8.6.41 Scrub typhus 1252

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section 8 Infectious diseases 1252 8.6.41 Scrub typhus Daniel H. Paris and Nicholas P.J. Day ESSENTIALS Orientia spp. are obligate intracellular Gram-negative bacteria that cause scrub typhus, historically known as ‘tsutsugamushi disease’, a febrile illness characterized by early nonspecific ‘flu-like’ symptoms, and sometimes a diffuse, macular, or maculopapular rash and/or a necrotic lesion eschar at the inoculation site. Leptotrombidium mites transmit Orientia spp. to humans via the bite of the larval stage, while all mite stages act as bacterial reservoirs through ver- tical transovarial and transstadial transmission. Scrub typhus is a leading cause of treatable undifferentiated febrile illness in many regions of Asia, and unfortunately remains an underappreciated neglected disease, mainly due to diagnostic difficulties and lack of awareness among medical staff. Complications include meningo- encephalitis, respiratory and renal failure, and severe multiorgan failure. Scrub typhus can be treated effectively with tetracyclines, macrolides, and chloramphenicol. Humans are dead-end hosts and do not participate in the Orientia life cycle, hence treatment does not affect overall disease incidence. Currently there is no vac- cine available as the heterogeneity of Orientia strains, the weak and transient cross-protection among divergent isolates, and the ap- parent loss of heterologous protection within months after natural infection pose major hurdles in the development of diagnostics and vaccines. Introduction Historically, the Rickettsia were classified into three major serological groups, but recent discoveries of novel Rickettsia spp. have challenged this classification. Based on genetic classification, the Rickettsia genus is now divided into four major groups: ‘typhus group’ (R. prowazekii, R. typhi); ‘spotted fever group’ (R. rickettsii, R. conorii and many others); ‘ancestral group’ (R. bellii and R. canadensis) and the ‘transitional group’ (R. akari, R. australis and R. felis). In 1996 O. tsutsugamushi was moved into its own Orientia genus on the basis of genotyping— this genus currently comprises the two human-pathogenic species O. tsutsugamushi and O. chuto sp. nov. Although scrub typhus probably is the world’s most important rickettsial illness in terms of disease burden, the available know- ledge and literature about Orientia spp. remains rather limited. In Japanese, the jungle mite is called ‘tsutsuga-mushi’ (tsutsuga = dan- gerous and mushi = insect). The earliest clinical accounts compatible with scrub typhus were found in the ‘Zhouhofang’, a Chinese clinical manual produced in 313 BC, and the term ‘tsutsugamushi disease’ was first applied to mite-associated fevers in the Niigata prefecture in Japan in 1810. Since then, Orientia spp. have been found and de- scribed across Asia and the Pacific region, but also recently in Africa, Europe, and South America, following a tropical to subtropical dis- tribution (Fig. 8.6.41.1). Aetiology and epidemiology Orientia are Gram-negative, nonflagellated, small coccobacilli found within the cytoplasm of host cells. They are transmitted to humans Fig. 8.6.41.1 World distribution of Orientia spp. Orientia spp. were thought to be geographically restricted to the Asia-Pacific

region. However, recent identification of Orientia spp. in febrile patients from the Arabian Peninsula and Chile (culture and sequencing), in rodents from Southern France and Senegal (Orientia-specific PCR), and serologically in Kenya, Congo and Cameroon suggest that scrub typhus could be more widely distributed in the tropical/subtropical belt around the world than previously assumed.

