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EMERGING TROPICAL DISEASES (K BARR, SECTION EDITOR)

Scrub Typhus: an Update*

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Abstract

Purpose of Review Scrub typhus has recently assumed public importance. This article expounds current understanding of the epidemiology, clinical features, diagnosis, treatment, and control.

Recent Findings It is a zoonotic disease caused by several strains of the rickettsial bacterium *Orientia tsutsugamushi* and is spread by the bite of larvae of *Leptotrombidium* mites. Until recent times, the disease was confined to rural areas in the "tsutsugamushi triangle," but now it is reported beyond it also. Pathogenesis involves endothelial injury with consequent vasculitis and systemic inflammatory response. It presents as fever with or without a wide range of complications. Multiorgan dysfunction carries high mortality. There are a number of accurate diagnostic modalities, and treatment of choice is doxycycline with several alternatives. There are concerns regarding emergence of drug resistance, and no vaccine is available.

Summary Scrub typhus is resurging infection, and development of an effective control program and sensitization of medical community is the need of the hour.

Keywords Scrub typhus · *Orientia tsutsugamushi* · Rickettsial · Treatment · Complications · Diagnosis

Introduction

Scrub typhus is caused by the bacterium *Orientia tsutsugamushi*. It belongs to the family Rickettsiaceae which comprises of Gram-negative bacteria that are obligate intracellular parasites and are spread by the bite of insect vectors. The terms "tsutsuga" and "mushi" are derived from Japanese and literally translate to disease and bug, respectively [1]. There are at least 30 distinct strains of *O. tsutsugamushi*, arising due to variation in the 56 kDa outer membrane protein [2]. The chief strains that produce human disease include Gilliam, Kato, Karp, Boryang, and Kawasaki. Scrub typhus is a zoonotic infection that is spread to several mammals by the bite of larvae (chiggers) of mites belonging to the genus *Leptotrombidium*, which commonly inhabit areas with low lying and dense or sparse vegetation [3]. The nymph and adult stages do not transmit the disease as they prey only on insect eggs. The mites transmit the pathogen to progeny via transovarian mode. In nature, the mites and rodents serve as reservoirs. Rodents are the natural hosts but do not suffer from disease, while humans are accidental end hosts. Growth of the mite population contributes to the spurt in cases during rainy season [4].

Epidemiology

The epidemiology of scrub typhus is changing to involve a greater part of the world. This may be due to global warming, increasing international travel and rapid industrialization [5]. The disease garnered interest during the Second World War, when outbreaks were reported among many soldiers stationed in camps [6]. Until the start of the twenty-first century, its occurrence was thought to be restricted to the "tsutsugamushi triangle" that is formed by connecting Pakistan, Japan, and northern Australia (Fig. 1). However, it has now been documented outside this region with cases without a history of travel here being reported from Middle East, Africa, and South America [7•]. Back in 1999, the World Health Organization (WHO) acknowledged the possibility of scrub typhus being under-diagnosed in the Asia Pacific region [8].

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Fig. 1 World map depicting Tsutsugamushi triangle

This is despite the fact that it has the potential to cause very severe disease, and the response to treatment is excellent. Recently, outbreaks have been reported from many countries in the Indian subcontinent and Southeast Asia that were relatively oblivious to its presence for many decades [9]. The disease is also increasingly reported from urban areas although it was originally associated with rural areas with farmlands and forests. The factors leading to this dispersal are incompletely understood. These may include migration of the mites via travelers and the destruction of their natural habitat by deforestation [10, 11]. Certain studies have estimated the seroprevalence in general population to be 68.4% in Japan, 35.2% in South Korea, 31.8% in India, 23.7% in Bangladesh, 21% in Thailand, and 10% in China [12–17]. Most of the cases have been known to occur after monsoons, but the seasonal distribution is also undergoing a transformation, and outbreaks are now also reported in winters [18].

Pathogenesis

The bacterium is introduced into the dermis by the bite of the vector, and incubation period varies from 5 days to 2 weeks [19]. Macrophages and dendritic cells are the initial targets for infection that then undergoes hematogenous and lymphatic dissemination. The bacterium enters the target cells by endocytosis. Affliction of the endothelial cells produces vasculitis-like pathologic and clinical expressions [20]. Microvascular damage is characterized by perivascular infiltration by mono- and polymorphonuclear infiltrate along with capillary leakage and luminal thrombosis that leads to downstream tissue hypoperfusion and injury. Histopathologic examination of organs such as the liver, spleen, kidneys, lungs, brain, and heart by immunohistochemical staining or electron microscopy demonstrates the presence of bacteria within the endothelial cells and macrophages. Both humoral and cellular immune responses are elicited [21]. The primary humoral immune response is characterized by production of IgM antibodies that reach a detectable level within the first week of infection and IgG antibodies which start to appear after the second week in first infection and within first week in subsequent infections. The sensitized cytotoxic T-lymphocytes attack the infected host cells. These CD8+ cells constitute a potent defense mechanism and play an important role in clearance of the pathogen. Simultaneously, systemic inflammatory response is induced by release of pro-inflammatory cytokines such as interferon-γ, interleukin-10, interleukin-1 β, and tumor necrosis factor-α [22].

