Scrub typhus

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ABSTRACT

Scrub typhus is an acute febrile illness caused by *orientia tsutsugamushi*, transmitted to humans by the bite of the larva of trombiculid mites. It causes a disseminated vasculitic and perivascular inflammatory lesions resulting in significant vascular leakage and end-organ injury. It affects people of all ages and even though scrub typhus in pregnancy is uncommon, it is associated with increased foetal loss, preterm delivery, and small for gestational age infants. After an incubation period of 6-21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. A primary papular lesion which later crusts to form a flat black eschar, may be present. If untreated, serious complications may occur involving various organs. Laboratory studies usually reveal leukopenia, thrombocytopenia, deranged hepatic and renal function, proteinuria and reticulonodular infiltrate. Owing to the potential for severe complications, diagnosis, and decision to initiate treatment should be based on clinical suspicion and confirmed by serologic tests. A therapeutic trial of tetracycline or chloramphenicol is indicated in patients in whom the diagnosis of scrub typhus is suspected. The recommended treatment regimen for scrub typhus is doxycycline. Alternative regimens include tetracycline, chloramphenicol, azithromycin, ciprofloxacin, rifampicin, and roxithromycin. Treatment of pregnant women with azithromycin was successfully done without relapse and with favorable pregnancy outcomes. Hence, early diagnosis and treatment are essential in order to reduce the mortality and the complications associated with the disease. We searched the English-language literature for reports of scrub typhus in children, pregnant women, and non-pregnant patients with scrub typhus, using the MEDLINE/PubMed database, which includes citations from 1945 to the present time. We used the search terms 'scrub typhus', 'scrub typhus' and 'pregnancy', 'scrub typhus' and 'children', 'scrub typhus' and 'complications', 'scrub typhus' and 'treatment'.

Key words: Doxycycline, eschar, *orientia tsutsugamushi*, scrub typhus, serologic assays, tsutsugamushi disease, Weil-Felix test

INTRODUCTION

Also known as tsutsugamushi disease,[1] this acute febrile disease is caused by *orientia tsutsugamushi* [Japanese word tsutsuga ("dangerous"), mushi ("bug")],[1] which is a small Gram-negative, obligate intracellular organism whose polysaccharides bear an antigenic relationship to proteus OX-K, which is thus used in serologic tests to confirm scrub typhus.[1] O. tsutsugamushi is transmitted to humans by the bite of the larva of trombiculid mites (chiggers) which are almost microscopic, often brilliantly colored (red).[1] Infected chiggers are found particularly in areas of heavy scrub vegetation during the wet season, (therefore this disease has also been called river/flood fever[1]) when mites lay eggs.[2] usually June through November.[3] The word "scrub" was applied because of the type of vegetation that maintains the chigger−mammal relationship even though other regions also support rodents and mites.[1]

Scrub typhus is endemic to a part of the world known as the "tsutsugamushi triangle." This extends from Japan, Taiwan, China, South Korea,[4] Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales.[5] In India, the presence of scrub typhus has been known for several years. The disease is widely spread all over the

country, and was reported in several states - Haryana, Jammu, and Kashmir, Himachal Pradesh, Uttaranchal, West Bengal, Assam, Maharashtra, Kerala and Tamilnadu.[6] During World War II, there was an outbreak of this disease in Assam and West Bengal, in the 1965 Indo-Pak war and in 1990 and in a unit of an army deployed at the Pakistan border of India.[7] These reports showed a resurgence of this disease in India.

O. tsutsugamushi invades endothelial cells to produce disseminated vasculitic and perivascular inflammatory lesions, which results in significant vascular leakage and ensuing end-organ injury.[1,3]

CLINICAL FEATURES AND DIAGNOSIS

Illness varies from mild and self-limiting to fatal.[2] After an incubation period of 6-21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms.[1] The classic case description includes a primary papular lesion (where the chigger has fed and can occur anywhere on the body), which enlarges, undergoes central necrosis, and crusts to form a flat black eschar. This is associated with regional and later generalized lymphadenopathy (enlarged and tender nodes). The symptoms gradually increase in severity and a macular rash may appear on the trunk.[8] If untreated, the patient may become stuporous as meningoencephalitis develops. Various cranial nerve deficits have been noted in untreated patients.[3] Pulmonary findings are often absent despite radiographic evidence of interstitial pneumonia. Signs of cardiac dysfunction, including minor electrocardiographic abnormalities - first-degree heart block and inverted T waves - can appear. In patients with myocarditis, there may be a gallop rhythm, poor-quality heart sounds, and systolic murmurs.[3] Sometimes, palpable spleen (and occasionally liver) may also be present. Deafness, dysarthria, and dysphagia may occur but are usually transient, although deafness can last for several months. Patients with untreated disease remain febrile for about 2 weeks and have a long convalescence of 4 to 6 weeks thereafter.[1]

