

## Efficacy and Safety of Azithromycin for Uncomplicated Typhoid Fever: An Open Label Non-comparative Study

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An open-labelled, non-comparative study was conducted in 117 children aged 2-12 years to evaluate the efficacy and safety of azithromycin (20mg/ kg/day for 6 days) for the treatment of uncomplicated typhoid fever. Of the patients enrolled based on a clinical definition of typhoid fever, 109 (93.1%) completed the study. Mean (SD) of duration of fever at presentation was 9.1(4.5) days. Clinical cure was seen in 102 (93.5%) subjects, while 7 were withdrawn from the study because of clinical deterioration. Mean day of response was 3.45±1.97. BACTEC blood culture was positive for *Salmonella typhi* in 17/109 (15.5%) and all achieved bacteriological cure. No serious adverse event was observed. Global well being assessed by the investigator and subjects was good in 95% cases which was done at the end of the treatment. Azithromycin was found to be safe and efficacious for the management of uncomplicated typhoid fever.

**Key words:** Azithromycin, Children, Management Typhoid fever.

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Widespread emergence of multidrug-resistant *S. typhi* has necessitated the search for other therapeutic options for typhoid fever. Fluoroquinolones have proven effective, but to date they are not recommended for use in children, and quinolone-resistant strains of *S. typhi* have been reported [1]. Azalides, are another class of antibiotics which have shown promise in the treatment of typhoid fever. Azithromycin, the first drug of this class and studies comparing the efficacy of azithromycin with cefixime in adults and children with typhoid fever have reported it to be safe and efficacious [2-4]. Few studies are exclusively reported in children [5,6]. We planned this open-labeled, study to assess the safety and efficacy of single daily dose of azithromycin for uncomplicated typhoid fever in children.

### METHODS

This multicentre study was conducted with prior approval of the study protocol from the Institutional Ethics Committee of both participating institutions. We planned to enroll 120 children from outpatient department of the two centres. Children aged 2-12 years with fever (axillary/oral temperature  $\geq 38.5^{\circ}\text{C}$ ) for at least 4 days with clinical features suggestive of uncomplicated typhoid fever (abdominal pain and tenderness, diarrhea or constipation, and hepatosplenomegaly) were enrolled. Only those children whose guardians were able to record body temperature and note down all information in the case diary for assessment during study visits and were telephonically available, were included. Written informed parental consent was taken from all subjects prior to enrolment.

Children with complicated typhoid fever (those with gastro-intestinal bleeding, suspected intestinal perforation, pneumonia, stupor, coma) or those taking antibiotics other than amoxicillin, ampicillin, cotrimaxazole or chloramphenicol in the last 4 days were excluded. Children with history of documented *S. typhi* and/or paratyphi infection within last 12 weeks or history of hypersensitivity reactions to azithromycin were also excluded.

On day of recruitment a complete medical, treatment and vaccination history was recorded. Complete physical examination was carried out and blood collected for complete blood count, malarial parasite, BACTEC blood culture. BACTEC blood culture was carried out as per standard procedure. Isolates were identified by standard microbiological methods and disc susceptibility testing was performed by the modified Kirby Bauer method. Study medication was dispensed and monitoring instruction provided to the patient. The subjects received azithromycin dispersible tablet/suspension at a dose of 20mg/kg/body weight in a single daily dose for 6 days. Paracetamol 15mg/kg body weight orally was used as antipyretic. No antibiotics other than the study medications were dispensed.

Children were treated at their home and reassessed in the out-patient department on day 4, day 7 and day 10 after the start of the treatment. On day 4 and day 7 temperature chart and symptom diary was evaluated with a complete physical examination. Drug compliance was assessed by history collecting the empty wrappers/bottles. The overall compliance

was categorized compliant if >80% of study medication consumed according to prescribed regimen.

Children who were BACTEC blood culture positive were evaluated on day 10 also for repeat blood culture. A window period of  $\pm 2$  days was admissible for each visit. If the temperature increased or the clinical condition of the patient worsened or there was a serious drug reaction, patient was taken off from the study and treated with ofloxacin (15mg/kg/day oral) or intravenous ceftriaxone (100mg/kg/day). All follow ups were carried out in the out-patient department of the hospital.

