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*Review Article*

# All about scrub typhus

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## ABSTRACT

**Introduction:** Rickettsia is Gram-negative, non-motile, obligate intracellular proteobacteria. They stay in various forms such as coccus, bacillus, and threads. At times, they are regarded as coccobacilli. No human-to-human transmission is there. They always need a vector such as fleas, lice, mite, and ticks for transmission. Rickettsiae species were classically divided into spotted fever and typhus groups. Scrub typhus also known as bush typhus is an important cause of acute febrile illness in South and East Asia and Pacific. It is caused by the intracellular parasite *Orientia tsutsugamushi*, a gram negative alpha proteobacterium of family Rickettsiaceae which was first isolated and identified in 1930 in Japan. It is distinct from other Rickettsiae in that it lacks both peptidoglycan and lipopolysaccharide in its cell wall. Like other vasculotropic rickettsiae, it affects vascular endothelial cells causing vasculitis. It also affects macrophages and cardiac myocytes.

**Objectives:** This review will give a way forward regarding all information about scrub typhus in detail.

**Materials and Methods:** Various clinical profile especially clinical features, presence or absence of ESCHAR, organ invovement, investigations, treatment and final outcome was studied in detail.

**Results:** Clinical results, investigations were analysed to stamp the diagnosis. Different modalities of management has interpreted well.

**Conclusion:** Among all rickettsial infections, scrub typhus being most common is seen all over Indian states and UTs. A child presenting to ER with fever of unknown origin, nephropathy, acute encephalitic syndrome, hepatosplenomegaly, lymphadenopathy, and also hypotension pointing toward possibility of scrub, hence, a detailed search for ESCHAR being essential in clinical examination.

**Keywords:** Rickettsia, Scrub typhus, Orientia, Vasculitis

## INTRODUCTION

An estimated 1 billion people are at risk for scrub typhus and 1 million cases occur annually.[1] Scrub typhus occurs mostly in Asia including areas delimited by Korea, Pakistan, and North Australia. In India, it is reported from almost all states and union territories. The 1st case was reported from Punjab (Juyal *et al*., 1992). Infections commonly occur in rainy months mostly June–October. Once thought to be disease of rural population, these infections are being increasingly reported from urban areas of India.

## TRANSMISSION

The infection is transmitted through the bite of chigger (larval mite) of a trombiculid mite (*Leptotrombidium*), which serves as both vector and reservoir. Vertical transovarial transmission

(passage of the organism from infected mites to their progeny) is the major mechanism. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved.

## PATHOGENESIS

From the regional node rickettsia, they find their way to different organs through blood stream. Like malaria parasite entering RBC, these coccobacilli enter endothelial cells. The main pathologic change is focal or disseminated vasculitis caused by the destruction of endothelial cells and the perivascular infiltration of leukocytes.[2] The process may be stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions. They have special affliction for small and medium vessel wall causing diffuse endothelial infection (infective vasculitis). This, in turn, causes microvascular leakage and vascular lumen obstruction causing edema, hypotension, and hypoalbuminemia. There is immune-mediated inflammation leading to non-occlusive thrombosis, tissue infarction, and hemorrhage ensuing end-organ damage most often manifested in brain and lungs.

## MATERIALS AND METHODS

Varied clinical presentations indicating specific investigations will point towards final diagnosis.

## CLINICAL FEATURES

IP ranges from 1 to 2 weeks. Scrub typhus can be mild or severe in children and can affect almost every organ system. Clinicians should be aware of four systemic presentations:

1. Central nervous system (CNS)
2. Respiratory
3. Renal
4. Gastric intestinal tract (GIT).

Diagnosis is mainly based on strong clinical suspicion in a background of undifferentiated fever/fever without focus for more than 5 days, high grade, abrupt onset associated with headache, myalgia, arthralgia not responding to conventional antibiotics, and a presence of eschar. Hepatosplenomegaly, regional and generalized lymphadenopathy, and edema (periorbital edema, pedal edema, and anasarca) have also been reported. It can even mimic sepsis of unclear etiology or dengue-like disease picture.

