Rickettsial Infections: Indian Perspective

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Context: Underdiagnosed and misdiagnosed rickettsial infections are important public health problems. They also lead to extensive investigations in children with fever of undetermined origin contributing to financial burden on families. The present review addresses the epidemiology, clinical features, diagnosis and management issues of these infections, primarily for a practicing clinician.

Evidence acquisition: We did a PubMed, Medline and Cochrane library search for literature available in last 40 years.

Results : Rickettsial infections are re-emerging and are prevalent throughout the world. In India, they are reported from Maharashtra, Tamil nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and West Bengal. In view of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnosic test, these infections are notoriously difficult to diagnose. Failure of timely diagnosis leads to significant morbidity and mortality. With timely diagnosis, treatment is easy, affordable and often successful with dramatic response to antimicrobials. As antimicrobials effective for rickettsial disease are usually not included in empirical therapy of nonspecific febrile illnesses, treatment of rickettsial disease is not provided unless they are suspected. Knowledge of geographical distribution, evidence of exposure to vector, clinical features like fever, rash, eschar, headache and myalgia alongwith high index of suspicion are crucial factors for early diagnosis.

Key words : *Rickettsia, Spotted fever, Typhus fever, Vasculitis, Weil-Felix test.*

Rickettsial diseases are some of the most covert re-emerging infections of the present times. They are generally incapacitating and notoriously difficult to diagnose; untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treated(1). Rickettsial infection has been one of the great scourges of mankind, occuring in devastating epidemics during times of war and famine. Napoleon's retreat from Moscow was forced by rickettsial disease breaking out among his troops. Lenin is said to have remarked, in reference to rickettsial disease rampant during Russian revolution, that "either socialism will defeat the louse or the louse will defeat the socialism"(2). Rickettsial infection in the past have taken more lives than all the wars combined together(3). Tickborne rickettsial diseases (TBRD) continue 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(4).

EPIDEMIOLOGY

Except Antartica, rickettsial infections are prevalent throughout the world. For India, the reported numbers are an underestimate due to lack of community based data and non-availability of confirmatory laboratory tests(5). Rickettsial disease in India has been documented from Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu(1,6-8). Batra has reported a high magnitude of scrub typhus, spotted fever and Indian tick typhus caused by *R. conorii*(1). An extensive study on tickborne rickettsiosis in Pune district of

Maharashtra revealed that Indian tick typhus exists as zoonosis(9).

MICROBIOLOGICAL ASPECTS

Family Rickettsiaceae comprise a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. Rickettsiae are small, nonflagellate, gram negative pleomorphic cocco-bacilli adapted to obligate intracellular parasitism and transmitted by arthropod vectors. They are primary parasites of arthropods like lice, fleas, ticks and mites, in which they are found in the alimentary canal. In vertebrates, including humans, they infect vascular endothelium and reticulo-endothelial cells. Family Rickettsiaceae comprises three genera namely *Rickettsia, Orientia* and *Ehrlichia*. Former members of this family, *Coxiella burnetii* which causes Q fever and *Rochalimaea quintana* causing trench fever have been excluded because the former is not primarily arthropod-borne and the latter not an obligate intracellular parasite(2). Being obligate intracellular parasites, these organisms donot grow on cell free media and need tissue cultures and laboratory animals for their isolation. Various members of this family can be grouped into four biogroups based on the lipopolysaccharide group antigen, as shown in *Table* **I**.

PATHOGENESIS

These organisms grow in alimentary canal of arthropods. Arthropods maintain the infection naturally by either transovarial transmission (passage of the organism from infected arthropods to their progeny seen in spotted fever group and scrub typhus) wherein arthropods act as vector as well as reservoir; or without transovarial transmission seen in typhus fever group, wherein arthropods act only as vector. Man is an accidental host except for louse borne epidemic typhus caused by *Rickettsia prowazekii*. Transmission to humans occurs by infected arthropod vector or exposure to infected animal reservoir host. Vector to human transmission occur as vector defaecate while feeding (flea feeding reflex) so that faces contaminate pruritic bite wounds (seen with typhus fever group) or primarily by bite, where regurgitation of infected saliva occurs during feeding (seen with spotted fever group and scrub typhus).They are not transmissible directly from person to person except by blood transfusion or organ transplantation(10).

