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Research Article

Comparative Safety and Adverse Drug Reaction Profiles of Four Antibiotics in Paediatric Enteric Fever: A Prospective Pharmacovigilance Cohort Study

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ABSTRACT

Background: Safety comparisons among antibiotics used for paediatric enteric fever are limited, and adverse symptoms may be influenced by the infection, treatment route, and intensity of follow-up.

Methods: A prospective observational cohort included 200 children and adolescents aged 5–18 years with culture-confirmed uncomplicated enteric fever treated in routine care with cefixime (n=58), ceftriaxone (n=54), aztreonam (n=32), or azithromycin (n=56). Suspected adverse drug reactions (ADRs) were monitored through day 28. Causality was classified using Naranjo categories and severity using modified Hartwig–Siegel categories. Cohort comparisons used exact tests; an eight-predictor logistic model for any ADR was considered exploratory.

Results: Thirty-one participants (15.5%) experienced an ADR: 4/58 (6.9%) with cefixime, 7/54 (13.0%) with ceftriaxone, 4/32 (12.5%) with aztreonam, and 16/56 (28.6%) with azithromycin (p=0.016). Nausea/vomiting was most frequent (29.0% of ADRs), followed by diarrhoea and injection-site reactions (16.1% each). Twenty reactions (64.5%) were classified as probable, 21 (67.7%) as mild, and 2 (6.5%) as severe. Serious ADRs occurred in two participants. Compared with cefixime, adjusted odds were higher with azithromycin (OR 7.03, 95% CI 2.07–23.87) and ceftriaxone (OR 4.33, 95% CI 1.01–18.65), but estimates were imprecise.

Conclusion: Recorded ADR incidence differed across cohorts and was highest with azithromycin, although most reactions were mild or moderate. Non-randomised treatment selection, limited event counts, and possible differences in monitoring and symptom attribution preclude causal safety ranking.

Keywords: Enteric fever, paediatric, adverse drug reaction, pharmacovigilance, azithromycin, ceftriaxone, cefixime, aztreonam

INTRODUCTION

Enteric fever continues to affect children and adolescents in endemic regions, and antimicrobial treatment remains necessary even as vaccination, water, sanitation, and hygiene measures expand.[1-3] Treatment choices are increasingly shaped by changing susceptibility, with third-generation cephalosporins and azithromycin commonly used in contemporary practice.[4]

Effectiveness alone is insufficient for choosing therapy. Oral and parenteral agents differ in

gastrointestinal tolerability, hepatic monitoring needs, injection-site burden, feasibility, and the intensity with which adverse symptoms are observed. In enteric fever, nausea, abdominal discomfort, diarrhoea, rash, and biochemical abnormalities may also arise from the illness itself, complicating attribution to the medicine.

Structured causality and severity methods can improve consistency in pharmacovigilance. The Naranjo algorithm categorises the likelihood that an event is drug related, while the modified Hartwig-Siegel scale grades clinical severity according to treatment changes, additional therapy, and consequences such as prolonged admission.[5,6] These methods support transparent comparison but do not remove confounding or replace clinical judgment.

We therefore described the incidence, pattern, seriousness, causality, and severity of ADRs across four routine-care antibiotic cohorts and explored associations between participant characteristics, care context, and recorded ADR occurrence.

METHODS

STUDY DESIGN AND PARTICIPANTS

This prospective pharmacovigilance analysis was embedded within a comparative observational cohort in the Department of Paediatrics, Index Medical College and Hospital, Indore, Madhya Pradesh. Children and adolescents aged 5-18 years with culture-confirmed uncomplicated S. Typhi or S. Paratyphi A infection were followed through day 28. The treating paediatrician selected cefixime, ceftriaxone, aztreonam, or azithromycin as initial routine-care monotherapy; no treatment was assigned by the investigator.

Protocol exclusions included complicated or critical illness, known hypersensitivity to the selected antibiotic, severe renal or hepatic dysfunction likely to affect treatment or safety assessment, immunocompromise, a concurrent bacterial infection requiring another systemic antibiotic, and more than 24 hours of effective pretreatment. The analysis file contained 200 complete core records but did not include screening and exclusion counts.

SAFETY ASSESSMENT

Suspected ADRs were recorded during inpatient or outpatient monitoring and scheduled assessments on days 3, 7/end of treatment, 14, and 28. A suspected ADR was defined as a noxious and unintended response considered potentially related to the index antibiotic. Recorded fields included reaction type, seriousness, causality category, and severity category.

Causality was classified using the Naranjo algorithm as probable or possible in the observed dataset.[5] Severity was graded with modified Hartwig-Siegel categories as mild, moderate, or severe.[6] Seriousness was recorded separately. Because the available analysis file did not include dose, route, treatment duration, co-medications, exact onset time, dechallenge details, or laboratory values, the present paper analyses the coded safety outcomes rather than independently re-adjudicating individual reports.

STATISTICAL ANALYSIS

ADR incidence was reported as number and percentage within each treatment cohort. Cohort differences were assessed using Pearson chi-square or Fisher-Freeman-Halton Monte Carlo exact tests when cell counts were small. Reaction type, Naranjo category, and Hartwig-Siegel severity were summarised among the 31 participants with an ADR.

