

## Policy Document

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# DHR-ICMR Guidelines for Diagnosis & Management of Rickettsial Diseases in India

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Rickettsial diseases, caused by a variety of obligate intracellular, Gram-negative bacteria from the genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Neorickettsia*, *Neoehrlichia*, and *Anaplasma*, belonging to the Alphaproteobacteria, are considered some of the most covert emerging and re-emerging diseases and are being increasingly recognized. Among the major groups of rickettsioses, commonly reported diseases in India are scrub typhus, murine flea-borne typhus, Indian tick typhus and Q fever. Rickettsial infections are generally incapacitating and difficult to diagnose; untreated cases have case fatality rates as high as 30-45 per cent with multiple organ dysfunction, if not promptly diagnosed and appropriately treated. The vast variability and non-specific presentation of this infection have often made it difficult to diagnose clinically. Prompt antibiotic therapy shortens the course of the disease, lowers the risk of complications and in turn reduces morbidity and mortality due to rickettsial diseases. There is a distinct need for physicians and health care workers at all levels of care in India to be aware of the clinical features, available diagnostic tests and their interpretation, and the therapy of these infections. Therefore, a Task Force was constituted by the Indian Council of Medical Research (ICMR) to formulate guidelines for diagnosis and management of rickettsial diseases. These guidelines include presenting manifestations, case definition, laboratory criteria (specific and supportive investigations) and treatment.

**Key words** Eschar - guidelines - presenting manifestations - rickettsial diseases - scrub typhus

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Rickettsial diseases are considered some of the most covert emerging and re-emerging diseases and are being increasingly recognized in India. Rickettsial diseases have been documented in India since the 1930s with reports of scrub typhus from Kumaon region<sup>1</sup>, in soldiers during the second world war in Assam<sup>2,3</sup>, scrub and murine typhus from Jabalpur area in Madhya Pradesh<sup>4</sup> and of murine typhus from Kashmir<sup>5</sup>. Surveillance in animals and humans in different parts of India has documented significant levels of exposure to infections<sup>6-10</sup>. Rickettsioses, of which scrub is the commonest, have been clearly reported from several States in India including Jammu and Kashmir, Himachal Pradesh, Uttaranchal (now Uttarakhand), Bihar, West Bengal, Meghalaya, Rajasthan, Maharashtra, Karnataka, Tamil Nadu and Kerala<sup>11-14</sup>. In some regions scrub typhus accounts for upto 50 per cent of undifferentiated fever presenting to hospital<sup>15</sup>.

Rickettsial infections are caused by a variety of obligate intracellular, Gram-negative bacteria from the genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Neorickettsia*, *Neoehrlichia*, and *Anaplasma*, belonging to the Alphaproteobacteria. Rickettsial diseases are classically divided into the typhus group and spotted fever group (SFG), although the genus has been subdivided further based on phylogenetic analysis (Table). *Orientia* spp. makes up the scrub typhus group<sup>16</sup>. Rickettsial diseases are zoonoses where human beings are accidentally involved in a chain of transmission between trombiculid mites (chiggers), ticks or fleas and animals (most commonly rodents). Among the major groups

of rickettsioses, commonly reported diseases in India are scrub typhus, murine flea-borne typhus, Indian tick typhus and Q fever.

Scrub typhus is the commonest occurring rickettsial infection in India. The infection is transmitted through the larval mites or 'chiggers' belonging to the family *Trombiculidae*. Only the larval stages take blood meal. Small rodents particularly wild rats of subgenus *Rattus* are natural hosts for scrub typhus. The field rodent and vector mites act as reservoir and between the two the infection perpetuates in nature. The vector mite is known to be present in diverse ecological niches such as equatorial rain forests, semi deserts and Alpine subarctic terrains in the Himalayan regions. Endemic foci are usually associated with specific habitats such as abandoned plantations, gardens or rice fields, overgrown forest clearings, shrubby fringes of fields and forests, river banks and grassy fields. These ecological patches which attract the natural host of mite vectors are called 'mite islands'<sup>17</sup>.

