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Research Article

Comparative Effectiveness of Cefixime, Ceftriaxone, Aztreonam and Azithromycin in Culture-Confirmed Paediatric Enteric Fever: A Prospective Observational Cohort Study

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ABSTRACT

Background: Contemporary head-to-head evidence for antibiotics used in paediatric enteric fever is limited and treatment selection in routine care is influenced by illness severity, route, and susceptibility.

Methods: This prospective comparative observational cohort study included 200 children and adolescents aged 5–18 years with culture-confirmed uncomplicated enteric fever. Initial routine-care therapy was cefixime (n=58), ceftriaxone (n=54), aztreonam (n=32), or azithromycin (n=56). The primary outcome was time to sustained defervescence. Kaplan–Meier methods, log-rank testing, Holm-adjusted pairwise comparisons, and multivariable Cox regression were used. Secondary outcomes included cure, failure, rescue therapy, complications, relapse by day 28, length of stay, and laboratory normalisation.

Results: S. Typhi accounted for 183 (91.5%) isolates, and 193 (96.5%) index-drug results were susceptible. Median times to sustained defervescence were 92.7 hours with cefixime, 82.9 hours with ceftriaxone, 115.1 hours with aztreonam, and 78.0 hours with azithromycin (overall log-rank $p<0.001$). Compared with cefixime, adjusted defervescence rates were faster with ceftriaxone (hazard ratio [HR] 1.61, 95% CI 1.03–2.54) and azithromycin (HR 2.24, 95% CI 1.49–3.36). Clinical cure was 92.5% overall; cohort differences in cure, failure, rescue therapy, complications, and relapse were not statistically significant.

Conclusion: Fever-clearance time differed among treatment cohorts, whereas definitive clinical outcomes did not. Because treatment was not randomised and important baseline imbalances remained, the findings support susceptibility-guided, individualised treatment rather than causal ranking of the four antibiotics.

Keywords: Enteric fever, paediatric, cefixime, ceftriaxone, aztreonam, azithromycin, defervescence, observational cohort

INTRODUCTION

Enteric fever remains an important cause of morbidity among children and adolescents in endemic settings. Although improvements in water, sanitation, hygiene, and typhoid vaccination are central to prevention, timely antimicrobial therapy is still required to shorten illness and reduce complications.[1-3]

Therapeutic choices have changed as classical multidrug resistance and widespread fluoroquinolone non-susceptibility have emerged. Third-generation cephalosporins and azithromycin are now commonly used, yet recent Indian surveillance has detected ceftriaxone resistance and increasing azithromycin minimum inhibitory concentrations.[4] Local culture and susceptibility data therefore remain essential.

Cefixime offers an oral cephalosporin option, ceftriaxone provides predictable parenteral exposure, azithromycin achieves high intracellular concentrations, and aztreonam may be selected in specific clinical or allergy contexts. Earlier comparative studies support activity of these agents, but they were conducted under heterogeneous resistance patterns and used variable definitions of response.[5-13]

Routine-care comparisons are complicated by confounding by indication: children prescribed parenteral treatment may be more severely ill or more likely to require admission than those receiving oral treatment. We therefore compared prespecified effectiveness outcomes across four antibiotic exposure cohorts and adjusted the primary time-to-event analysis for major baseline differences.

METHODS

STUDY DESIGN AND SETTING

A prospective, comparative, observational cohort study was conducted in the Department of Paediatrics, Index Medical College and Hospital, Indore, Madhya Pradesh, with collaboration from Pharmacology, Microbiology, and Biostatistics. The study covered a protocol-defined three-year period after Institutional Ethical Committee approvals. Treatment was selected by the attending paediatrician, and the investigator did not randomise participants or assign a regimen. Reporting follows STROBE principles.[15]

PARTICIPANTS AND EXPOSURE COHORTS

Children and adolescents aged 5-18 years were eligible if they had fever of at least 38.0 °C for three or more consecutive days, blood culture positive for S. Typhi or S. Paratyphi A, uncomplicated disease, initial monotherapy with one of the four study antibiotics, and planned follow-up through day 28. Patients with severe or complicated enteric fever, major renal or hepatic dysfunction, immunocompromise, a concurrent bacterial infection requiring additional systemic treatment, known hypersensitivity, or more than 24 hours of effective pre-treatment were excluded according to the protocol.