An exploratory maximum-likelihood logistic model evaluated any ADR using treatment cohort, age, sex, baseline severity score, prior antibiotic exposure, and inpatient status. Cefixime was the treatment reference. With 31 events and eight coefficients, the model had limited event-per-variable density; estimates and nominal p values were therefore interpreted cautiously. All tests were two-sided with $p<0.05$ used as a descriptive threshold rather than proof of causal drug effects.

RESULTS

PARTICIPANT AND CARE CONTEXT

Among 200 participants, 58 received cefixime, 54 ceftriaxone, 32 aztreonam, and 56 azithromycin. Mean age was 11.2 years, 105 (52.5%) were male, and 115 (57.5%) were managed as inpatients. Inpatient proportions differed substantially: 27.6% with cefixime, 87.0% with ceftriaxone, 87.5% with aztreonam, and 42.9% with azithromycin ($p<0.001$). Prior antibiotic exposure was recorded in 50 (25.0%) participants. These care-context differences are relevant because monitoring intensity, route-related reactions, and symptom reporting may vary by setting.

ADR INCIDENCE AND SERIOUSNESS

Thirty-one participants (15.5%) experienced at least one recorded ADR. Incidence differed among cohorts (p=0.016) and was highest with azithromycin (28.6%), followed by ceftriaxone (13.0%), aztreonam (12.5%), and cefixime (6.9%) (Table 1). Two serious ADRs were recorded-one in a ceftriaxone recipient and one in an azithromycin recipient-with no significant cohort difference (p=0.677).

Table No. 1: Adverse drug reactions by antibiotic cohort

Safety outcome	Cefixime (n=58)	Ceftriaxone (n=54)	Aztreonam (n=32)	Azithromycin (n=56)	p value
Any ADR	4 (6.9%)	7 (13.0%)	4 (12.5%)	16 (28.6%)	0.016
Serious ADR	0 (0.0%)	1 (1.9%)	0 (0.0%)	1 (1.8%)	0.677

Note: Values are n (%). ADR, adverse drug reaction. Exact testing was used when expected counts were small**.**

REACTION PATTERN, CAUSALITY AND SEVERITY

Nausea or vomiting was the most frequent recorded reaction (9/31; 29.0%). Diarrhoea and injection-site reactions each accounted for 5/31 (16.1%), while abdominal discomfort, elevated transaminases, and rash each accounted for 4/31 (12.9%) (Table 2). The six categories accounted for all 31 coded ADRs.

Twenty events (64.5%) were classified as probable and 11 (35.5%) as possible by Naranjo category. By modified Hartwig-Siegel severity, 21 (67.7%) were mild, 8 (25.8%) moderate, and 2 (6.5%) severe (Table 3).

Table No. 2: Types of recorded adverse drug reaction

ADR type	Number	Percentage of ADRs
Nausea/vomiting	9	29.0%
Diarrhoea	5	16.1%
Injection-site reaction	5	16.1%
Abdominal discomfort	4	12.9%
Elevated transaminases	4	12.9%
Rash	4	12.9%

Note: Percentages use the 31 participants with an ADR as the denominator; the coded categories sum to 31.

Table No. 3: Causality and severity classifications among participants with an ADR

Assessment	Category	Number	Percentage of ADRs
Naranjo causality	Probable	20	64.5%
Naranjo causality	Possible	11	35.5%
Hartwig-Siegel severity	Mild	21	67.7%
Hartwig-Siegel severity	Moderate	8	25.8%
Hartwig-Siegel severity	Severe	2	6.5%

Note: ADR, adverse drug reaction. Causality and severity were coded using the Naranjo and modified Hartwig-Siegel frameworks, respectively.

EXPLORATORY ADJUSTED ANALYSIS

Compared with cefixime, the adjusted odds of a recorded ADR were higher with azithromycin (OR 7.03, 95% CI 2.07-23.87; p=0.002) and ceftriaxone (OR 4.33, 95% CI 1.01-18.65; p=0.049). The aztreonam estimate was elevated but imprecise (OR 4.40, 95% CI 0.86-22.53; p=0.076). Inpatient status was associated with lower recorded ADR odds (OR 0.35, 95% CI 0.14–0.92; p=0.033), while age, sex, severity, and prior antibiotic exposure were not significant (Table 4).

Table No. 4: Exploratory multivariable model for any recorded ADR

Predictor	Adjusted OR	95% CI	p value
Ceftriaxone vs cefixime	4.33	1.01-18.65	0.049
Aztreonam vs cefixime	4.40	0.86-22.53	0.076
Azithromycin vs cefixime	7.03	2.07-23.87	0.002
Age, per year	1.05	0.91-1.20	0.494
Male sex	0.98	0.43-2.24	0.958
Baseline severity, per point	0.93	0.74-1.16	0.518
Prior antibiotic exposure	0.51	0.19-1.42	0.199
Inpatient	0.35	0.14-0.92	0.033

Note: Reference cohort: cefixime. OR, odds ratio. With 31 events and eight coefficients, estimates are exploratory and confidence intervals are wide.