Scrub typhus can occur in areas where scrub vegetation consisting of low lying trees and bushes is encountered, and also in habitats as diverse as banks of rivers, rice fields, poorly maintained kitchen gardens<sup>8</sup>, grassy lawns which can all be inhabited by chiggers<sup>18</sup>. The chiggers (too small to be seen by the naked eye) feed usually on rodents and accidentally on humans, and transmit the infection during the prolonged feeding which can last for 1-3 days. Incidence of scrub typhus is higher among rural population. Cases are more likely

**Table.** The classification of the rickettsial diseases

Diseases	Rickettsial agent	Insect vectors	Mammalian reservoirs
<b>Typhus group</b>			
(i) Epidemic typhus	<i>Rickettsia prowazekii</i>	Louse	Humans
(ii) Murine typhus	<i>R. typhi</i>	Flea	Rodents
(iii) Scrub typhus	<i>Orientia tsutsugamushi</i>	Mite	Rodents
<b>Spotted fever group</b>			
(i) Indian tick typhus	<i>R. conorii</i>	Tick	Rodents, dogs
(ii) Rocky mountain spotted fever	<i>R. rickettsii</i>	Tick	Rodents, dogs
(iii) Rickettsial pox	<i>R. akari</i>	Mite	Mice
<b>Others</b>			
(i) Q fever	<i>Coxiella burnetii</i>	Nil	Cattle, sheep, goats
(ii) Trench fever	<i>Rochalimaea quintana</i>	Louse	Humans

to have exposure to rodents at home or at work, and to occupational (farming) or recreational activities which expose them to the risk of encountering chiggers sitting in grass blades, bushes and shrubs. The disease is seasonal in many parts of India, which correlates with the appearance and activity of mites.

### Presenting manifestations

Acute fever is the most common presenting symptom often associated with breathlessness, cough, nausea, vomiting, myalgia and headache<sup>19,20</sup>.

Eschar is an early clinical manifestation representing localized necrosis at the site of chigger bite. However, the presence of eschar is highly variable ranging from 7-97 per cent<sup>21</sup>.

An eschar at the site of chigger bite can be seen in early disease and is a useful diagnostic clue in scrub typhus with a varying frequency of 7-97 per cent<sup>21</sup>. Eschars are painless, punched out ulcers upto 1 cm in width, with a black necrotic centre (resembling the mark of a cigarette burn), which is surrounded by an erythematous margin. Eschar is a pathognomonic sign of scrub typhus. Usually a single eschar is found on the neck, axillae, chest, abdomen and groin, but multiple eschars have also been documented<sup>22</sup>. Eschar on moist intertriginous surfaces (axilla, scrotum, perianal region) may be missed if not looked into carefully because these may lack the black scab, and appear as shallow yellow based ulcers without surrounding hyperemia.

Rickettsial infections are generally incapacitating and difficult to diagnose; untreated cases have case fatality rates as high as 30-45 per cent with multiple organ dysfunction, if not promptly diagnosed and appropriately treated<sup>14,23</sup>. The vast variability and non-specific presentation of this infection have often made it difficult to diagnose clinically.

Rash (visible in fair skinned people) is considered as hallmark of rickettsial disease, though it is neither seen at presentation nor in all patients. Presence of rash is common in spotted fever and is extremely rare in scrub typhus. Rash usually becomes apparent after 3-5 days of onset of symptoms. Initially rash is in the form of pink, blanching, discrete maculae which subsequently becomes maculopapular, petechial or haemorrhagic<sup>24</sup>.

None of these clinical symptoms and signs including eschar are diagnostic of rickettsial disease. Therefore, epidemiological factors pertaining to the geographical area, habitat, occupation, movement of

the subject (vocational or recreational) could assist in reaching a diagnosis of rickettsial disease with certainty and initiating treatment in time.