Consecutive sampling was planned until 200 analysable participants were reached. Participants were grouped according to the initial antibiotic prescribed during routine care: cefixime, ceftriaxone, aztreonam, or azithromycin. The analysis file did not contain dose, route, frequency, duration, or exact dose-timing fields; the exposure should therefore be interpreted as the initial drug cohort rather than a fully specified regimen.

OUTCOMES AND FOLLOW-UP

The primary outcome was time from the first index-antibiotic dose to sustained defervescence, defined as the first temperature below 38.0 °C that remained below 38.0 °C for at least 48 hours without antipyretics. Participants who had not achieved sustained defervescence by day 7 were censored at 168 hours.

Secondary outcomes were defervescence by day 7, clinical cure, treatment failure, rescue or change of antibiotic, complications, relapse through day 28, length of stay, and days to laboratory normalisation. Clinical cure required resolution of fever and major symptoms without rescue therapy or complication. Treatment failure included persistent fever beyond day 7, deterioration, a complication, death, or treatment change for inadequate response.

Baseline demographic, clinical, care-context, microbiological, and susceptibility variables were recorded within 24 hours of the first dose. Temperature, symptoms, treatment changes, and complications were monitored during admission or outpatient care, with scheduled assessment on days 3, 7/end of treatment, 14, and 28.

STATISTICAL ANALYSIS

Continuous variables were summarised as mean ± SD and median (IQR), and categorical

variables as number and percentage. Baseline continuous variables were compared using one-way analysis of variance with Kruskal-Wallis sensitivity checks. Categorical variables were compared using Pearson chi-square or Fisher-Freeman-Halton Monte Carlo exact tests when expected counts were small.

Time to sustained defervescence was analysed using Kaplan-Meier methods and the overall log-rank test. Pairwise log-rank p values were corrected using the Holm method. A Cox proportional-hazards model with Breslow handling of ties included age, sex, duration of fever before treatment, baseline severity, prior antibiotic exposure, index-drug susceptibility, inpatient status, culture organism, and treatment cohort. A hazard ratio above 1 indicates faster defervescence. All tests were two-sided with $p<0.05$ considered statistically significant. The adjusted treatment-failure model was exploratory because only 15 failures occurred.

RESULTS

PARTICIPANT PROFILE

The analysis included 200 unique culture-confirmed participants: 58 received cefixime, 54 ceftriaxone, 32 aztreonam, and 56 azithromycin. The mean age was 11.2 years and 105 (52.5%) participants were male. S. Typhi accounted for 183 (91.5%) isolates and S. Paratyphi A for 17 (8.5%). The index drug was susceptible in 193 (96.5%) cases.

Age, weight, fever duration, baseline temperature, sex, prior antibiotic exposure, organism, and organomegaly were broadly similar among cohorts. However, baseline severity differed (p=0.008), ceftriaxone and aztreonam recipients were much more likely to be inpatients (p<0.001), and index-drug susceptibility was lower in the aztreonam cohort (p=0.002) (Table 1). Screening, refusal, and pre-enrolment exclusion counts were not available in the analysis file, so a participant flow before the 200 analysable records could not be reconstructed.

