Orientia tsutsugamushi

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GENERAL DESCRIPTION

The scrub typhus rickettsiae are Gram-negative obligate intracellular bacteria, cococcoid in shape, which multiply by binary fission in the cytoplasm of infected cells. Typical in vivo target cells include vascular endothelial cells and macrophages. The rickettsiae fail to grow on axenic media but grow well in cell culture, the yolk sac of embryonated eggs, and laboratory animals including the mouse. Due to major differences from other members of the genus Rickettsia, the genus "Orientia" tsutsugamushii has been proposed (26).

Scrub typhus, (synonyms: chigger-borne rickettsiosis, tsutsugamushi disease, rural typhus) is an acute zoonotic febrile illness in which humans are incidental dead-end hosts. The symptoms and signs are based upon a disseminated vasculitis involving focal infection of the endothelial vascular cells lining the small blood vessels. The agent is transmitted by the bite of infected larval trombiculid mites or "chiggers," which serve as both reservoir and vector. Infection does not occur until 6 to 8 hours after tick attachment, and fever begins 7 to 10 days later (18). Often a local lesion or eschar appears at the site of the chigger bite. Absence of the eschar or a rash can make the diagnosis difficult. Severity of disease depends upon the virulence of the infecting strain and age and immune status of the patient. Left untreated, the clinical disease may last for up to 2 weeks and have a mortality rate of up to 35% (14). The disease is endemic within an area generally bordered by Papua New Guinea and Queensland, Australia, north to Kamchatka peninsula, Russia, and from Afghanistan east to the Philippines. The endemic region includes Burma, Thailand, Vietnam, Cambodia, Malaysia, India, Pakistan, Japan, Taiwan, Indonesia, China, Korea, and Pacific islands of that region.

The tetracyclines and chloramphenicol have been extremely effective agents for treatment of scrub typhus. However, a recent report from Thailand of drug-resistant strains is alarming (29). Alternative agents, including rifampin, clarithromycin, and azithromycin appear promising but require further clinical evaluation.
Specific immunity following recovery can last up to 3.5 years following reinfection with the homologous strain, but immunity is short-lived with heterologous strains (19). Isolates exhibit a high degree of antigenic diversity, complicating the development of vaccines.

**SUSCEPTIBILITY IN VITRO AND IN VIVO**

Since rickettsiae are obligate intracellular parasites, susceptibility testing cannot be accomplished with traditional culture methods. Experimental systems used for testing susceptibility include cell culture, the murine animal model, and embryonated eggs. In vitro cell culture tests of rickettsial susceptibility are usually performed by plaque reduction assays, dye uptake, or direct counts of infected cells. All of these assays require multiple preparation of tests at each of several concentrations of antibiotics and are not generally available.

The rickettsiostatic antibiotics chloramphenicol and the tetracyclines are traditionally used to treat scrub typhus. Cephalosporins, penicillin, and aminoglycoside antibiotics are not effective. Clinical efficacy is supported by experimental in vitro cell culture models and in vivo animal models (8, 9, 12, 15, 28). Correlation between in vitro and in vivo models is not always consistent; however, and testing methods have not yet been standardized. For example, ciprofloxacin was found to have very good activity in vivo (3, 6) but diminished in vitro susceptibility by the direct cell culture method (8: Strickman, unpublished data).

Until recently, clinically relevant antibiotic-resistant scrub typhus was unreported. Claims of antibiotic-resistant *O. tsutsugamushi* isolates recovered from patients in northern Thailand are supported by both in vitro and in vivo susceptibility testing (29). It remains possible that enhanced virulence, rather than decreased antibiotic susceptibility is contributing to the poorer clinical response to traditional antibiotics among these patients (Kelly, unpublished data). If antibiotic resistance is indeed an emerging problem, new antibiotic agents are needed for successful treatment of patients infected with these strains. Rifampin is known to be active in vitro (9) and is currently undergoing clinical evaluation in Thailand (Watt, unpublished data). The new azalide antibiotic azithromycin has been shown to be active against the doxycycline-resistant strain of *O. tsutsugamushi* (24).

