IAP Task Force Report: Management of Enteric Fever in Children

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The timely appropriate management of typhoid fever, can considerably reduce both morbidity and mortality. General supportive measures like use of antipyretics, maintenance of hydration, appropriate nutrition and prompt recognition and treatment of complications are extremely important for a favorable outcome. The child should continue to have normal diet and no food should be restricted.

In areas of endemic disease 90% or more of typhoid cases can be managed at home with proper oral antibiotics and good nursing care(1). Close medical follow up is necessary to look for development of complications or failure to respond to therapy.

Patients with persistent vomiting, inability to take oral feed, severe diarrhea and abdominal distension usually require parenteral antibiotic therapy preferably in a hospital.

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Antimicrobial Therapy

Since 1990s *Salmonella typhi* has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin) and are known as Multi Drug Resistant typhoid fever (MDRTF). There are some reports of re-emergence of fully susceptible strain to first line drugs(2). But these reports are few and unless antibiotic sensitivity testing shows the organisms to be fully susceptible to first line drugs they are not advocated for empirical therapy in typhoid.

Fluoroquinolones are widely regarded as the most effective drug for the treatment of typhoid fever(3). But unfortunately, some strains of *S. typhi* have shown reduced susceptibility to fluoroquinolones(4,5). On routine disc testing with the recommended break points, organisms showing suspectibility to fluoroquinolones show poor clinical response to actual treatment. These organisms when tested by disc testing with nalidixic acid show resistance. So in other words resistance to nalidixic acid is a surrogate marker which predicts fluoroquinolones failure and can be used to guide antibiotic therapy. The resistance to fluoroquinolones may be total or partial. The nalidixic acid resistant *S typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones.

With the development of fluoroquinolones resistance third generation cephalosporins were used in treatment but sporadic reports of resistance to these antibiotics also followed(6). Recently, azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever(7). Aztreonam and imipenem are also potential third line drugs which are used recently(3).

There is now considerable amount of evidence from the long term use of fluro-

quinolones in children that neither they cause bone or joint toxicity nor impairment of growth.

Ciprofloxacin, ofloxacin, perfloxacin and fleroxacin are common fluoroquinolones proved to be effective and used in adults. In children the first two are only used in our country and there is no evidence of superiority of any particular fluroquinolones. Norfloxacin and nalidixic acid do not achieve adequate blood concentration after oral administration and should not be used. Fluoroquinolones have the advantage of lower rates of stool carriage than the first line drugs(8). However, fluoroquinolones are not approved by Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and is suffering from life threatening infection.

Of the third generation cephalosporins oral cefixime has been widely used in children(9-11). Amongst the third generation cephalosporins in injectable form ceftriaxone, cefotaxime and cefoperazone are used of which ceftriaxone is most convenient.

Fluoroquinolones like ofloxacin or ciprofloxacin are used in a dose of 15 mg/kg of body weight per day to a maximum of 20 mg/kg/day.

Of the oral third generation cephalosporins, oral cefixime is used in a dose of 15-20 mg per kg per day in two divided doses. Parenteral third generation cephalosprins include ceftri-

TABLE I–*Treatment of Uncomplicated Enteric Fever*

Susceptibility	First line oral drug			Second line oral drug		
	Antibiotic	Daily dose (mg/kg)	Days	Antibiotic	Daily dose (mg/kg)	Days
Fully sensitive	3rd Gen. Cephalosporin *e.g.,* Cefixime	15-20	14	Chloramphenicol Amoxicillin TMP-SMX	50- 75 75-100 8 TMP 40 SMX	14-21 14 14
Multidrug resistant	3rd Gen. Cephalosporin *e.g.,* Cefixime	15-20	14	Azithromycin	10-20	14

TABLE II–*Treatment of Severe Enteric Fever*

Susceptibility	First line parenteral drug			Second line parenteral drug		
	Antibiotic	Daily dose (mg/kg)	Days	Antibiotic	Daily dose (mg/kg)	Days
Fully sensitive	Ceftriaxone or Cefotaxime	50-75	14	Chloramphemicol Ampicillin TMP-SMX	100 100 8 TMP 40 SMX	14-21 14 14
Multidrug resistant	Ceftriaxone or Cefotaxime	50-75	14	Aztreonam	50-100	14

Messages

- Multidrug resistant typhoid cases, resistant to first line drugs, namely chloramphenicol, co-trimoxazole and ampicillin are reported since 1990. They need to be treated with second line drugs like third generation cephalosporins.
- Most of the typhoid cases can be managed at home with oral antibiotics and good nursing care.
- For severe cases with persistent vomiting, inability to take oral feeds, severe diarrhea, abdominal distension, parenteral antibiotic, will be needed preferably in a hospital.
- Though some strains have shown reemergence of sensitivity to first line drugs still it is too early for their recommendation in emperic therapy.
- The nalidixic acid resistant *S. typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones.
- Third generation cephalosporins, both oral and injectables are recommended for first line treatment. Of the oral third generation cephalosporins, cefixime and cefpodoxime proxelil are used commonly and of parenteral preparation ceftriaxone, cefotaxime, and cefoperazone are used, of which ceftriaxone is most convenient. Oral third generation cephalosporin is to be used in higher dose in typhoid fever.
- Azithromycin is used as an alternative agent in treatment of uncomplicated typhoid fever.
- Aztreonam and Imepenem are potential second line drugs.
- For life threatening infection resistant to all other recommended antibiotics fluoroquinolones may be used.

axone 50-75 mg per kg per day in one or two doses; cefotaxime 40-80 mg per kg per day in two or three doses and cefoperazone 50-100 mg per kg per day in two doses. Azithromycin is used in a dose of 10-20 mg per kg given once daily.

Fluoroquinolones are the most effective drug for treatment of typhoid fever. For nalidixic acid sensitive *S. typhi* (NASST) 7 days course is highly effective. Though shorter courses are advocated but they should be reserved for containment of epidemics. For nalidixic acid resistant *S. typhi* (NARST) 10-14 days course with maximal permitted dosage is recommended. Courses shorter than seven days are not satisfactory.

In case of uncomplicated typhoid oral third generation cephalosporin *e.g.*, cefixime should be the drug of choice as empiric therapy. If by 5 days there is no clinical improvement and the culture report is inconclusive add a second line drug *e.g.*, azithromycin or any other drug effective against *S. typhi* depending upon the sensitivity pattern of the area.

For complicated typhoid the choice of drug is parenteral third generation cephalosporin *e.g.*, ceftriaxone. In severe life threatening infection fluoroquinolones may be used as a last resort. Aztreonam and imepenem may also be used.

Combination therapy though practiced all over needs substantiation with adequate data from studies.

Tables I, II show various antibiotics used in the management of both complicated

and uncomplicated typhoid with different sensitivity patterns

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Annexure I

List of participants of the workshop organized by IAP Task Force on Guidelines for Diagnosis and Management of Enteric Fever in Children under IAP Action Plan 2006.

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