Clinical Features

The initial manifestations are non-specific, comprising of fever, chills, malaise, lymphadenopathy, headache, arthralgia,

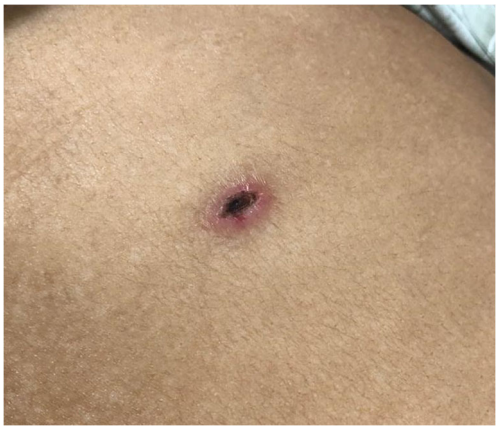

Fig. 2 The eschar present at the site of mite bite

myalgia, rash, jaundice, nausea, vomiting, and abdominal pain [19]. These features are un-differentiable from certain other infections that share similar epidemiology, such as dengue, malaria, influenza, leptospirosis, acute viral hepatitis, and enteric fever. Co-infections of scrub typhus with these diseases are frequently reported [23–28].

Localized cutaneous necrosis at the site of bite can lead to formation of the characteristic eschar (Fig. 2), which is a black-colored painless and non-pruritic scab overlying an area of erythema [29]. The eschar eventually shrinks and leaves behind an area of hyperpigmentation that clears up over time. The eschar is useful in clinical diagnosis in the endemic areas. It can be concealed under the clothes; hence, a thorough physical examination should be carried out in suspected cases. It can be inconspicuous and difficult to detect in people with a dark complexion [30]. Its occurrence has been variably reported in 7–80% of the cases in different studies [31].

The spectrum of complications reported is diverse, and they occur second week onwards. The array of laboratory abnormalities and complications that can be seen are mentioned in Table 1 [32–47]. The course can be marked by multiorgan dysfunction that carries high mortality. The disease severity varies with the strain and is directly proportional to the bacterial DNA load [48].

Delayed administration of antibiotics has been shown to be associated with more complications and, hence, mortality [49]. In a large review of around 20,000 patients not treated with antibiotics, the mortality was found to be 6% and varied among the various studies from 0 to 70% [50]. There were notable differences in the outcome depending on the region, and mortality was higher in older patients. Studies have also demonstrated lower mortality in children as compared to adults [51]. In timely treated patients, the mortality is as low as 1.4% [19].

The clinical profile and severity in pregnancy are the same as general population. However, the incidence of obstetric complications including prematurity, abortion, and fetal death

Table 1 Laboratory abnormalities and complications that can be seen in scrub typhus

Laboratory abnormalities	
Hematological	Anemia, thrombocytopenia, leucopenia, leukocytosis, coagulopathy
Biochemical	Electrolyte imbalance, urea and creatinine elevation, transaminase elevation, hyperbilirubinemia, hypoalbuminemia, cardiac enzyme elevation, amylase and lipase elevation, inflammatory marker elevation
Radiological	Pleural effusion, pulmonary infiltrates, pulmonary consolidation, hepatomegaly, splenomegaly, ascites, gall bladder edema, bulky pancreas, dilated bowel, cerebral edema, myocardial hypokinesia, meningeal enhancement, intracranial bleed, white matter hyperintensities
Complications	
Neurologic	Encephalopathy, seizures, meningoencephalitis, PRES, cerebellitis, intracranial bleed, cerebral venous thrombosis, parkinsonism, opsoclonus, myoclonus, Guillain-Barre syndrome, psychosis, transverse myelitis, ADEM, cranial and peripheral neuropathies
Gastrointestinal	Intestinal bleed, ileus, hepatitis, acute liver failure, cholecystitis, cholangitis, acute pancreatitis, splenic infarction
Hematological	Bleeding tendency, DIC, deep venous thrombosis, hemophagocytic lymphohistiocytosis, bone marrow suppression
Renal	AKI, hematuria, albuminuria, acute pyelonephritis
Cardiovascular	Myocarditis, arrhythmias, shock
Respiratory	Pneumonitis, pleural effusion, ALI, ARDS, pulmonary thromboembolism
Others	Arthritis, retinal vein occlusion, cerebral salt wasting