PATHOLOGY

These organisms after entering human body, multiply locally and enter the bloodstream. Then they invade their target cells, which are vascular endothelium, reticuloendothelial cells and in case of Ehrlichiosis and Anaplasmosis, blood cells. Once inside host cells, organisms multiply and accumulate in large numbers before lysing the cell (in case of typhus group) or they escape from cell, damaging its membrane and causing influx of water (in case of spotted fever group). Unlike rickettsiae in the spotted fever group, which can survive and replicate for several days after the death of their host cells,

TABLE I BIOGROUPS OF RICKETTSIACEAE(12)

Biogroup	Disease	Vector	Host	Organism
Spotted fever	Rocky Mountain spotted fever (RMSF)	tick	dogs, rodents	*Rickettsia rickettsii*
	Rickettsialpox	mite	mice	*Rickettsia akari*
	Indian tick typhus / Boutonneuse fever/ Mediterranean spotted fever (MSF)	tick	dogs, rodents	*Rickettsia conorii*
Typhus	Epidemic louse borne typhus	louse	human	*Rickettsia prowazekii*
	Brill-Zinsser disease (recrudescent typhus)	louse	human	*Rickettsia prowazekii*
	Endemic/Murine flea borne typhus	flea	rats	*Rickettsia typhi*
Scrub typhus	Scrub typhus	chigger	rodents	*Orientia tsutsugamushi*
Miscellaneous	Ehrlichioses and Anaplasmosis	tick	deer,dogs,rodents	*Ehrlichia , Anaplasma*
	TIBOLA (tick borne lymphadenopathy)	tick	wild boar	*Rickettsia slovaca*
	DEBONEL	tick	wild boar	*Rickettsia slovaca*

DEBONEL: Dermacentor borne necrosis-eschar-lymphadenopathy.

rickettsiae of the typhus group die rapidly after killing their host cells(11).

Vasculitis is the basic pathogenetic mechanism. Vasculitis is responsible for skin rash, microvascular leakage, edema, tissue hypoperfusion and end-organ ischemic injury. Formation of thrombi can lead to tissue infarction and hemorrhagic necrosis. Inflammation and vascular leakage leads to interstitial pneumonitis, noncardiogenic pulmonary edema, cerebral edema and meningoencephalitis. Infection of endothelial cells also induces procoagulant activity that promotes coagulation factor consumption, platelet adhesion and leucocyte emigration and may result in clinical syndrome similar to disseminated intravascular coagulation(12).

CLINICAL FEATURES

Early signs and symptoms of these infections are nonspecific and mimic benign viral illnesses, making diagnosis more difficult(13). Symptomato-logy may vary from mild to severe. Unless there is a high index of suspicion, it is likely to be missed as the clinical presentation may mimic other common infections in the tropics(14). Incubation period of various rickettsial infections varies between 2-21 days. Clinical manifestations of rickettsial infections are detailed herein.

Fever: Fever of undetermined origin is the most frequent presentation of rickettsial disease. Fever is usually abrupt onset, high grade, sometimes with chills, occasionally with morning remissions and associated with headache and myalgia. Diagnosis of rickettsial disease should always be considered in patients with acute febrile illness accompanied with headache and myalgia, particularly in endemic areas with history of tick exposure or contact with dogs. In one study, 24% among 180 children (less than 14 years age) admitted with acute febrile illness in whom other common causes for fever were excluded, were clinically and serologically confirmed to have scrub typhus or other rickettsial infections. Scrub typhus formed the largest group (62.8%) followed by spotted fever (32.6%) and endemic typhus fever (4.7%)(15).

Headache and Myalgia: Severe frontal headache and generalised myalgia specially in muscles of the lumber region, thigh and calf is seen in variable proportion of cases. Headache is noted less frequently in young children than in adults, but when it occurs, it is often intractable to therapy(16).