DISCUSSION

This structured safety analysis found an overall recorded ADR incidence of 15.5%, with a statistically significant difference among treatment cohorts. The azithromycin cohort had the highest crude incidence, and its adjusted odds remained elevated relative to cefixime. Most reactions were mild or moderate, and only two were classified as serious or severe.

Gastrointestinal events formed the largest share of the safety profile. Nausea or vomiting, diarrhoea, and abdominal discomfort together accounted for 58.0% of recorded ADRs. These symptoms are clinically plausible during antimicrobial therapy but can also occur as manifestations of enteric fever, making attribution difficult without detailed timing, dose, dechallenge, and co-medication information. Elevated transaminases and rash were less frequent but remain relevant for clinical monitoring.

Injection-site reactions represented route-related harm and occurred in the context of parenteral care. Safety comparisons should therefore consider not only systemic pharmacology but also administration burden, vascular access, local reactions, and monitoring requirements. Conversely, oral treatment may permit more active patient or caregiver reporting of gastrointestinal symptoms outside the inpatient environment.

The lower adjusted odds of recorded ADRs among inpatients should not be interpreted as a protective effect of admission. It may reflect selection, route, differential documentation, competing disease symptoms, or differences in the threshold for coding an event as drug related. The finding reinforces that recorded ADR incidence is partly a property of the surveillance process as well as the medicine.

The Naranjo assessment classified nearly two-thirds of events as probable, and the Hartwig-Siegel distribution indicated that most required little or modest clinical intervention.[5,6] These structured categories increase reproducibility but do not eliminate observer judgment. Rechallenge is rarely appropriate in paediatric antimicrobial care, and alternative causes such as infection-related symptoms may remain unresolved.

Previous paediatric comparative trials generally reported favourable tolerability with azithromycin and ceftriaxone, but safety definitions and event ascertainment varied and some trials were not powered for uncommon harms.[7] Contemporary treatment recommendations appropriately balance effectiveness, susceptibility, feasibility, and toxicity rather than selecting therapy on a single safety outcome.[8,9] The present results support counselling about gastrointestinal symptoms and clinically indicated liver monitoring with azithromycin, as well as local and parenteral-care monitoring with ceftriaxone or aztreonam.

Strengths include prospective follow-up through day 28, four defined exposure cohorts, complete coded safety fields, and use of recognised causality and severity frameworks. Limitations include non-randomised treatment selection, a single centre, only 31 ADRs, broad confidence intervals, absence of dose and duration data, no coded co-medications or exact onset times, possible overlap between infection symptoms and ADRs, and potential differences in detection between inpatient and outpatient care. The adjusted model was exploratory and may be overfitted.

Accordingly, the results describe observed pharmacovigilance signals rather than causal comparative toxicity. Replication should use

active surveillance with time-stamped events, independent adjudication, exposure dose and duration, co-medications, laboratory trajectories, and standardised follow-up across care settings.

CONCLUSION

Recorded ADR incidence differed across the four antibiotic cohorts and was highest in the azithromycin group, but most reactions were mild or moderate. Gastrointestinal reactions predominated, while serious or severe events were uncommon. Because treatment and care setting were not randomised, event counts were limited, and surveillance intensity may have differed, the findings should guide counselling and monitoring rather than establish a causal safety hierarchy.

REFERENCES

1. World Health Organization. Typhoid [Internet]. Geneva: WHO; 2023. [cited 2026 Jul 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/typhoid
2. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. Lancet. 2015;385(9973):1136-1145. Doi: 10.1016/S0140-6736(13)62708-7.
3. John J, Bavdekar A, Rongsen-Chandola T, Dutta S, Gupta M, Kanungo S, *et al*. Burden of typhoid and paratyphoid fever in India. N Engl. J Med. 2023;388(16):1491-1500. Doi: 10.1056/NEJMoa2209449.
4. Sahai N, Jacob JJ, Arunachalam DK, Das BK, Kapil A, Pandey S, *et al*. Antimicrobial susceptibility trends of S. Typhi and S. Paratyphi in a post-COVID-19 pandemic India, from a multicenter surveillance network. Sci Rep. 2025;15:13777. Doi: 10.1038/s41598-025-93170-7.
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245. Doi: 10.1038/clpt.1981.154.
6. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49(9):2229-2232. Doi: 10.1093/ajhp/49.9.2229.
7. Frenck RW Jr, Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, *et al*. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis. 2000;31(5):1134-1138. Doi: 10.1086/317450.
8. Kuehn R, Stoesser N, Eyre D, Darton TC, Basnyat B, Parry CM. Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins. Cochrane Database Syst. Rev. 2022;11:CD010452. Doi: 10.1002/14651858.CD010452.pub2.
9. Parry CM, Qamar FN, Rijal S, McCann N, Baker S, Basnyat B. What should we be recommending for the treatment of enteric fever? Open Forum Infect Dis. 2023;10(1):S26-S31. Doi: 10.1093/ofid/ofad179.
10. Indian Council of Medical Research. National ethical guidelines for biomedical and health research involving human participants. New Delhi: ICMR; 2017.