**ANTIMICROBIAL THERAPY**

**Drug of Choice**

The tetracyclines and chloramphenicol are standard effective treatments for scrub typhus. As is true with all antibiotics known to be active against scrub typhus, these antibiotics are rickettsiostatic, not rickettsicidal. Patients receiving tetracycline have been reported to respond more rapidly than those receiving chloramphenicol (17) and, unless contraindicated, tetracycline is the preferred agent. Tetracycline and its long-acting analogue doxycycline can be used interchangeably, although compliance may be better with doxycycline. The usual dose of tetracycline for adults is 500 mg every 6 h, and the usual adult oral dose of doxycycline is 200 mg once followed by 100 mg every 12 h (5). Single-dose (200 mg) doxycycline therapy has been reported to be effective (1). Although not frequently used in the United States, minocycline has been used successfully in Japan to treat scrub typhus (10, 11). Antibiotics are usually continued 7 to 15 days. Response is rapid, usually with improvement in 24 to 36 h. In general, treatment with tetracyclines is associated with favorable outcomes. Failure to defervesce within 48 h suggests an alternate diagnosis or antibiotic resistance as described by Watt (29). In earlier studies, shorter courses of tetracycline or doxycycline or initiation of therapy before day 5 of illness were sometimes associated with relapses 5 to 10 days after therapy (1, 17, 27). However, more recently, a 3-day doxycycline course was found to be as effective as a standard 7-day tetracycline course, with no relapses occurring with either regimen (22).

The tetracyclines are associated with adverse effects that limit their utility. Due to toxic effects on developing teeth and bones, tetracyclines are contraindicated in pregnancy and in

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**TABLE 1 • Antibiotic Treatment Recommendations for Scrub Typhus**

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<th>Clinical Situation</th>
<th>Recommended Treatment Adults</th>
<th>Children</th>
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| Routine treatment: | Doxycycline, 200 mg, day 1 (100 mg every 12 h), followed by 100 mg/day, 3 days* (single 200-mg dose may be adequate) | <100 lb: doxycycline 5 mg/kg/day, 7 days; ≥100 lb adult dosage
| Alternative        | Chloramphenicol, 500 mg every 6 h, 7–15 days* | Chloramphenicol, 50 mg/kg/day (divided dose every 8 h), 5 d<sup>a</sup> c <7 week old, 25 mg/kg/day; 1–4 weeks old, 25 mg/kg/12 h |
| Alternative        | Tetracycline, 25 mg/kg/day (4 divided doses) 3–7 days<sup>b</sup> | |
| Pregnancy          | Chloramphenicol, 500 mg every 6 h, 7–15 days* | |
| Doxycycline failure* | Azithromycin 500 mg/day, 3 days<sup>c</sup> | |

*Relapses reported when therapy initiated before 5th febrile day. A repeated dose has been effective.

<sup>a</sup>Permanent tooth discoloration reported with prolonged use in children up to 8 years old (less common with doxycycline).

<sup>b</sup>Not approved. Therefore, for this indication.

<sup>c</sup>Failure to defervesce within 48 h suggests resistance; defervescence normally occurs within 24 to 36 h.
children under 12 years old. Photosensitivity and gastrointestinal symptoms are also not uncommon.

Chloramphenicol is a broad-spectrum rickettsiostatic antibiotic useful for treatment of scrub typhus (23). Usual adult dosage is 500 mg every 6 hours for 7 to 15 days, and in children, 50-75 mg/kg/day orally for 5 days. It is associated with prolonged fever following initiation of treatment (compared with tetracycline) and in rare cases causes aplastic anemia. It is therefore used as an alternative in situations in which a tetracycline is contraindicated. Patients in whom chloramphenicol therapy is initiated fewer than 5 days after onset of fever often exhibit recrudescence symptoms upon cessation of therapy (17).

Special Situations

There is currently no effective vaccine for scrub typhus. Single-dose chemoprophylaxis with either chloramphenicol (4 g weekly (20)) or doxycycline (200 mg weekly (13, 27)) has been found effective. Both can effectively suppress disease, provided treatment is continued 4 to 6 weeks after exposure, but neither drug is effective when prophylaxis is discontinued shortly after the end of exposure.