Table No. 1: Selected baseline characteristics by antibiotic cohort

Characteristic	Cefixime (n=58)	Ceftriaxone (n=54)	Aztreonam (n=32)	Azithromycin (n=56)	p value
Age, years	11.3±3.1	11.1±3.1	10.8±3.2	11.5±2.7	0.778
Baseline severity score	5.6±1.8	6.3±1.9	5.5±1.7	5.1±1.8	0.008
Male sex	31 (53.4%)	31 (57.4%)	19 (59.4%)	24 (42.9%)	0.357
Inpatient	16 (27.6%)	47 (87.0%)	28 (87.5%)	24 (42.9%)	<0.001
Prior antibiotic exposure	9 (15.5%)	13 (24.1%)	11 (34.4%)	17 (30.4%)	0.160
S. Paratyphi A	4 (6.9%)	5 (9.3%)	2 (6.2%)	6 (10.7%)	0.890
Index drug susceptible	57 (98.3%)	54 (100.0%)	27 (84.4%)	55 (98.2%)	0.002

Note: Continuous values are mean±SD; categorical values are n (%). One-way ANOVA or Pearson chi-square/Fisher-Freeman-Halton exact tests were used as appropriate.

TIME TO SUSTAINED DEFERVESCENCE

Median sustained-defervescence time was shortest with azithromycin (78.0 hours), followed by ceftriaxone (82.9 hours), cefixime (92.7 hours), and aztreonam (115.1 hours). The overall Kaplan–Meier curves differed (log-rank $\chi^2=30.41$, 3 df, p<0.001) (Table 2 and Figure 1).

After Holm correction, cefixime differed from ceftriaxone (p=0.047) and azithromycin (p=0.002); ceftriaxone differed from aztreonam (p<0.001); and azithromycin differed from aztreonam (p<0.001). Ceftriaxone and azithromycin did not differ significantly (p=0.300) and the cefixime-aztreonam comparison did not remain significant (p=0.067).

Table No. 2: Time to sustained defervescence by antibiotic cohort

Cohort	n	Events	Censored at day 7	Observed hours, mean ± SD	KM median, hours	KM median, days
Cefixime	58	54	4	102.9±27.1	92.7	3.86
Ceftriaxone	54	50	4	88.4±28.1	82.9	3.45

Aztreonam	32	27	5	118.0±28.0	115.1	4.80
Azithromycin	56	54	2	81.6±26.4	78.0	3.25

Note: KM, Kaplan-Meier. Overall log-rank $\chi^2=30.41$, df=3, $p<0.001$.

