



# **TYPHOID**

## Management Guidelines 2022





## Medical Microbiology & Infectious Diseases Society of Pakistan

# Typhoid Management Guidelines – 2022

## Introduction

Typhoid fever is endemic in Pakistan. With the emergence of the extensively drug resistant *Salmonella Typhi*, its management has become a challenge. This document is intended to guide all physicians regarding the appropriate management of typhoid in the setting of high antimicrobial resistance.

## Presentation

Typhoid and paratyphoid fevers are commonly grouped together under the collective term 'enteric fever'. Typhoid fever is caused by *Salmonella enterica* serovar Typhi and paratyphoid fever is caused by either *Salmonella Paratyphi A*, *B*, or *C*. Both *S. Typhi* and *S. Paratyphi* cause a fecal oral transmitted systemic disease, however, *S. Paratyphi* causes a less severe illness.

Typhoid fever is an acute, life-threatening, febrile illness. The clinical syndromes associated with *S. Typhi* and *Paratyphi* are indistinguishable. Typhoid fever begins 7-14 days after ingestion of the organism. Signs and symptoms are likely to develop gradually — often appearing one to three weeks after exposure to the disease. 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.

The clinical presentation of typhoid fever varies from a mild illness with low grade fever, headache, fatigue, malaise, loss of appetite, cough, constipation and skin rash or rose spots to in some cases, a fatal complications such as intestinal perforations, gastrointestinal hemorrhages, encephalitis and cranial neuritis.

Any patient presenting with fever with no clear focus of infection in an endemic setting, for more than 3 days should be suspected to have typhoid fever.

In the early course of the disease, the patient is likely to experience:

- Fever that starts low and increases daily, possibly reaching as high as 104.9° F (40.5° C)
- Headache
- Coated tongue
- Weakness and fatigue
- Muscle aches
- Sweating
- Dry cough
- Loss of appetite and weight loss
- Abdominal pain
- Diarrhea or constipation
- Rash
- Abdominal distension

In the later course of the disease, if timely management is not initiated, the patient may become delirious and life threatening complications may develop. In some cases, signs and symptoms may return up to two weeks after the fever has subsided.

## Laboratory findings

- The criterion standard for diagnosis of typhoid fever has long been culture isolation of the organism. Cultures are widely considered 100% specific.
- Most patients with typhoid fever are usually anemic, have normal blood counts, a slightly raised erythrocyte sedimentation rate (ESR), occasional thrombocytopenia, and relative leucopenia. CRP is not required.
- Liver transaminase and serum bilirubin values usually rise to twice the reference range. LFTs should be done to differentiate from acute viral hepatitis, which can begin with non-localizing fever.
- Mild hyponatremia and hypokalemia are common.
- Dengue and malaria should also be ruled out

## Microbiological Diagnosis

- The culture of *S. Typhi* can be done from many body fluids such as blood, bone marrow, urine, rose spot biopsy extracts, duodenal aspirates and stool, while the blood culture remains the mainstay of definitive diagnosis
- Positive serological tests (such as Widal and Typhidot) are not recommended for diagnosis of enteric fever.

Blood culture is the gold standard test for the diagnosis of typhoid and must be sent before starting antibiotics

- Blood cultures are positive in 40-80% of cases usually early in the course of the disease. Culture of bone marrow aspirate is 90% sensitive until at least 5 days after commencement of antibiotics. However, this technique is extremely painful, which may outweigh its benefit.
- Cultures from stool are usually not positive in early disease.
- Empirical treatment for typhoid should not be commenced without obtaining blood cultures. Blood cultures can be taken even if patient is currently afebrile.
- Blood cultures can still be sent even if the patient is already on antibiotics.
- A blood culture report is available in around 7 days after sample submission in cases where there is no growth of any microorganisms.
- In case of a positive blood culture, a report with organism identification and antibiotic sensitivity testing will be available in as early as 3 to 4 days.
- A negative culture does not exclude typhoid and may warrant a repeat blood culture if the fever is not responding in 7-9 days of commencing treatment.
- The volume of blood cultured is one of the most important factors in the isolation of *S. Typhi* from typhoid patients.
  - At least 20ml of blood should be obtained from an adult patient and inoculated (10ml each) in to the aerobic and anaerobic blood culture bottles.
  - For children the following volumes are recommended in the single pediatric bottle:
    - 3-5 ml- for children < 5years
    - 5-10ml –from children 5-12 years
    - 10-15ml –from children >12 years
- A preliminary report of gram negative rods, which is followed by growth of oxidase negative non-lactose fermenters from a blood culture sent while suspecting enteric fever, is highly suggestive of *Salmonella* species and should be treated on the lines of typhoid fever

## Serological Tests

- Serological tests (Widal and Typhidot) are not recommended in the diagnosis of typhoid. Both have low sensitivity and specificity and do not provide information on antimicrobial sensitivity.