In children, scrub typhus may be mild or severe. Most patients present with fever and regional/generalized lymphadenopathy. A single painless eschar, maculopapular rash[3] hepatomegaly, splenomegaly and gastrointestinal symptoms (abdominal pain, vomiting, and diarrhoea) may be present. Case fatality rate in untreated patients may be as high as 30%, although deaths in children are infrequent.[3]

It is necessary to determine the predictors that identify markers of severe disease in order to reduce the mortality, complications and the delay in treatment. The potential markers for developing complications were age (≥60 years); scrub typhus patients who presented to the hospital without an eschar; laboratory findings such as WBC counts >10, 000/mm and serum albumin level ≤3.0 g/dL.[3,9]

Laboratory studies usually revealed:
- Leukopenia[1] and thrombocytopenia[3] with subsequent increase of white blood cell counts to normal levels.[1] In children, leukocyte and platelet counts are usually within normal ranges, although thrombocytopenia and leukocytosis may also occur[3]
- Coagulopathy[1]
- Elevation of liver enzymes and bilirubin - indicating hepatocellular damage[1]
- Proteinuria[1]
- Elevation of creatinine[3]
- Reticulonodular infiltrates (most common finding on chest radiograph).[8] Chest X-rays also reveal transient perihilar or peribronchial interstitial infiltrates[3]
- Cerebrospinal fluid (CSF) examinations show a mild mononuclear pleocytosis with normal glucose levels.[3]

Owing to the potential for severe complications, diagnosis, and decision to initiate treatment should be based on clinical suspicion and confirmed by serologic tests.[3] Serological tests have their own limitations in which clinicians need to be aware of. Although agreement exists that a ≥ four-fold increase in antibody titre between two consecutive samples is diagnostic, such a diagnosis is retrospective and cannot guide initial treatment.[10,11]

Weil-Felix
The Weil-Felix agglutination test, oldest test in current use, detects cross-reacting antibodies to proteus mirabilis OXK.[12] Diagnostic Weil-Felix agglutination (detectable after 5 to 10 days following the onset)[6] shows ≥four times rise in titre to proteus OX-K and no reaction to proteus OX-2 or OX-19 (in 50-70% of patients); a single titre ≥1:160 is also diagnostic (normal is ≤1:40.).[13] About 50% of patients have diagnostic titres.[1,3] This test is inexpensive, easy to perform, and results are available overnight; however, it lacks specificity and sensitivity.[11] The Weil-Felix test is still used because of its low cost,[12] and in conditions where other serologic tests are not available/possible e.g., in

rural areas. Even though this test is not a very sensitive test but when positive, it is rather specific test.[14]

ENZYME-LINKED IMMUNOSORBENT ASSAY

Kits for the detection of antibodies against infectious agents use pooled human sera as reference material to establish cut-off values and to routinely confirm test integrity.[15] The 56-kDa protein (located on the outer membrane of O. Tsutsugamushi) is highly reactive with patient sera, and therefore preferred for use in the diagnosis of scrub typhus.[16] ELISA using whole cell antigen and r56 from the Karp, Kato, and Gilliam strains of O. Tsutsugamushi (KpKtGm-wc ELISA and KpKtGm r56 ELISA)[17,18] were used and the final concentrations of antibodies were then measured by a Microplate Reader. In a study by Jiang et al.,[17] this trivalent ELISA appears to be superior in terms of sensitivity, to the other ELISA tests, owing to the presence of large amounts of conserved and/or variable regions of the r56-kD protein from the three strains of O. Tsutsugamushi. Jones et al.,[19] described genetically engineered chimeric IgG, IgM, and IgA antibodies as an alternative positive control for inclusion in a commercial ELISA kit, and found that the purified protein have a much greater specificity for the scrub typhus antigen than the serum-derived controls. Jang et al.[16] described a rapid and reliable IgM capture ELISA based on the capture of IgM antibodies in sera, and concluded that IgM capture ELISA carries a high sensitivity and specificity. It is also a reliable and useful diagnostic method for early detection of scrub typhus, besides a large number of sera can be tested at a time.