8.6.41 Scrub typhus 1253 by the bite of larval trombiculid mites, called ‘chiggers’ (family Trombiculidae, genus Leptotrombidium), within which the bacteria are maintained transovarially and transstadially over multiple gen- erations. Incidence is seasonal, with an increase in cases just before and during the rainy season in Southeast Asia and at harvest time in Japan. The transmitting trombiculid mites can be found from sea level to mountainous heights in Borneo (Sabah, Sarawak) and India (Kashmir, Himachal Pradesh, Sikkim and Arunachal Pradesh), in alpine conditions in the Pakistan Himalayas, in rain forests, shrubby fringes between fields and forest, abandoned paddy fields, rubber plantations, beaches, riverbanks, semiarid deserts, and commonly in areas with secondary vegetative growth (Fig. 8.6.41.2). Pathogenesis/Pathology The outer membrane proteins of Orientia attach to host cells via syndecan and fibronectin receptors that engage integrins and trigger bacterial endocytosis and internalization. The intracellular pre- ferred location of Orientia is in the glycogen and ATP-rich peri- nuclear region of the cytoplasm, to which the bacteria are thought to translocate via microtubules. Infected cells express and secrete in- flammatory and chemotactic cytokines, which involve activation of NF-κB and the MAPK pathways. The systemic vasculopathy of scrub typhus involves prominent perivascular cuffing with mononuclear cells and fibrinoid necrosis of the vascular wall. These dense infiltrates contain Orientia in monocytes, lymphocytes, and macrophages (Fig. 8.6.41.3). Scrub typhus infection is typically associated with prominent systemic mononuclear cell activation, and strong pro-inflammatory co- agulation activation in vivo. Skin biopsies of scrub typhus eschars show Orientia to be mainly within dermal dendritic cells and tissue monocytes and rarely within endothelial cells. Orientia-infected cells that have the capacity to re-circulate in lymphatic or blood vasculature (Trojan horse phenomenon) enable the pathogen to escape from the eschar via lymph nodes to the systematic circula- tion and reach parenchymal organs. This period of dissemination usually occurs between 3 and 14 days after the onset of fever, and during this ‘rickettsaemic window’ Orientia can be detected in the blood (i.e. using polymerase chain reaction (PCR) assays). The natural immune response to scrub typhus is challenged by the great immunogenic diversity of Orientia strains, usually re- sulting in weak and transient cross-protection to infection with different isolates, and waning of heterologous protection within months. This short-lived immune protection is associated with high re-infection rates, especially in people living in endemic areas. The mechanisms of protective immunity against Orientia are under in- vestigation, but remain poorly understood. Validated experimental models to study the pathogenesis of scrub typhus are lacking, al- though infected Rhesus macaques have similar clinical and patho- physiological features as humans. Clinical features The clinical presentation starts with a nonspecific ‘flu-like’ syn- drome, including fever, fatigue, frontal headaches, myalgia, cough, (d) (e) (a) (b) (c) Fig. 8.6.41.2 Vegetation associated with scrub typhus transmission. Rodents infested with trombiculid mites excavate burrows along the dried-mud walkways in disused paddy fields (a). Mite islands—locations with high mite densities inhabiting the soil—typically found along waterways, amidst bamboo groves, disused paddy fields, and in hilly coffee plantations (b, c, and d). Aerial view of Chiang Rai (north Thailand) shows the disused paddy fields with streams, jungle, plantations, and shrubby vegetation which represent high-risk areas for acquiring scrub typhus (e). (a) (c) (d) (b) Fig. 8.6.41.3 Orientia tsutsugamushi in cell culture and skin biopsies. Obligate intracellular Orientia spp. require cells for in vitro propagation, and typically

locate to the glycogen and ATP-rich perinuclear region (immunofluorescence and immune histochemistry staining, (a) and (c), magnification ×650). Eschar biopsies from scrub typhus patients reveal the typical perivascular cuff formation with high densities of bacteria, monocytes, lymphocytes, and antigen-presenting cells (CD14-pos. monocytes (b) and T lymphocytes (d) stained red, Orientia in green, magnification ×400). Images provided by DHP, panels (b) and (d) were published in PLoS Negl Trop Dis, 2012 Jan; 6(1):e1466. doi: 10.1371/journal.pntd.0001466.