## Case Definition of Typhoid:

Probable/Suspected case of typhoid fever	A patient with documented fever (38°C and above) for at least 5 days prior to presentation, with rising trend in fever and having no other focus to explain the cause of the fever (e.g. UTI, pneumonia, abscess etc.) OR A clinically compatible case that is epidemiologically linked to a confirmed case of typhoid fever
Confirmed case of typhoid fever	A patient with persistent fever (38 °C or above) lasting 3 or more days and <i>S. Typhi</i> isolated on blood or bone marrow culture.
Chronic carrier	An individual excreting <i>S. Typhi</i> in the stool or urine for longer than one year after a blood culture confirmed episode of typhoid fever. In the absence of a culture confirmation of prior illness it is not possible to label a person as a carrier

**Note: Positive serological tests (such as Widal and TyphiDOT) are not recommended for diagnosis of enteric fever and are not included in case definitions of Typhoid**

The confirmed cases of typhoid fever can be classified as drug-sensitive/ non-resistant, multi-drug resistant (MDR), extensively drug resistant (XDR) or extended spectrum beta-lactamase positive typhoid fever, based on drug susceptibility patterns.

### Classification of Typhoid Fever Cases by Drug Resistance Status, Pakistan, 2018

Classification	Case Definition
Non-resistant typhoid fever	Typhoid fever caused by <i>S. Typhi</i> and or <i>S. Paratyphi</i> A, B or C strains which are sensitive to first-line drugs <sup>1</sup> and third generation cephalosporins <sup>2</sup> , with or without resistance to second-line drugs <sup>3</sup> .
Multi-drug resistant typhoid fever	Typhoid fever caused by <i>S. Typhi</i> and or <i>S. Paratyphi</i> A, B or C strains which are resistant to first-line drugs <sup>1</sup> , sensitive to third generation cephalosporins <sup>2</sup> , with or without resistance to second-line drugs <sup>3</sup> .
Extensively drug resistant typhoid fever	Typhoid fever caused by <i>S. Typhi</i> strains which are resistant to first and second-line drugs and 3 <sup>rd</sup> generation cephalosporins <sup>4</sup> .
ESBL positive typhoid fever <sup>4</sup>	Typhoid fever caused by <i>S. Typhi</i> strains which are resistant to third generation cephalosporins but may be sensitive to chloramphenicol, cotrimoxazole or fluoroquinolones.

<sup>1</sup>Chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole

<sup>2</sup>Cefixime is recommended by the International Academy of the Philippines (IAP) for uncomplicated typhoid fever. Ceftriaxone is recommended for complicated typhoid fever.

<sup>3</sup>Fluoroquinolones

<sup>4</sup>MMIDSP has added a further category to this classification on reports of *S. Typhi* strains that are resistant to third generation cephalosporins but sensitive to chloramphenicol, cotrimoxazole or fluoroquinolones.

## Management guidelines:

- In bacteraemic patients, automated blood cultures can turn positive as early as 4 hours, with final identification and susceptibility results being available in the following 48 hours.
- Two sets of blood culture are optimal before starting antibiotic therapy and in those patients who are already on antibiotics but not responding to therapy.
- Serological tests should never be ordered or relied upon to diagnose or rule out enteric fever.
- It is important to rule out malaria, dengue and other possible causes of febrile illness in a patient who presents with acute febrile illness of more than 3 days of duration
- After sending baseline investigations, including blood cultures, commence empirical treatment for suspected enteric fever with either oral cefixime or IV ceftriaxone depending on the severity of the disease.
- In the absence of a positive blood culture or if a blood culture shows no growth, re-evaluate the diagnosis and stop or modify antibiotics if not typhoid.
- Fever defervescence is prolonged in typhoid fever and may take 5-7 days to improve. Do not rush to change antibiotics, monitor for improvement in frequency and intensity of fever.
- The appetite and general condition of the patient may improve before improvement in fever is noticed.
- Monitor for complications like abdominal distension, tenderness, vomiting, alteration of GCS and laboratory parameters like bicytopenia.