Alternative Therapy

Macrolide antibiotics such as azithromycin, clarithromycin, and erythromycin are active in vitro and in vivo against scrub typhus, but there is little clinical experience to support their routine clinical use (7, 24). Azithromycin has been used successfully to treat a few patients in Thailand, including in areas where antibiotic resistance is known to occur (Silppapajakul, Pacharee, unpublished data). Clarithromycin was used successfully at a dose of 400 mg/day for 12 to 19 days to treat three patients in Japan (7). Ciprofloxacin, 500 mg every 12 h, was also used to treat a patient in Nepal (3). The patient defervesced within 24 h. Studies are ongoing in Thailand to evaluate the clinical efficacy of rifampin (Watt, unpublished data).

ENDPOINTS FOR MONITORING THERAPY

Successful therapy is associated with rapid defervescence following initiation of treatment. Most patients become afebrile within 48 h. Failure to respond promptly should raise the suspicion of an alternate diagnosis or the possibility of antibiotic resistance. There are no useful laboratory parameters of successful treatment. Serology cannot be used, since antibody titers can continue to rise during otherwise effective therapy (10). While potentially useful in establishing diagnosis, the polymerase chain reaction (PCR) is of limited value as a treatment monitor, since circulating rickettsiae can be detected by PCR up to 8 days after initiation of antibiotic (10). Viable scrub typhus rickettsiae have been recovered from the lymph nodes of patients from 5 to 15 months after effective treatment, but spontaneous recurrence of clinical disease has not been observed (21). Specific IgM and IgG antibodies rise late in the first week of illness, and serodiagnosis can be done by the standard indirect fluorescent antibody (IFA) test, indirect immunoperoxidase (IIP) test (4), or dot-ELISA (30) (Dip-S-Ticks, Integrated Diagnostics, Baltimore, MD). The latter test was shown to be positive as early as the fifth febrile day (30).

CAVEATS AND COMMENTS

The origin of reported chloramphenicol and tetracycline resistance in Thailand is not obvious because the nature of the host-vector relationship suggests an absence of selective pressure toward drug resistance. An alternative explanation may be that these strains are more virulent, a phenomenon that has been observed in preliminary in vitro studies with strains from other regions of Thailand (Kelly, unpublished data). This issue is clinically relevant because several scrub typhus patients in the region of northern Thailand where resistance is found died while receiving appropriate antibiotic therapy (Watt, unpublished data). Use of chemoprophylaxis in such areas might present cause for concern. Currently there is no evidence of resistance occurring anywhere outside Thailand.

Disease incidence appears to be on the rise as well (16, 25). The apparent increase in Japan may be partially explained by increased use of β-antibiotics in the 1970s for treatment of febrile illnesses in place of chloramphenicol and the tetracyclines.

Scrub typhus may be difficult to diagnose as the clinical presentation can be similar to several other febrile illnesses such as dengue fever, hantavirus, leptospirosis, and typhoid. Often the pathognomonic eschar is not present, or the typical rash may not be apparent if the patient has dark skin. The Weil-Felix test, while relatively specific, is somewhat insensitive, often as low as 50% early in the course of disease and should be supplemented by the more sensitive and specific IIP, IFA, or other commercial tests (2, 4, 30). However, these tests are not yet widely available. Often prompt defervescence following empirical treatment with chloramphenicol, tetracycline, or doxycycline is used to confirm the clinical impression. Thus, patients who fail to respond in typical fashion might be missed.

In view of evidence for emerging strains that respond poorly to standard treatment and possible antibiotic resistance as well as the need to identify drugs acceptable for the safe, effective treatment of children and pregnant women, continued development of new antibiotics and vaccines is needed. The possible spread of untreatable scrub typhus threatens to return us to the preantibiotic era such as occurred during World War II when tens of thousands of cases occurred in Asian and European soldiers in the Asia-Pacific region (14). While a disease described over 2000 years ago by Chinese physicians may not be classed as "emerging," an appreciation of its ubiquity and potential severity is reemerging.

REFERENCES