RAPID LATERAL FLOW-ASSAY

Consists of a single strip (IgG, IgM), where the Kp r56 protein was conjugated to gold particles as the indicator system.[17,20]

WESTERN BLOT

Assay r56 from the Karp, Kato, and Gilliam strains of O. Tsutsugamushi (KpKtGm r56),[17] using electrophoresis. Results are interpreted as positive or negative with the presence or the absence of a 41-kD band (for the truncated 56-kD recombinant protein) on the film, respectively.

IMMUNOCHROMATOGRAPHIC TEST

A rapid diagnostic test in which serum was applied to the reagent pad of the ICT strip. The results were recorded as positive, equivocal, or negative for the presence of the control and the IgM or total antibody lines. Blacksell et al.[21] assessed the diagnostic capacity of a rapid ICT and found that the sensitivity and specificity for the detection of IgM were 96.8 and 93.3%, respectively. For the detection of total antibodies, the sensitivity was 97.6% but the specificity was much lower, at 71.4%.

THE INDIRECT FLUORESCENT ASSAY

First described by Bozeman et al. 1963.[22] IFA has been considered as the gold standard for serologic detection of scrub typhus antibodies,[23] and is also currently the reference standard.[10] The specific serologic test for a conclusive diagnosis is the detection of significant increases (≥four-fold) of IFAs in paired serum specimens obtained 2 weeks apart.[1] The end point of each IFA titre was defined as the lowest serum concentration demonstrating definite fluorescence. The test is more sensitive and faster but costly and antigenic variation is common.[11]

INDIRECT IMMUNOPEROXIDASE

Eliminates the expense of a fluorescent microscope in which fluorescein is replaced by peroxidise.[24] This test has the advantage in that any rickettsial strain can be used as the antigen, either IgG or IgM antibodies can be titrated individually, gives a permanent preparation (for re-examination), and all cells (infected and uninfected) can be observed. It is easy, however the readings are subjective.[25]

PCR AMPLIFICATION OF ORIENTIA GENES

Samples from eschars and blood are useful, and may be the most sensitive diagnostic test.[3] Since O. tsutsugamushi is an intracellular organism, thus whole blood or the buffy coat is considered to be the preferred samples for PCR tests.[26] Nested PCR test, based on specific primers derived from the 56-kDa major outer membrane protein antigen of O. Tsutsugamushi, can detect the organism as early as 1-3 days of the fever phase and is known to be 100 times more sensitive than performing single PCR.[26-28]

ISOLATION/INOCULATION

O. tsutsugamushi can be isolated and cultured from a patient's blood by inoculating it intraperitoneally, into white mice. However, it requires biosafety level-3 facilities,[29] costly and laborious, hence not appropriate for the routine diagnosis of scrub typhus.[11] Guinea pig

inoculation - scrotal reaction following intra peritoneal injection of blood into male guinea pig. (Test is often not used at present.) – Negative in scrub typhus.[13] Table 1 shows a list of diagnostic tests for scrub typhus.

Complications

Scrub typhus involves multiple organs and is characterized by microangiopathies - focal vasculitis or perivasculitis.[1] Pulmonary involvement is a well-documented complication of scrub typhus infection with pleural effusion being a common radiographic feature in 12-55% of patients in previous studies.[1,2,30] Other pulmonary manifestations include varying degrees of bronchitis/interstitial pneumonitis

Table 1: Diagnostic tests for scrub typhus		
Test	**Comments/Results**	**Recommendation**

Weil Felix	Detects cross-reacting antibodies to Proteus mirabilis OXK
	Diagnostic Weil-Felix agglutination shows ≥four times rise in titre to proteus OX-K and no reaction to Proteus OX-2 or OX-19 (in 50-70% of patients)
	
	Single titre ≥1:160 is also diagnostic (normal is ≤1:40)
	Agglutinating antibodies (mainly IgM) are detectable after 5 to 10 days following the onset of symptoms
	Lacks specificity and
	Sensitivity
		Can be used when other specific tests are not available because of the following reasons:
		  Inexpensive
		  Easy to perform
		  Results are available overnight
		  Is not a very sensitive test but when positive, it is rather specific test

ELISA
  KpKtGm-wc
  KpKtGm r56
  IgM capture
	Detect antibodies against infectious agents by using pooled human sera as reference material
	
