestinal haemorrhage – typhoid meningitis – surgical interventin*

## 1. Introduction

Typhoid fever is caused by *Salmonella typhi*, a Gram-negative bacterium. Often less severe disease is caused by *Salmonella* serotype *paratyphi* A.[1]. Typhoid is spread via faeco-oral transmission. The infective dose (the minimum number of organisms required to cause infection) is relatively high at around 100,000 organisms. Typhoid may be spread from person-to-person by direct contact, or through ingestion of contaminated food or water. Infection becomes apparent after an incubation period of 10-14 days (range 5-21 days).[2] . Clinical characteristic typhoid fever as a syatemic illness are: 1) fever that is intermittent during the first week, but becomes sustained (lasting > 48 hours) thereafter; 2) headache (43-90%), 3) gastrointestinal symptoms such as abdominal pain/cramps, nausea and vomiting, constipation or diarrhoea. Other uncommon clinical signs include a relative bradycardia (a lower heart rate than would be expected in the presence of fever and illness), a skin rash ('rose spots') which are faint-pink spots 2-4cm in diameter which develop on the chest, abdomen and back, hepatosplenomegaly (enlarged liver and spleen. The symptoms of typhoid overlap with a number of other infectious diseases important in the tropical region such as malaria, dengue fever and leptospirosis.[3].

Diagnostic criteria of Typhoid Fever are *Confirmed enteric fever*: Fever  $\geq 38^{\circ}\text{C}$  for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi*. *Probable enteric fever*: Fever  $\geq 38^{\circ}\text{C}$  for at least three days, with a positive serodiagnosis or antigen detection test but without *S. Typhi* isolation. *Chronic carrier state*: Excretion of *S. typhi* in stools or urine (or repeated positive bile or duodenal string cultures) for longer than one year after the onset of acute enteric fever; sometimes, *S. typhi* may be excreted without any history of enteric fever.[4]

## 2. General management

Supportive measures are important in the management of typhoid fever, such as oral or intravenous hydration, the use of antipyretics, and appropriate nutrition and blood transfusions if indicated. More than 90% of patients can be managed at home with oral antibiotics, reliable care and close medical follow-up for complications or failure to respond to therapy. However, patients with persistent vomiting, severe diarrhoea and abdominal distension may require hospitalization and parenteral antibiotic therapy.[5].

## 3. Antimicrobial therapy

Efficacy, availability and cost are important criteria for the selection of first-line antibiotics to be used in developing countries. The fluoroquinolones are widely regarded as optimal for the

treatment of typhoid fever in adults. They are well tolerated and more rapidly and reliably effective than the former first-line drugs, chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole. The fluoroquinolones attain excellent tissue penetration, kill *S. typhi* in its intracellular stationary stage in monocytes/macrophages and achieve higher active drug levels in the gall bladder than other drugs. They produce a rapid therapeutic response, i.e. clearance of fever and symptoms in three to five days, and very low rates of post-treatment carriage. However, the emergence of MDR strains has reduced the choice of antibiotics in many areas. There are two categories of drug resistance: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (MDR strains) and resistance to the fluoroquinolone drugs. Resistance to the fluoroquinolones may be total or partial.

In developing countries Chloramphenicol or Thiamphenicol, are still widely prescribed for the treatment of typhoid fever. The optimal dosage is 75 mg per kg per day for 14 days divided into four doses.. The usual adult dose is 500 mg given four times a day. Oral administration gives slightly greater bioavailability than intramuscular or intravenous administration of the succinate salt. Trimethoprim-sulfamethoxazole, can be used orally or i.v. in adults at a dose of 160 mg TMP plus 800 mg SMZ twice daily for 14 days. Of the third-generation cephalosporins, oral cefixime 20 mg per kg per day for adults. Azithromycin in a dose of 500 mg (10 mg/kg) given once daily for seven days has proved effective in the treatment of typhoid fever in adults. A dose of 1 g per day for five days was also effective in adults. If intravenous antibiotics are required, i.v. cephalosporins can be given in the following doses: ceftriaxone, 50-75 mg per kg per day (2-4 g per day for adults) in one or two doses; cefotaxime, 40-80 mg per kg per day (2-4 g per day for adults) in two or three doses; and cefoperazone, 50-100 mg per kg per day (2-4 g per day for adults) in two doses. Ciprofloxacin, ofloxacin and pefloxacin are also available for i.v. use.

