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REVIEW

Scrub typhus: risks, diagnostic issues, and management challenges

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Abstract: Scrub typhus is an acute febrile illness in the "tsutsugamushi triangle", transmitted by chiggers that can be treated effectively if detected early. Laboratory testing, including molecular and serological assays, is needed for confirming the diagnosis, especially in the absence of the pathognomonic eschar. In this review, factors that play a role in disease occurrence and clinical clues for diagnosis, in addition to risk factors contributing to disease severity, including mortality, are discussed in detail. Moreover, issues related to diagnostic assays, treatment, and mixed infections are also enumerated and described.

Keywords: *Orientia tsutsugamushi*, disease severity, mortality predictors, diagnosis, coinfections, treatment

Introduction

Scrub typhus is a vector-borne zoonosis endemic in South Asia, Southeast Asia, East Asia, the Pacific Islands, and Northern Australia (the "tsutsugamushi triangle"), with reports of similar infections from Africa, the Middle East, and South America.[1] This infection is caused by *Orientia tsutsugamushi*, which is transmitted to humans by the bite of infected chiggers (larvae) of trombiculid mites.[2] The name "tsutsugamushi disease" was given by Hashimoto in 1810.[3] The tsutsugamushi triangle is home to more than half the world's population,[4] with 2 billion at risk and 1 million cases of scrub typhus occurring per year.[5] Clinical manifestations range from asymptomatic to severe disease. The mortality rate varies and can be as high 50%,[6] such that the mortality among 1 million infections in a single year is likely enormous.[7] This is because the organism responsible affects the vascular endothelium and mononuclear macrophages. Therefore, all organs, including the lungs, liver, kidneys, and central nervous system, can be affected.[8] Misdiagnosis and underdiagnosis is also known to occur due to lack of availability of diagnostic tests and the aspecific nature of symptoms, especially when the characteristic eschar is not present.[7,9–11]

Scrub typhus is not transmitted directly from person to person; it is only transmitted by the bites of vectors.[12] The vector responsible is the chigger of the trombiculid mite belonging to the genus *Leptotrombidium*, but recently newer vector genera have been discovered that are capable of transmitting this agent. Tilak et al reported that *Schoengastiella ligula* (northeast India) transmitted *O. tsutsugamushi* in tea-garden workers,[13] while Lee et al discovered this agent could be transmitted by *Euschoengastia koreaensis* in South Korea.[14] Knowledge of the vector, including species, distribution, density, and habitats, is important to understand the epidemiology of scrub typhus in

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a given area or region.[15] Vector activity is related to temperature, rainfall (climate), land use (ecology), and various socioeconomic factors.[4,8,15–17] An increase in vector density contributes to increased transmission, due to more humans being bitten by infected chiggers.

O. tsutsugamushi serotype distribution varies from region to region in the tsutsugamushi triangle, and strain types are identified by sequencing the 56 kDa gene.[18–20] In South Korea, the Boryong serotype is predominantly encountered, the Karp and Gilliam serotypes are common in Taiwan, and the Gilliam serotype is prevalent in China.[18] In India, based on a 56 kDa analysis, strains similar to Kato and Karp are common, whereas in Japan Kato, Karp, Gilliam, Kawasaki, and Kuroki types are observed.[19]

Scrub typhus without the eschar is a febrile illness without any evidence of localization, and is hence termed "acute undifferentiated fever".[21–24] This illness is thus clinically indistinguishable from malaria, dengue fever, other rickettsioses, leptospirosis, and enteric fever, which are common causes of acute undifferentiated fever in the Asia-Pacific region.[10,22,23,25–29] In this review, factors describing populations at risk, severity predictors, clinical clues, diagnostic assays, coinfections observed, and drugs available for treatment of scrub typhus are described.

Risk factors for acquiring scrub typhus

The abundance of the chigger of the trombiculid mite, which is the vector for scrub typhus, determines the chance of acquiring scrub typhus, which in turn determines the prevalence of scrub typhus in a given region.[4] There is always a spurt of cases during certain seasons in the endemic areas described, and this varies from country to country and is dependent on the climate[1] and environment. Additionally, within a country, certain regions show increased prevalence.

