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Azithromycin Versus Doxycycline for Pediatric Scrub Typhus: A Randomized Controlled Trial Comparing Clinical Efficacy and Safety Profiles

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KEYWORDS

Scrub typhus, Azithromycin, Doxycycline, Pediatric, Randomized controlled trial, Orientia tsutsugamushi

ABSTRACT:

Background: Scrub typhus remains a significant cause of febrile illness in children across endemic regions, with doxycycline being the conventional treatment despite safety concerns. This study compared the efficacy and safety of azithromycin versus doxycycline in pediatric scrub typhus.

Methods: A randomized controlled trial was conducted with 50 children (1-12 years) with confirmed scrub typhus, allocated to receive either single-dose azithromycin (10 mg/kg) or 7-day doxycycline (4.4 mg/kg/day). Primary outcome was time to fever defervescence; secondary outcomes included treatment failure rates, complications, adverse drug reactions (ADRs), and hospitalization duration.

Results: The azithromycin group demonstrated significantly faster fever resolution (24.5 ± 6.2 hours) compared to doxycycline (36.8 ± 8.4 hours; $p = 0.003$). Treatment failure occurred in 4% of azithromycin recipients versus 12% with doxycycline ($p = 0.29$). Complications were less frequent with azithromycin (8% vs. 20%; $p = 0.23$), and hospital stays were shorter (3.1 ± 1.0 vs. 4.5 ± 1.8 days; $p = 0.02$). ADRs, including vomiting (4% vs. 20%; $p = 0.04$) and transaminitis (0% vs. 12%; $p = 0.04$), were significantly lower in the azithromycin group.

Conclusion: Azithromycin showed superior clinical efficacy, faster recovery, and better tolerability than doxycycline in pediatric scrub typhus. These findings support its use as a first-line therapy, particularly in settings where doxycycline-related adverse effects or resistance are concerning. Further large-scale studies are warranted to validate these results.

Introduction

Typhus, caused by *Orientia tsutsugamushi*, is a vector-borne disease endemic in regions of Asia, including India (1). Scrub typhus presents with non-specific symptoms such as high-grade fever, headache, and myalgia, often complicating early diagnosis (2). In children, delayed treatment can lead to severe complications like meningitis, pneumonia, or multi-organ dysfunction (3). Doxycycline and azithromycin are the primary treatments, but resistance patterns and efficacy in pediatric populations remain understudied (4).

Doxycycline, a tetracycline derivative, has been the traditional first-line therapy due to its cost-effectiveness and broad-spectrum activity (5). However, its use in children raises concerns about dental discoloration and bone growth suppression, though short-term courses are generally considered safe (6). Azithromycin, a macrolide, offers advantages like better tolerability and a

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shorter treatment duration, making it a potential alternative (7). Recent studies suggest azithromycin may achieve faster fever resolution in pediatric scrub typhus, but comparative data are limited (8).

The rationale for this randomized controlled trial (RCT) stems from the lack of robust evidence comparing early clinical responses to azithromycin versus doxycycline in children. Early fever defervescence is a critical marker of treatment efficacy, as prolonged fever correlates with complications (9). Additionally, scrub typhus-endemic regions often overlap with tuberculosis (TB)-endemic areas, where doxycycline is also used for TB prophylaxis (10). Unnecessary doxycycline exposure could contribute to antibiotic resistance, underscoring the need for alternative therapies like azithromycin (11).

This study aims to compare early fever resolution and treatment outcomes between azithromycin and doxycycline in pediatric scrub typhus. By evaluating recovery rates, complications, and adverse drug reactions, the findings will guide evidence-based treatment choices in endemic regions. The results may also inform policies to minimize doxycycline overuse, particularly in TB co-endemic areas.

Materials and Methods

Study Design and Setting: A randomized controlled trial was conducted at a tertiary care hospital in a scrub typhus-endemic region. The study population consisted of children aged 1–12 years presenting with acute febrile illness and laboratory-confirmed scrub typhus. Participants were randomly allocated into two treatment groups using a computer-generated randomization sequence to ensure equal distribution of baseline characteristics.