## Treatment

- Supportive treatment:
  - Antipyretics as required

- Adequate rest, hydration, and correction of fluid-electrolyte imbalance
- Adequate nutrition: a soft, easily digestible diet should be continued unless the patient has abdominal distension or ileus
- In case of severe illness monitor blood pressure, blood sugar, electrolytes, hemoglobin, platelet counts and liver functions as indicated
- **Empiric treatment**
  - Antibiotic treatment should be started as soon as possible to prevent complications, relapse, and the development of chronic carriage.
  - Typhoid is usually treated with a single agent antibiotic.
  - It is important to obtain appropriate specimens before treatment so that antimicrobial susceptibilities can be determined to guide treatment.
  - Based on clinical status, start oral or intravenous empiric treatment, until blood culture results are available.
    - Oral Azithromycin or  
IV Carbapenem
  - If the initial therapy was PO, switch to IV Carbapenem if:
    - there are no clinical signs of improvement after 5 days of treatment or
    - any signs of complications appear
  - Once the results of blood culture are available, modify antibiotic regimen based on the final antibiotic sensitivity results. Refer to section on Definitive treatment for further details.
  - Refer the patient to a secondary or tertiary care centre, in cases where no clinical signs of improvement are not seen despite switching to IV antibiotics (for at least 48 hours) and blood cultures remain negative.
- **Definitive treatment**
  - **Susceptible typhoid or Non-resistant typhoid fever:** This includes typhoid caused by *S. Typhi* strains that are sensitive to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, third-generation cephalosporins and/or fluoroquinolones. Treatment can be de-escalated to any of the first-line options. Please refer to the table below for dosage. Complete 14 days of treatment.
  - **MDR typhoid fever:** This includes typhoid caused by *S. Typhi* strains that are resistant to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, and/or fluoroquinolones.

These strains are sensitive to third-generation cephalosporins. Treatment can be de-escalated to Cephalosporins in this scenario. IV antibiotics can be switched to oral cefixime. Please ensure at least 14 days of therapy with cephalosporins is completed. Shorter courses may lead to relapse.

- XDR typhoid fever: This includes typhoid caused by S. Typhi strains, that are resistant to all recommended antibiotics for typhoid fever, but is sensitive to carbapenems and azithromycin. In this scenario, proceed as follows:
  - **If the patient is clinically stable** start azithromycin with dose according to body weight.
  - For a patient weighing <60kg, give 1gm loading dose orally, followed by 500mg PO q24hr for 7-10 days.
  - For those weighing > 60kg - give PO 1 gm q24hr for 7-10 days
  - **If the patient is unable to take orally, is hemodynamically unstable, deteriorating rapidly or develops complications, admit or refer to a tertiary care centre. Choice of antibiotic in this situation would be:**
    - **Imipenem:** 500mg q6h for 10 or 14 days or
    - **Meropenem:** 1gm q8hr for 10 - 14 days or
    - **Ertapenem:** 1gm q24hr for 10 - 14 days

*Note: The treatment may be de-escalated to oral Azithromycin once the patient is clinically improving and is able to tolerate oral medication to complete a total of 14 days of therapy*

- **ESBL positive typhoid fever:** If the blood culture shows growth of an ESBL positive strain of S. Typhi that is resistant to third- generation cephalosporins and sensitive to carbapenems, azithromycin, as well to chloramphenicol, cotrimoxazole or fluoroquinolones, then chose one of the first line options, if the patient is clinically stable or de-escalate to the first line option after initial therapy with carbapenems or azithromycin. Complete 14 days of treatment.
- Always aim to switch from IV to PO, once the patient is clinically stable and is able to take orally. Also in case of isolation of a susceptible strain, aim to de- escalate from a broad spectrum to a narrow spectrum drug.
- Despite completion of treatment, patients should be monitored for relapse or complications for 3 months after treatment has commenced.



## Complicated typhoid:

- Suspected or culture proven enteric fever with jaundice, drowsiness, severe abdominal pain and intestinal haemorrhage, severe sepsis or septic shock.
- Patients with complicated enteric fever should be managed at tertiary care centres.

## Prevention:

Vaccines: Two vaccines against typhoid are currently available in Pakistan.