Chiggers are abundant in locales with high relative humidity (60%–85%), low temperature (20°C–30°C), low incidence of sunlight, and a dense substrate-vegetative canopy.[2,30,31] As such, they are found in great numbers in forest clearings, riverbanks, and grassy regions. Humans acquire scrub typhus on exposure to infected larvae (chiggers) of trombiculid mites. The density of chiggers of *Leptotrombidium pallidum* and *L. scutellare* is very high from September to November in South Korea, with a consequent rise in scrub typhus in humans. This provides evidence that an increase in chigger density of the vector species is responsible for the high seasonal prevalence in endemic areas.[17] This variation in chigger activity gives rise to the seasonality of scrub typhus.

Peak prevalence in South Korea occurs in autumn (September–November), in Japan increased cases are observed in autumn and winter, in north China (Shandong) in September–November, and in south China in June–September. In south India, scrub-typhus cases occur mostly in the cooler months (August–January), while in Southeast Asia scrub-typhus cases are highest in July–November.[32] Incidence of scrub typhus can vary from country to country and also region in large countries like India and China. It has been reported that each 1°C and 1% change in temperature can cause an increase in incidence,[16] as evidenced by a 15% rise in scrub-typhus cases in Guangzhou, China.[8]

In addition to temperature, secondary vegetation and rainfall also increase the incidence of scrub typhus.[33] Occupational risk is higher in farmers (aged 50–69 years), females,[6] and those working in vegetable fields, harvesting in autumn,[34] and rural highlands.[35] In a study by Kweon et al, outdoor activities like resting on a grass field without a mat, working in short sleeves and bare hands, and defecating and/or urinating outdoors while squatting increased risk for scrub typhus.[12] In a case-control study from South Korea, individuals engaged in fruit farming, gathering chestnuts, and taking breaks in areas adjacent to agricultural operations had an increased risk of contracting scrub typhus compared to controls. The authors opined that providing a health-education program would lower the risk in these individuals and similar groups.[36] Land use is another determinant, as scrub-typhus incidence increases when forest lands are converted to fields, palm oil, and rubber plantations,[2]and also when urbanization occurs.[36]

Clinical clues favoring a diagnosis of scrub typhus

Presence of eschars

The presence of eschars is considered pathognomonic. It has been reported that eschar incidence varies from 7% to 97% in endemic areas[5] and is painless.[37] Eschars are often found in covered areas of the body, such as the groin, axilla, chest, and lower back, including the buttocks.[9,10,38–40] Recently, there have been reports of multiple eschars[41,42] and atypical eschars,[43] which were punched-out ulcers with slough. This could also be due to the original eschar scab being removed by scratching[44] or falling away, especially during bathing. This seems plausible, because the eschar appears at the chigger-bite site a few days before the onset of symptoms.[37] Therefore, a thorough examination becomes necessary and improves eschar detection, leading in turn to improvement in the diagnosis of scrub typhus in a clinical setting. This has been observed at our center: eschar incidence improved from

<10% in 2003[45] to 55% in 2013.[46] Eschars of scrub typhus appear a few days after at chigger-bite sites, before the disease manifests. The eschar is painless and consists of a black scab, with an erythematous halo and minimal edema.[44,47] Detection of eschars is dependent not only on the clinical experience of the examining physician but is also influenced by skin color (eschars are more easily seen on the fair-skinned than the dark-complexioned) and also on the thoroughness of the physical examination.[48] The differentials for a scrub-typhus eschar include insect bites (including spider bites) and post-traumatic scabs,[49] which can all be ruled out with a little patience and perseverance. The eschar of anthrax, though painless, is surrounded by extensive or marked edema that is gelatinous and stretches the skin, and is often preceded by a pruritic papule.[50,51] Table 1 gives a summary of clinical and laboratory findings favoring or not favoring a diagnosis of scrub typhus.[23,25,28,52–58]

Use of clinical prediction rules

As given in Table 1, a few clinical clues other than eschars are available for suspecting or diagnosing scrub typhus in the clinic or at the bedside. It is to be noted that even at a referral hospital in endemic countries, the diagnosis of scrub typhus is usually based on the clinical findings.[54] As definitive diagnosis requires laboratory testing, clinical prediction rules have been tried. Chen et al observed a 100% negative predictive value for clinical criteria combining the presence of eschars, atypical lymphocytes in peripheral blood smear, and contact history.[59] A clinical rule formulated for scrub typhus by Jung et al uses five predictors with a maximum score of 8 points. The scoring criteria include age ≥65 years (2 points), recent history of fieldwork/outdoor activities (1 point), onset of illness during an outbreak period of scrub typhus (2 points), myalgia (1 point), and eschars (2 points). A score below 3 rules out scrub typhus, while 100% sensitivity was observed for a score ≥3. the authors felt that this could be used for selecting patients for empirical therapy in resource-poor situations or for performing specific laboratory tests.[23] Similarly, Siriwongpan et al devised and validated a clinical risk scoring system using a set of 526 patients with scrub typhus based on the World Health Organization (WHO) case definition.[60–62]

