

## Role of Azithromycin in Enteric Fever

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**T**here is an urgent need to explore the utility and safety of alternate drugs in treatment of enteric fever due to emergence of multi-drug resistant (MDR) and nalidixic acid resistant (NARST) strains of *Salmonella typhi*. Azithromycin is a potentially useful drug in treatment of typhoid fever because of its high intracellular tissue penetration and a long elimination half life (72 hours). This systematic review from the Cochrane Library addresses the available evidence on the efficacy and safety of azithromycin in treating enteric fever.

### SUMMARY

Seven randomized trials enrolling 773 patients with uncomplicated (without overwhelming toxemia, intestinal hemorrhage, intestinal perforation, shock, psychosis, or convulsions) typhoid or paratyphoid fever (confirmed by blood, bone marrow, urine or stool culture) were included in this systematic review. Three trials each were conducted in Egypt and Vietnam, and one multicentric trial was reported from India. Three trials exclusively included adults, two included children, and two included both adults and children; all were hospital inpatients. Many of the cases included in the trials had infections with MDR or/and NARST strains. Two trials each compared azithromycin with ceftriaxone and ofloxacin, whereas one each compared it with ciprofloxacin, gatifloxacin and chloramphenicol. Azithromycin was used orally in dosage of 20 mg/kg/day in children and 500 mg to 1g for adults; the duration of treatment was 5-7 days. Compared with fluoroquinolones, azithromycin significantly reduced clinical failure (OR: 0.48, 95% CI: 0.26 to

0.89; 564 participants, 4 trials) and duration of hospital stay (mean difference: -1.04 days, 95% CI: -1.73 to -0.34 days; 213 participants, 2 trials). Compared with ceftriaxone, azithromycin significantly reduced relapse (OR 0.09, 95% CI: 0.01 to 0.70; 132 participants, 2 trials) but not other outcome measures. Few adverse events were reported, and most were mild and self-limiting. The authors concluded that azithromycin appears to be better than fluoroquinolones for treatment of enteric fever including drug-resistant strains and may be better than ceftriaxone in reducing relapse rates.

### COMMENTARY

#### *Are the results valid?*

The clinical question raised by this systematic review is relevant. The search of relevant studies was as per Cochrane group criteria and all studies up to August 2008 were included. Randomization was adequate but blinding was not done in any of the study. The outcomes assessed (clinical cure, fever clearance time and relapse rate) were functionally important for influencing the policy and recommendations. The heterogeneity of the studies was an issue because of the different drugs used and the different definitions of clinical cure. Also, the proportions of MDR and NARST strains (1.5%-83% and 52%-96.5%, respectively) varied between the trials.

Separate analysis was not done for pediatric age group because of the small sample size of the review and possibly because of lack of segregated data from the studies. However, there is no reason to believe that the result of the antibiotic therapy in children

**KEY MESSAGE**

- Azithromycin reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of typhoid fever in populations with multidrug resistant typhoid fever.

and adolescents would be different from adults. The results of the comparison of azithromycin with fluoroquinolones are rather more important for pediatric age group because of the concerns related to licencing of fluoroquinolones in this age group.

*How precise and clinically significant is the treatment effect?*

The review reported a 6.8% absolute reduction in risk of clinical failure with azithromycin in comparison to fluoroquinolones. In other words, we need to treat about 17 patients of enteric fever with azithromycin to prevent one treatment failure (Number needed to treat 'NNT'=17). There was also a decrease in the duration of hospital stay by an average of one day with the use of azithromycin. It may not be valid to comment on microbiological failure and relapse because of low occurrence of these events in either arm. In comparison to ceftriaxone, there was an absolute risk reduction of 13.6% i.e. 7 patients need to be treated with azithromycin to prevent one relapse (NNT=7). This appears reasonably good especially when the use of azithromycin was not associated with any serious adverse event and it has the convenience of oral usage. However, it is again to be noted that this result is also based on the analysis of a small number of patients ( $n=132$ ) from only two studies. Surprisingly, the fever clearance time with use of azithromycin was not different from any other drug despite the benefits in terms of other outcomes.

#### *Implications for Practice and Policy*

Evidence from this review show that azithromycin appears to be marginally better than fluoroquinolones in terms of reducing clinical failure and duration of hospital stay, and ceftriaxone in terms of reducing relapse. Azithromycin is recommended as a 2nd line drug in multi-resistant typhoid fever(1). The duration of 14 days treatment

with azithromycin recommended in this IAP document, however, seems to be a typographical error as none of the studies has used it beyond 7 days for treatment of typhoid fever(1).

The results of the review are however based on relatively small number of patients. Large trials involving pediatric patients are needed especially in outpatient settings to compare azithromycin with other first line drugs such as oral 3rd generation cephalosporins. The use of azithromycin should be restricted to children with confirmed diagnosis of enteric fever with inadequate response to the first line drugs such as fluoroquinolones or oral 3rd generation cephalosporins to prevent the emergence of resistant strains.

#### *Note*

A couple of issues were observed in reporting of the results of this systematic review. In the text of the review, the authors report at many places (including Table 5) that no serious adverse effect was reported in any of the subjects allocated to azithromycin or any other drug. However, in the forest plot (Analysis 2.6), they have shown 10 serious adverse events (7 with azithromycin and 3 with fluoroquinolones). Another issue is that the authors have reported the results for all outcomes in terms of 'Odd's ratio' and not 'Relative Risk' which is a more useful way to measure the results from prospective randomized studies.

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#### **REFERENCE**

1. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK; IAP Task Force. IAP Task Force Report: Management of enteric fever in children. *Indian Pediatr* 2006; 43: 884-887.