COMMENTARY

Monotherapy is Recommended in the Treatment of Scrub Typhus and Doxycycline Resistance is a Misconception

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Scrub typhus, initially documented in China in 313 AD, is a zoonotic infection transmitted by mites carrying *Orientia tsutsugamushi*. It stands as a significant rickettsial infection globally, often causing acute undifferentiated febrile illness (AUFI).[1] Human transmission occurs through the bite of these infected trombiculid mites. Clinical manifestations closely resemble those of other common tropical infections like dengue, chikungunya and leptospirosis, typically presenting with fever and constitutional symptoms. Nonetheless, neurological, hematological, respiratory, cardiovascular, or renal complications may develop over time. Infection by *O. tsutsugamushi* induces generalized perivascular inflammation and vasculitis, leading to substantial vascular leakage and subsequent end-organ damage.[2] Early diagnosis and comprehensive understanding of therapy are imperative to mitigate mortality and associated complications due to the disease. Antibiotics, namely, doxycycline and azithromycin, constitute the primary treatment options.[3] Despite numerous studies and randomized controlled trials comparing the efficacy of these drugs, a consensus on the most appropriate treatment regimens remains elusive.

So far, six antibiotics have been used successfully for treating scrub typhus and they include doxycycline, azithromycin, tetracycline, rifampicin, chloramphenicol, and roxithromycin. Doxycycline is a broad-spectrum antibiotic belonging to the tetracycline family.[4] It has very good intracellular penetration, with bacteriostatic activity on a wide range of gram-positive and negative organisms. It binds allosterically to the 30S prokaryotic ribosomal unit, hindering the attachment of charged aminoacyl-tRNA (aa-tRNA) to the ribosomal A site, thereby halting the elongation phase of protein synthesis. Doxycycline remains the standard reference treatment for scrub typhus. A quick therapeutic response (within 48 hours) to this drug is often considered as a very important diagnostic clue for this infection. In stable patients, oral doxycycline is recommended at the dose of 100 mg twice daily for at least 1 week; however, in severely ill patients with features of multiorgan dysfunction and shock, the absorption of this drug is often unreliable. In such cases, it is judicious to use it through intravenous route. It is relatively safe in patients with renal impairment. Most of the studies have shown that azithromycin is almost equally efficacious as doxycycline. Recently, some researchers have seen delayed defervescence of fever with the use of doxycycline alone, thereby pointing towards the resistance of the said drug. Some studies have recommended the usage of combination therapy in the treatment of Scrub typhus, although there is paucity of large studies or randomized controlled trials regarding the same.

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The establishment of doxycycline as the standard therapy in scrub typhus gave rise to the dictum that—no response to treatment within 48 hours of commencement of a tetracycline antibiotic suggests an alternate diagnosis other than scrub typhus. In 1996, physicians working in Northern Thailand drew attention to a concerning observation.[5] Despite 1 week course of doxycycline, 7 out of 19 serologically confirmed scrub typhus patients failed to show defervescence. Susceptibility testing was performed on three selected clinical isolates and a reference Karp strain, employing both a mouse survivability model and cell culture. Among them, one *O. tsutsugamushi* isolate (AFC-3) demonstrated resistance to doxycycline, with a minimum inhibitory concentration (MIC) surpassing 4 μg/mL, whereas another isolate (AFC-27) exhibited at least partial resistance to the said drug. In a separate regional investigation, an *O. tsutsugamushi* isolate (AFSC-4), acquired from a patient with a delayed response to antibiotic therapy, showed diminished susceptibility to doxycycline when contrasted with the reference Karp strain. Nevertheless, azithromycin demonstrated efficacy against both strains.[6] The doxycycline MIC for AFSC-4 was estimated to range from at least 0.25 to 0.5 μg/mL, while for Karp, it was 0.0625 μg/mL. As a result, the authors concluded that AFSC-4 demonstrated resistance to doxycycline. Recent clinical investigations from Southern India, South Korea, and Northeastern

Thailand have underscored severe, treatment-resistant illness and instances of mortality, prompting speculation regarding the potential role of doxycycline resistance.[7–9] Additionally, reports have emerged of prophylactic failure among military people in Southeast Asia and Australia, attributed to suspected doxycycline resistance.[10,11] The question arises: "If doxycycline resistance in *O. tsutsugamushi* is not innate but acquired, what was the source of the selective pressure for the antibiotic?" Suggestions have been made that the emergence of resistance could be linked to antibiotic exposure from animal feeds or environmental influences, but these factors are not unique to northern Thailand. Other theories have proposed that spontaneous mutations, unrelated to selective pressure, might be responsible for acquired doxycycline resistance. This speculation is rooted in observations of the elevated rates of homologous recombination in *O. tsutsugamushi* or the potential presence of previously unidentified strains. inherently resistant to doxycycline.[12–14] It is worth emphasizing that there is still no globally accepted reference standard for antibiotic susceptibility testing (AST) of *O. tsutsugamushi*. Despite the contentious nature of reports dating back to the 1990s, there has been surprisingly little independent verification of the findings.

