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Severe scrub typhus infection: Clinical features, diagnostic challenges and management

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Abstract

Scrub typhus infection is an important cause of acute undifferentiated fever in South East Asia. The clinical picture is characterized by sudden onset fever with chills and non-specific symptoms that include headache, myalgia, sweating and vomiting. The presence of an eschar, in about half the patients with proven scrub typhus infection and usually seen in the axilla, groin or inguinal region, is characteristic of scrub typhus. Common laboratory findings are elevated liver transaminases, thrombocytopenia and leukocytosis. About a third of patients admitted to hospital with scrub typhus infection have evidence of organ dysfunction that may include respiratory failure, circulatory shock, mild renal or hepatic dysfunction, central nervous system involvement or hematological abnormalities. Since the symptoms and signs are non-specific and resemble other tropical infections like malaria, enteric fever, dengue or leptospirosis, appropriate laboratory tests are necessary to confirm diagnosis. Serological assays are the mainstay of diagnosis as they are easy to perform; the reference test is the indirect immunofluorescence assay (IFA) for the detection of IgM antibodies. However in clinical practice, the enzyme-linked immuno-sorbent assay is done due to the ease of performing this test and a good sensitivity and sensitivity when compared with the IFA. Paired samples, obtained at least two weeks apart, demonstrating a $\geqslant$ 4 fold rise in titre, is necessary for confirmation of serologic diagnosis. The mainstay of treatment is the tetracycline group of antibiotics or chloramphenicol although macrolides are used alternatively. In mild cases, recovery is complete. In severe cases with multi-organ failure, mortality may be as high as 24%.

Key words: Rickettsia; Diagnosis; Management; Outcome; Multi-organ failure

Core tip: Scrub typhus is an important differential diagnosis in patients who present with acute undifferentiated fever in South East Asia. Since the presentation may be non-specific, with features of organ failure in those with severe infection, early diagnosis and appropriate management is crucial. The presence of an eschar suggests scrub typhus infection. The diagnosis may be confirmed on serological assays, the reference test being the indirect immunofluorescence test for the detection of IgM antibodies. In those with mild infection, fever defervescence occurs in about 2-d with Doxycycline therapy.

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INTRODUCTION

Scrub typhus infection is an important aetiology of acute undifferentiated fever in south-east Asia and India[1,2]. It is a zoonotic rickettsial illness caused by *Orientia tsutsugamushi* and is endemic in the "Tsutsugamushi triangle" that extends from northern Japan and far eastern Russia to northern Australia in the south and Pakistan in the west[3]. The reservoirs for infection are the chiggers (larva of trombiculid mite) and rats and humans are accidentally infected. It is transmitted by trombiculid mites in long grasses and in dirt-floor homes, with infection characterized by a flu-like illness of fever, headache and myalgia lasting approximately one week. In some, the illness progresses to multi-organ dysfunction syndrome and death.

DISTRIBUTION OF DISEASE

Scrub typhus is seen in several parts of South-East Asia including India[4-11], Bangladesh[12], China[13], Taiwan[14], South Korea[15], Japan[16] and Northern Australia[17]. Although scrub typhus has been reported from isolated parts of these countries[2,5,9,13,14], it is likely that this disease is ubiquitous. The majority of cases are from the rural areas given that these mites thrive in those environments. However acute infection as well as serological evidence of infection has been published from metropolitan cities[10,11,13]. Outbreaks generally occur during the cooler months of the year after monsoons[12].

In the endemic Asia-Pacific region, one billion people are estimated to be at risk of infection and one million cases of scrub typhus occur every year[18]. The disease is responsible for nearly 1/4th of the febrile episodes in endemic areas[19]. Mortality in severe case or with improper treatment may be as high as 30%[20,21].

PATHOPHYSIOLOGY

The pathophysiological hallmark of scrub typhus is disseminated vasculitis[22] with subsequent vascular injury that involves organs such as skin, liver, brain, kidney, meninges and the lung. The organism multiplies at the site of inoculation that progresses on to necrosis and evolves into an eschar with regional lymphadenopathy[22]. Within a few days, patients develop rickettsemia with infection of the vascular endothelium resulting in vascular injury in several organs. The injury causes disseminated intravascular coagulation (DIC) with platelet consumption, vascular leak, pulmonary edema, shock, hepatic dysfunction and meningoencephalitis[23-26].