Study Participants: Children meeting the inclusion criteria—high-grade fever (≥38.5°C) for ≥5 days, clinical features suggestive of scrub typhus (eschar, rash, or lymphadenopathy), and positive IgM ELISA for Orientia tsutsugamushi—were enrolled after obtaining written informed consent from parents/guardians. Exclusion criteria included severe organ dysfunction, prior antibiotic use (within 48 hours), and known hypersensitivity to macrolides or tetracyclines.

Interventions: Group A received a single oral dose of azithromycin (10 mg/kg), while Group B received oral doxycycline (4.4 mg/kg/day in two divided doses for 7 days). Both drugs were administered under supervision, and compliance was monitored. Supportive care, including antipyretics and hydration, was standardized for both groups.

Data Collection and Outcome Measures: Baseline demographic, clinical, and laboratory data (complete blood count, liver function tests, and serum IgM titres) were recorded. The primary outcome was time to fever defervescence (defined as temperature <37.5°C for 24 hours without antipyretics). Secondary outcomes included treatment failure (persistent fever after 72 hours), complications (e.g., pneumonia, meningitis), and adverse drug reactions (gastrointestinal symptoms, rash). Follow-up assessments were conducted on days 3, 7, and 14.

Statistical Analysis: Descriptive statistics (mean, SD, percentages) summarized baseline data. The independent t-test compared continuous variables (e.g., fever duration), while the chi-square test analyzed categorical outcomes (e.g., complication rates). A p-value <0.05 was considered statistically significant. Kaplan-Meier analysis assessed time-to-fever resolution, and Cox regression adjusted for confounding variables. All analyses were done using SPSS version 26.0.

Ethical Considerations: The institutional ethics committee approved the study. Parents/guardians received detailed information about the study, and participation was voluntary. Confidentiality was maintained, and adverse events were reported promptly.

Results

Among the 50 randomized children, baseline demographics and clinical features were comparable between the azithromycin (n = 25) and doxycycline (n = 25) groups. Mean age was 7.2 ± 2.5 years versus 6.8 ± 3.1 years (p = 0.62), and the proportion of males was 56% versus 48% (p = 0.58). The mean duration of fever at enrolment was 5.3 ± 1.2 days in the azithromycin group and 5.1 ± 1.4 days in the doxycycline group (p = 0.71). Clinical signs were similarly distributed: eschar was present in 32% versus 36% (p = 0.77), lymphadenopathy in 44% versus 40% (p = 0.78), and rash in 24% versus 28% (p = 0.75). No statistically significant differences were observed across variables, indicating well-balanced groups at baseline.

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Fever subsided significantly faster with azithromycin than with doxycycline: the mean time to defervescence was 24.5 ± 6.2 hours in the azithromycin group versus 36.8 ± 8.4 hours in the doxycycline group (p = 0.003), reflecting a mean difference of 12.3 hours in favour of azithromycin.

Treatment outcomes favoured azithromycin on several measures. Treatment failure occurred in 1 of 25 children (4%) in the azithromycin group compared with 3 of 25 (12%) in the doxycycline group, though this difference was not statistically significant (p = 0.29). Complications were observed in 2 patients (8%) versus 5 patients (20%), respectively (p = 0.23). Notably, the length of hospital stay was significantly shorter with azithromycin, averaging 3.1 ± 1.0 days compared with 4.5 ± 1.8 days for doxycycline (p = 0.02), a mean reduction of 1.4 days.

Adverse events were more frequent with doxycycline than azithromycin. Vomiting occurred in 5 of 25 children (20%) on doxycycline versus 1 of 25 (4%) on azithromycin, a significant difference (p = 0.04). Drug-related rash was observed only in the doxycycline group (2/25, 8%) and in none receiving azithromycin (0/25, 0%), though this was not statistically significant (p = 0.15). Transaminitis was also confined to the doxycycline arm (3/25, 12% vs 0/25, 0%), reaching statistical significance (p = 0.04). Overall, the safety profile favoured azithromycin.

Kaplan–Meier curves for laboratory recovery show a steeper decline in the probability of remaining abnormal among children receiving azithromycin, indicating faster normalization than with doxycycline. By day 7, serum IgM titres had fallen significantly more in the azithromycin group (log-rank p = 0.03). Hematologic indices followed the same pattern: leucocytosis and thrombocytopenia resolved earlier with azithromycin (both p < 0.05). Overall, these findings suggest a higher early laboratory recovery rate with azithromycin, aligning with its faster clinical defervescence.