Risk factors determining severity and outcome in scrub typhus

Severity of disease based on genotype

The severity of scrub typhus varies considerably, which might correlate with the virulence of the particular *O. tsutsugamushi* strain responsible for the infection. There is evidence that frequency of eschars and rash in scrub typhus is dependent on the infecting genotype. South Korean individuals with the Boryong genotype have significantly higher incidence (97%) of eschars and skin rash compared to 74% with the Karp genotype.[63] Karp genotypes (summer scrub typhus, isolated in Guangdong, Fujian, Hainan provinces in southern China) were found to be more virulent and caused more severe disease than Kawasaki genotypes (autumn–winter scrub typhus) isolated in Shandong and northern Jiangsu provinces in northern China.[48] Eschar presence was not significant in severe and nonsevere scrub typhus.[64]

Clinical and laboratory parameters predicting severity in scrub typhus

Patients with possible scrub typhus with low body temperature, rapid pulse rate, presence of crepitation, low percentage of lymphocytes, low serum albumin, elevated aspartate aminotransferase, elevated serum creatinine, and positive urine albumin should be monitored closely for severity progression.[60] Tables 2 and 3 provide a summary of the significant features predicting severity and outcome of scrub typhus. Parameters that show very significant *P*-values (0.01) by multivariate logistic regression analysis have been included in the tables. In a meta-analysis of 89 studies (19,644 patients with scrub typhus), fatal outcome was reported in 2,488 patients, with an overall mortality of 12.7%. Though increasing age

Table 1 Parameters compatible and incompatible with a diagnosis of scrub typhus ($P<0.01$)

Supporting a diagnosis of scrub typhus	Against a diagnosis of scrub typhus (usually diagnosed)
Eschar	Bone pain (dengue)
Regional lymphadenopathy	Bleeding manifestations (dengue)
Total fever ≥8 days	Loose stools (enteric fever)
CRP >32 mg/L	White blood-cell counts <5,000/mm^3 (dengue)
ALT/AST >1	Platelets <50,000/mm^3 (dengue)
Defervescence within 48–72 hours of specific therapy	Bilirubin >2 mg/dL (malaria, hepatitis A)
	AST >500 U/L (dengue)
	ALT <100 U/L (malaria)
	ALT >500 U/L (hepatitis A)

Table 2 Predictors of mortality in patients diagnosed with scrub typhus ($P<0.01$)

Parameter	Significant value	OR (95% CI)	Study
Age	>65 years	14.5 (1.3–166.4)	Thipmontree et al[66]
Creatinine	>1.5 times normal	12.8 (1.8–92.1)	
Total bilirubin	>3 mg/dL	24.8 (2.1–286.6)	
Hemoglobin	≤10 g/dL	32.1 (2.6–393.8)	Park et al[67]
Inotropic support	BP <90 mmHg	10.1 (4.5–22.9)	Varghese et al[68]
Creatinine	>2 mg/dL	3.5 (1.7–7.1)	
CNS dysfunction	–	6 (2.8–12.8)	
Metabolic acidosis	Venous HCO_3 <17 mmol/L	6.1 (1.8–21.3)	Chrispal et al[21]
ARDS	Bilateral pulmonary infiltrates (CXR); peak flow ratio <200; normal CVP	3.6 (1.2–10.7)	
Altered sensorium	Historical or observed altered sensorium	3.1 (1–9.9)	
Shock	Systolic BP <90 mmHg	3.1 (1–9.8)	

Abbreviations: OR, odds ratio; CI, confidence interval; CNS, central nervous system; ARDS, acute respiratory distress syndrome; CXR, chest X-ray; CVP, central venous pressure; BP, blood pressure.

