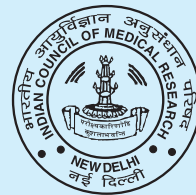


DHR-ICMR

GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF RICKETTSIAL DISEASES IN INDIA



DEPARTMENT OF HEALTH RESEARCH



INDIAN COUNCIL OF MEDICAL RESEARCH

2015

DHR-ICMR

GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF RICKETTSIAL DISEASES IN INDIA

Disclaimer: These guidelines on diagnostic 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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Foreword

In reference to rickettsial disease, rampant during Russian revolution, Lenin is said to have remarked that “either socialism will defeat the louse or the louse will defeat the socialism”. Rickettsial infection occurring in adversary epidemics, during times of war and famine has been one of the great bedevil of mankind. Historically going back, the disease was first reported during Peloponnesian War, but more accurate descriptions begin in 1489 with the Spanish siege of Granada. Rickettsial infections in the past have taken more lives than all the wars combined together.

In this era of modernization, the disease is still responsible for modern outbreaks; continues to cause severe illness and death in otherwise healthy adults and children, despite availability of low cost, effective antibiotic therapy. The greatest challenge to clinician is the difficult diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective. With the possible threat posed by such infections, there is the need to put in place sufficient safeguard measures to protect the citizens of our country and the world from the threat posed by rickettsial infections.

The present DHR-ICMR guidelines comprehensively address the various concerns regarding the clinical assessment, treatment, and laboratory diagnosis of rickettsial diseases in India and the world. I hope the physicians, health care worker, scientific community, the regulatory agencies, public health care professionals and the public at large will be benefited by these guidelines.



Dr. M. D. Gupte



डॉ विश्व मोहन कटोच
एम डी, एक एन ए एससी, एक ए एम एस, एक ए एससी, एक एन ए
सचिव, भारत सरकार
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स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
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Preface

Rickettsial diseases continue to be the source of severe illness and death in healthy adults and children, in spite of the availability of low cost, effective antimicrobial therapy. The greatest challenge is the difficult diagnostic dilemma posed by these infections early in their clinical course, when antibiotic therapy is most effective. Early signs and symptoms of these illnesses are notoriously nonspecific or mimic benign viral illnesses, making diagnosis difficult.

The care and management of people with rickettsial diseases is done primarily by the general practitioners and physicians. However, there are no clear directions or Guidelines for its management. A need for availability of a set of Guidelines which can be used by doctors, scientists and public health workers all over the country was strongly felt. With this in view, Department of Health Research (DHR) and Indian Council of Medical Research (ICMR) took the initiative to formulate the guidelines for the diagnosis and management of Rickettsial diseases in India. A Task Force was constituted to examine various management guidelines available and deliberate on the relevant issues keeping in view the local conditions. The guidelines formulated and presented in this document define a framework for recognizing manifestations, identifying appropriate diagnostic tests and initiating prompt and effective treatment.

These guidelines have been developed for scientific purpose with the aim to provide physicians and health care workers with practical information to assist with the diagnosis and care of patients with Rickettsial infections and also stimulate thinking among scientists interested in developing this area in the country at the various levels of health care and thus help the people to lead a normal and healthy life.

V.M. Katoch

V.M.Katoch

Acknowledgements

The emergence of Rickettsial infection has necessitated the development of consensus amongst health care delivery personnel for appropriate timely diagnosis and management. Consequently, DHR-ICMR has taken the initiative in developing the “DHR-ICMR Guidelines for diagnosis and management of Rickettsial diseases in India”. We gratefully acknowledge the help rendered by all the people involved in the formulation of these guidelines.

We are very grateful and indebted to our Secretary (DHR) & DG (ICMR) Dr. V. M. Katoch, for his vision, guidance and support given to develop the ‘Guidelines for diagnosis and management of Rickettsial diseases in India’. We extend our sincere thanks to Dr. M. D. Gupte, Co-Chair for identifying and highlighting the significant issues to be included in the guidelines on Rickettsial Infections and steering the deliberations during formulation of the guidelines. We also express our gratitude to Lt. Gen. D.Raghunath, Co-Chair for his continuous guidance, support and encouragement in this endeavor.