Rash: Though rash is considered as hallmark of rickettsial disease, it is neither seen at presentation nor in all the patients(17,18). Thus it should be remembered that spotted fevers could be spotless too! Rash usually becomes apparent after 3-5 days of onset of symptoms. Initially rash is in the form of pink, blanching, discrete macules which subsequently becomes maculopapular, petechial or hemorrhagic (*Fig.*1). Sometimes palpable purpura (typical of vasculitis) is seen. Occasionally petechiae enlarge to ecchymosis and gangrenous patches may develop. Rarely gangrene of digits, earlobes, scrotum, nose or limbs may occur secondary to vasculitis and thrombosis. Distribution of rash is initially near ankles, lower legs and wrists. Thereafter rash spreads centripetally to involve whole body. Presence of rash on palms and soles, considered so typical of rickettsial disease, can be seen in other diseases like infective endocarditis, syphilis, meningococcemia, enteroviral diseases and adverse drug reactions. The rash of typhus group rickettsioses is quite atypical, initially appearing on trunk, spreading centrifugally and usually sparing palms and soles.

Eschar: A necrotic eschar at the inoculating site is seen in variable proportion of Indian tick tuphus, scrub typhus and rickettsialpox cases. The site of initial tick bite is inapparent in other rickettsial infections. Eschar, a black necrotic area, resembles the skin burn of cigarette butt (*Fig.*2). A necrotic eschar usually has an erythematous rim and is associated with regional lymphadenopathy.

Generalised lymphadenopathy and hepato-splenomegaly are seen in majority of scrub typhus patients(19).

Systemic features: Clinical features referable to various systems are sometimes seen in rickettsial infections. Gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhea are seen with varying frequency. Constipation is seen particularly in epidemic typhus. Respiratory

FIG. 1 *Hemorrhagic rash of rickettsial infection.*

FIG. 2 *Eschar in left inguinal region.*

symptoms include cough and distress are sometimes seen. Neurological manifestations like dizziness, drowsiness, disorientation, tinnitus, photophobia, delirium, meningismus, and visual disturbances; are seen more commonly with typhus group rickettsioses. The word 'typhus' refers to cloudy state of consciousness ('*typhos*': cloud or smoke).

Miscellaneous: Periorbital edema, conjunctival hyperemia, epistaxis, acute reversible hearing loss and arthralgia are sometimes reported.

SEVERE MANIFESTATIONS AND COMPLICATIONS

Rickettsial infections sometimes produce severe life threatening manifestations and takes a fulminant course. Fulminant course of rickettsial infections, particularly spotted fever group is known to occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Following are the life threatening manifestations of rickettsial infections.

1. *Respiratory*: Interstitial pneumonitis and noncardiogenic pulmonary edema secondary to pulmonary microvascular leakage are occasionally observed.

2. *Neurological*: Meningoencephalitic syndrome is known to occur with rickettsial infections. In fact, rickettsial infections should be included in differential diagnosis of aseptic meningitis and encephalitis in patients exposed to endemic areas specially when accompanied by renal insufficiency and/or jaundice(20, 21).

3. *Renal*: Acute renal failure is associated with bad prognosis and can be a presenting feature of rickettsial disease. The possibility of scrub typhus should be borne in mind whenever a patient of fever present with varying degree of renal insufficiency particularly if eschar exists alongwith history of environmental exposure(22,23).

4. *Disseminated intravascular coagulation* like syndrome, hepatic failure, gangrene and myocarditis are sometimes seen in rickettsioses.

LABORATORY FINDINGS

No single laboratory finding is specific for early diagnosis. Various laboratory abnormalities found in rickettsial diseases are described below.

Hematology: Total leucocyte count, during early course of the disease, is normal to low normal with marked shift to left. Later in the course of the disease, it shows leucocytosis in 30% of cases(24). Low platelet counts are present in about 60% cases(16). Erythrocyte sedimentation rate is usually high.