Table 3 Parameters associated with adverse events in patients with scrub typhus ($P<0.01$)

Patient group	Outcome	Variable/parameter	Significant value	OR (95% CI)	Study
Elderly (>60 years)	Severe disease (AKI)	WBC count	>10,000/mm^3	2.6 (1.3–5.1)	Jang et al[69]
		MDRD GFR	<60 mL/min	3.5 (1.9–6.7)	
		Albumin	≤3 g/dL	5 (2.7–9.3)	
		APACHE II score	>10 points	3.3 (1.8–60.9)	
Adults (>16 years)	ICU admission	WBC counts	>11,000/mm^3	1.3 (1–1.5)	Lee et al[70]
		Pulmonary infiltrates	Present	25 (4–161)	
Adults (>16 years)	Hospital stay >10 days	MODS	Two or more organs damaged	10 (2.3–43.9)	Lee et al[70]
Adults (>16 years)	Severe scrub typhus	Rash	Present	3.7 (1.3–10.5)	Zhang et al[64]
Adults (>18 years)	Severe scrub typhus	WBC counts	>10,000/mm^3	4.6 (1.6–7.9)	Kim et al[71]
		Serum albumin	≤3 g/dL	8.5 (1.7–14.9)	
		Age	≥60 years	3.1 (1.5–6.4)	
		Eschar	Absent	6.6 (1.2–35.8)	
Adults (>18 years)	AKI	Comorbidity	Htn and/or DM and/or CKD	6.5 (2.8–15.2)	Sun et al[72]
Children (<14 years)	MODS	AST	>160 IU/mL	4.7 (1.4–15.6)	Zhao et al[73]
Not mentioned	AKI	ICU admission	–	2.9 (1.4–5.8)	Attur et al[74]
Children and adults	Severe scrub typhus	Pulse rate	>100/min	3.2 (1.9–5.4)	Sriwongpan et al[61]
		Crepitations	Present	3 (1.6–5.4)	
		AST	>160 IU/mL	2.9 (1.9–4.4)	
		Serum albumin	≤3 g/dL	4.7 (3–7.5)	
		Serum creatinine	>1.4 mg/dL	8.2 (5.1–13.4)	

Abbreviations: OR, odds ratio; CI, confidence interval; AKI, acute kidney injury; WBC, white blood cell; MDRD, Modification of Diet in Renal Disease; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; MODS, multiple-organ dysfunction syndrome; Htn, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease.

was associated with fatality, presence or absence of eschars did not affect the outcome.[65]

Laboratory diagnosis of scrub typhus

Scrub typhus can mimic other acute febrile illnesses common in the tropics, especially when pathognomonic eschars are absent.[10] Therefore, laboratory tests become mandatory for confirmation of the diagnosis.[38,75,76] Methods available include direct methods like isolation of the pathogen in cell cultures (HeLa, L929, Vero, and BHK21) and detection of scrub typhus-specific DNA like 56 kDa, 47 kDa, 16S ribosomal RNA, and GroEL gene targets by polymerase chain reaction (PCR). Indirect methods include detection of antibodies to *O. tsutsugamushi* by immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA),[77] and rapid diagnostic assays.[78,79] Tables 4 and 5 give performance characteristics of the available assays for laboratory confirmation of scrub typhus.

Real-time PCR assays like the 47 kDa, 56 kDa, and GroEL are increasingly used, and these detect 10–50 copies/μL of *O. tsutsugamushi*. Real-time PCR specificity is higher if type-specific genes are used (eg, 56 kDa and 47 kDa genes for *O. tsutsugamushi*) than if genus-specific genes are used (17 kDa genes for *Rickettsia* spp.), which again are stronger than nonspecific conserved "housekeeping" genes like *HSPD1* (GroEL) and 16S ribosomal RNA.[27] The drawback

Table 4 Performance of nonmolecular diagnostic tests used for detection of scrub typhus

Type of assay	Sensitivity (%)	Specificity (%)
Cell culture[49,81,95,96]	5–56	100
Antigen detection[97]	65–100	100
IgM IFA[49,98–103]	70–100	84–100
IgM + IgG IFA[98,99,102]	78–97	98–100
IgM ELISA[29,49,76,85,89,90,98,100,101,104–106]	70–100	87–100
IgG ELISA[90,100,105,106]	58–96	92–98
IgM ICT[78,79,87,90,95,98]	47–99	95–100
IgM + IgG ICT[76,79,98,107,108]	61–100	74–100