#### **4. Management of Severe Typhoid Fever**

In severe typhoid the fluoroquinolones are given for a minimum of 10 days (Table 1). Both outpatients and inpatients with typhoid fever should be closely monitored for the development of complications. Timely intervention can prevent or reduce morbidity and mortality. Typhoid fever patients with changes in mental status, characterized by delirium, obtundation and stupor, should be immediately evaluated for meningitis by examination of the cerebrospinal fluid. If the findings are normal and typhoid meningitis is suspected, should immediately be treated with high-dose intravenous dexamethasone in addition to antimicrobials. If dexamethasone is given in an initial dose of 3 mg/kg by slow i.v. infusion over 30 minutes and if, after six hours, 1 mg/kg is administered and subsequently repeated at six-hourly intervals on seven further occasions. Administering dexamethasone has been shown to reduce fatalities among such patients; however if used, patients must be monitored closely because dexamethasone may mask abdominal complications. Furthermore, steroid treatment beyond 48 hours may increase the relapse rate. Mortality can be reduced by some 80-90% in these high-risk patients.[1,3,7]. Once patients have clinically improved, treatment can be completed with oral antibiotics (e.g.oral ciprofloxacin). Intestinal bleeding, perforations or ulcerations are life-threatening and may require immediate fluid resuscitation, surgical interventions (e.g. closure, drainage of peritoneum, and/or small-bowel restriction for multiple-perforations) and broad-spectrum

antimicrobial coverage for polymicrobial peritonitis. Metronidazole and gentamicin or ceftriazone should be administered before and after surgery because a fluoroquinolone is not being used to treat leakage of intestinal bacteria into the abdominal cavity. Early intervention is crucial, and mortality rates increase as the delay between perforation and surgery lengthens.[7]

**Table1. Treatment of Severe Typhoid Fever.[1]**

Susceptibility	Optimal parenteral drug			Alternative effective parenteral drug		
	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 resistant	Fluoroquinolone	15	10–14	Ceftriaxone or cefotaxime	60 80	10–14
Quinolone resistant	Ceftriaxone or cefotaxime	60 80	10–14	Fluoroquinolone	20	7–14

## 5. Conclusion

Management of severe typhoid need to early diagnostic and appropriate administration of the sensitive antibiotic by IV and monitoring and control of the complication, such as dehydration, gastrointestinal bleeding and surgical intervention if perforation occure. Metronidazole and gentamicin or ceftriazone should be administered before and after surgery because a fluoroquinolone is not being used to treat leakage of intestinal bacteria into the abdominal cavity. Early intervention is crucial, and mortality rates increase as the delay between perforation and surgery lengthens.

## References

- [1]. WHO. 2003, Background document:The diagnosis, treatment and prevention of typhoid Fever, World Health Organization, Department of Vaccines and Biologicals, CH-1211 Geneva 27, Switzerland, Avilable from: [www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/), Accessed Oct 20, 2017.
- [2]. NICD. 2017, Typhoid – caused by *Salmonella* Typhi Frequently Asked Questions, Outbreak Response Unit, Division of Public Health Surveillance and Response Centre for Enteric Diseases, Available from: [http://www.nicd.ac.za/assets/files/Typhoid\\_FAQ.pdf](http://www.nicd.ac.za/assets/files/Typhoid_FAQ.pdf), Accessed Oct 20, 2017.

- [3]. Upadhyay R, Nadkar RM, Muruganathan A et al. 2015, API Recommendations for the Management of Typ, *Journal of The Association of Physicians of India*, Vol. **63**, November 2015.
- [4]. Bruschi JL. 2017, Typhoid Fever Workup, *Medscape*, Available from: <https://emedicine.medscape.com/article/231135-workup>, Accessed 20 Oct, 2017.
- [5]. WHO. 2011, Guidelines for the Management of Typhoid Fever, Available from: <http://apps.who.int/medicinedocs/documents/s20994en/s20994en.pdf>, Accessed Oct 19, 2017
- [6]. Bruschi JL, 2017, Typhoid Fever Medication, *Medscape*, Available from: <https://emedicine.medscape.com/article/231135-medication>, Accessed Oct 20, 2017.
- [7]. NICD. 2016, Typhoid: NICD recommendations for diagnosis, management and public health response, *Guidelines\_typhoid\_20160125*.