PRES posterior reversible encephalopathy syndrome, *ADEM* acute demyelinating encephalomyelitis, *DIC* disseminated intravascular coagulation, *AKI* acute kidney injury, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome

is greatly increased [52]. Suntharasaj et al. have reported vertical transmission in a pregnant woman with the fetus having detectable IgM antibodies [53]. This needs to be interpreted with caution, considering dearth of more literature. The risk factors for mortality have been evaluated in certain studies as shown in Table 2 [32, 35, 54–57].

Diagnosis

The gold standard test for serological diagnosis is indirect immunofluorescence assay (IFA) [58]. In this technique, the patient's antibodies from the collected serum bind to the artificially exposed scrub typhus antigen. This complex then binds to the secondary anti-human antibody that is conjugated with a fluorescent dye and can be detected with fluorescent microscopy. IFA involves use of expensive equipment and extensive training of the involved personnel. The diagnostic antibody titers vary from region to region (generally 1:320 or greater), depending on local prevalence of the disease. When serial samples are available, more than fourfold increase in titer with a baseline of 1:50 is almost always diagnostic. The sensitivity and specificity of IFA for IgM antibodies are 85% and 98%, respectively [59].

A cheaper alternative and satisfactory alternative to IFA is the indirect immunoperoxidase assay which used peroxidase-labeled antibodies and negates the need for expensive equipment for fluorescence microscopy [60]. The most widely used modality in endemic regions is enzyme-linked immunosorbent assay (ELISA) due to its lower cost and acceptable results with sensitivity and specificity concordance of up to 93% and 97.5%, respectively, with IFA [61]. A rapid diagnostic test based on immunochromatography is also utilized in countries such as Korea and Thailand. It has been found to have sensitivity of 68% and specificity of 95%. It can be used for point-of-care diagnosis [62]. The Weil Felix OX-K agglutination test, based on the principle of antigenic cross-reactivity between Proteus and certain Rickettsial species, has poor sensitivity and specificity. It is easy to perform, and results are available quickly. The test is still valuable in extremely resource poor settings [4].

Direct molecular diagnosis by polymerase chain reaction (PCR) also permits identification of the strain. Currently tests are available targeting the outer membrane proteins (56 kDa and 47 kDa) and 16S rRNA gene product [63]. The samples can be blood or the eschar. Since the eschar is not universally present, its usefulness for PCR is limited. PCR can detect the disease on the third day of infection, even before the production of antibodies. However, its high cost and skill requirement hinder its widespread use as many of the endemic regions are comprised of developing countries. Furthermore, prior antibiotic treatment can lead to false-negative results. Culture is not useful for diagnosis as it is technically difficult and growth can take 3–4 weeks [64]. Cell lines such as Vero cells, HeLa cells, and BHK-21 cells have successfully been used as media.

Treatment and Control

As with other rickettsial infections, doxycycline is the treatment of choice and is superior to all other drugs [65•]. Oral or intravenous forms are used in a dose of 100 mg every 12 h for at least 1 week. Empirical therapy is used frequently in the endemic regions when clinically suspected, especially in the presence of an eschar. The response to doxycycline is excellent, and the lack of defervescence or advancement of complications after 2 days of treatment in the absence of diagnostic doubt should raise suspicion of antibiotic resistance. The complications require individualized specific supportive therapies. Alternatively, tetracycline can be used in a dose of 500 mg every 6 h for a week, and it has been found to be equally potent [66].