Abbreviations: IFA, immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; ICT, immunochromatographic test.

of molecular assays is that the best yield is seen with eschar biopsy, followed by buffy coat, whole blood, and blood clots.[29,38,80–82] As obtaining eschar biopsies is challenging, eschar-swab specimens have been used and found to be adequate for detection of scrub typhus-specific DNA.[29,82] In contrast to eschar PCR, buffy-coat positivity by PCR (scrub typhus) falls to 10%, 4 days after treatment.[83] Sometimes, typical eschars are not observed, and in such situations PCR or immunohistochemical staining methods using eschar-like crust lesions will be useful.[80,84]

Though determination of scrub-typhus antibodies is the mainstay of scrub-typhus diagnosis,[85] definitive evidence of causation by serology is provided only when paired sera demonstrate a fourfold rise in titer or seroconversion.[86] As paired sera are seldom available, a single cutoff titer for IFA, ELISA, and rapid diagnostic tests can be used for diagnosis, provided the background noise in the population has been determined.[76,87,88] Serology can determine past and recent exposure to *O. tsutsugamushi*, and thus is useful for disease surveillance.[82] Though considered the gold standard, IFA is now under threat as the reference test for scrub-typhus diagnosis.[5,7,29,49,82,88,89] The IFA (which uses cell culture-grown *O. tsutsugamushi* as antigens) can be used to differentiate IgM and IgG classes of antibodies. It is semiquantitative, as antibody concentration is reported as a titer (inverse of the highest dilution giving a positive reaction). Moreover, it requires fluorescence microscopy, is very labor-intensive, and despite adequate training of personnel is reported to have a high incidence of interassay and intra-assay variability.[5,38,88] ELISA, on the other hand, can be automated and thus used to screen large numbers of sera, is objective (optical density value), economical, technically simpler, and able to detect antibody levels also.[82] Due to strain variation, 56 kDa antigen cocktails are being used for detection of scrub-typhus antibodies.[90] As there is evidence that ELISA is more accurate than IFA,[48] it is being recommended as an alternative to the IFA.[88,89,91] Rapid diagnostic tests are becoming important, as a rapid diagnosis can be made with a certain degree of certainty, especially in endemic areas.[79] The Weil–Felix agglutination test is definitely a cheap option for diagnosis of rickettsial infections, including scrub typhus, in resource-poor settings.[76] Though it has poor sensitivity, it can have good specificity[85,92] and is a good test in resource-poor situations for demonstrating the presence of scrub typhus or rickettsioses, though most workers feel it has poor specificity.[76,82]

Bayesian latent-class modeling has been used to determine diagnostic test performance, as it does not consider any test as perfect.[49] In addition, composite criteria involving culture, PCR, and serological positivity like scrub typhus-infection criteria have been used.[81] Moreover, a WHO case definition for scrub typhus also is available,[93] as is an expert-derived Indian Council of Medical Research case definition.[94] Lim et al concluded that combinations of IgM ICT and presence of eschars have good specificity and can be

Table 5 Summary of performance characteristics of molecular assays for diagnosis of scrub typhus

Target	Assay	Sensitivity (%)	Specificity (%)
56 kDa	Conventional PCR[109–111]	0–96	100
	Nested PCR[18,20,49,80,81,83,96,109,110,112–119]	16–100	88–100
	qPCR[120,121]	65–73	100
47 kDa	Conventional PCR[110,111]	3–7	100
	Nested PCR[110,111]	81–85	100
	qPCR[49,81,110,122]	63–81	90–100
	LAMP[123,*]	52	94
16S rRNA	Conventional PCR[111,119]	45–87	100
	qPCR[124]	52	100
GroEL	Conventional PCR[111]	66	100
	Nested PCR[125]	90.4	100
	qPCR[49,81,126,127]	56.4	96.2
	LAMP[81,127]	87.5	100

Note: *An evaluation done using 24 eschar samples from scrub typhus-confirmed cases showed sensitivity and specificity of 83.3% and 100%, respectively (Prakash, unpublished data, 2012).