	Limitations: *O. tsutsugamushi*, is difficult to grow, tests are costly and requires bio-safety level 3 facilities to produce whole cell antigens
		High sensitivity and specificity therefore preferred if available

Rapid lateral flow-assay	Assays using recombinant proteins Positive result: Purple color on the control test lines of the cassette strip for either IgG or IgM Negative result: Purple color only on control line of the cassette strip	Results can be obtained after 10 min; therefore can be use for fast detection
KpKtGm r56 Western blot	Positive result: Presence of a 41-kD band (for the truncated 56-kD recombinant protein) on the film Negative result: absence of the 41-kD band	High sensitivity and specificity; therefore can be done, if available
Immunochromatographic Test	Results: Recorded as positive, equivocal, or negative for the presence of the control and the IgM or total antibody lines	Rapid and have a high sensitivity and specificity therefore should be done if available

The Indirect Fluorescent Assay	Considered as the gold standard test and is also currently the reference standard
	
	Conclusive diagnosis: Is the detection of significant increases (≥ fourfold) of IFAs in paired serum specimens obtained 2 weeks apart. Presence of specific IgG and IgM ≥1:400 strongly favours diagnosis
	The end point of each IFA titre was defined as the lowest serum concentration demonstrating definite fluorescence
	Limitation: Expensive and requires considerable training
		Preferable because:
		  More sensitive
		  Results can be obtained in a few hours

Indirect Immunoperoxidase	Any rickettsial strain can be used as the antigen, and either IgG or IgM antibodies can be titrated individually Limitation: Readings are subjective	Can be done only if other more sensitive/specific tests are not available
PCR amplification of Orientia genes	Can be detected as early as 1-3 days of the fever phase which is before the appearance of specific antibodies in the blood	Most sensitive diagnostic test. Therefore should be the preferred test, but facilities are not available everywhere and it is very expensive
Isolation	O. tsutsugamushi can be isolated and cultured by inoculating it, intraperitoneally, into white mice and can be demonstrated in the tissues of the mice, by Giemsa (or Diff-Quick) staining Requires biosafety level-3 facilities and culture on cell monolayers and median time to positivity is 27 days Expensive and laborious	Not appropriate for the routine diagnosis of scrub typhus, hence not recommended
Inoculation	Scrotal reaction following intra peritoneal injection of blood into male guinea pig	Obsolete and test is often not used at present

ELISA – Enzyme-linked immunosorbent assay; PCR – Polymerase chain reaction; OX K – Serogroup O3 of proteus mirabilis; OX 19 – Serogroup O1 of proteus vulgaris; OX 2 – Serogroup O2 of proteus vulgaris; IgG – Immunoglobulin G; IgM – Immunoglobulin M; IFA – Indirect flourescent assay

progressing to acute respiratory distress syndrome,[9] pneumonitis with patchy consolidation, cardiomegaly, pulmonary oedema, hilar adenopathy, focal atelectasis, reticulonodular opacities, bronchial wall thickening, and centrilobular nodules.[1,2] Radiologic findings may be of value in differentiating scrub typhus from other febrile diseases. The incidence of CXR abnormalities in patients with scrub typhus varied from 59.4 to 78%.[1-3,31] In their study, Wu *et al.*,[32] found that the incidence of CXR abnormalities was higher in the older age groups and that the CXR patterns could be different at different stages of the same disease. Patients with abnormal CXR findings had a higher rate of serious complications (such as septic shock, congestive heart failure (CHF), acute respiratory failure, severe jaundice and acute renal failure, and requirement for ICU care and prolonged length of hospital stay) compared with patients with negative CXR results.[32]

SCRUB TYPHUS AND ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS (defined as an acute and persistent lung inflammation with increased vascular permeability)[33] is a well known complication of scrub typhus, which is rarely reported but serious.[34] Initial symptoms of dyspnea and cough, higher WBC counts, lower hematocrit, higher total bilirubin counts, and delayed treatment with appropriate antibiotics were significantly predictive variables in these patients; with albumin, prothrombin time, and delayed use of appropriate antibiotics being independent predictors.[35] The risk factors for the development of ARDS are older age, thrombocytopenia, and the presence of early pneumonitis.[34] The major cause of mortality is a delay in diagnosis, but with appropriate antibiotic therapy, patients usually recover without any major sequelae.[34] In a study by Wang *et al.*,[35] 11.1% of their scrub typhus patients developed ARDS, and the mortality rate for such patients was 25%. Pandey *et al.*,[36] reported three cases of scrub typhus with ARDS who showed dramatic response to doxycycline. Hence, scrub typhus patients should be carefully evaluated for potential progression to ARDS if they initially have respiratory symptoms.