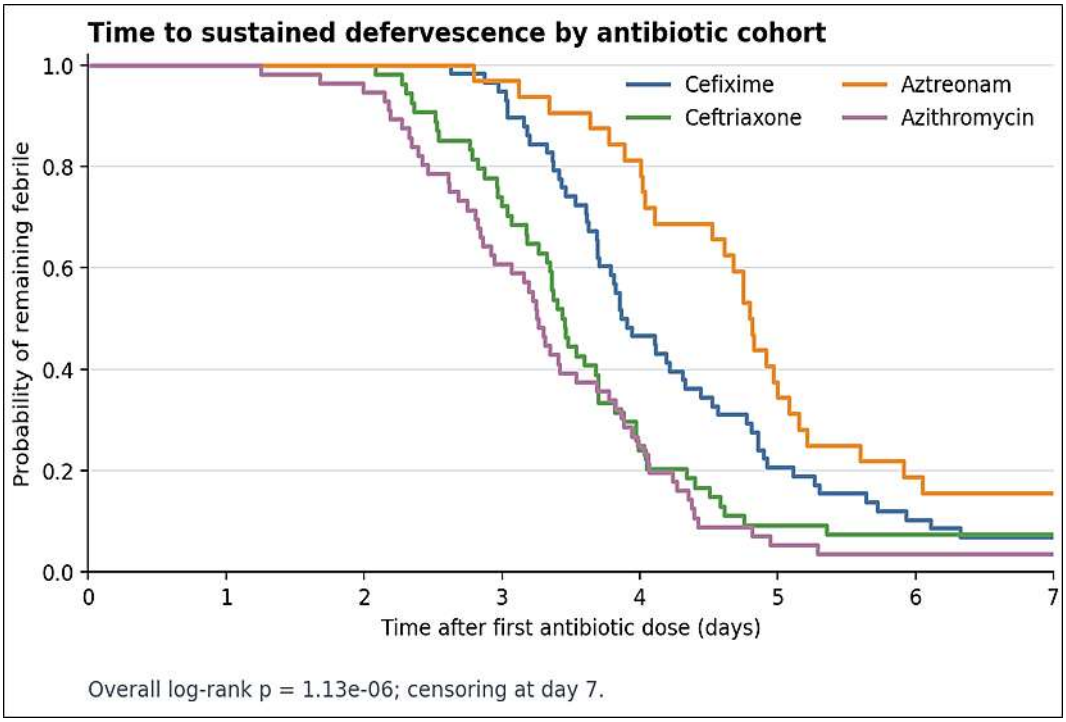

Figure No. 1: Kaplan-Meier probability of remaining febrile by antibiotic cohort

Note: A lower curve indicates faster sustained defervescence. Participants without sustained defervescence by day 7 were censored at 168 hours.

ADJUSTED DEFERVESCENCE ANALYSIS

In multivariable Cox regression, ceftriaxone was associated with a 61% higher instantaneous defervescence rate than cefixime (adjusted HR 1.61, 95% CI 1.03-2.54; p=0.038), while azithromycin was associated with more than twice the rate (HR 2.24, 95% CI 1.49-3.36; p<0.001). The aztreonam estimate suggested slower defervescence but included the null (HR 0.60, 95% CI 0.35-1.02; p=0.060). Higher baseline severity and prior antibiotic exposure were associated with slower defervescence, whereas index-drug susceptibility was associated with faster defervescence (Table 3).

Table No. 3: Multivariable Cox regression for sustained defervescence

Predictor	Adjusted HR	95% CI	p value
Ceftriaxone vs cefixime	1.61	1.03-2.54	0.038
Aztreonam vs cefixime	0.60	0.35-1.02	0.060
Azithromycin vs cefixime	2.24	1.49-3.36	<0.001
Age, per year	1.04	0.99-1.10	0.102
Male sex	1.15	0.85-1.57	0.359
Fever before treatment, per day	1.08	0.98-1.19	0.098
Baseline severity, per point	0.80	0.73-0.88	<0.001
Prior antibiotic exposure	0.70	0.49-1.00	0.047
Index drug susceptible	3.75	1.44-9.73	0.007
Inpatient	1.31	0.91-1.91	0.150
S. Paratyphi A	1.11	0.66-1.87	0.699

Note: Reference cohort: cefixime. HR>1 indicates faster sustained defervescence. Breslow handling of ties was used.

SECONDARY OUTCOMES

Clinical cure occurred in 185 (92.5%) participants and treatment failure in 15 (7.5%). Cure ranged from 84.4% in the aztreonam cohort to 96.4% in the azithromycin cohort, but the four-group comparison was not significant (p=0.255). Rescue therapy was used in 15 (7.5%), complications occurred in 6 (3.0%), and relapse by day 28 occurred in 8 (4.0%); none differed significantly among cohorts (Table 4).

Among inpatients, median stay was 3.0 days with azithromycin, 4.0 days with cefixime, and 6.0 days with both ceftriaxone and aztreonam (p<0.001). Median laboratory-normalisation time was shortest with azithromycin and longest with aztreonam (p<0.001). These outcomes were closely linked to admission and treatment-selection practices and should not be interpreted as direct pharmacological effects.