Abbreviations: qPCR, quantitative polymerase chain reaction; LAMP, loop-mediated isothermal amplification; rRNA, ribosomal RNA.

used in resource-poor situations as point-of-care diagnostic tests, whereas performance of a PCR would be very useful in centers with facilities for same.[49]

Coinfections and scrub typhus

In endemic areas, coinfections have been described, and these include infections with other pathogens causing similar illness. Table 6 enumerates the grading of coinfections according to Phommasone et al,[27] and Tables 7 and 8 describe such infections.

A few scenarios are described for our understanding. The first is by Sonthayanon et al, who found that among the 82 serological coinfections observed, molecular assays were positive for leptospirosis in 43 (52%), scrub typhus in nine (11%), and both in five (6%), whereas 25 (30%) were negative for both leptospirosis and scrub typhus. Possible explanations for the difference observed between serologic and molecular results include low sensitivity of the molecular assay, failure to test a sample obtained during the window of bacteremia in leptospirosis, serologic cross-reactivity, and acute infection caused by one pathogen in the background of a recent but inactive infection caused by the second pathogen.[128]

Second, in the presence of eschars, testing for *Leptospira* serology is unwarranted, according to Lee and Liu, as four of the seven cases who were *Leptospira* serology-positive had eschars.[26] As treatment with doxycycline or azithromycin is very effective against *Leptospira* and *Orientia*, serological cross-reaction or coinfection does not matter, as treatment with either will be beneficial to the patient with an acute febrile illness when both serologies are positive.[129]

Third, dual and triple infections occur, as reported by Ahmad et al, who described malaria, dengue, and scrub typhus in five cases, 21 were dengue cross-reactive, malaria smears were positive in 14, and nine individuals had IgM antibodies to scrub typhus and dengue. Further clarification regarding which was a cross-reaction could have been determined if information regarding presence or absence of

Table 6 Grading of coinfections

Grade	Tests	Specificity	Sensitivity
I	Culture, NAATs, and antigen detection	Best	Poor
II	Seroconversion Rise in titer in paired sera Western blot-positive	Good	Good
III	Single serological value above cutoff	Poor	Very good

Abbreviation: NAATs, nucleic acid-amplification tests.

Table 7 Coinfections (dual) demonstrated in scrub-typhus patients

Evidence grade	Coinfecting pathogen (test positive)	Positive	Diagnostic test positive for scrub typhus
Grade I	*Rickettsia typhi* (PCR)[132]	3	PCR
	Plasmodium falciparum (smear)[133]	2	PCR
	Leptospira (culture, PCR, MAT)[53]	5	Culture and/or PCR
	Dengue (NS1 antigen, PCR)[53]	10	
	Rickettsia spp. (PCR)[53]	3	
	Mycoplasma pneumoniae (PCR)[134]	1	PCR
	Leptospira (PCR)[128]	5	PCR
Grade I and II	*Leptospira* (culture, PCR, MAT)[135]	4	Culture, PCR, and IFA
Grade II	*Leptospira* (culture, MAT, IFA)[136]	62	IFA
	Leptospira (MAT)[26]	7	IFA
	Leptospira (culture, MAT)[129]	11	IFA
	Coxiella burnetii (IFA)[137]	5	IFA
	Dengue (NS1-antigen ELISA)[138]	1	IFA
	JEV (IgM ELISA)[53]	26	Culture and/or PCR
	Leptospira (MAT)[139]	1	IFA
	Leptospira (MAT)[140]	1	IFA
	Severe fever with thrombocytopenia syndrome (PCR)[141]	3	IFA
Grade III	Leptospira (MAT)[142]	9	Dot-blot assay
	Dengue (NS1 antigen)[131]	6	IgM ELISA
	Leptospira (IgM ELISA)[143]	8	IgM ELISA
	Dengue (IgM ELISA)[130]	21	IgM ELISA
	Malaria (smear)[130]	14	
	Spotted fever, group rickettsia (IFA)[144]	3	IFA
	R. typhi (IFA)[144]	1	

Abbreviations: PCR, polymerase chain reaction; MAT, microscopic agglutination test; IFA, immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; JEV, Japanese encephalitis virus.