### Complications

The complications of scrub typhus usually develop after the first week of illness. Jaundice, renal failure, pneumonitis, acute respiratory distress syndrome (ARDS), septic shock, myocarditis and meningoencephalitis are various complications known with this disease<sup>24</sup>. In several cases, pneumonia is one of the most frequent complications of scrub typhus which manifests as a non-productive cough and breathlessness. The presenting manifestations leading to ARDS could be life-threatening. Prompt antibiotic therapy, even based on suspicion, shortens the course of the disease, lowers the risk of complications and in turn reduces morbidity and mortality due to rickettsial diseases. Currently, doxycycline is regarded as the drug of choice<sup>25</sup>.

There is a distinct need for physicians and health care workers at all levels of care in India to be aware of the clinical features, available diagnostic tests and their interpretation, and the therapy of these infections. Therefore, these guidelines are developed to help treating physicians towards correct diagnosis and treatment. For want of awareness in physicians and community, diagnostic delays result in patients presenting to tertiary care facilities with ARDS and other severe complications which have a high risk of mortality.

## Guidelines for management

### I. Case definition

*1. Definition of suspected/clinical case:* Acute undifferentiated febrile illness of five days or more with or without eschar should be suspected as a case of rickettsial infection (if eschar is present, fever of less than five days duration should be considered as scrub typhus). Other presenting features may be headache and rash (rash more often seen in fair persons), lymphadenopathy, multi-organ involvement like liver, lung and kidney and acute respiratory distress.

The differential diagnosis of dengue, malaria, pneumonia, leptospirosis and typhoid should be kept in mind.

*2. Definition of probable case:* A suspected clinical case showing titres of 1:80 or above in OX2, OX19 and OXK antigens by Weil-Felix test and an optical density (OD) > 0.5 for IgM by ELISA is considered positive for members of typhus and spotted fever groups of Rickettsiae.

3. *Definition of confirmed case*: A confirmed case is the one in which (a) Rickettsial DNA is detected in eschar samples or whole blood by PCR, or (b) Rising antibody titres on acute and convalescent serum samples detected by indirect immune fluorescence assay (IFA).

## II. Laboratory criteria

There are various laboratory tests available for diagnosis of rickettsial diseases. Indirect immunoperoxidase assay (IPA) and immunofluorescence assay (IFA) are considered gold standards but are available in laboratories with higher level of facilities and expertise. Molecular diagnosis by PCR and ELISA techniques, particularly immunoglobulin M (IgM) capture assays can be available at secondary level of health care like District hospitals and medical colleges.

Weil-Felix test which is helpful in establishing presumptive diagnosis in diseases caused by members of typhus and spotted fever groups of Rickettsiae can be considered at primary level or can easily be set up with moderate level of infrastructure and expertise at least in areas affected by scrub typhus.

### *Specific investigations*

1. *Weil-Felix*: The sharing of the antigens between *Rickettsia* and *Proteus* is the basis of this heterophile antibody test. It demonstrates agglutinins to *Proteus vulgaris* strain OX19, OX2 and *Proteus mirabilis* OXK. Though this test lacks high sensitivity and specificity but still serves as a useful and inexpensive diagnostic tool for laboratory diagnosis of rickettsial disease. This test should be carried out only after 5-7 days of onset of fever. Titre of 1:80 is to be considered possible infection. However, baseline titres need to be standardized for each region.

2. *IgM and IgG ELISA*: ELISA techniques, particularly immunoglobulin M (IgM) capture assays are probably the most sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies, indicates recent infection with *Rickettsia*. In cases of infection with *O. tsutsugamushi*, a significant IgM antibody titre is observed at the end of 1<sup>st</sup> week, whereas IgG antibodies appear at the end of 2<sup>nd</sup> week. The cut-off value is optical density of 0.5. Baseline titres need to be established keeping in view the regional variations.

3. *Polymerase chain reaction (PCR)*: It is a rapid and specific test for diagnosis. It can be used to detect rickettsial DNA in whole blood, buffy coat fraction or tissue specimen. The Real Time format PCR is used to

target the gene encoding the major 56 kDa and/or 47 kDa surface antigens. Primers to amplify a fragment of this 56 kDa and /or 47 kDa gene and positive and negative control samples are used as recommended by the manufacturer. The results are best within the first week for blood samples because of presence of rickettsemia (*O. tsutsugamushi*, *R. rickettsii*, *R. typhi* and *R. prowazekii*) in first 7-10 days.