Myocarditis in scrub typhus is usually subclinical and therefore many times ignored.[37] The main pathologic findings are vasculitis, perivasculitis, and cellular infiltrations consisting of primarily lymphocytes and plasma cells, with interstitial haemorrhage and oedema.[38] Cardiomegaly and CHF may be present,

which could be secondary to myocardial or pericardial involvement.

Gastrointestinal involvement is also frequently reported.[32,39] Some studies reported elevation of liver enzymes[37] and hepatic dysfunction[40] with elevation of serum bilirubin.[40] Most patients showed a peak value in their abnormal liver function tests 2 weeks after the onset of symptoms.[40] The major endoscopic features in scrub typhus are superficial mucosal haemorrhage, multiple erosions, and ulcers without any preferred site, and unusual vascular bleeding.[39] Acute pancreatitis associated with pancreatic abscess in a patient with multiple organ failure has been reported.[41] The mechanism responsible for the development of acute pancreatitis may involve an intrinsic inflammatory process *via* vasculitis, but the precise nature of this mechanism is not well understood.[42] Hyperamylasemia and hyperlipasemia have also been reported.[32,43]

Many studies[32,41] reported renal failure as one of the major complications. One study showed that during the febrile phase of the illness, 20% of the patients had abnormal urinalysis, showing proteinuria almost exclusively.[44] The renal pathology usually shows characteristic focal interstitial lesions, cloudy swelling of the tubular epithelium, occasional evidence of severe vascular damage, and glomerular injury.[45]

Central nervous system (CNS) complications range from aseptic meningitis to frank meningoencephalitis. Meningoencephalitis is a constant autopsy finding in fatal cases of scrub typhus, and is present in 10% of children.[3] Pai and co-workers[46] have even demonstrated amplified O. tsutsugamushi DNA in CSF specimens by means of nested PCR. Other studies[32] reported slight pleocytosis with mild protein elevation and normal sugar values in CSF. In other series involving small numbers of pediatric patients (15-30 patients), aseptic meningitis ranged from 3 to 20%.[42,47]

Multi organ failure was also reported in various studies.[37,43]

DIFFERENTIAL DIAGNOSIS

Scrub typhus is a recognized cause of obscure tropical fevers, especially in children.[4] The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue,

leptospirosis, malaria, hemorrhagic fevers, and infectious mononucleosis.[3] The headache may mimic trigeminal neuralgia.[8]

Prognosis, treatment, prevention and control

The case-fatality rate for untreated classic cases is 7% but would probably be lower if all mild cases were diagnosed.[2] Poor prognostic factors include requiring care in an intensive care unit, high APACHE-II scores, and the absence of an eschar (making diagnosis more difficult).[8] According to some reports, the rate of eschar formation varies[48,49] and is much less in the Indian subcontinent,[49] and could be related to the different virulence, load of pathogen, and host immunity. Concurrent scrub typhus may inhibit the replication of HIV[3] and HIV infection does not appear to influence the severity of scrub typhus.[8]

A therapeutic trial of tetracycline or chloramphenicol is indicated in patients in whom the diagnosis of scrub typhus is suspected. Defervescence should occur within 24 h. The recommended treatment regimen for scrub typhus is doxycycline (2.2 mg/kg/dose bid PO or IV, maximum 200 mg/day for 7-15 days).[2,3] For prophylaxis, 200 mg may be taken as a single dose. In patients in whom oral therapy is not feasible, it may be given as the hyclate by slow intravenous infusion.[50] It does not accumulate significantly in patients with renal impairment.[50] Recent reports suggest that natural resistance to doxycycline and other antibiotics make selection of appropriate antimicrobial therapy difficult.[3]

Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 h PO, maximum 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 h IV, maximum 3 g/24 h, or 500 mg qid orally for 7-15 days for adults). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL.[3] Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3-4 days to avoid relapse.[3] Chloramphenicol is best avoided during pregnancy and reduced doses should be given in hepatic impairment.[50]