GI symptoms such as abdominal pain, nausea, vomiting, diarrhea, hepatitis, surgical abdomen, and acute gastroenteritis occur in 40% of patients. Even acute renal failure can be a presenting feature of rickettsial disease. It can cause fever with cough and pulmonary infiltrates or community acquired pneumonia and even non-cardiogenic pulmonary edema. Aseptic meningitis, meningoencephalitis, and acute encephalitic syndrome (AES) are potential fatal complications of scrub. High index of suspicion is required to diagnose scrub meningoencephalitis in a child presenting with fever, headache, and altered sensorium with or without convulsion. Neurological manifestation is either due to systemic (CNS) vasculitis or direct invasion by the organism.

ESCHAR is typical for SCRUB TYPHUS and is seen in 7–68% of cases. It is a crusty necrotic lesion with or without surrounding erythematous halo. It is usually single, painless, non-pruritic and about 1 cm in diameter resembling the skin burn of cigarette and caused by necrosis of dermal and epidermal tissues with superficial crust densely infiltrated with lymphocytes, histiocytes, damaged capillaries, and venules. One should search for eschar in the area of draining lymphadenopathy as painful regional lymphadenopathy is a marker of hidden or developing eschar. Eschar is considered as pathognomonic of rickettsial diseases, though it can be seen in anthrax, bacterial ecthyma, spider bite, and rat bite fever [Figures 1 and 2].

## LABORATORY RESULTS

Laboratory investigations reveal normal to low total leukocyte count, thrombocytopenia, raised ESR and CRP, hyponatremia, hypoalbuminemia, and elevated hepatic transaminases serum glutamic pyruvic transaminase {SGPT>SGOT) serum glutamic-oxaloacetic transaminase. Cerebrospinal fluid (CSF) examination reveals mild mononuclear pleocytosis with normal glucose levels. Chest radiography reveals transient perihilar peribronchial interstitial infiltrates. Rash in scrub typhus is maculopapular, uncommon than spotted fever group seen in 30–43% of cases.

Although rickettsiae can be isolated from or detected in clinical specimens, serological tests still remain an indispensable tool in the diagnosis.[3] Diagnosis is confirmed by rickettsial DNA detected in whole blood or tissue samples, or 4-fold rise in antibody titers on acute and convalescent sera by immunofluorescence assay (IFA) or immunoperoxidase assay. IFA is the gold standard test but has disadvantages of being expensive, not easily available and requiring expertise sophisticated instruments. Orientia serological tests such as indirect fluorescent antibody are >90% sensitive with 11 days or more fever. Rickettsia can be cultivated using tissue culture methods. In India, where PCR and IFA are not easily available, properly performed paired serological like IgM ELISA has high positive predictive value.

Weil-Felix (heterophile agglutination) has lower sensitivity but better specificity, inexpensive, easily available, not

requiring expertise instruments. It gives a positive result with OXK titer of 1:80 or more in scrub typhus.

## RISK FACTORS

People having animal sheds in proximity of homes or exposure to rodents, living in or travel to areas endemic for rickettsial diseases, overcrowding and poor personal hygiene, war, famines all predisposes to these infections.

## DIFFERENTIAL DIAGNOSIS

D/D includes fever of unknown origin, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, infectious mononucleosis, meningococcemia, adverse drug reactions, and vasculitis such as Kawasaki disease, COVID vasculitis, MISC during COVID pandemic, and thrombotic thrombocytopenic purpura.

## TREATMENT

Suspected cases are treated empirically for management protocol see Figure 3. Careful hemodynamic management should be done to avoid pulmonary and cerebral edema.