We are grateful to all the Task Force members for their scientific contribution in preparing guidelines and refinement of the manuscript. We also acknowledge the inputs received from representatives of different organizations present in the scientific deliberations and the suggestions received from others following posting of draft guidelines.

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Abbreviations

%	:	Percent
ARDS	:	Acute Respiratory Distress Syndrome
<i>C.burnetii</i>	:	<i>Coxiella burnetii</i>
cc.mm	:	Cubic Millimetre
cm	:	Centimetre
DNA	:	Deoxyribonucleic acid
ELISA	:	Enzyme-Linked Immunosorbent Assay
Fig.	:	Figure
i.e.	:	that is
IFA	:	Immunofluorescence Assay
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IPA	:	Indirect Immunoperoxidase Assay
IV	:	Intravenous
Kda	:	Kilodalton
Kg	:	Kilogram
mg	:	Milligram
<i>O. tsutsugamushi</i>	:	<i>Orientia tsutsugamushi</i>
OD	:	Optical Density
PCR	:	Polymerase Chain Reaction
<i>R.akari</i>	:	<i>Rickettsia akari</i>
<i>R. conorii</i>	:	<i>Rickettsia conorii</i>
<i>R. prowazekii</i>	:	<i>Rickettsia prowazekii</i>
<i>R.rickettsii</i>	:	<i>Rickettsia rickettsii</i>
<i>R.typhi</i>	:	<i>Rickettsia typhi</i>
SFG	:	Spotted Fever Group

DHR-ICMR Guidelines for diagnosis and management of Rickettsial diseases in India

1. Introduction

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 ¹, Assam in soldiers during the second world war ²⁻³, of scrub and murine typhus from Jabalpur area in Madhya Pradesh ⁴ and of murine typhus from Kashmir ⁵. Surveillance in animals and humans in different parts of India has documented significant levels of exposure to infections. ⁶⁻¹⁰ Rickettsioses, of which scrub is the commonest, has been clearly reported from several states in India including Jammu and Kashmir, Himachal Pradesh, Uttaranchal (now known as Uttarakhand), Bihar, West Bengal, Meghalaya, Rajasthan, Maharashtra, Karnataka, Tamil Nadu and Kerala ¹¹⁻¹⁴. In some regions scrub typhus accounts for upto 50% of undifferentiated fever presenting to hospital.¹⁵

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. Rickettsia are classically divided into the typhus group and spotted fever group (SFG), although the genus has been subdivided further based on phylogenetic analysis. **Orientia** spp. makes up the scrub typhus group.¹⁶ 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).

Given below is the classification of the Rickettsial diseases

Diseases	Rickettsial agent	Insect vectors	Mammalian reservoirs
Typhus group a. Epidemic typhus b. Murine typhus c. Scrub typhus	<i>R.prowazekki</i> <i>R.typhi</i> <i>O.tsutsugamushi</i>	Louse Flea Mite	Humans Rodents Rodents
Spotted fever group a. Indian tick typhus b. Rocky Mountain spotted fever c. Rickettsial pox	<i>R.conorii</i> <i>R.rickettsii</i> <i>R.akari</i>	Tick Tick Mite	Rodents, dogs Rodents, dogs Mice
Others a. Q fever b. Trench fever	<i>C.brunetti</i> <i>Rochalimaea Quintana</i>	Nil Louse	Cattle, sheep, goats Humans

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. A number of 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" ¹⁷

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 ⁸, grassy lawns which can all be inhabited by chiggers.¹⁸ 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 1-3 days. Incidence of scrub typhus is higher among rural population. Cases are more likely 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, shrubs. The disease is seasonal in many parts of India, which correlates with the appearance and activity of mites.

2. Presenting manifestations

Rickettsial infections are generally incapacitating and difficult to diagnose; untreated cases have case fatality rates as high as 30-45% with multiple organ dysfunction, if not promptly diagnosed and appropriately treated. ¹⁴ The vast variability and non-specific presentation of this infection have often made it difficult to diagnose clinically. Given below are some of the presenting symptoms and signs of rickettsial infections:

Acute fever is the most common presenting symptom often associated with breathlessness, cough, nausea, vomiting, myalgia and headache ¹⁹⁻²⁰

An eschar at the site of chigger bite can be seen in early disease and is useful diagnostic clue in scrub typhus, though its frequency varies from 7-97% ²¹. Eschars are painless, ulcers upto 1 cm in size, with a black necrotic centre (resembling the mark of a cigarette burn). Usually a single eschar is found on the neck, axillae, chest, abdomen and groin, but multiple eschars have also been documented.²² Eschar on moist intertriginous surfaces (axilla, scrotum, perianal region) may be missed if not looked into carefully because they may lack the black scab, and appear as shallow yellow based ulcers without surrounding hyperemia.