Biochemistry: Hyponatremia and hypoalbuminemia, reflecting increased vascular permiability, are sometimes helpful in differentiating rickettsial infections from other acute infections. Thrombocytopenia, hyponatremia and normal to low leucocyte count are certain clues to early diagnosis. Hepatic transaminase values are frequently elevated. Blood urea is elevated due to prerenal mechanisms.

Serology: Microimmunoflorescence, immunoperoxidase assay, latex agglutination, indirect hemagglutination, enzyme-linked immunosorbent assay, dot blot immunoassay (including dipstick test) and Weil-Felix test are the various serological methods available for diagnosis of rickettsial diseases. Of these, only Weil-Felix test is easily available in India. As all these tests detect antibodies, they would be able to make diagnosis only after 5-7 days of onset of disease and hence play no role for initiation of therapy in a suspected case.

(*a*) *Weil-Felix test:* The sharing of antigens between rickettsia and proteus is the basis of this heterophile antibody test. It demonstrates agglutinins to *Proteus vulgaris* strain OX 19, OX 2 and OX K. Most of the Western literature has advised against performing this test for diagnosis of rickettsial infections(12). The poor sensitivity of the WF test is now well demonstrated but a good correlation between the results of the WF test and detection of IgM antibodies by an indirect immunofluorescence assay (IFA) is often observed(25). This can be used as a screening test, which detects more cases than misdiagnosed ones and when positive, is reasonably specific. In spite of all its drawbacks, Weil-Felix test still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease(1). Either four fold rise in agglutinin titre in paired sera or single titre of more than 1:320 is considered diagnostic for infection with these febrile agents. The use of this test is accepted in

conditions where definitive investigations are not available(26,27). Isaac, *et al*.(28) have demonstrated that the sensitivity of Weil-Felix was 30% at a breakpoint titre of 1:80, but the specificity and positive predictive value were 100%. Hence Weil-Felix test is still not entirely obsolete but has to be interpreted in the correct clinical context(6).

(b) *IFA:* This is a reference serological method for diagnosis of rickettsial diseases and is considered 'gold standard'. It is not available in India. As with all other serological methods, it usually provides retrospective diagnosis and sensitivity is enhanced by testing paired sera (acute and convalescent).

Polymerase chain reaction assay: It can be used to detect rickettsial DNA in whole blood, buffy coat fraction or tissue specimen. It is the most rapid assay for the diagnosis. It has certain disadvantages like varying levels of sensitivity, high cost and nonavailability.

Immunohistochemistry and isolation of organism: in cell culture or laboratory animals are other methods restricted to research laboratories.

DIAGNOSIS

No rapid laboratory tests are available to diagnose rickettsial infection early in the course of disease. It is emphasized again that the only crucial factor for early diagnosis is high index of suspicion. Following five factors taken together should help in diagnosis, which can then be confirmed with serology.

1. *Compatible clinical presentations:* Various clinical situations where a diagnosis of rickettsial disease should be considered are fever without source, pyrexia of unknown origin (PUO), fever with rash (rash which is petechial, involving palms and soles, having centripetal spread), fever with eschar, meningoencephalitis or aseptic meningitis, acute renal insufficiency with eschar, and infective vasculitidis.

2. *Tick bite or tick exposure:* Tick bite is painless and histoty of tick bite is present in less than 50% of cases. Hence absence of tick bite should not dissuade

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KEY MESSAGES

- Rickettsial infections are prevalent in various parts of India.

- These are one of the most difficult infections to diagnose in their early course and high index of suspicion is the key to early diagnosis.

- Fever, rash, headache, myalgia, lymphadenopathy and eschar are various clinical features of these infections.

- Epidemiological features and history of exposure to vector are crucial for diagnosis.

- Failure of early diagnosis is associated with significant mortality and morbidity and also leads to expensive PUO workup.

- Therapy is easy and affodable with dramatic results and needs to be started on clinical suspicion, as there is no specific test for early diagnosis.

- Doxycycline is the drug of choice and it can be used safely even in chldren below 8 years of age.