Table No. 4: Clinical and selected recovery outcomes by antibiotic cohort

Outcome	Cefixime	Ceftriaxone	Aztreonam	Azithromycin	p value
Defervescence by day 7	54 (93.1%)	50 (92.6%)	27 (84.4%)	54 (96.4%)	0.255
Clinical cure	54 (93.1%)	50 (92.6%)	27 (84.4%)	54 (96.4%)	0.255
Treatment failure	4 (6.9%)	4 (7.4%)	5 (15.6%)	2 (3.6%)	0.256
Rescue antibiotic	3 (5.2%)	4 (7.4%)	4 (12.5%)	4 (7.1%)	0.661
Complication	2 (3.4%)	2 (3.7%)	1 (3.1%)	1 (1.8%)	0.947
Relapse by day 28	5 (8.6%)	0 (0.0%)	1 (3.1%)	2 (3.6%)	0.122
Inpatient stay, days	4.0 (3.8-5.0)	6.0 (5.0-7.0)	6.0 (6.0-7.0)	3.0 (2.0-4.0)	<0.001
Laboratory normalisation, days	5.8 (4.9-6.9)	5.8 (5.0-6.6)	7.0 (6.0-7.8)	5.0 (4.3-6.0)	<0.001

Note: Categorical outcomes are n (%); inpatient stay and laboratory normalisation are median (IQR). Exact tests were used for sparse categorical outcomes; Kruskal-Wallis tests were used for continuous recovery outcomes.

DISCUSSION

This prospective observational cohort identified different fever-clearance trajectories across four routinely prescribed antibiotics. Azithromycin and ceftriaxone were associated with faster adjusted defervescence than cefixime, while the aztreonam estimate suggested a slower response. In contrast, high clinical cure was observed across cohorts and there was no statistically reliable difference in failure, rescue therapy, complications, or relapse.

Earlier paediatric trials reported high cure with both azithromycin and ceftriaxone,[7,11] comparable outcomes with cefixime and ceftriaxone,[8] and slower clinical response with aztreonam in historical comparisons.[9,10] The present findings are directionally consistent with those reports but add a standardised time-to-event analysis in routine care. Exact fever-clearance times should not be compared mechanically across studies because resistance patterns, case definitions, prior treatment, temperature schedules and definitions of sustained normothermia differ.

The association between index-drug susceptibility and faster defervescence was clinically plausible, but it was estimated from only seven non-susceptible observations and therefore remains imprecise. Its main implication is practical: cultures should be obtained before antibiotics whenever feasible, and therapy should be refined using individual susceptibility results and current institutional surveillance.[4,13,14]

Baseline severity and prior antibiotic exposure were independently associated with slower fever clearance. These factors may reflect greater illness burden, partial treatment before referral, altered microbial dynamics, or delayed effective therapy. Their influence illustrates why unadjusted treatment rankings are especially vulnerable to bias in non-randomised antimicrobial studies.

The absence of statistically significant differences in cure or failure should not be interpreted as therapeutic equivalence. Only 15 failures and 8 relapses occurred, producing wide uncertainty for rare outcomes. A future

multicentre pragmatic study should be powered for failure and relapse, document dose, route, duration, adherence and co-medications, and use randomisation or stronger causal-inference methods where feasible.

The study's strengths include culture confirmation, prespecified exposure cohorts, an objective sustained-defervescence definition, censoring at day 7, day-28 follow-up, multiplicity correction, and multivariable adjustment. Important limitations were the single-centre design, non-randomised prescribing, unequal cohort sizes, residual confounding, unavailable dose and duration data, lack of screening counts, and limited detail on laboratory trajectories. The proportional-hazards assumption also could not be evaluated with the depth expected in a larger confirmatory study.

These results should therefore be regarded as comparative-effectiveness estimates rather than evidence that one antibiotic is universally superior. Treatment selection should integrate susceptibility, severity, oral tolerance, route feasibility, prior exposure, monitoring capacity, and reliable follow-up.

CONCLUSION

In culture-confirmed uncomplicated paediatric enteric fever, time to sustained defervescence differed among routine-care antibiotic cohorts, with faster adjusted fever clearance in the ceftriaxone and azithromycin cohorts than in the cefixime cohort. Ultimate cure, failure, rescue-treatment, complication, and relapse rates did not differ significantly. Because the study was observational and clinically important baseline imbalances were present, the findings support susceptibility-guided, individualised treatment rather than causal ranking of the four agents.

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