MOLECULAR CHARACTERISTICS

O. tsutsugamushi expresses a type-specific protein, the 56-kDa protein, which is unique and not expressed by other bacteria or Rickettsiae. Since this protein sequence is unique, and contains cross-reacting epitopes, variations in this have resulted in the genetic diversity of *O. tsutsugamushi*[27]. This protein has also been explored in the development of vaccines[28]. Commonly reported strains include the prototype Karp strain and closely related strains (Karp-like strains), which are most frequent in endemic areas, as well as Gilliam, Kato, Kawasaki, TA763 and others[28,29].

CLINICAL FEATURES

Scrub typhus presents as an acute undifferentiated fever. The incubation period for symptoms is between six and twenty-one days from exposure[30]. The clinical picture is characterized by sudden onset fever with chills, headache, backache and myalgia, profuse sweating, vomiting and enlarged lymph nodes[30]. In some patients, an eschar may develop at the site of chigger feeding, usually at sites where the skin surfaces meet, such as axilla, groin and inguinal areas[31]. Although the eschar is reported to be less frequently observed in South Asian patients than in East Asian or Caucasians[31], 55% of patients had an eschar in a recent study from South India[27]. In a large retrospective analysis of 418 patients with confirmed scrub typhus and an eschar, a significant difference in the distribution of eschar was noted between males and females[32]. In females it was primarily present in the chest and abdomen (42.3%), while in males it was present in the axilla, groin and genitalia (55.8%). Unusual sites of eschar were reported to be in the cheek, ear lobe and dorsum of the feet[32].

Five to eight days after the onset of fever, a macular or maculopapular rash may appear on the trunk and later extend to the arms and the legs in a small proportion of patients[31]. Complications of scrub typhus infection include pneumonia[33], acute respiratory distress syndrome (ARDS) like picture[34,35],

myocarditis[36], encephalitis[37], hepatitis[38], DIC[39], hemophagocytic syndrome[40], acute kidney injury[41], acute pancreatitis[42], transient adrenal insufficiency[43], subacute painful thyroiditis[44] and presentation as an acute abdomen[45].

Several neurological manifestations have been observed in the setting of scrub typhus infection. The most common neurological presentation in scrub typhus is as meningitis, meningoencephalitis or encephalitis[46]. Others include cerebral venous thrombosis[47], Guillain-Barre Syndrome[48], transient Parkinsonism and myoclonus[49], opsoclonus[50], cerebellitis[51], transverse myelitis[52], polyneuropathy[53], facial palsy[54], abducens nerve palsy[55] and bilateral optic neuritis[56].

Multi-organ dysfunction is not uncommon in severe scrub typhus infection. In a recently published study of 116 patients admitted to an intensive care unit with severe scrub typhus infection, the admission Acute Physiology and Chronic Health Evaluation (APACHE) II score was 19.6 ± 8.2[20]. Ninety-one patients in this cohort had dysfunction of 3 or more organs and 16 patients (15%) had evidence of dysfunction of all six organs. Respiratory dysfunction was predominant (96.6%) with ventilatory support required in 87.9%. Cardiovascular dysfunction was present in 61.7% and hepatic dysfunction in 63.8%. Thirteen patients (11.2%) were dialyzed. Hospital mortality in this ICU cohort was 24.1%[20]. On logistic regression analysis, APACHE-II score and duration of fever were independently associated with mortality.

DIAGNOSIS

Acute febrile illness (AFI) may be categorized as differentiated fever, where there is an obvious focus of infection (*e.g.*, respiratory tract, urinary tract) or an undifferentiated fever. In an undifferentiated fever, where there is no obvious focus of infection and the symptoms and signs are quite nonspecific, several diagnostic possibilities are considered, particularly in the tropics[2]. This includes scrub typhus, malaria, enteric fever, dengue, leptospirosis, spotted fever rickettsioses and Hanta virus[2]. Thus, in this setting, it is particularly important that a detailed clinical history and examination are done and relevant diagnostic tests performed to diagnose the cause of AFI. The presence of an eschar makes the diagnosis of scrub typhus highly likely and this should be carefully looked for.