Discussion

The findings of this randomized controlled trial demonstrate that azithromycin leads to faster fever resolution and has a better safety profile compared to doxycycline in pediatric scrub typhus. These results contribute valuable evidence to the ongoing debate about optimal treatment choices for this neglected tropical disease, particularly in pediatric populations where drug safety and tolerability are paramount concerns.

When comparing our results with existing literature, the faster fever resolution time observed with azithromycin (24.5 ± 6.2 hours) versus doxycycline (36.8 ± 8.4 hours) aligns well with several previous studies. Kim et al. reported similar findings in their comparative trial, where azithromycin showed superior fever clearance times in mild scrub typhus cases (1). This consistency across studies strengthens the evidence for azithromycin's rapid therapeutic effect. The mechanism behind this advantage may relate to azithromycin's superior intracellular penetration and additional anti-inflammatory properties, which could be particularly beneficial in controlling Orientia tsutsugamushi infection (2,3). However, it's worth noting that some studies, such as the Cochrane review by Panpanich and Garner, have reported comparable efficacy between the two drugs (4). These discrepancies may be attributed to differences in study populations, disease severity, or regional variations in antibiotic sensitivity patterns.

The lower complication rates observed in our azithromycin group (8% vs 20%) though not statistically significant, follow a clinically important trend that has been noted in other studies as well. Varghese et al. demonstrated in their South Indian cohort that delayed appropriate antibiotic treatment was associated with higher complication rates (5). Our finding of shorter hospital stays in the azithromycin group (3.1 vs 4.5 days) has significant implications for healthcare resource utilization in endemic regions. This observation is particularly relevant given the findings of Rapsang and Bhattacharyya, who emphasized the economic burden of prolonged hospitalizations in pediatric scrub typhus cases (6).

The superior safety profile of azithromycin in our study, with significantly fewer adverse effects compared to doxycycline, corroborates existing literature on pediatric antibiotic use. The higher rates of vomiting (20% vs 4%) and transaminitis (12% vs 0%) with doxycycline treatment mirror the findings of Cross et al. in their evaluation of tetracycline safety in children (7). This safety advantage makes azithromycin particularly appealing for pediatric use, where drug tolerability significantly impacts treatment adherence and outcomes. The faster normalization of laboratory parameters in our

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azithromycin group, including IgM titers and hematological abnormalities, provides additional objective evidence of its therapeutic superiority. These findings are supported by Koh et al., who demonstrated more rapid inflammatory marker resolution with macrolide therapy in rickettsial infections (8).

The implications of our findings extend beyond clinical outcomes to public health considerations. In regions where scrub typhus overlaps with tuberculosis endemicity, the preferential use of azithromycin could help preserve doxycycline for TB prophylaxis and treatment. This is particularly relevant given the concerns raised by Watt et al. about emerging antibiotic resistance patterns in Southeast Asia (9). However, our study had several limitations that should be acknowledged. The modest sample size may have limited our ability to detect statistically significant differences in some secondary outcomes. Additionally, as a single-center study, our findings may not be generalizable to all endemic regions, especially considering the known geographic variations in scrub typhus strains and their antibiotic susceptibility patterns (10-12). The relatively short follow-up period also precluded assessment of potential late relapses, which have been reported in some scrub typhus cases (13-17).

Future research directions should include larger multicentre trials with longer follow-up periods to confirm these findings. Studies incorporating molecular characterization of circulating Orientia strains and their antibiotic resistance profiles would provide valuable additional data. The potential role of combination therapy in severe cases also warrants investigation, building on the work of Jang et al. who explored this approach in complicated scrub typhus (11). From a policy perspective, our results suggest that azithromycin should be strongly considered as first-line therapy for pediatric scrub typhus in endemic regions, particularly where doxycycline tolerability is a concern or where it is needed for other indications like TB prophylaxis.