section 8 Infectious diseases 1254 and restlessness/insomnia. The presence of an eschar is a valuable diagnostic clue, but like the rash, is not always present. An eschar is a necrotic and painless inoculation lesion following a mite bite, typic- ally found in areas associated with compression; restrictive clothing like shirt cuffs, bra, underwear, sarong, or in intertriginous areas, like axillae, under the breasts, groin, or buttock regions. The finding of this important diagnostic clue is often missed, as eschars are com- pletely painless—patients are often unaware of their presence—and the affected body regions often difficult to examine due to cultural sensitivities. The diffuse, macular, and/or maculopapular rash can present within 3–10 days following onset of disease (Fig. 8.6.41.4). Lymphadenopathy is a common feature, more so than in other rick- ettsial infections, such as murine typhus. Reversible partial hearing loss has been described and appears to be a specific feature of scrub typhus. The underlying pathophysiology of this symptom is cur- rently not understood. Complications in scrub typhus include gastrointestinal symp- toms, respiratory and renal failure, encephalitis, and very rarely disseminated intravascular coagulation. The major serious compli- cations are central nervous system infection, acute respiratory dis- tress syndrome, and multiple organ dysfunction syndrome, which are associated with mortality rates reaching 20%, even if treated. Untreated scrub typhus mortality rates average around 6–8%, but can reach 40% in certain geographical regions, depending on the strain of Orientia and the immune competence of the patient. Diagnosis The Weil–Felix test historically separated scrub typhus from the other forms of typhus and was based on the detection of cross-reactive anti-Orientia antibodies to Proteus mirabilis—specifically the OX- K (Kingsbury) strain. The Weil–Felix test is unreliable, with poor diagnostic accuracy and has been replaced by the newer indirect immunofluorescent assay (IFA) and indirect immunoperoxidase test (IIP). These assays use cell-culture-derived Orientia antigens to detect and titrate specific antibodies in paired admission and conva- lescent samples. However, these tests are rarely standardized across laboratories, require considerable expertise, and are usually not available in rural tropical areas where they are most needed. Recently, anti-Orientia IgM and IgG-based rapid diagnostic tests and Enzyme-Linked Immunosorbent Assays (ELISAs) have become available, and are replacing the suboptimal IFAs or IIPs. Both assays use cell culture-derived O. tsutsugamushi antigens or recombinant proteins to detect Orientia-specific antibodies and are inexpensive, sensitive, specific, and reproducible; rapid diagnostic tests are either immunochromatographic or semi- quantitative immuno dot blot assays, whereas ELISAs facilitate higher throughput of serum samples, and enable performing mul- tiple tests at one time. PCR methods detect different target genes of Orientia spp. and with their high sensitivities and specificities, these assays have be- come a central diagnostic pillar in scrub typhus, as they enable earlier diagnosis during the bacteraemic dissemination phase be- fore specific antibodies are sufficiently produced for serology. Target genes include the 47kDa, 56kDa, 16S rRNA, and groEL genes. Orientia spp. can be cultured from blood, though this requires special tissue culture techniques and Bio-Safety Level 3 facilities, and can take several weeks. Samples taken from necrotic eschars or eschar crust can be useful for both PCR-based or immuno histochemical diagnosis which, due to their high bacterial loads and isolation from blood circulation, can be used