- o **A single dose of injectable Vi polysaccharide vaccine** for children > 2 years of age. Revaccination is needed every 3 years for continued protection.
- o **A single dose typhoid conjugate vaccine** is approved for use in children  $\geq$  6 months of age. Offers protection for at least 3 years to adults, children, and infants over 6 months of age. Revaccination schedule is under study at the moment.
- o Neither vaccine is 100 percent effective and would require repeat immunizations, as vaccine effectiveness diminishes over time.
- o Vaccinate everyone, including:
  - All household members of a confirmed case (including adults and children over 6 months of age)
  - All healthcare workers
  - All food handlers
- Because vaccines do not provide complete protection, or protection against other water/food borne infections following preventive strategies should be followed:
  - o Hand washing
  - o Boiling of water before consumption
  - o Avoid raw vegetables and fruits that cannot be peeled. When you eat raw fruit or vegetables that can be peeled, wash them thoroughly and peel them yourself. (Wash your hands with soap first.) Do not eat the peelings.
  - o Avoid foods and beverages from street vendors.
  - o Ask for drinks without ice unless the ice is made from boiled or treated water; avoid flavored ice and juice
  - o Consume foods that have been thoroughly cooked and served hot
  - o Control of flies: Ensure that cooked food is covered to protect it from flies.

## Antibiotic choices for treatment of typhoid

Antibiotic	Route	Adult dosage/day	Dosage: mg/kg/day	Duration in days
Azithromycin	Oral	Patient weight <60kg: 1gm loading dose PO, then 500mg q24hr for 7-10 days.	8-10 mg/kg	7 - 10
		Patient weight > 60kg: 1 gm q24hr		
Meropenem	IV	1 gm q8hr	60mg/kg/day: in 3 doses	10-14
Imipenem	IV	500mg q6hr or 1g q8hr	20-60mg/kg/day: in 3/4 doses	10-14
Ertapenem	IV	1 gm q24hr	-	10-14

### For Drug-sensitive Typhoid fever (if susceptibility result is available)

Antibiotic	Route	Adult dosage/day	Dosage: mg/kg/day	Duration in days
Ceftriaxone	IM, IV	1gm q12hr or 2 gm q24hr	50-75 mg/kg	10-14
Cefixime	Oral	400 mg q12hr	15-20 mg/kg: in 1-2 doses	10-14
Ciprofloxacin	Oral/IV	500 - 750 mg q12hr PO/400 mg q12hr IV	-	10-14
Chloramphenicol	Oral, IV	500 mg q6hr	50 mg/kg in 4 doses	14
Trimethoprim-Sulfamethoxazole	Oral, IV	160/800 mg q12hr	4-20 mg/kg: in 2 dose	14
Ampicillin/Amoxicillin	Oral, IV, IM	1000-2000 mg q6hr	75-100 mg/kg: in 4 doses	14

## References

- A. <https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/>
- B. Current Trends in the Management of Typhoid Fever. SP Kalra et al. MJAFI 2003; 59 : 130-135
- C. World Health Organization. (2003). Background document: the diagnosis, treatment and prevention of typhoid fever. Geneva: World Health Organization.  
<http://www.who.int/iris/handle/10665/68122>

- These guidelines have been made in reference to the currently available literature on typhoid and in consultation with Medical Microbiology and Infectious Diseases experts of the MMIDSP.
- For any queries in reference to these guidelines, please send an email at:  
[Mmidsp123@yahoo.com](mailto:Mmidsp123@yahoo.com), [gsmmidsp@gmail.com](mailto:gsmmidsp@gmail.com)
- For more information and FAQs, please refer to the section: FAQs on typhoid fever, on the MMIDSP website

### MMIDSP Officer Bearers:

President	General Secretary	Treasurer
Prof. Bushra Jamil (AKUH)	Dr Faisal Hanif (AM College)	Dr Shobha Lakshmi (NICVD)

Website: <https://www.mmidsp.com>    Twitter: [@MMIDSP](https://twitter.com/MMIDSP)    Facebook: [MMIDSP](https://www.facebook.com/MMIDSP)

# Simple steps to protect yourself from typhoid fever and extensively drug-resistant (XDR) typhoid fever

The bacteria that cause typhoid fever spread through contaminated food and water

**Protect yourself from typhoid fever:**

**Water:** bring to a rolling boil for 1 minute, or chlorinate, especially from open sources

**Food:** wash with safe water, peel and properly cook or boil. Do not eat food which you did not prepare if you are unsure of its safety

**Sanitation:** do not use open defecation

**Sanitation:** separate waste water from water for washing or food preparation

**Sanitation:** Wash your hands often, especially before eating and after using the toilet

**Sanitation:** Cover food when you are not eating to keep flies away

Seek prompt medical attention from a qualified doctor if you have the following symptoms