Azithromycin is also highly efficacious and is commonly used in a dose of 500 mg for up to 5 days [67]. Single 1 gm dose is effective in mild infections, and in severe disease, it may be followed by 500 mg a day. It is the drug of choice in pregnancy, since doxycycline is contraindicated. It is also the preferred treatment in children. Chloramphenicol had been used for treatment until the development of new and safer antibiotics. Its use has fallen out of favor now [68]. The usual

Table 2 Significant risk factors for mortality

Study	Risk factors
Varghese et al. (2006)	AKI, hyperbilirubinemia
Lee et al. (2009)	Higher APACHE II score, absent eschar
Park et al. (2011)	Higher APACHE II score, serum osteopontin > 100 ng/mL
Kumar et al. (2014)	AKI, ARDS, hyperbilirubinema
Thipmontree et al. (2016)	AKI, hyperbilirubinemia, age > 65 years
Gaba et al. (2019)	Higher SOFA score, AKI, myocarditis, DIC, severe hepatitis, shock

AKI acute kidney injury, *APACHE* acute physiology and chronic health evaluation, *ARDS* acute respiratory distress syndrome, *SOFA* sequential organ failure assessment, *DIC* disseminated intravascular coagulation

regimen is 500 mg every 6 h, for a week. It carries the risk of bone marrow suppression and requires strict monitoring. Although not currently significantly relevant outside of the regions from where it is reported, strains resistant to doxycycline have been detected recently in Thailand [69]. Possible doxycycline resistance, in view of treatment failures, has also been reported from India and South Korea [18, 70]. The AFC-3 and AFSC-4 strains, first identified from Thailand, are particularly known to be resistant to doxycycline [71]. It has also been found to have higher infectivity in vitro, and the mechanism of resistance is not fully understood [69].

Wangrangsimakul et al. have boldly challenged the notion of doxycycline resistance and claimed that the treatment failures are actually due to certain host factors and antibiotic quality issues as in vitro resistance is not seen when stringent laboratory methodologies are adopted [72••]. They have stressed the need for more research. Fluoroquinolones have been found to be inappropriate for treatment of scrub typhus. The mechanism of resistance has been elucidated in Kato and Boryong strains in studies which attributed it to mutations in the quinolone resistance determining region of gyrA gene [73, 74]. It codes for subunit A of DNA gyrase, one of the targets of fluoroquinolones.

Rifampicin may be an effective alternative in doxycycline resistance. A study, from a region of Thailand where doxycycline resistance is present, confirmed its usefulness and found that a greater proportion of patients (79% versus 77%) receiving 900 mg a day became afebrile after 48 h of the first dose, as compared to those receiving 600 mg a day [75]. The study, however, included only patients with mild disease. Another apprehension was regarding emergence of rifampicin resistance in patients who had concurrent tuberculosis. Combination drug therapy has not been found to be better than monotherapy. Azithromycin currently remains the antibiotic of choice in treatment failures due to suspected doxycycline resistance.

Absence of an approved vaccine is a major impediment to the disease control. Significant antigenic variation among the various strains and little cross-reactivity are the major challenges in development of an effective vaccine [19]. Immunity lasting up to 2 years from a live vaccine has been demonstrated in humans, and trials of heat-killed vaccines have been unsuccessful [76]. The general measures to reduce exposure to the vector include wearing clothes that minimize the area of exposed body surface, avoiding walking through densely vegetated areas, and use of insecticides and insect repellants [77]. Post-exposure prophylaxis is currently not recommended; however, doxycycline has shown the potential in one trial [78].

Conclusion

Scrub typhus used to be a time-worn disease, but now it is undergoing revival, and it has a potential to be a major public health problem. It is now widespread and has not yet received the attention it deserves from the healthcare community. The disease should be suspected in all patients with an undifferentiated febrile illness in the endemic areas and should also be considered as a possibility in other areas. The gamut of complications is vast, and more data continues to pour in. Early diagnosis and antibiotic treatment is the key to a better outcome. More research is needed for clarification of drug resistance and development of a robust vaccine.

- The manuscript has not been submitted to more than one journal for simultaneous consideration.
- The submitted work is original and has not been published elsewhere in any form or language.
- Results have been presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. Authors have adhered to discipline-specific rules for acquiring, selecting, and processing data.
- No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works have been given.

Code Availability Not relevant.

Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Saurabh Gaba, Monica Gupta, Ruchi Gaba, and Sarabmeet Singh Lehl. The first draft of the manuscript was written by Saurabh Gaba, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The idea for the article was conceived by Saurabh Gaba and Monica Gupta. Saurabh Gaba, Monica Gupta, and Ruchi Gaba performed the literature search and data analysis, and Saurabh Gaba, Monica Gupta, and Sarabmeet Singh Lehl drafted and critically revised the work.

As required all authors whose names appear on the submission have (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not involve human or animal participants.

Ethics Approval Not relevant.

Informed Consent from Patient The participant has consented to the submission of the picture of eschar to the journal (Fig. 2). Patients has signed informed consent regarding publishing their data and photographs.

Research Involving Human Participants, Their Data, or Biological Material Not relevant.

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- • Of importance
- •• Of major importance

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