The diagnostic methods available for laboratory confirmation include identification of the organism in cell culture, detection of the antigen by immunehistochemical methods or the antibodies by the indirect immunofluorescence assay (IFA) and finding specific nucleic acid targets using molecular methods. The success of a test in confirming the diagnosis of scrub typhus is dependent on the type of sample taken[57] and the timing of the specimen. Cell culture or molecular assays performed using eschar (when present) or buffy coat are more likely to be positive in the first two weeks of illness[58]. Antibody levels reach detectable levels by day seven; paired sera obtained at least two weeks apart are necessary for serologically confirming the diagnosis by demonstration of a ⩾ 4 fold rise in titre[59].

Isolation of *Orientia tsutsugamushi* in culture is definitive and can be performed using cell culture[60]. Cell lines like HeLa cells, L929 cells (mouse fibroblast cells), Vero cells, BHK-21 cells have been used to cultivate *Orientia tsutsugamushi*. The L929 mouse fibroblast cell line is commonly used for the isolation of *O. tsutsugamushi* from the blood. Isolation of *Orientia tsutsugamushi* is not routinely done as it requires a cell culture facility, trained personnel, strict bio-safety precautions and a BSL (Bio Safety level) Ⅲ facility. As the organism doubling time is 9-18 h[61], it takes an average of four weeks for identification by culture[57]. This further precludes the use of culture as a routine diagnostic test. Currently, reference laboratories use culture techniques for isolation of *Orientia tsutsugamushi* for definitive identification, research and for obtaining antigen for immunofluorescence[62].

Since antigen detection tests have low sensitivity/specificity and require biopsy specimens, in the clinical setting, serological assays are the mainstay of diagnosis[63] as they are simple and comparatively easy to perform[64]. The serological reference test is the indirect IFA for the detection of IgM antibodies. This assay has drawbacks which include retrospective nature, requirement of well trained personnel and equipment which may not be available in many diagnostic laboratories[65]. Currently most diagnostic laboratories use the enzyme-linked immunosorbent assay (ELISA) for the detection of IgM antibodies in scrub typhus as it provides an objective result and has sensitivity similar to that of IFA[64]. Detection of IgM antibody is considered to be diagnostic of an acute infection when compared to IgG antibodies which suggest a previous infection especially in endemic areas[66]. Rapid tests to detect IgM antibodies to scrub typhus have sensitivity ranging from 34.7% to 96.7% and specificity between 93.3% and 99.7%[66-68].

PCR assays, either conventional or real-time, targeting the 56 kDa gene, 47 kDa gene, *16 S rRNA* and *groEL* gene have also been explored and reported to have specificity approaching 100%[24]. Sensitivity of the nested PCR assays using 56 kDa or the *16 S rRNA* genes can be as low as 22.5% to 36.1%[9]. Real-time PCR assays show a better sensitivity ranging from 45%[69] to 82%[70]. In recent times, LAMP assays targeting the *GroEl* and the 47 kDa gene have been described[71,72]. The LAMP assay has the advantage that it can be performed using simpler equipment. In addition it is not inhibited by heme as is the case with PCR[73].

In the clinical setting, a diagnosis of scrub typhus is considered when a patient with an AFI has an eschar and a positive IgM ELISA for scrub typhus and other causes of fever excluded[74]. In the absence of an eschar, a positive IgM ELISA in the appropriate clinical setting with defervescence within 48-h of initiation of

Table 1 Commonly used antimicrobial agents in scrub typhus infection

Name of drug	Dose and administration in adults	Comments
Doxycycline[75,77]	100 mg twice daily for 7 d	Drug of choice Intravenous preferred for sicker patients Rapid defervescence within 48 h
Tetracycline[76]	500 mg four times daily	No difference between doxycycline and tetracycline
Azithromycin[75,77]	Mild infections: 500 mg single dose Severe infections: 500 mg once daily for 3 to 5 d; 1 g loading dose may be given	Preferred drug in pregnancy In mild cases symptom duration similar when compared with doxycycline Recommended when doxycycline resistance is present
Telithromycin[80]	800 mg daily for 5 d	As effective as doxycycline
Chloramphenicol[75,77]	500 mg every 6 h for 7 d	Most common alternative to tetracycline Contraindicated in pregnancy Risk of aplastic anemia
Rifampicin[78]	600 to 900 mg daily for 7 d	Combination with doxycycline not more efficacious than either Rifampicin or doxycycline in mild scrub typhus Shorter duration of fever with Rifampicin in Northern Thailand when compared with Doxycycline Caution in tuberculosis endemic areas