even after initi- ation of treatment. Differential diagnosis The following infectious diseases can cause ‘typhus-like illnesses’, and can present with similar clinical features: scrub typhus, murine typhus, dengue, leptospirosis, typhoid, melioidosis, malaria, and chikungunya fever. Typhus (Rickettsia and Orientia infections)—distinguished molecularly using PCR with genotyping or serologically by specific cross-adsorption tests and Western blotting in paired acute and con- valescent samples (IFA, IIP, ELISA). Malaria—direct pathogen detection via stained blood films, antigen detection assays Arbovirus infections (e.g. dengue, Chikungunya)—diagnosis using combined antigen and antibody-based detection algorithms (nonstructural proteins and IgM detection). The dengue rash is more erythematous and homogenous than in scrub typhus and is often accompanied by pronounced thrombocytopenia. Leptospirosis—diagnosed by PCR (whole blood), serology incl. microscopic agglutination testing and/or culture (blood, urine, cere- brospinal fluid (CSF)—recently possible on solid agar). Relapsing fever (lice or tick transmitted)—direct demonstration of Borrelia spirochetes in blood smears, and/or via serology and/ or PCR. Meningococcal disease—conventional blood and CSF cultures. Typhoid—conventional blood and bone marrow cultures, and recently by rapid diagnostic testing of blood culture fluid. Viral fevers—with maculopapular skin rash, as in Epstein–Barr virus, infectious mononucleosis, or primary HIV infections, are dis- tinguished serologically or via PCR assays. (a) (d) (e) (f) (b) (c) Fig. 8.6.41.4 Inoculation eschar lesions and rash in scrub typhus. Eschars in the umbilicus (a), at a T-shirt cuff line (b), the belt/sarong line (c), and buttocks (f). Eschars and rash are not always present. The rash is typically erythematous, macular, or maculopapular, and can be very faint or difficult to discern, especially in deep skin tones (d and e). Images (a), (d), (e), and (f) were generously provided by Dr Rattanaphone Phetsouvane, from Laos and images (b) and (c) by Dr Hugh Kingston, from Cambodia and Bangladesh, respectively.

8.6.41 Scrub typhus 1255 Treatment Scrub typhus is very responsive to treatment with appropriate anti- biotics (doxycycline, azithromycin, chloramphenicol), and empirical treatment should be considered early if this diagnosis is suspected. Doxycycline: Unless contraindicated, doxycycline is the standard treatment with an adult oral dose of 100 mg twice daily for 7 days. Tetracycline 500 mg q6 h for 7 days can also be used. In uncom- plicated scrub typhus, studies have shown that shorter regimens of 3 days performed equally well as 7 days. No failures or relapses and similar fever clearance times were observed in either treatment group in a Korean study that compared a 3-day course of doxycyc- line (100 mg every 12 hours) to a 7-day regimen of tetracycline (500 mg every 6 hours). Similarly, a Malaysian study showed that a single dose of doxycycline 200 mg was equivalent to one week of tetracyc- line 500 mg every 6 hours for treating patients with scrub typhus— no relapses occurred in the 2-week follow up period. Azithromycin: An alternative drug with comparable efficacy is azithromycin (1000 mg or 500 mg on the first day, followed by 500 or 250 mg daily for another 2 days—3-day regimen). Azithromycin has also been shown to be as effective as doxycycline, when used as a single-dose treatment in uncomplicated disease. Azithromycin is particularly useful if tetracyclines are contraindicated, such as in pregnancy, although doxycycline can be considered safe until the 25th week of pregnancy. Trials of shorter courses are underway for both doxycycline and azithromycin-based regimens. Azithromycin has been suggested as alternative treatment for doxycycline-resistant scrub typhus in northern Thailand, although robust data on the na- ture of resistance and treatment options is lacking. Chloramphenicol is an excellent drug, and a good alternative to doxycycline, although its haematological side effects (1:21 600) and the very rare occurrence of grey baby syndrome in premature infants (circulatory collapse) have led to significant reduction of its use (500 mg q6 h in