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a pediatrician from considering the diagnosis of rickettsial disease. Patient should be completely exposed to look for ticks on body and clothing. Outdoor actvities in areas with high uncut grass, weeds, low bushes or animal sheds where ticks are often seen is a definite risk factor. Contact with family dog in whom history of tick attachment or tick removal is forthcoming can be useful.

3. *Epidemiological data:* Diagnosis should be considered in areas known for rickettsial disease. But in absence of multicentric studies, one would not know prevalence in particular area. Occurrence of similar illness (like index case) simultaneously or sequentially in family members or family pets can be a useful link as small 'islands' of infected ticks may occur in discrete geographic units such as neighborhood or parks(16).

4. *Suggestive laboratory features:* Normal to low leucocyte count with marked left shift, thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases are compatible with diagnosis of rickettsial disease, although absence of these does not rule it out.

5. *Rapid defervescence with appropriate antibiotics:* It is so characteristic that it can be used as a diagnostic test for rickettsial disease. In fact if fever fails to respond in 48 hours, one should review the diagnosis. Severely ill patients with multiple organ dysfunction may take longer period of time to respond.

Thus, rickettsial infection should be suspected in presence of above clinical features in a patient with likelihood of tick exposure. They should undergo relevant hematological and biochemical testing and those with high probability of rickettsial infection should be treated with appropriate antimicrobials. Failure of defervescence within 48 hours should lead to search for alternative diagnosis.

DIFFERENTIAL DIAGNOSIS

Rickettsial diseases can be easily confused with a variety of viral (measles, enteroviral exanthems, dengue, infectious mononucleosis), protozoal (malaria), bacterial (meningococcemia, typhoid, leptospirosis, toxic shock syndrome, scarlet fever) and collagen vascular (Kawasaki disease, other vasculitis) diseases, and adverse drug reactions. Invasive meningococcal disease may not be reliably distiguished from rickettsial disease clinically, hence one may need to treat for both conditions, after sending cerebrospinal fluid and blood for appropriate studies(4). The possibility of rickettsial disease should be considered in those leptospirosis patients who present with atypical features or respond poorly to therapy(29).

TREATMENT

Definitive treatment should be instituted on the basis of clinical and epidemiological clues as early as possible to avoid severe disease and fatal outcome(30,31). Various antibiotics useful for treating rickettsial diseases are tetracyclines,

preferably doxycycline, chloramphenicol, macro-lides(32,33) specially, azithromycin, clarithromycin, roxythromycin, and fluroquinolones, specially ciprofloxacin, ofloxacin, pefloxacin, levofloxa-cin(12). Doxycycline is the drug of choice. Oral treatment is used unless patient is vomiting or obtunded. Dose is 5 mg/kg/day in two divided doses for children below 45 kg and 200 mg/day in two divided doses for children above 45 kg. Duration of therapy should be at least 3 days after defervescence or minimum 5-7 days.

Use of tetracycline to treat children below 8 years is no longer a subject of controversy (34-36). It has been observed that cosmetically perceptible staining of teeth require six or more multiple day courses of therapy. Because TBRD can be life threatening and limited courses with tetracycline class antibiotics donot pose a substantial risk for tooth staining, the American Academy of Pediatrics committee on infectious diseases revised it's recommendations in 1997 and has identified doxycycline as the drug of choice for treating presumed or confirmed RMSF in children of any age(37).

Chloramphenicol has more side effects and needs hematological monitoring. On many occasions, fluroquinolones are associated with clinical failures despite good in vitro activity. Clarithromycin can be considered a valid alternative to tetracycline and chloramphenicol, especially for children less than 8 years of age(32,33). Occasional cases with resistance to doxycycline are treated with macrolides or rifampin. Sulfonamides are contraindicated in rickettsial diseases as they increase morbidity and mortality either by delaying institution of appropriate antibiotics or directly stimulating the growth of organisms.

Good supportive therapy is needed in critically ill patients as iatrogenic cerebral and pulmonary edema is easily precipitated due to preexsisting micro-vascular leakage. Judicious use of corticosteroids is advocated by some in meningoencephalitis(12). Supportive care is also needed for hypovolemia, coagulopathy, seizures and intercurrent infections.

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