

Drug-Resistant Scrub Typhus

TO THE EDITOR—Wangrangsimakul and colleagues dismiss doxycycline-resistant scrub typhus as a misconception [1], but they present insufficient evidence to do so and misrepresent the clinical data supporting the concept. Diminished susceptibility to doxycycline was primarily demonstrated by an attenuated clinical response to treatment in patients with mild scrub typhus [2, 3]. Mouse mortality results correlated closely with response to treatment in humans [2, 3], allowed identification of rifampicin and azithromycin as effective against Chiangrai strains of *Orientia tsutsugamushi* [4], and demonstrated a spectrum of doxycycline susceptibility in Chiangrai isolates. The third but least dependable resistance marker was in vitro antibiotic susceptibility testing (AST), some limitations of which are pointed out by Wangrangsimakul [1]. AST is the main focus of their critique.

There was a significantly shorter fever clearance time in control group patients from Mae Sot, western Thailand, than in individuals from Chiangrai in the north [2]. Wangrangsimakul misleadingly states that “patients from Chiangrai were ill for longer and were older than their counterparts from Mae Sot.” There were no statistically significant differences in age or duration of illness. Mean duration of fever was 5.7 days in Chiangrai vs 4.7 days in Mae Sot. Do these authors seriously propose that this nonsignificant difference could confound treatment outcome? In a subsequent Chiangrai study, not referenced by Wangrangsimakul, only 13 of 28 doxycycline-treated patients were afebrile at 48 hours, a clear indication of attenuated therapeutic response [3]. Median age was 31 years, virtually identical to the Mae Sot patients’ mean age of 30.3 years.

The evidence cited by the authors against doxycycline resistance is weak—1 case of prolonged fever clearance with an

isolate not proven to be doxycycline resistant [5]. Doxycycline minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90} s) for 2 Chiangrai isolates were higher than for 5 reference strains, but were below drug levels achieved in vivo in human plasma [6]. Clinical findings from Chiangrai show decreased susceptibility to doxycycline, not absolute resistance. Patients did not fail therapy; rather, fever and other clinical signs resolved more slowly than expected historically and compared to controls. The MIC results cited by the authors are consistent with these clinical findings. Antibiotic exposure through animal feeds could drive resistance. The authors disingenuously dismiss this mechanism by stating that adding antibiotics to animal feeds is not unique to northern Thailand and mistakenly cite my article [2] to support this claim. Animal feed differences between Chiangrai and elsewhere have not been carefully investigated. There is simply no evidence that the host, pharmacological, and immunological factors hypothesized by Wangrangsimakul explain diminished doxycycline response, and considerable evidence against.

I agree with the authors that further studies of the response of scrub typhus infection to doxycycline and other antibiotics should be performed and lament the lack of further, careful studies. However, whether referred to as resistance or decreased susceptibility, there is a proven attenuated response to doxycycline in Chiangrai scrub typhus [2, 3]. A diminished therapeutic response in mild cases could translate to increased morbidity and mortality in severe infections. Administering an antibiotic to which *O. tsutsugamushi* is not fully susceptible could be life-threatening.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Clinical Infectious Diseases® 2020;71(6):1580

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Reply to Watt

TO THE EDITOR—We thank the author for his letter [1]. At the heart of the debate is the issue of how antibiotic resistance for *Orientia* species should be defined. We applied strictly microbiological criteria to doxycycline resistance, based on minimum inhibitory concentrations (MICs) and the pharmacokinetic/pharmacodynamic (PK/PD) properties of the tested antibiotics [2]. Doxycycline MICs obtained for AFC-3 and AFSC-4 *Orientia tsutsugamushi* isolates were recently reported at 0.125 mg/L and 0.250 mg/L,

respectively [3]. These values fall within the expected wild-type distribution of doxycycline MICs (median of 0.125 mg/L \pm one to two 2-fold dilution steps) in 5 reference strains (including Karp and Gilliam, prototypical strains considered doxycycline susceptible) and 51 clinical isolates from Laos and Thailand, and remain well below the plasma concentrations achieved in humans at standard doses (100–200 mg/day, peak serum concentrations of 1.7–5.9 mg/L) [3–5]. The small differences between doxycycline MICs observed are likely due to technical variation rather than major differences in susceptibility.

The author stipulates that attenuated clinical response to doxycycline implies diminished susceptibility and dismisses other important factors known to influence infection such as bacterial virulence and host immunity [1]. We do not dispute that some scrub typhus patients in Chiangrai have prolonged fever clearance times despite appropriate antibiotic treatment. However, fever clearance times ≥ 72 hours were observed in some patients receiving doxycycline, rifampicin, azithromycin, and chloramphenicol as part of clinical trials conducted in Thailand and in South Korea [6–10].

Results of the mouse survivability assay may be influenced by virulence of the infecting *O. tsutsugamushi* isolates [11]. The differences in pharmacokinetics of antibiotics in mice and lack of comparison to other reference and clinical isolates from patients with appropriate responses to treatment are additional weaknesses [12, 13]. The author's work shows that mouse survivability rates were similar for doxycycline and azithromycin when infected with Chiangrai *O. tsutsugamushi* isolates [14]. If diminished antibiotic susceptibility is determined by attenuated clinical response and reduced mouse survivability, then resistance in scrub typhus to the main antibiotics used appear widespread. Current evidence suggests that other factors described in our article influence clinical response and that a microbiological basis for doxycycline resistance in *O. tsutsugamushi* is lacking.

Chiangrai patients from the author's original study were on average febrile for longer prior to admission than patients from Mae Sot [13]. Although statistical significance was not reached, the differences may have potentially affected outcome, and larger studies to assess the relationship between age and duration of fever to outcome are required. We referenced the author's work while discussing potential sources of antibiotic selective pressure. There is evidence for the widespread use of antibiotics in animal feed globally and in Thailand, but we agree that detailed comparative studies at the provincial level are unavailable [15–18].

We believe that antibiotic susceptibility for *O. tsutsugamushi* should be based on MICs and PK/PD data and advocate the use of antimicrobial susceptibility tests that are accurate and reproducible, allowing for standardization and harmonization of results. Current trials embedding analysis of these important aspects should provide further clarity.

Notes

Financial support. T. W., W. P., P. N. N., and N. P. J. D. are funded by the Wellcome Trust, United Kingdom, as part of the Mahidol-Oxford Tropical Medicine Research Unit Tropical Health Network institutional funding support.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Clinical Infectious Diseases® 2020;71(6):1580–1

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DOI: 10.1093/cid/ciz1192