Symptoms appear on average 8-14 days after ingesting contaminated food or water

A fever higher than 38° C

Weakness/fatigue

Nausea, stomach pain, loss of appetite

Headache

Diarrhea, constipation

A rash of flat, rose-colored spots

If you are being treated for typhoid fever:

Do not prepare or serve food for other people

Ask your qualified health professional to vaccinate your children

**Protect yourself from XDR typhoid fever:**

Follow all the steps for typhoid fever, and additionally:

Only take medication prescribed by a qualified health professional

Before taking any medication, wait for your qualified health professional to complete necessary laboratory tests (these are called culture and antibiotic sensitivity test)

Always complete antibiotics courses prescribed by your qualified health professional

Consult your qualified health professional if your condition does not improve after taking medicine

Proper treatment for someone with XDR typhoid must be given at a health facility, not at home

## ٹائیفائیڈ (معیاری) بخار اور ادویات سے شدید درجہ مزاحم ٹائیفائیڈ بخار سے بچاؤ کے ساتھ اقدامات

ٹائیفائیڈ بخار کو پھیلانے والا جرثومہ (بیکٹریا) آلودہ غذا اور پانی کے ذریعے بیماری کا باعث بنتا ہے۔

**آپ خود کو ٹائیفائیڈ بخار سے محفوظ رکھ سکتے ہیں**

مکھیوں سے بچاؤ کیلئے کھانے والی چیزوں کو ڈھانپ کر رکھیں

**کھانا:** اپنی خوراک کو مکھیوں سے محفوظ رکھنے کے لئے ڈھانپ کر رکھیں۔ کھانے کی اشیاء کو صاف پانی سے دھوئیں۔ کچی سبزیاں اور چھل وغیرہ خود تیار کریں اور انہیں اچھی طرح پکا کر یا بال کر استعمال کریں۔ ایسی خوراک ہرگز استعمال نہ کریں جس کے محفوظ ہونے کا یقین نہ ہو۔

**پانی:** پانی کو (ایک منٹ تک) ابال کر یا کلورین کے ذریعے صاف کر کے استعمال کریں خصوصاً جب یہ غیر محفوظ ذرائع سے حاصل کیا گیا ہے۔

**ذاتی صفائی:** کھلے میں پاخانہ کرنے سے گریز کریں۔

**حفظان صحت اور ذاتی صفائی:** کھانا کھانے سے پہلے اور لیٹرین کے استعمال کے بعد اپنے ہاتھ صابن سے ضرور دھوئیں۔

### درجہ ذیل علامات ظاہر ہونے کی صورت میں فوری طور پر مستند معالج سے مشورہ کریں

اگر آپ ٹائیفائیڈ بخار میں مبتلا ہیں اور اپنا علاج کروا رہے ہیں تو



دوسروں کے لئے کھانا بنانے یا ان کو کھانا پیش کرنے سے گریز کریں

مستند عملہ صحت سے اپنے بچوں کو ٹائیفائیڈ سے بچاؤ کے حفاظتی ٹیکوں کے لئے رابطہ کریں



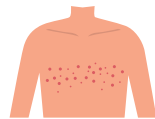
اگر تجویز کردہ ادویات استعمال کرنے کے باوجود آجکی طبیعت بہتر نہیں ہو رہی تو اپنے مستند معالج سے دوبارہ رابطہ کریں



شدید مزاحم ٹائیفائیڈ بخار میں مبتلا مریض کو ہسپتال میں داخل کروا کر علاج کروائیں



جسم پر سرخی مائل دانے ہوں



سر درد ہو



متلی، پیٹ میں درد یا جھوک میں کمی ہو جائے



کمزوری یا تھکاؤٹ محسوس ہو



پتلا پاخانہ یا قبض ہو



درجہ حرارت 38C سے زیادہ ہو

ٹائیفائیڈ بخار سے بچاؤ کے طریقوں پر عمل کے ساتھ ساتھ مندرجہ ذیل اضافی تدابیر اختیار کریں

کوئی بھی علاج شروع کرنے سے پہلے اپنے مستند معالج کو انتہائی ضروری لیبارٹری ٹیسٹ مکمل کر لینے دیں۔



صرف مستند اور اہل معالج کی تجویز کردہ ادویات کا استعمال کریں۔

مستند معالج کا تجویز کردہ اپنی ہائیڈک ادویات کا کورس مکمل کریں۔



# Medical Microbiology & Infectious Diseases Society of Pakistan



Academic Partner:



**SAMI Pharmaceuticals (Pvt.) Ltd.**<sup>®</sup>