Table 8 Details of infections with two other pathogens in scrub-typhus patients

First pathogen (test)	Second pathogen (test)	Third pathogen (test)	Number (evidence)
Orientia tsutsugamushi (PCR)	*Rickettsia typhi* (PCR)	*Mycobacterium tuberculosis* (culture)	1 (Grade I)[135]
O. tsutsugamushi (PCR)	*R. typhi* (PCR)	*Salmonella enterica*, group D (culture)	1 (Grade I)[135]
O. tsutsugamushi (PCR)	Leptospirosis (PCR)	JEV (IgM-capture ELISA)	2 (Grade II)[53]
Plasmodium vivax (RDT)	*O. tsutsugamushi* (PCR)	Dengue (NS1 antigen)	1 (Grade I)[145]
Malaria (smear)	Dengue (IgM ELISA)	*O. tsutsugamushi* (IgM ELISA)	5 (Grade III)[130]
O. tsutsugamushi (IFA)	*R. typhi* (IFA)	Spotted fever, group rickettsia (IFA)	6 (Grade III)[144]

Abbreviations: PCR, polymerase chain reaction; JEV, Japanese encephalitis virus ELISA, enzyme-linked immunosorbent assay; RDT, rapid diagnostic test; IFA, immunofluorescence assay.

eschars was available[130] or determination of NS1-antigen positivity, as was done by Basheer et al.[131]

Management challenges

Atypical clinical features and absence of eschars may result in delayed diagnosis, complications, or death.[76] Scrub typhus responds promptly to effective treatment, with patients becoming afebrile within 24–48 hours,[41,94] so much so that when enteric fever, septicemia, and malaria are ruled out, empirical treatment with doxycycline (even when given late in the disease) is clinically useful.[146] Therefore, empirical therapy with doxycycline is to be encouraged in regions or locales where scrub typhus is endemic or reemerging. This will lead to a reduction in complications, with a corresponding decrease in morbidity and mortality.[146] Treatment for scrub typhus has been reviewed extensively by Peter et al[86] and Rajapakse et al.[147] Doxycycline is useful as an empirical treatment, because of its high cost-effectiveness and wide spectrum of activity, and is considered safe in children <8 years of age.[44] There is grade B evidence for lack of dental staining in children given short-course doxycycline, as may be given in scrub typhus.[148–151] Moreover, doxycycline reaches good concentrations in cerebrospinal fluid, as does minocycline, though use of the latter is limited by dose-related vestibular side effects.[151] Fluoroquinolones are not good drugs for treatment,[150,152] nor are penicillins, clarithromycin, and cephalosporins.[153] *O. tsutsugamushi* with reduced susceptibility has been observed for doxycycline and chloramphenicol in Chiang Rai, northern Thailand.[154–156] This may not have been true resistance, but due to delayed treatment or tolerance.

Data on scrub typhus in pregnancy are scanty. Among the 82 cases reviewed from the literature till 2014 by McGready et al, 2.5% were associated with maternal mortality. Miscarriage occurred in 17%, and poor neonatal outcomes (stillbirth, preterm labor, and low birth weight) were documented in 42%. Macrolide antibiotics, such as azithromycin, are safe in pregnancy, but doxycycline, which is cheaper, can also be used if the former is not available.[157] The aim of therapy is to save both mother and child,[158] and the benefits of therapy with doxycycline outweigh the risks.[148–151] Cross et al opined that doxycycline treatment should be used in children and pregnant women for treating scrub typhus, as the infection-associated risks are too large and thus overwhelmingly against avoiding therapy with this agent.[151] Recently, Jang et al reported that intravenous azithromycin was efficacious in the treatment of severe scrub typhus.[159]

The major concern is that misdiagnosis occurs when the characteristic eschars are absent.[153] This is of importance, as treatment with an appropriate antibiotic (doxycycline, tetracycline, or chloramphenicol) renders patients afebrile within 48 hours, such that pyrexia persisting beyond 72 hours rules out scrub typhus. Such patients have jaundice (icteric sclera and/or total bilirubin >1.5 mg/dL), no headache, and relative bradycardia (<110/min).[25]

Conclusion

Scrub typhus is an important cause of febrile illness in the Asia-Pacific region. The main management challenge is institution of specific therapy in a timely and an effective manner, as stated elsewhere in this review. For this, rapid and accurate diagnosis becomes necessary, especially in the absence of eschars. In resource-poor endemic settings, clinical prediction rules have been defined and found useful. In addition, a battery of tests is needed for increasing diagnostic yield and sorting out the issue of coinfections. Finally, appropriate treatment should be initiated, keeping in mind the risk and benefits afforded by such treatment.

Disclosure

The author reports no conflicts of interest in this work.

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