adults or 50–75 mg/kg/day in children for 7 days). Combinations and drug–drug interactions for dual treatment: The idea of achieving shorter fever clearance times using combin- ation therapy is attractive, especially in pregnancy with the aim of reducing adverse pregnancy outcomes. However, rifampicin co-treatment with doxycycline, azithromycin, or chloramphenicol might decrease the levels and effects of these drugs; hence dose ad- justment might be required. These combinations should be used with caution until reliable data become available. Combinations of doxycycline plus azithromycin or chloramphenicol are beneficial and no negative interactions are described to date. Prognosis/Outcome Severe scrub typhus patients typically present with multiple organ dysfunction syndrome in approximately a third of hospitalized pa- tients, and high APACHE-II admission scores, as recently reported in a large study in India. However, despite the high frequency of multiple organ dysfunction syndrome, the mortality remains rela- tively low with overall case fatality rate at approximately 9%. In pa- tients with central nervous system (CNS)-related complications a higher mortality rate of 18% was observed in a large recent study in Laos. This study showed that Rickettsia spp., Orientia spp. and Leptospira spp. infections are important causes of CNS infections in Laos, observed significantly more frequently than conventional bac- terial aetiologies (Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Streptococcus suis). Scrub typhus in pregnancy is potentially worse than malaria with a high rate of poor neonatal outcome, with stillbirth, prematurity, and low birth weight occurring in just over 40% of pregnancies. Despite these data, the current evidence to support the use of doxy- cycline or azithromycin in pregnancy for scrub typhus is weak, and the optimum antimicrobial treatment for undifferentiated fevers in pregnancy remains unknown. In summary, treatment delays, diagnostic limitations, and lack of awareness are important reversible contributing factors to the cur- rently poor outcome of scrub typhus. Antibiotics effective against scrub typhus, such as doxycycline, are often not routinely given as part of empirical treatment strategies. Hence, particularly as diagnosis is difficult, scrub typhus is often undertreated, contributing to the dis- ease burden associated with this important but neglected disease. Entomology Leptotrombidium mites are the main reservoir and vectors of Orientia spp. They are usually characterized by the form of their dorsal shield structure called ‘scutum’ and the pattern of setae and sensillae hairs attached to it (Fig. 8.6.41.5). The trombiculid life cycle consists of (a) (c) (d) (b) Fig. 8.6.41.5 Morphological characteristics of chigger mites. Chigger mites are small—a typical trombiculid mite larva is approx. 0.2 mm and has three pairs of legs, whereas adult mites have four pairs (a, scale 100 um). Morphological mite identification requires description of mouthparts (chelicerae), palpal and tarsal claws, segmentation of the legs (b, scale bar 20 um), and the characteristic dorsal shield-like plate termed scutum (c and d, scale bars 20 um). The scutum of Aschoschoengastia sp. have a rectangular shape with fine setae hairs at the outer edges, and two hairy clubbed sensillae, the feeler hairs (c). The scutum of Gahrlipia sp., subgenus Walchia have a shield-shaped scutum and also clubbed sensillae (d). The bases of the sensillae are often mistaken for the eyes—these are actually pale discs located next to the scutum (arrows). Images taken with the support of Dr Sungsit Sungvornyothin, Medical Entomology Dept., Mahidol University.

 four stages: eggs, larvae, nymphs, and adults; only the larval forms (‘chiggers’) feed on vertebrate hosts, whereas nymphs and adult mites live in the soil and feed on the eggs of insects. Chiggers penetrate the skin with chelicerae and use their enzyme-rich saliva to digest a tube-like structure (termed ‘stylostome’) through the epidermal layer and inoculate Orientia, as high pathogen concentrations are found in the saliva. Mites of all stages can harbour Orientia, which are maintained through the various stages in the mite life cycle, and vertically via transovarial transmission over many generations. O. tsutsugamushi infections in

