Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Enteric Fever

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Introduction

Enteric fever is acute generalized infection of reticuloendothelial system with predilection for intestinal lymphoid tissue and gallbladder.

The term includes *typhoid fever caused by Salmonella typhi* (around 80% of all cases worldwide) and *paratyphoid fever caused by Salmonella paratyphi A or B* (20% of all cases). The bacterium is gram negative and nonlactose fermenting.

Diagnosis

- ☑ *Mainly clinical:* The most common cause of fever without focus.
  - *Infant to children up to 5 years:* Fever, vomiting, and diarrhea.
  - *Older children:* Fever in increasing trend (step ladder pattern) over 5–7 days, anorexia, abdominal pain, cough followed by toxic look, lethargy, tender abdomen, soft splenomegaly, hepatomegaly, and relative bradycardia.
  - *Rash:* Rose spots described in Western textbooks is almost never seen in Indian children.
- ☑ *Laboratory diagnosis*:
  - *Hemogram:* Total leukocyte count: normal or low, with neutrophilia and thrombocytopenia. Eosinopenia is remarkably consistent with typhoid fever. There may be mild elevation of transaminases.
  - *Culture and sensitivity:* It is the gold standard and the most important investigation for diagnosis. Automated blood culture systems like BACTEC have improved recovery and are cost-effective in the long run. *Salmonella* is an easy organism to culture and antimicrobial sensitivity results are important for treatment.
    - *Blood culture*: 90% yield in first week and up to 40% in the fourth week of illness. Send paired cultures with total volume of blood to be sent as 5–10 mL with a blood: broth ratio of 1:5.

Diagnosis

- Bone marrow culture is an important investigation in pyrexia of unknown origin (PUO) in later stages of the illness as it remains positive even after antibiotic therapy.
- Stool and urine cultures are not recommended due to poor yield.

- *Serology*: These tests are not diagnostic, may be supportive and should not be relied upon for patient management decisions.
  - *Widal test*: It detects presence of immunoglobulin M (IgM) and IgG antibodies against H (flagellar antigen) and O (somatic antigen) of *S. typhi* and *paratyphi A and B* in the second week of illness. Tube method is better than the slide method.

    Antibody titer of both O and H in range of 1:160 dilution or more is taken as a positive test. Fourfold rise in titer in paired samples 1 week apart is the conventional method, however, it is less practical.

    As sensitivity and specificity are low, widal may come false positive in malaria, rickettsial infection, or infection with other *Enterobacteriaceae*.

    It may come false negative in patients treated with prior antibiotics.
  - *Typhi dot/enzyme immune assay (EIA) test*: It detects IgM and IgG antibodies against 50 kd outer membrane protein antigen which is specific for *S. typhi*. Specificity is only 37% and anamnestic reactions may be seen in other infections. A Cochrane database review in 2017 concluded that the rapid diagnostic serologic tests need further robust evaluation.

Treatment

Choice of empirical therapy for typhoid fever is shown in **Table 1**.

TABLE 1: Choice of empirical therapy for typhoid fever.

Patient's condition	***First-line choice***	***Second-line choice***
Severe illness Indoor patient Any complications	Ceftriaxone	Cefotaxime (concomitant hepatitis) Aztreonam (penicillin allergy)
Outpatient department	Cefixime	Azithromycin (penicillin allergy)

Drug dosage guideline is presented in **Table 2**.

TABLE 2: Drug dosage guideline.

Drug	***Dose (mg/kg/day)***	***Maximum dose (per day)***
Ceftriaxone	100	4 g
Cefotaxime	150–200	8 g
Cefixime	20	1,200 mg
Azithromycin	20	1 g
Aztreonam	50–100	8 g

Duration of Treatment

Treat for at least 7 days after defervescence or a total of 14 days, whichever is later. Azithromycin is used for a total of 7 days.

Role of Steroids

Steroids are indicated only in severe illness. If the patient presents with shock, coma, or in altered sensorium, dexamethasone in the dose of 3 mg/kg followed by 1 mg/kg every 6 hours for 2 days may be given. Prolonged use of steroids can increase the relapse rate and cause adverse effects, hence use judiciously.

Delayed Defervescence

If by day 7 of antibiotics, defervescence has not occurred but child looks less toxic, there is increase in duration between fever spikes or quick response to antipyretics, same antibiotics can be continued till day 10.

Clinical Failure

No defervescence and child looks toxic with increase in fever spikes after 7 days of starting *optimal* treatment is clinical failure.

In such a scenario, rule out:

- ☑ Complications such as abscess formation and infection-associated hemophagocytic lymphohistiocytosis (HLH)
- ☑ Coinfections such as malaria and hepatitis A
- ☑ Drug fever or thrombophlebitis
- ☑ If the child was culture negative, review the diagnosis with careful history, physical examination, and repeat investigations.

Special Therapeutic Concerns

- ☑ *Culture positive report* empowers the clinician, gives confidence even in late defervescence and *prevents unnecessary use of azithromycin which must be kept as a reserve drug*.
- ☑ *Quinolones* are contraindicated in pediatric age group and *should not be used for treatment of enteric fever*.
- ☑ *Aminoglycosides* like amikacin *have no role in management* as their site of action is extracellular while *Salmonella* is an intracellular organism.
- ☑ In the era of antimicrobial resistance (AMR), it is very important that laboratories give drug sensitivity reports with minimum inhibitory concentrations (MICs) and its interpretation. *In enteric fever, MIC ≤1 for ceftriaxone is associated with excellent clinical outcome*. Rising ceftriaxone MICs are being reported from India. *MIC breakpoints for resistance to ceftriaxone are [≥4 as per Clinical and Laboratory Standards Institute (CLSI)] and [>2 as per European Committee on Antimicrobial Susceptibility Testing (EUCAST)]*. *Azithromycin* is the drug of choice in ceftriaxone resistant isolates. If such a child is hemodynamically unstable or the disease is severe, then *meropenem* may be used.

Relapse

Even after adequate treatment, enteric fever has a relapse rate of 5–20%. Recurrence of fever 2–3 weeks after its initial resolution is called relapse. It is usually milder. Treatment of relapse is with the same drug used for initial therapy. Relapse can be differentiated from reinfection only by molecular typing.

Carrier State

It is defined as an asymptomatic person who sheds *Salmonella* in stool or urine beyond 3 months of an episode of enteric fever. It is uncommon in pediatric age group hence post illness screening for *S. typhi* carriage is not recommended. If detected treat with trimethoprim-sulfamethoxazole (10 mg/kg/day for 6–12 weeks) or high dose amoxicillin (75–100 mg/kg/day for 4–6 weeks) to decrease the risk to close contacts.

Further Reading

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