The drug of choice is doxycycline (4.4 mg/kg/day divided every 12 h PO or IV (max200 mg/day). Intravenous doxycycline (monotherapy) is sufficient to treat children with meningoencephalitis (total duration 7 days). It is broad-spectrum antibiotic of tetracycline class. It inhibits bacterial protein synthesis by binding to 30s ribosomal subunit. It has bacteriostatic activity against a broad range of Gram – ve and Gram +ve bacteria. Oral/intravenous is safe during breastfeeding. Therapy should be continued for a minimum 5 days and until the patient is afebrile for at least 3 days.

Side effects are diarrhea, nausea, vomiting, increased risk of sunburn, and use during the first trimester causes permanent discoloration of teeth.

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 max 4 g/day). It is preserved for pregnant women and for patients with doxycycline allergy.

Macrolides such as clarithromycin (15–30 mg/kg/day per oral divided every 12 h, max 1 g/day) or azithromycin (10 mg/kg PO on day 1, then 5 mg/kg PO; maximum: 500 mg/day), fluoroquinolones, and rifampicin (especially used for pregnant women) are other effective regimens. Sulfonamides are contraindicated.

As per Mathai *et al*., 17 patients treated with doxycycline recovered in 1–3 days, as well as two patients who received chloramphenicol. In five patients who received ciprofloxacin,

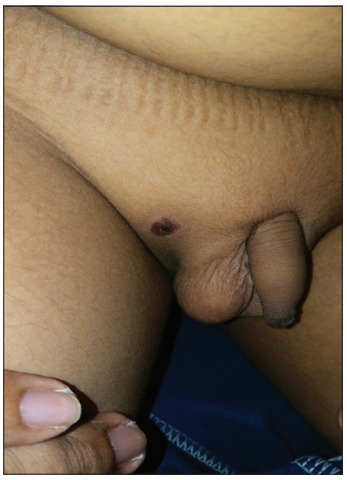

**Figure 1:** An eschar in R inguinal region.

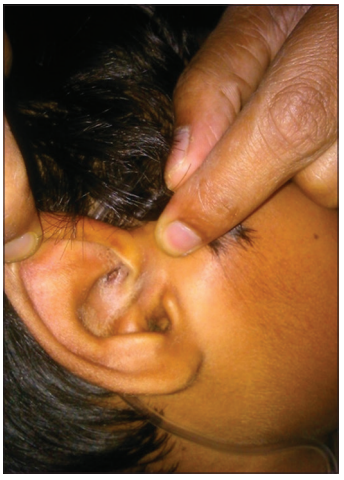

**Figure 2:** An eschar inside R pinna.

fever subsided only after 5 days. Finally, 3 patients (10.7%) died, including one patient treated with doxycycline.[4]

## COMPLICATION

Serious complications include pneumonia in 20–35% and meningoencephalitis in approximately 10–25% of children. Acute renal failure, myocarditis, and a septic shock-like syndrome occur much less often. Gangrene, acute respiratory distress syndrome, gastrointestinal bleed, neurological sequelae, hemophagocytic lymphohistiocytosis, purpura fulminans, myocarditis, and disseminated intravascular coagulation (DIC) can also occur. The infection carries a high of mortality (death rate up to 30%) if timely interventions not done.

Few cases of complicated scrub also revealed positive anti-COVID antibody. As of now in India, COVID vaccination has not started U18, it implied either COVID being as coinfection or mere a coincidental finding suggestive

