



Rickettsial diseases in children

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Abstract:

In a tropical country like India, fevers are caused by different etiological agents. Rickettsial infections, which have a global distribution is one of the differential diagnosis in such cases and are reported from almost all parts of India. Rickettsial diseases widely vary in severity from self-limited mild illnesses to fulminating life-threatening infections. They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells which makes it difficult to culture them on artificial culture medium.

With globalization there is rapid spread of disease across the continents and therefore, skills for diagnosis and management of the disease attains global importance.

Rickettsial diseases can be clinically classified as Spotted Fever group, typhus group, distinctive clinical rickettsiae and emerging rickettsiae. The clinical course will have incubation period, stage non-specific clinical signs and symptoms followed by typical/classical features depending on the type of rickettsiae infecting a person. However the clinical manifestation varies from one geographical area to another area for same species.

The rickettsial diseases once thought to have been eradicated from India are re-emerging in many parts of our country. Their presence has recently been documented in at least eleven states of our country. Greater clinical awareness, a higher index of suspicion, better use of available diagnostic tools would increase the frequency with which rickettsial diseases are diagnosed.

Key words: Rickettsial infections, typhus fevers, Weil Felix test, doxycycline

Introduction: (S.S.)

India being a tropical country, fevers are caused by different etiological agents. When a patient presents with history of fever with rash/ thrombocytopenia, rickettsial infections is one of the differential diagnosis along with dengue, measles, rubella, meningococcal infection, malaria, leptospirosis and other viral exanthems¹. Rickettsial infections have a global distribution and are reported from almost all parts of India². Rickettsial diseases widely vary in severity from self-limited mild illnesses to fulminating life-threatening infections.

The genus *Rickettsia* belongs to the bacterial tribe Rickettsiae, family Rickettsiaceae, and order Rickettsiales. They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells which makes it difficult to culture them on artificial culture medium. They are differentiated from virus in having a gram negative cell wall and susceptibility to antibiotics³. These organisms typically have an animal reservoir and an arthropod vector; exceptions are *R. prowazekii*, for which humans are the primary reservoir. These organisms are primarily parasites of arthropods such as lice, fleas, ticks and mites, in which they are found in the alimentary canal. There may be transovarial (Rocky mountain spotted fever) maintenance of the organism in the vectors⁴.

Classification: (S.S.)

Rickettsia can be classified into three major groups based on serological characteristics, namely the 'typhus group', 'spotted fever group' and 'scrub typhus group'. By DNA sequencing, the first two are assigned to the genus *Rickettsia* while causative organisms of scrub typhus belongs to the related genus *Orientia*⁵.

Spotted fever group

- Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii*

- Rickettsial pox, caused by *Rickettsia akari*
- Boutonneuse fever (i.e. Kenya tick-bite fever, African tick typhus, Mediterranean spotted fever, Israeli spotted fever, Indian tick typhus, Marseilles fever)

Typhus group

- Louse-borne (epidemic) typhus caused by *Rickettsia prowazekii*
- Brill-Zinsser disease (i.e. relapsing louse-borne typhus) caused by *Rickettsia prowazekii*
- Murine (endemic or flea-borne) typhus by *Rickettsia typhi*

Scrub typhus group (Tsutsugamushi disease)

- Scrub typhus (Chigger bite) caused by *Orientia tsutsugamushi*

Pathophysiology:^{3,7} (S.S.)

Rickettsiae are introduced into the local site of the arthropod bite directly by the bite or when the feces is rubbed into the bite. They multiply at the site and produce a local lesion (eschar). The outer membrane proteins act as adhesins and allow the organisms to adhere to the host cell and undergo phagocytosis. The organisms survive within in the cytoplasm of the host cells. To avoid phagocytosis within the cells, they secrete phospholipase D and hemolysin C, which disrupt the phagosomal membrane. The organisms are seeded in various organs through hematogenous spread. They have an affinity for the endothelial cells of small blood vessels throughout the body. Inside the host cell, the rickettsial organisms either multiply and accumulate in large numbers to be released by lysing of cell (typhus group) or they escape from the cell, damaging its membrane which results in the influx of water (spotted fever group). The endovascularitis (*R. rickettsia*) causes a petechial rash, encephalitic signs, and gangrene of skin and tissues. Patients seriously ill with a rickettsial disease of the typhus or spotted