mites can alter the sex ratio in some mite species, resulting in most progeny being female. Although mites transmit O. tsutsugamushi to vertebrate hosts such as rodents very effectively, only a small proportion of uninfected mites acquire Orientia during feeding on infected animals. Free-living mites are typically collected using black plates and black cloths placed on the ground and/or on grass, on to which they are attracted. Mite larvae (chiggers) are best collected by trapping of rodents and collected dir- ectly from ears and genital areas—their preferred sites for attach- ment and feeding (Fig. 8.6.41.6). Areas of uncertainty, controversy, and future developments Drug resistance Scrub typhus patients usually become afebrile within 48 hr of starting appropriate treatment, but in 1996 both chloramphenicol and doxycycline resistance were reported in Chiangrai in nor- thern Thailand; only 40% of patients cleared their fever within 72 hours, compared to 100% in patients from Mae Sod on the Thai Myanmar border; median fever clearance times in Chiangrai were 80 h (range 15–190 h) compared to 30 h in Mae Sod (range 4–58 h). The underlying nature of these possibly resistant infections has not been investigated further. Considering the current case fa- tality rate of 13% in hospitalized patients in this region, it is of great clinical relevance to determine if the infecting Orientia strains are truly antibiotic resistant, or whether there are other explanations for this poor clinical response. The genome of O. tsutsugamushi The genome of O. tsutsugamushi is the largest in the order Rickettsiales with a single chromosome of approx. 2.0 Mb in size. It is eccentric, as it contains the highest number of repetitive sequences of any bacterial organisms known to date; 47% of the genome are repeats derived from integrative, conjugative, and transposable elements. Both massive gene amplification and degradation have generated a huge number of repeated genes with intensive genome shuffling, but the proliferation of mobile elements and the selective pressures influencing them remain unexplained. The adaptation of rickettsia to an obligate intracellular lifestyle is associated with an increased reliance on host cellular functions. As the bacteria discard many of their enzymes over time (reduc- tive genome evolution), an increasing supplementation with host cell metabolites and substrates takes place. Large-scale comparative genomic analyses suggest that gene loss has been a driving force for obligate intracellular bacterial genomes (and not acquisition of viru- lence factors) to adapt to particular host-associations in eukaryotic cells. Rickettsia and Orientia genomes have revealed interesting con- troversies between reductive evolutionary forces on metabolic genes observed in all species, but proliferation of mobile genetic elements in only some. These evolutionary effects highlight the influence of chance, adaptation, and host cell exploitation during the evolution of intracellular bacteria, but the underlying mechanisms remain poorly understood.

FURTHER READING

Cross R, et al. (2016). Revisiting doxycycline in pregnancy and early childhood—time to rebuild its reputation? Expert Opin Drug Saf, 15, 367–82. Dittrich S, et al. (2015). Orientia, rickettsia, and leptospira pathogens as causes of CNS infections in Laos: a prospective study. Lancet Glob Health, 3, e104–12. Kim YS, et al. (2004). A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub ty- phus. Clin Infect Dis, 39, 1329–35. Koh GC, et al. (2010). Diagnosis of scrub typhus. Am J Trop Med Hyg, 82, 368–70. McGready R, et al. (2014). Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. PLoS Negl Trop Dis, 8, e3327. Panpanich R, Garner P (2002). Antibiotics for treating scrub typhus. Cochrane Database Syst Rev, 3, CD002150. Paris DH, et al. (2012). Orientia tsutsugamushi in human scrub typhus eschars shows tropism for dendritic cells and monocytes rather than endothelium. PLoS Negl Trop Dis, 6, e1466. Paris DH, et al. (2013). Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. Am J Trop Med Hyg, 89, 301–7. Peter JV, et al. (2015). Severe scrub typhus infection: clinical features, diagnostic challenges and management. World J Crit Care Med, 4, 244–50. (c) (d) (a) (b) Fig. 8.6.41.6 Methods for capturing soil and rodent-borne mites in the field.

Ongoing epidemiological field surveys serve to characterize mites transmitting scrub typhus to humans. Black plastic plates of approx. 30 cm length are placed on the ground or black cloth is placed on shrubby grass for a few minutes and free-living mites crawl onto these (a) and (b). Mites are easily identified on the black background and are collected for microscopic morphological and molecular identification. The mite life cycle takes place in the upper soil layers, and topsoil can be collected for subsequent isolation of mites using a Berlese Funnel (c). In (d), a freshly captured rodent has chigger mites in its ears (orange or cream-coloured spots) and distributed along the edge of the ear (arrows).

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