doxycycline or scrub IgM ELISA seroconversion on convalescent sera with other etiologies of AFI ruled out with appropriate investigations also suggests scrub typhus infection[2].

TREATMENT

Supportive treatment

Patients with mild disease presenting with fever without organ dysfunction may require only antipyretics along with antibiotics. Patients presenting with organ dysfunction would need organ support depending on the nature and extent of organ dysfunction[20]. Patients with respiratory failure could be supported either by means of non-invasive or invasive mechanical ventilation based on standard criteria in the management of respiratory failure. Those with circulatory shock can be treated with fluid resuscitation and vasoactive therapy if the blood pressure does not improve with fluids. Acute kidney injury, which is not uncommon in scrub typhus, may need renal replacement therapy. Those with DIC with clinical bleeding would require transfusion of blood products depending on the nature of coagulation derangement.

Specific treatment

The drug treatment options in scrub typhus have been evaluated and summarized in a recent meta-analysis[75]. In the 17 studies that were included in the meta-analyses, six antibiotics were used and included doxycycline, chloramphenicol, azithromycin, rifampicin, roxithromycin and tetracycline. Conventionally, the treatment of scrub typhus involves the use of the tetracycline group of antibiotics[76] or chloramphenicol[75]. Since these drugs are contraindicated in pregnancy and in children, alternative agents such as quinolones and macrolides are used for the treatment of scrub typhus in this setting[75].

In the four studies that compared azithromycin with chloramphenicol, chloramphenicol treatment was associated with significantly shorter median time to clearance of fever and lower adverse events when compared with azithromycin[75]. Six studies compared doxycycline with chloramphenicol; symptom clearance time was significantly shorter with doxycycline[75]. No significant differences were observed in symptom duration comparing azithromycin with doxycycline (3 studies), roxithromycin with doxycycline (3 studies) and doxycycline with either rifampicin or tetracycline (2 studies each)[75].

Doxycycline is the preferred drug in the treatment of scrub typhus. A therapeutic response to doxycycline therapy is used as a diagnostic test[2]. In less sick patients oral doxycycline can be administered at 100 mg twice daily. The duration of treatment is 7 d. In critically ill patients, particularly those in shock, the absorption of enterally administered doxycycline may be problematic. In such situations, intravenous doxycycline should be used; where unavailable, intravenous azithromycin may be used in isolation or combined with enteral doxycycline[20,74]. Azithromycin is also the recommended drug for treatment of scrub typhus in pregnancy[77]. Rifampicin may be considered where doxycycline resistance is present[77]. In one trial of patients with mild scrub typhus, Rifampicin was found to have shorter defervescence time when compared with doxycycline[78]. However, in tuberculosis endemic countries, rifampicin should be avoided for the treatment of scrub typhus. Although there is some evidence for the use of quinolones in scrub typhus, recent reports of quinolone resistance suggests that this treatment should not be used in critically ill patients[79]. Preliminary reports suggest that Telithromycin is a promising new antibacterial agent for patients with mild to moderate scrub typhus[80]. The different anti-microbial agents used in scrub typhus are summarized in Table 1.

COURSE

Patients with mild disease usually recover fully. In a

study of 261 patients from Taiwan, no mortality was observed[81]. In a recently published large cohort of 623 patients hospitalized with scrub typhus of varying illness severity from mild to critically ill, the mortality was 9%[35]. Reducing mortality over a 4-year period was reported in this study. Favourable maternal and fetal outcome may be expected in appropriately managed patients with scrub typhus complicating pregnancy[82]. In sicker patients admitted to the ICU with multi-organ failure, the mortality is 24%[20]. These observations should encourage clinicians to approach scrub typhus infection with optimism.

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