Ciprofloxacin is a quinolone antibiotic that is effective against O. Tsutsugamushi. However, there is a substantial amount of data demonstrating that ciprofloxacin is not efficacious in the treatment of scrub typhus.[51] Another alternative is azithromycin (500 mg orally for 3 days). Clinical trials showed that azithromycin may be as effective,

and that rifampicin (600 to 900 mg/day) is superior to doxycycline in such cases. A retrospective analysis in Korean children with scrub typhus showed that roxithromycin (150 mg twice a day) was as effective as either doxycycline or chloramphenicol, suggesting a role as an alternative therapy for children or pregnant women.[3] Rifampin reduces the duration of fever by 1 day when used with doxycycline.[8] Intensive care may be required for haemodynamic management of severely affected individuals.[3]

Prevention is based on avoidance of the chiggers that transmit O. Tsutsugamushi, accomplished by insect repellents and by the use of protective clothing impregnated with benzyl benzoate.[1] Diethyltoluamide preparations are also effective and applying this chemical to socks is especially important in preventing chigger bites.[1] Infection provides immunity to reinfection by homologous but not heterologous strains; however, since natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection.[3] Vaccines were developed and tested, however, no single antigen has been identified that induces protection against all of the antigenically diverse strains of O. tsutsugamushi.[1] For short exposure, chemoprophylaxis with doxycycline (200 mg weekly) can prevent the disease but permits infection.[8] Prophylaxis for scrub typhus with doxycycline has shown promise when started before exposure to infection.

SCRUB TYPHUS IN PREGNANCY

The clinical manifestations of scrub typhus in pregnant women are similar to those of non-pregnant adults.[52] Studies reported that scrub typhus in pregnancy may be associated with increased foetal loss,[51,52] preterm delivery,[52,53] and small for gestational age infants.[51] There have been reports of vertical transmission[53,54] from transplacental infection and transmission in perinatal blood-borne infection during labor[54] causing neonatal scrub typhus in mothers with acute febrile illness during pregnancy. Diagnosis of scrub typhus during pregnancy is same as in non-pregnant women and is based on an exposure history, clinical symptoms, and confirmed serological studies.[52] The standard therapy for scrub typhus in non-pregnant adults is doxycycline and chloramphenicol. However, doxycycline, a class D drug (according to the U.S. Food and Drug Administration), has been associated with fetal risk and is contraindicated in pregnant women. One study reported a pregnant woman who had

received chloramphenicol, and despite the mother's high scrub typhus-specific IgG and IgM titers, IgM was not detected in the neonate's sera.[52] However, chloramphenicol, is classified as a class C drug and is prescribed with caution to late trimester pregnant women because of increase risk to the foetus at the time of delivery.[55] Tsui and co-workers[56] reported a pregnant woman who was successfully treated with minocycline, but it is difficult to define the safety of its use during pregnancy from this single limited report. Single dose of azithromycin 500 mg was successfully used in nine pregnant women suffering from scrub typhus without relapse and with favorable pregnancy outcomes.[57] Importantly, there is little evidence to suggest that azithromycin causes harm to the developing foetus.[58] Azithromycin seems to be an effective agent against scrub typhus because it efficiently penetrates polymorphonuclear leukocytes and macrophages, which are target cells for O. tsutsugamushi.[59] In addition, a long tissue half-life and long lasting post-antibiotic effects of azithromycin may explain no relapse despite the use of a single dose. The use of ciprofloxacin in pregnant women resulted in miscarriages;[51] therefore, ciprofloxacin should be selected with caution for the treatment of scrub typhus, especially during pregnancy.

Relevance to clinical anesthesiologists/intensivists

Scrub typhus is a killer disease where disseminated vasculitic and perivascular inflammatory lesions result in end-organ injury. Even though the disease shows dramatic response to appropriate antibiotics, these serious complications can occur and most of them proved to be fatal. In most of the intensive care units (ICU), these patients are usually admitted when such complications have already progressed, mainly due to undiagnosis/misdiagnosis and hence left un-treated. In the ICU, aggressive management (like appropriate ventilator strategy in ARDS patients, dialysis of renal failure patients, correction of haematological abnormalities etc.) of such patients is imperative to prevent the high mortality associated with these complications. Preventing sepsis and multi organ failure can be possible in the ICU with specific treatment protocols and supportive management. Hence, an anesthetist/intensivist have to be aware of such situations to prevent morbidity and mortality associated with this disease.

CONCLUSION

Scrub typhus is a growing and emerging disease,

which is grossly under-diagnosed in under developed/developing countries due to its non-specific clinical presentation, limited awareness, and low index of suspicion among clinicians and lack of diagnostic facilities. Hence, early diagnosis and treatment are imperative to reduce the mortality and the complications associated with the disease.

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