Table I: ⁶ Profile of Rickettsial diseases

Group	Species	Disease	Vector	Vertebrate reservoir	Distribution
Typhus	<i>R prowazekii</i>	Epidemic typhus	Louse	Human beings	World wide
	<i>R prowazekii</i>	Brill Zinsser disease	Louse	Human beings	America, Europe, Australia
	<i>R typhi</i>	Endemic typhus	Rat flea	Rat	World wide
Spotted fever group	<i>R rickettsia</i>	Rocky mountain spotted fever	Tick	Rabbit, dog, small rodents	North America
	<i>R conori</i>	Indian tick typhus, Boutonneuse, Kenyan tick typhus	Tick	Rodents	India, Mediterranean, Kenya
	<i>R siberica</i>	Siberian tick typhus	Tick	Cattle, Wild animals	Russia, Mongolia
	<i>R australis</i>	Queensland tick typhus	Tick	Bush rodents	N Australia
	<i>R akari</i>	Rickettsial pox	Gamasid mite	Mouse	USA, Russia
Scrub typhus	<i>O tsutsugamushi</i>	Scrub typhus	Trombiculid mite	Small rodents, birds	East Asia, Pacific islands, Australia

fever group may have ecchymotic skin necrosis, edema (due to increased vascular permeability), digital gangrene, circulatory collapse, shock, oliguria, anuria, azotemia, anemia, hyponatremia, hypochloremia, delirium, and coma. Regional lymphadenopathy is common with infection by *Orientia* species or members of the spotted fever group (except for *R. rickettsii*).

Clinical features of Rickettsiae:

(S.B.)

General- Rickettsial diseases form one of the most neglected emerging and re-emerging diseases.^{8, 9} With globalization

there is rapid spread of disease across the continents and therefore skills for diagnosis and management of the disease attains global importance.

Rickettsial diseases can be clinically classified as Spotted Fever group, typhus group, distinctive clinical rickettsiae and emerging rickettsiae. The clinical course will have incubation period, stage of non-specific clinical signs and symptoms followed by typical/classical features depending on the type of rickettsiae infecting a person. However, the clinical manifestations vary from one geographical area to another for the same species.^{3, 8}

Rickettsial group of diseases are arthropod borne diseases with an incubation period of 3 to 14 days. The disease begins with non-specific features like fever, myalgia and headache. Headache is usually quite severe, young children may not complain of pain. Onset of nausea, vomiting, pain abdomen, diarrhoea and abdominal tenderness occur in substantial number of children suggesting gastroenteritis or an acute surgical abdomen.

The specific features are as follows:

Rocky mountain spotted fever (RMSF):

The etiological agent is *Rickettsia rickettsii*. The rash, the major diagnostic sign, appear in a small number of cases on first day and in about 50% cases by third day, usually appear after 3-5 days of onset of fever and occurring up to 91% of patients overall. The rash typically begins around the wrists and ankle but may start on the trunk or be diffuse at the onset. Focal neurological deficits, transient deafness, meningismus and photophobia. In classic RMSF, death occurs 8 to 15 days after onset of symptoms when appropriate treatment is not given in a timely manner. In fulminant RMSF, death occurs within the first 5 days. The highest age-specific incidence of RMSF is among children <10 years of age and the disease is milder in children.

Other Spotted Fever Group Rickettsiae (SFG):

Among eight other SFG rickettsial species known to be pathogenic for humans, *R. conorii*, *R. siberica*, *R. japonica*, *R. australis*, *R. honei*, *R. africae* and *R. slovaca* are considered to be transmitted by tick bite. *R. conorii* infection has been designated by many geographic names: Marseilles fever, Mediterranean spotted fever, Kenya tick typhus and Indian tick typhus.

