Drug treatment of scrub typhus

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SUMMARY Scrub typhus is avector-borne disease caused by the pathogen Orientia tsutsugamushi.We review the published literature for evidence on drug treatment in scrub typhus. Doxycycline has a proven efficacy in several trials and a meta-analysis, although resistance has been documented in parts of northern Thailand. Macrolides are equally efficacious and have less adverse effects, but they are expensive. Azithromycin is the recommended drug in pregnancy and for children. Rifampicin is effective in areas where doxycycline resistance is present. Quinolones have shown some degree of efficacy but the evidence is scant. Most clinical evidence on drug treatment is from cases of mild-to-moderate scrub typhus. Further study is needed on the efficacy of different antibiotics in the treatment of severe, life-threatening scrub typhus.

Introduction: Scrub typhus is a vector-borne zoonosis caused by the organism Orientia tsutsugamushi.1 This often overlooked and under-diagnosed infection is endemic in the south eastern and far eastern countries of Asia (India, Sri Lanka, Pakistan, Japan, Thailand and Korea) and extends to Afghanistan in the west and further south as far as northern Australia. This geographical area is loosely termed the tsutsugamushi triangle.2 The natural hosts of the pathogen are trombiculid mites (Leptotrombidium deliense, L. palladium, etc.). 1 Infected larval stages of the mites (chiggers) inoculate humans (accidental hosts) while feeding. The pathogens multiply at the site of entry which later develops into an eschar.3 The term scrub typhus is descriptive of the typical habitat endemic to the vector, although its existence is not limited to such niches. It is estimated that there are one million new cases each year and that one billion people are at risk of infection.4 Often a simple febrile illness, scrub typhus is a disease with a potentially fatal outcome, causing multi-organ dysfunction in severe cases.5 Left untreated, mortality rates can be as high as 30%.6 Early diagnosis and treatment is, therefore, important. We review the current state of evidence on drug treatment of scrub typhus.

Methods :We searched MEDLINE using the search terms ‘scrub typhus’ or ‘Orientia tsutsugamushi’ with ‘treatment’, ‘antibiotics’ and the names of all standard antibiotics. There were 33 citations in the original search with these restrictions. Bibliographies of the cited literature were also searched. All abstracts were read through independently by the three authors and relevant papers were identified for full review. Eighteen relevant papers were identified.

Results : Relatively few antibiotics have been evaluated for the treatment of scrub typhus in clinical trials. Drugs which have shown efficacy are chloramphenicol, the tetracycline group antibiotics, macrolides, quinolones and rifampicin (Table 1). Other antibiotics have been shown to be ineffective. One of the earliest antibiotics used in treatment was chloramphenicol.7–9 However, an early study showed that tetracycline was more effective10 and, in view of the risks of aplastic anaemia, chloramphenicol is now seldom used to treat scrub typhus. Tetracyclines are the most widely used drugs for the treatment of scrub typhus. In one study, a single dose of doxycycline 200 mg was shown to be as

effective as a seven-day course of tetracycline.11 A three-day course of doxycycline was shown to be as effective as seven days of tetracycline in a multicentre randomized trial12 (n ¼ 116); a metaanalysis confirmed the efficacy of doxycycline.13 Treatment with doxycycline is associated with a rapid abatement of fever and this effect has even been considered almost diagnostic.14 Chung et al.15 demonstrate that this defervescence correlates with a rapid reduction of cytokines following treatment with doxycycline. In this study, serum levels of interleukin-10, tumour necrosis factor (TNF)-a, and interferon (IFN)-g declined in patients within 24 h after the start of treatment. Furthermore, reductions in expression of messenger RNA for these cytokines were seen within the first week of treatment. Similarly, organism clearance also occurs within the first week of treatment; Kim et al.16 assessed the organism's genomic products by nested polymerase chain reaction (PCR) before and after administration of doxycycline or rifampicin (n ¼ 129) and demonstrated