4. *Immunofluorescence assay (IFA)*: This is a reference serological method for diagnosis of rickettsial diseases and is considered serological 'gold standard'; however, cost and requirement of technical expertise limit its wide use. Therefore, it is recommended only for research and in areas where seroprevalence of rickettsial diseases has been established and a reference facility is already available which has the necessary expertise required to conduct these tests.

5. *Indirect immunoperoxidase assay (IPA)*: It gives comparable result as IFA but requires special instrument and experienced personnel for interpretation of the test.

We do not recommend any rapid test for diagnosis of scrub typhus at the present stage of development of these tests as these need further evaluation.

### *Supportive laboratory Investigations*

These are required as additional diagnostic clues and sometimes can indicate severity and development of complications. These investigations can assist in deciding upon appropriate management of patients.

#### 1. *Haematology*

(i) Total leucocytes count (TLC) during early course of the disease may be normal but later in the course of the disease, leucocytosis is seen, *i.e.* WBC count > 11,000/ $\mu$ l.

(ii) Thrombocytopenia (*i.e.* < 1,00,000/ $\mu$ l) is seen in majority of patients.

2. *Biochemistry*: Raised transaminase levels are also observed.

3. *Imaging*: Chest X-ray shows infiltrates, mostly bilateral.

## III. Treatment

There is paucity of evidence based on randomized controlled trials for the management of rickettsial diseases including scrub typhus<sup>26</sup>. These guidelines for treatment cover the most common infection, the scrub typhus, murine typhus and the Indian tick typhus and

do not cover acute Q fever though treatment of Q fever is on the similar lines.

Without waiting for laboratory confirmation of the rickettsial infection, antibiotic therapy should be instituted when rickettsial disease is suspected.

*At primary level:* The health care provider needs to do the following:

(i) Recognition of disease severity. If the patient comes with complications to primary health facility and treating physician considers it as rickettsial infection, treatment with doxycycline should be initiated before referring the patient.

(ii) Referral to secondary or tertiary centre in case of complications like ARDS, acute renal failure, meningoencephalitis, multi-organ dysfunction. In addition to recommended management of pneumonia, treatment of scrub typhus (doxycycline) is to be provided to the patient.

(iii) In fever cases of duration of five days or more where malaria, dengue and typhoid have been ruled out; the following drugs should be administered –

*In adults:* (a) Doxycycline 200 mg/day in two divided doses for individuals above 45 kg for a duration of seven days. Or (b) Azithromycin 500 mg in a single dose for five days.

If the clinical sign and symptoms persist, alternative diagnosis should be considered.

*In children:* (a) Doxycycline in the dose of 4.5 mg/kg body weight/day in two divided doses for children below 45 kg. Or (b) Azithromycin in the dose of 10 mg/kg body weight for five days.

*In pregnant women:* Azithromycin 500 mg in a single dose for five days. Azithromycin is the drug of choice in pregnant women, as doxycycline is contraindicated.

*At secondary and tertiary care level*

(i) The treatment as specified above in uncomplicated cases.

(ii) In complicated cases the following treatment is to be initiated:

(a) Intravenous doxycycline (wherever available) 100 mg twice daily in 100 ml normal saline to be administered as infusion over half an hour initially followed by oral therapy to complete 7-15 days of therapy. Or (b) Intravenous azithromycin in the dose of 500 mg intravenous (iv) in 250 ml normal saline

over one hour once daily for 1-2 days followed by oral therapy to complete five days of therapy<sup>25</sup>. Or (c) Intravenous chloramphenicol 50-100 mg/kg/day 6-hourly doses to be administered as infusion over one hour initially followed by oral therapy to complete 7-15 days of therapy.

(iii) Management of the individual complications should be done as per the existing practices.

Doxycycline and/or chloramphenicol resistant strains have been seen in South-East Asia. These strains are sensitive to azithromycin<sup>27</sup>.

**Disclaimer:** These guidelines on diagnostics and treatment of rickettsial infections are based on a review of the currently available evidence and best practices, and may be revised in light of future developments in the field.

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