Louse-Borne Typhus (Epidemic Typhus):

The prototype of the typhus group rickettsial diseases is Louse-borne typhus. The primary disease and its recrudescence form (Brill-Zinsser disease) are caused by *Rickettsia prowazekii*. It is also known as epidemic typhus, classic typhus, typhus exanthematicus, & jail fever. Absence of eschar is very specific to this group. The typhus rash appears on the second to fourth day of fever, begins in axillary folds and upper part of trunk and spreads centrifugally to limbs. Rashes of small irregular pink macules are seen which rapidly darken to a mulberry or purple colour and rarely become petechial. The petichae coalesce to a generalized patchy purple mottling under the skin may occur.^{3, 10, 11} Central nervous system involvement in the form of meningoencephalitis may occur in 50% with meningism, tinnitus, hyperacusis agitated delirium and coma. Deafness, dysphagia, dysphoria, may be associated features.

Murine Typhus (*Rickettsia typhi*):

Murine typhus has been recognized as a worldwide zoonosis and often unrecognized. The etiological agent of murine typhus is *Rickettsia typhi* (*Rickettsia mooseri*). It is also known as endemic and shop typhus. The presence of hepatomegaly (24%) and splenomegaly (10%) has also been reported. Neurological signs and symptoms have been reported in 1- 45% of patients including confusion, stupor, seizures and localizing signs such as ataxia. Rash is noted in 18% at presentation and will present in 50% (2-71%) over the course of illness. The rash is macular or maculopapular in 78% and petechiae are noted in about 10%. These lesions are most often distributed on the trunk (88%); childhood murine typhus is often mild and sometimes

seen is only night time fever with normal day time activity.

Scrub Typhus:

Although scrub typhus was a dreaded disease in pre-antibiotic era, it is an important disease which caused thousands of cases during Second World War. Scrub typhus was known in Japanese folklore to be associated with the jungle mite which was named "dangerous bug" (tsutsugamushi). The clinical manifestations of this disease range from sub-clinical disease to organ failure to fatal disease. Clinical picture of scrub typhus is typically associated with fever, chills, cough, rash, diarrhoea, myalgia and diffuse lymphadenopathy.^{3, 10, 11} A necrotic eschar at the bite site of the mite is pathognomonic of scrub typhus however it is reported to be rare in south Asian population.¹²

Distinctive group: The bite caused by a "strikingly big" engorged tick was almost uniformly located on the occipital scalp region. The infection occurred most commonly in young children: the larger half of the patients were less than 10 years of age. The main symptom, presented in all patients was the enlargement of painful lymph nodes in the region of the tick bite, causing us to name the infection Tick-Borne Lymphadenopathy (TIBOLA).¹³ Dermacentor-borne necrosis-eschar-lymphadenopathy (DEBONEL)- The clinical presentations include an eschar at the site of the tick bite, surrounded by an erythema and painful regional lymphadenopathy.¹⁴

Clinical diagnosis: Early clinical diagnosis of rickettsial disease is essential to reduce morbidity and mortality and early diagnosis can be done by the following approach-

- Knowledge of geographic distribution of type of rickettsial diseases and the transmitting agent

- History of travel to such areas although it is less important as children travel less often.
- High degree of suspicion of exposure to organisms prevalent in the geographical area
- Appearance of rash between 3-5 days after onset of illness and its morphology and distribution
- Presence of eschar

Differential Diagnosis:

Dengue, Kawasaki Disease, Leptospirosis, Malaria, Measles, Meningococcal Infections, Rubella, Streptococcal Infection, Group A, Syphilis, Toxic Shock Syndrome, Vasculitis and Thrombophlebitis

Complications:

Complications in RMSF infection include partial paralysis of the lower extremities; gangrene requiring amputation of fingers, toes, arms, or legs, hearing loss, loss of bowel or bladder control, movement disorders, and language disorders. In Typhus group, complications are not uncommon and includes pneumonia, myocarditis, meningoencephalitis, acute renal failure and gastrointestinal bleeding.

Laboratory diagnosis: (S.S.)

The clinical presentation is very non-specific in the early stages as it mimics viral exanthems even if there is any rash. This makes it difficult to detect the disease in the early stages and also the presence of eschar may be missed as it is usually in covered areas. Added to this there is lack of reliable diagnostic methods in the early stages.