Fig.1 Eschar at neck region



Fig.2 Eschar with the typical central black scab suggesting a cigarette burn on the skin.



Fig.3 Eschar in axilla



Fig. 4. Rash on body

- **Rash (in fair skinned people):** Though rash is considered as hallmark of rickettsial disease, it is neither seen at presentation nor in all patients. Presence of rash is common in spotted fever and 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 hemorrhagic ²³.

None of these clinical symptoms and signs including eschar are diagnostic of rickettsial disease. Therefore epidemiological factors pertaining to 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.

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 ²⁴.

Pneumonia is one of the most frequent complications of scrub typhus which manifests as a non-productive cough and breathlessness and leads to ARDS which could be life-threatening. Severe complications besides acute respiratory distress syndrome (ARDS) include hepatitis, renal failure, meningo-encephalitis and myocarditis with shock may occur in varying proportions of patients.²⁴

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. 25

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 centres with ARDS and other severe complications which have a higher risk of mortality.

3. Guidelines for Management:

3.1 Case Definition

3.1.1 Definition of Suspected/clinical case:

Acute undifferentiated febrile illness of 5 days or more with or without eschar should be suspected as a case of Rickettsial infection. (If eschar is present, fever of less than 5 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 involvement.

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

3.1.2 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 are considered positive for typhus and spotted fever groups of Rickettsiae.

3.1.3 Definition of Confirmed case:

A Confirmed case is the one in which:

- Rickettsial DNA is detected in eschar samples or whole blood by PCR
- Or
- Rising antibody titers on acute and convalescent sera detected by Indirect Immune Fluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA)

3.2 Laboratory criteria

There are various laboratory tests available for diagnosis of rickettsial diseases. Indirect Immunoperoxidase Assay (IPA) and Immunofluorescence Assay (IFA) are considered serological gold standards but are available at laboratories with higher level of facilities and expertise. Molecular diagnosis by PCR is available only at few centres in India. However, ELISA based tests, particularly immunoglobulin M (IgM) capture assays can be made available at secondary level and tertiary levels 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 of health care as they can be easily set up with moderate level of infrastructure and expertise atleast in areas affected by scrub typhus.

3.2.1 Specific Investigations:

- **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.
- **IgM and IgG ELISA:** ELISA techniques, particularly immunoglobulin M (IgM) capture assays for **serum**, are probably the most of sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies, indicate comparatively recent infection with rickettsial disease. In cases of infection with *O. tsutsugamushi*, a significant IgM antibody titre is observed at the end of 1st week, whereas IgG antibodies appear at the end of 2nd week. The cut off value is Optical Density of 0.5. Baseline titres need to be established keeping in view the regional variations.
- **Polymerase Chain Reaction (PCR):** It is a rapid and specific test for diagnosis. It can be used to detect rickettsial DNA in whole blood and eschar samples. The PCR is targeted at the gene encoding the major 56 Kda and/or 47 Kda surface antigen gene. The results are best within first week for blood samples because of presence of rickettsemia (*O.tsutsugamushi*, *R.rickettsii*, *R. typhi* and *R.prowazekii*) in first 7-10 days.
- **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 sero-prevalence of rickettsial diseases has been established and a reference facility is already available which has the necessary expertise required to conduct these tests.
- **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 they need further evaluation.

3.2.2 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.

a) Hematology

- Total Leucocytes Count during early course of the disease may be normal but later in the course of the disease; WBC count may become elevated to more than 11,000 / cu. mm.

- Thrombocytopenia (i.e. $< 1,00,000/ \text{cu.mm}$) is seen in majority of patients.

b) Biochemistry

- Raised Transaminase levels are commonly observed.