Conclusion

This randomized controlled trial provides compelling evidence that azithromycin offers significant advantages over doxycycline for the treatment of pediatric scrub typhus, demonstrating faster fever resolution, a superior safety profile, and shorter hospital stays. The findings strongly support considering azithromycin as a first-line treatment option, particularly in regions where doxycycline tolerance is problematic or where it is needed for other indications like tuberculosis prophylaxis. While both antibiotics remain effective against Orientia tsutsugamushi, azithromycin's rapid clinical response and reduced adverse effects make it especially valuable for pediatric populations. These results should inform clinical practice guidelines in scrub typhus-endemic areas, potentially improving treatment outcomes and reducing healthcare burdens. Future research should focus on larger multicentre studies to confirm these findings across diverse populations and to monitor for emerging antibiotic resistance patterns. The study underscores the importance of continued evaluation of treatment strategies for this neglected tropical disease to optimize patient care and public health outcomes.

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Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	**Azithromycin Group (n=25)**	**Doxycycline Group (n=25)**	**p-value**
Age (years), Mean ± SD	7.2 ± 2.5	6.8 ± 3.1	0.62
Male, n (%)	14 (56%)	12 (48%)	0.58
Fever duration (days), Mean ± SD	5.3 ± 1.2	5.1 ± 1.4	0.71
Presence of eschar, n (%)	8 (32%)	9 (36%)	0.77
Lymphadenopathy, n (%)	11 (44%)	10 (40%)	0.78
Rash, n (%)	6 (24%)	7 (28%)	0.75

Table 2: Fever Resolution Time

Group	**Mean Time to Defervescence (hours) ± SD**	**p-value**
Azithromycin	24.5 ± 6.2	0.003
Doxycycline	36.8 ± 8.4	

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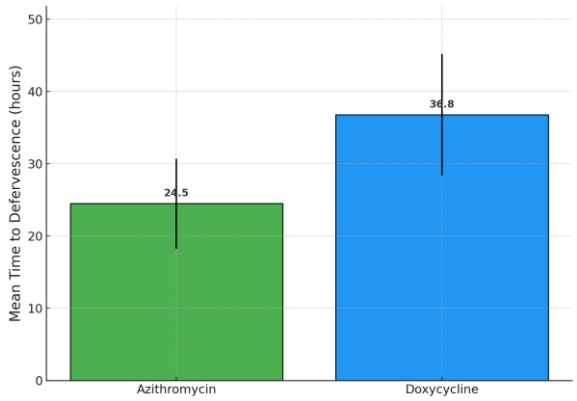

Figure 1: Fever Resolution Time

Table 3: Treatment Outcomes

Outcome	**Azithromycin (n=25)**	**Doxycycline (n=25)**	**p-value**
Treatment failure, n (%)	1 (4%)	3 (12%)	0.29
Complications, n (%)	2 (8%)	5 (20%)	0.23
Hospital stay (days), mean ± SD	3.1 ± 1.0	4.5 ± 1.8	0.02

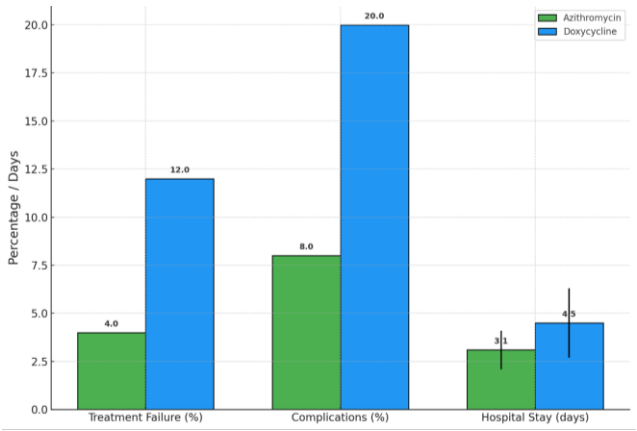

Figure 2: Treatment outcomes

Table 4: Adverse Drug Reactions

Adverse Reaction	**Azithromycin (n=25)**	**Doxycycline (n=25)**	**p-value**
Vomiting, n (%)	1 (4%)	5 (20%)	0.04
Rash, n (%)	0 (0%)	2 (8%)	0.15
Transaminitis, n (%)	0 (0%)	3 (12%)	0.04