Two independent groups re-examined the AFC-4 and AFSC-4 isolates. In the initial study, AFC-1, 3, 4 and Karp strains underwent testing following the methodology outlined in the original AFSC-4 report. Incubation lasted for 3 days, and bacterial growth was assessed using microscopy to count the number of orientia per 100 L929 cells. Growth inhibition was observed at 0.1 μg/mL of doxycycline across all four strains, challenging the concept of doxycycline resistance. In a subsequent study, which included five reference strains (Karp, Kato, Gilliam, UT76, and TA763) in addition to AFC-3 and AFSC-4 isolates, further evidence emerged against the presence of doxycycline resistance.[15] Wangrangsimakul et al., in their clinical investigation, documented a pediatric patient with an extended duration of fever clearance (150 hours). Antibiotic susceptibility testing of this particular isolate, employing the innovative quantitative PCR–based assay mentioned earlier, indicated an MIC90 of 0.0625 mg/L for doxycycline. This finding suggests that resistance to doxycycline was not the main factor in the prolongation of the fever clearance time (FCT) seen in this patient.[16]

Thus, based on current evidence, the notion of doxycycline resistance appears to be unfounded. There exist alternative, plausible explanations for the differences observed in the AFC-3 and AFSC-4 strains compared with other studied strains. These explanations may encompass various bacterial characteristics, alongside host and pharmacological factors, contributing to variations in treatment outcomes.

Monotherapy forms the cornerstone in treating patients with scrub typhus. Delayed fever defervescence poses a challenge in many clinical scenarios where the utility of combination antimicrobial usage might be explored. The comparative efficacy of different antibiotics in terms of FCT has been summarized in Table 1. As such, treatment outcomes with combination therapy and its effects on patients with severe illness have not been studied in detail. We came across only two such documentations in the literature. In a randomized controlled trial conducted by Watt et al., adult patients diagnosed with clearly defined, mild scrub typhus were initially assigned to one of three treatment groups: 1 week of daily oral administration of 200 mg of doxycycline (n = 40), 600 mg of rifampicin (n = 38) or a combination of both doxycycline and rifampicin (n = 11).[17] However, due to insufficient efficacy, the combined regimen was discontinued within the first year of treatment. Consequently, the combination arm was replaced with a regimen of 900 mg of rifampicin. More recently, an observational study in a hospital in South India, the authors investigated various treatment protocols for scrub typhus. This included monotherapy (using either doxycycline or azithromycin) and combination therapy (employing both doxycycline and azithromycin), with a focus on evaluating the incidence of delayed defervescence, overall outcomes, and the influencing factors.[18] In their investigation, the authors analyzed 177 hospitalized patients diagnosed with scrub typhus. Among them, combination therapy (consisting of both doxycycline and azithromycin) was administered to 74 subjects, while doxycycline alone was prescribed to 46 patients, and azithromycin alone to 57 patients. The duration of antimicrobial treatment for both monotherapy and combination therapy was standardized to 7 days. Combination therapy was favored particularly in cases of more severe illness, as indicated by a higher SOFA score (8.82). Univariate analysis showed that respiratory dysfunction was an independent factor associated

Table 1: Comparative efficacy of different antibiotics in terms of fever clearance time (FCT)

Study	*Sample size*	*Population*	*Intervention*	*FCT*
Arun Babu et al.[19]	510	Children ≤12 years	Oral azithromycin (10 mg/kg/d once daily for 7 days) Or Oral doxycycline (children<40 kg: 2.2 mg/kg twice daily; >40 kg: 100 mg twice daily for 7 days)	Azithromycin: 42 ± 24 hours Doxycycline: 48 ± 23 hours p = 0.001
Pachiappan and Gane[20]	107	Children ≤18 years	Oral doxycycline 5 mg/kg per day in two divided doses for 7 days. Or Oral azithromycin 10 mg/kg per day for 5 days.	Doxycycline: 21 hours (2–72) Azithromycin: 28 hours (4–82) p > 0.05
Watt et al.[17]	78	>18 years	Oral doxycycline 200 mg followed by 100 mg twice daily for 7 days Or Oral rifampicin 300 mg twice daily for 7 days Or Oral rifampicin 450 mg twice daily for 7 days	Doxycycline: 52 hours (4–108) Low-dose rifampicin: 27.5 hours (4–84) High-dose rifampicin: 22.5 hours (3–76) p = 0.01

(Contd...)

Table 1: *(Contd...)*

Study	*Sample size*	*Population*	*Intervention*	*FCT*
Lee et al.[21]	56	<18 years	Oral/Intravenous chloramphenicol 50 mg/kg 6 hourly for 7 days Or Oral azithromycin 10 mg/kg on day 1, followed by 5 mg/kg daily for 4 more days Or Oral chloramphenicol 15–30 mg/kg every 12 hours for 5 days	Clarithromycin: 0.83 ± 0.20 days Azithromycin: 1.80 ± 0.15 days Chloramphenicol: 1.26 ± 0.30 $p = 0.019$
Zhao et al.[22]	74	>18 years	Oral minocycline 200 mg followed by 100 mg twice daily for 7 days Or Oral azithromycin 500 mg once daily for 5 days	Minocycline: 16 hours (4–40) Azithromycin: 24 hours (6–126) $p = 0.03$

with delayed fever defervescence [risk ratio (RR), 2.50] and failed to show any statistical difference between the antibiotic groups with regards to the primary outcome. Thus, the authors concluded that combination therapy did not seem to have any added benefit compared to the monotherapy group.

Nonetheless, in a recent multicenter, double-blind, randomized controlled trial for assessing the effectiveness of intravenous doxycycline, azithromycin, or a combination thereof in managing severe scrub typhus, findings revealed that the combined therapy involving intravenous doxycycline and azithromycin emerged as a more effective treatment approach for severe scrub typhus when contrasted with the administration of either drug individually.[23]

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