Primary efficacy end-point was clinical cure rate at day 10 and bacteriological cure rate in children who were initially bacteriological positive. Clinical cure was defined as defervescence/fever clearance and subsidence of clinical symptoms. Fever clearance/defervescence was considered as sustained period of 72 hours with axillary temperature less than 37°C (98.6°F). Secondary efficacy end points were (i) clinical improvement rates at second follow up visit i.e. day 7 in percentage of subjects who do not achieve fever clearance but who show signs and symptoms of improvement (ii) tolerability/global assessment of well being assessed by the clinician at second follow up visit (day 7) to be measured on a 4 point Likert Scale (excellent=3, good=2, fair=1, poor=0) as assessed by the investigator and as reported by the patient or his guardian.

## RESULTS

A total of 117 children were enrolled, but 8 were lost

**TABLE I** CLINICAL CHARACTERISTICS OF STUDY CHILDREN AT BASELINE AND FOLLOW UP

Clinical findings	Visit 1 (Day 0)		Visit 2 (Day 4)		Visit 3 (Day 7)		Visit 4 (Day 10)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Fever >38.4°C	109	100	29	26.6	12	11	7	6.4
Headache	74	67.8	17	15.5	2	1.8	0	0.0
Constipation/diarrhea	61	55.9	8	7.3	0	0.0	0	0.0
Poor appetite	39	35.7	32	29.3	6	5.5	3	2.7
Abdominal pain	69	63.3	15	13.7	2	1.8	0	0.0
Splenomegaly	27	24.7	22	20.1	16	14.6	7	6.4
Hepatomegaly	73	66.9	56	51.3	35	32.1	15	13.7

### WHAT THIS STUDY ADDS?

- Azithromycin as a single daily dose therapy for 6 days was safe and efficacious for clinically diagnosed uncomplicated typhoid fever.

to follow up and 109 (93.5%) 68 males completed the study. Mean (SD) age was 7.5 (2.81) years. Only 22 subjects had prior history of typhoid vaccination (duration from receiving vaccine was less than 3 years in 9). Mean (SD) of duration of fever at presentation was 9.1 (4.5) days, of which 51 (46.7) presented within 7 days, 35 (32.1%) within 8-10 days and 23 (21.1%) of more than 11 days duration.

Only 23 (21.1%) children had received antibiotics (amoxicillin) before presentation. **Table I** shows the baseline clinical characteristics and that on follow up. Treatment failure was noticed in 7 (6.4%) patients by day 10. These were withdrawn from the study. Three of them received intravenous ceftriaxone and 4 received oral ofloxacin as an add-on therapy and all improved by day 7-15 of enrollment. All the patients had more than 80% compliance. Mean day of response to fever was 3.4 (1.9) days.

BACTEC blood culture was positive in 17 (15.5%) patients, of which one patient did not complete the study. Hence, 16/109 were BACTEC blood culture positive (**Table II**). All of these patients achieved bacteriological cure at 10th day. Five of these subjects required add on antibiotics. We did not have any case of multidrug resistant typhoid. Resistance to quinolones including ciprofloxacin was significantly high. Clinical characteristics and response rates were similar in BACTEC blood culture positive and BACTEC blood culture negative cases. No serious adverse effects were observed except worsening of diarrhea in two subjects.

Clinical improvement on day 7 was seen in 92 (84.4%) subjects. Global well being assessed by the investigator on day 10 was excellent in 54.6%, good in 37.9%, fair in 4.62% and poor in 0.92%. Global well-being as assessed by the subjects was excellent 44.2%, good in 47.2%, fair in 3.7% and poor in 1.8%.

### DISCUSSION

Azithromycin appears to be an effective drug for treating uncomplicated typhoid fever in children with efficacy rate of more than 90%. Treatment failure rates of 9.3% have been observed in earlier studies on azithromycin [4]. Two other studies have reported a clinical cure rate of 82% and 92% [5,7]. Sensitivity pattern seen in our study is also similar to other Indian study demonstrating a nalidixic acid resistance of 88% [8], hence the importance of azithromycin.

This study was not a randomized controlled trial or a comparative trial which is one of the limitations of the study. Of the subjects studied, 21.1% received amoxicillin before enrolment, this could have influenced the BACTEC blood culture results, though culture positivity was similar in those received antibiotics and those who did not.

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*Competing interests:* AOP is Associate Vice President of Alembic Ltd, which manufactures azithromycin.

**TABLE II** *IN VITRO* SUSCEPTIBILITY OF *S.TYPHI* ISOLATES FROM BACTEC CULTURE POSITIVE SUBJECTS (N=17)

Drug	Susceptible (%)
Amoxicillin	100
Cefixime	100
Ceftriaxone	100
Chloramphenicol	100
Cotrimoxazole	94.4
Ofloxacin	83.3
Ciprofloxacin	77.7
Azithromycin	77.7
Nalidixic Acid	16.6

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