3.3.3 Imaging

- Chest X-Ray showing infiltrates, mostly bilateral.

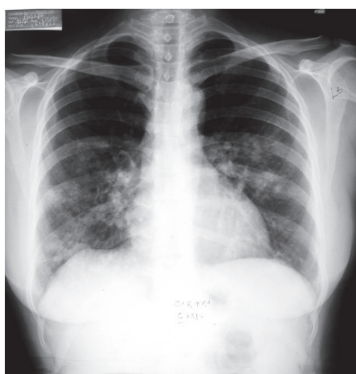


Figure: 5

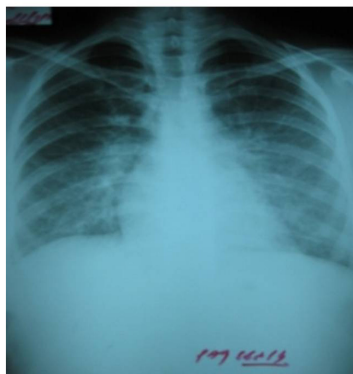


Figure: 6

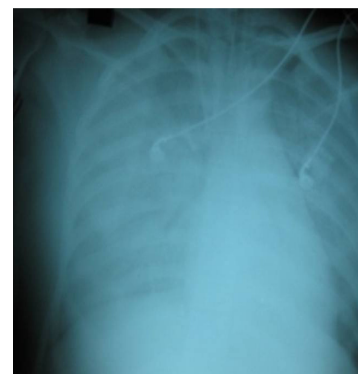


Figure: 7

Figure 5: X-ray of a patient with scrub typhus showing bilateral lower lobe interstitial infiltrates

Figure 6: X-Ray of a 30-year old woman presenting with fever of 10 days, non-productive cough of 5 days and complaining of breathlessness. X-ray shows bilateral reticulonodular (interstitial) opacities in the lower lobes before treatment.

Figure 7: X-ray of the same patient taken 2 days after admission to a tertiary care centre with severe breathlessness. X-ray now shows bilateral extensive air-space consolidation suggestive of an acute respiratory distress syndrome.

3.3 Treatment

There is paucity of evidence based on randomized controlled trials for the management of rickettsial diseases including scrub typhus.²⁵

These guidelines for treatment cover the most common infection, the scrub typhus, murine typhus and Indian Tick typhus and do not cover acute Q fever though treatment of Q fever is on similar lines.

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

3.3.1 At Primary level: The Health Care provider needs to do the following:

- a) Recognition of disease severity. If the patients come with complications to primary health facility and treating physician considers it as rickettsial infection, treatment with doxycycline should be initiated before referring the patient.
- b) Referral to secondary or tertiary centre in case of complications like ARDS, acute renal failure, meningo-encephalitis, multi-organ dysfunction. In addition to recommended management of

community acquired pneumonia, doxycycline is to be initiated when scrub typhus is considered likely.

- c) In fever cases of duration of 5 days or more where malaria, dengue and typhoid have been ruled out; following drugs should be administered when scrub typhus is considered likely –

Adults

- a) Doxycycline 200 mg/day in two divided doses for individuals above 45 kg for duration of 7 days. Patients should be advised to swallow capsules with plenty of fluid during meals while sitting or standing

Or

- b) Azithromycin 500 mg in a single oral dose for 5 days.

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 single dose of 10mg/kg body weight for 5 days.

Pregnant women

- a) Azithromycin 500 mg in a single dose for 5 days.

- b) Azithromycin is the drug of choice in pregnant women, as doxycycline is contraindicated

3.3.2 At secondary and tertiary care:

- a) The treatment as specified above in uncomplicated cases.

- b) In complicated cases the following treatment is to be initiated –

- i) Intravenous doxycycline (wherever available) 100mg 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

- ii) Intravenous Azithromycin in the dose of 500mg IV in 250 ml normal saline over 1 hour once daily for 1-2 days followed by oral therapy to complete 5 days of therapy. ²⁶

Or

- iii) Intravenous chloramphenicol 50-100 mg/kg/d 6 hourly doses to be administered as infusion over 1 hour initially followed by oral therapy to complete 7-15 days of therapy.

- iv) 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 ²⁷

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