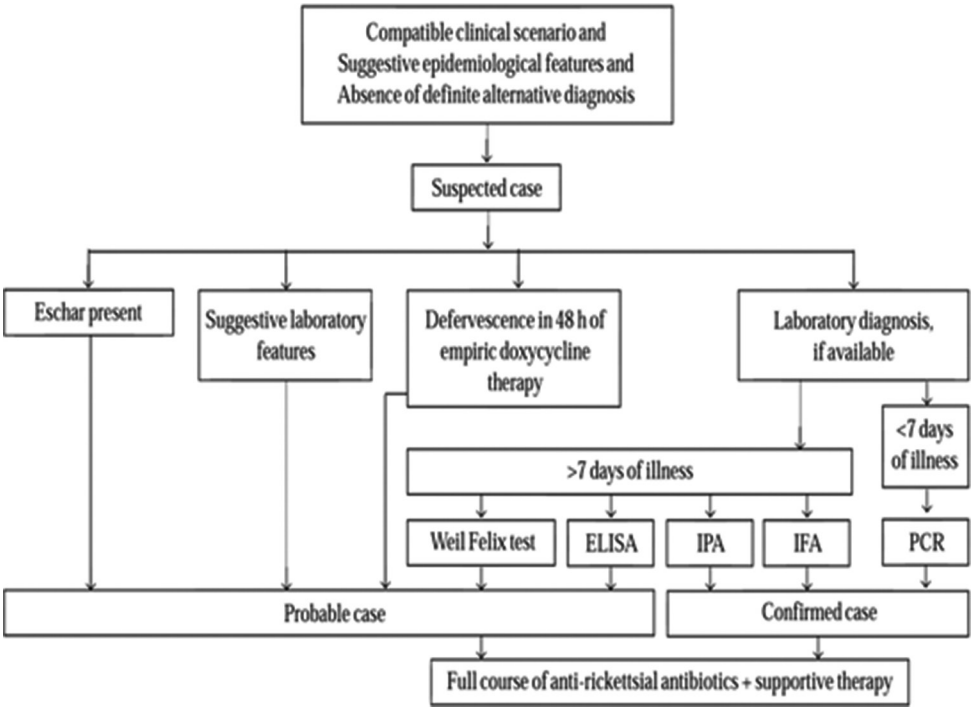


**Figure 3:** Management algorithm for rickettsial infections. ELISA: Enzyme-linked immunosorbent assay, IPA: Immunoperoxidase assay, IFA: Immunofluorescent assay, PCR: Polymerase chain reaction.

of past infection. Few cases admitted as multisystem inflammatory syndrome in children (MISC) and treated in line with intravenous immunoglobulin/intravenous (IVIG/IV) methylpred shown remarkable improvement after doxycycline as per coexistent scrub diagnosis. However, COVID and MISC in children being new entity more study and research needed to understand scrub versus MISC.

As per Thap *et al*., scrub typhus with septic shock patients results in organ failure: Respiratory failure and DIC was predominant followed by renal and hepatic involvement. Laboratory findings revealed that almost all of the patients had a mild leukocytosis, reduced hematocrit, and thrombocytopenia; SGOT, alkaline phosphatase (ALP), direct bilirubin, total bilirubin, blood urea nitrogen (BUN), and creatinine (CR) were elevated; hypoalbuminemia was noted.[5]

## POOR PROGNOSTIC FACTORS

G6PD deficiency, alcoholic liver disease, younger age, shorter incubation period, absence of rash, diabetes mellitus, delayed institution of anti-rickettsial drugs, and early multisystemic organ dysfunction.

## PREVENTION

Vector control, avoiding over-crowding, clean protective clothing, proper hygiene practices, permethrin based (on cloth) and 20–50% DEET(N-diethy-m-toluamide)-based (on skin) insect repellants to be used, prevention of vector bite, and prompt removal of mites.

## CONCLUSION

Due to low index of suspicion, non-specific clinical features in early course of disease and absence of easily available sensitive and specific diagnostic tests, these infections are difficult to diagnose. Strong clinical suspicion in a background of high fever, edema, and hepatosplenomegaly not responding to conventional antibiotics must be kept in mind. ESCHAR search, especially in flexural and intertriginous areas, should be included in routine examination of every patient with continued fever. Scrub meningoencephalitis is an upcoming differential diagnosis of acute encephalitis syndrome (AES). Cure rates are very high if treatment started on time. The clinical manifestations range from subclinical disease to organ failure and soon become fatal. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. Doxycycline is the gold standard drug and should be used judiciously. No vaccine is available due to marked genetic heterogeneity of strains.

## FUTURE PROSPECTS

Research and development to focus on following issues: Vaccine development and rapid diagnostic card test for antigen and antibody.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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