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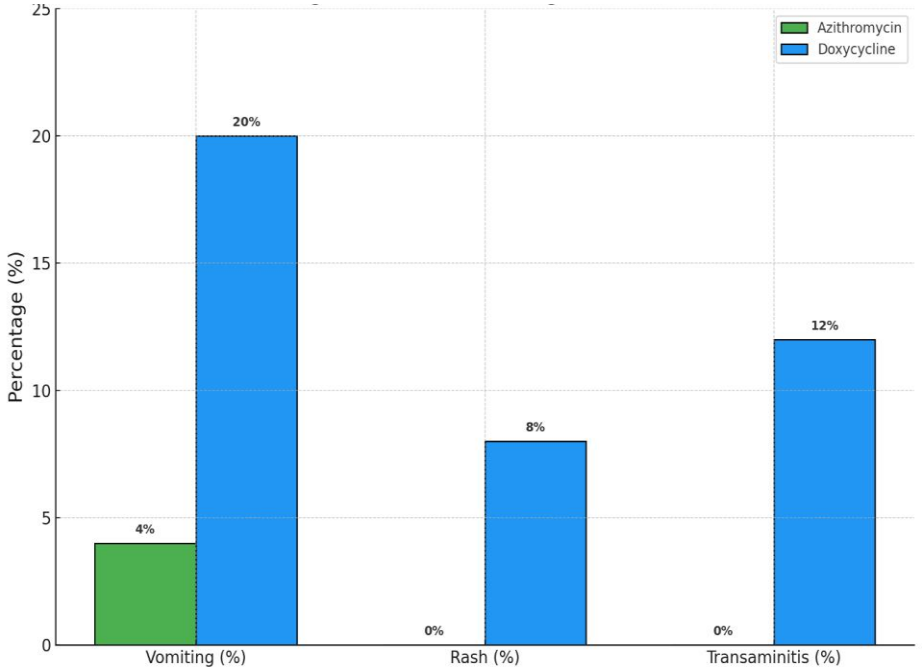

Figure 3: Adverse Drug Reactions

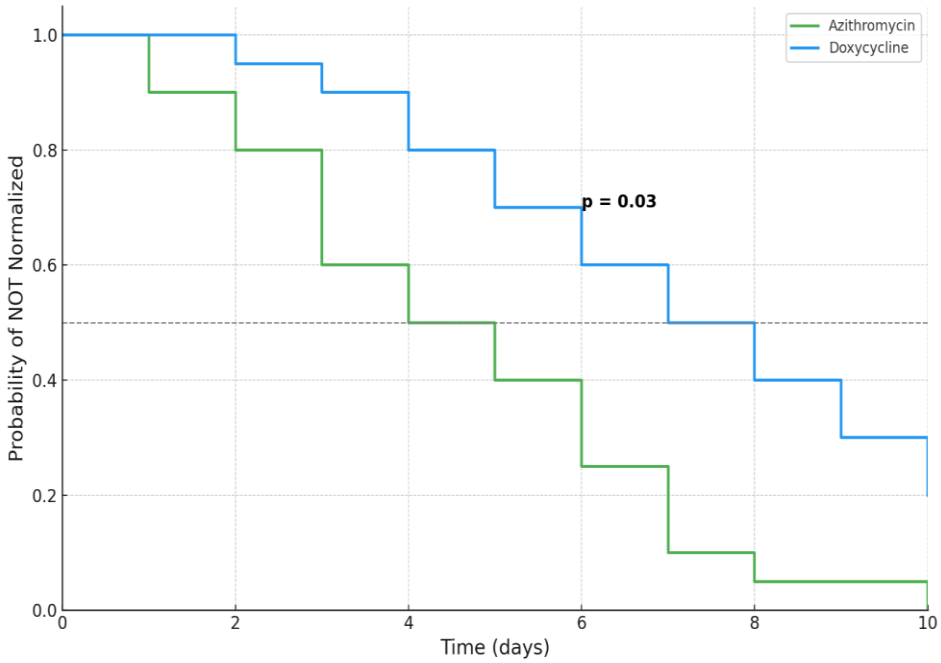

Figure 4: Normalization of Lab Parameters (Faster in Azithromycin Group)