Serological methods like Weil Felix test, Immunofluorescence and ELISA are used to detect the presence of IgM or IgG antibodies against rickettsial infections. Weil Felix test is a heterophile antibody test using the antigens of *Proteus* species

Table II: Interpretation of Weil Felix test¹⁶

Rickettsial infection	OX 19	OX 2	OX K
Epidemic typhus	++++	+	0
Brill Zinsser disease	++++	+	0
Murine typhus	++++	+	0
Scrub typhus	0	0	+++
RMSF	++++	+	0
Other tick borne infection	+	++++	0
Indian tick typhus	+	++++	0

for diagnosing the antibodies against rickettsial infections. Antibodies are usually positive by 7 – 10 days after infection. This test is not very specific as it can be positive in case of other related infections. But in countries like India, this is the test which is easily available and affordable. This test can be used as a screening test and correlated with the clinical symptoms. It also helps the physician in terms of titers in diagnosis and prognosis of the disease.² Testing of paired sera to demonstrate the rising titre is confirmatory in case of any serological tests as antibodies may persist in the body after an initial exposure to the organism.³ Immunofluorescence is the reference serological test which can be considered as the gold standard⁴. But this test is not available in India. ELISA test to confirm the IgM antibodies against Scrub typhus can be used once the OX K antigen is positive by Weil Felix test¹⁵ (**Table II**) Isolation of rickettsiae from clinical specimens like the tissue biopsy from the rash area can be attempted in cell culture, in laboratory animals like mice or guinea pigs, or in embryonated chicken eggs.⁶

This provides confirmed diagnosis of rickettsial infection. The clinical sample is inoculated intraperitoneally into the animals and observed for 3- 4 weeks for rise in temperature. Smears from the peritoneum, tunica and spleen of infected animals may be stained by Giemsa or Gimenez methods to demonstrate rickettsiae. In case of embryonated eggs, rickettsia grow well in the yolk sac but are not useful for isolation from clinical specimens. Cell cultures like Verocell MRC 5 can be used to isolate rickettsiae from clinical samples in 3 – 5 days.¹⁶ Growth is identified by immunofluorescence using group- and strain- specific monoclonal antibodies. These methods require high end facilities and expertise which may not be feasible for all diagnostic laboratories.

Detection of rickettsiae in tissue samples is attempted by immunohistochemistry. This method is 100% specific and 70% sensitive. Intracellular rickettsiae can be visualized even after 48hours of initiation of appropriate treatment.

Polymerase chain reaction: Detection of rickettsial DNA by molecular methods is

more rapid and specific but this test is not widely available. Highly conserved gene of rickettsial group can be detected and then to identify the species, restriction fragment length polymorphism analysis or DNA sequencing may be attempted. 56 k Da protein gene of *O. tsutsugamushi* is used to diagnose scrub typhus by PCR.¹⁶

Epidemiological Aspects: (A.J.)

Rickettsial Diseases in India-

Rickettsial diseases are one of the common mis-diagnosed or under-diagnosed diseases in the current scenario of re-emerging infections. The Rickettsiaceae family is maintained in nature through a cycle involving reservoir in mammals and arthropod vectors. The public health impact of these on lives or productivity lost is largely unmeasured, but suspected to be quite high worldwide.³

Worldwide distribution of the disease occurs within an area of about 13 million sq.km including- Afghanistan and Pakistan to the west, Russia to the north, Korea and Japan to the northeast; Indonesia, Papua New Guinea, and northern Australia to the south and some smaller islands in the western Pacific. It was first observed in Japan, where it was found to be transmitted by mites. The disease was, therefore, called tsutsugamushi (from tsutsuga meaning dangerous and mushi meaning insect or mite). This is found only in areas with a suitable climate, plenty of moisture and scrub vegetation. Recently, rickettsioses has been an emerging disease along the Thai-Myanmar border. There are reports of emergence of scrub typhus in Maldives Islands and Micronesia.

Rickettsial infections are unique in various aspects. They occur across all countries and are reported from almost all parts of India. Rickettsial infection in the past has taken more lives than all the wars combined together.¹⁷ As no single laboratory finding is specific for early diagnosis, treatment needs to be started

empirically on clinical and epidemiological suspicion.¹⁵ Physicians, including paediatricians, usually do not include Rickettsial infection in their differential diagnosis¹⁸ and hence antimicrobials effective for Rickettsial disease are usually not included in empirical therapy of non-specific febrile illnesses. 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. Knowledge of geographical distribution, evidence of exposure to vectors, clinical features like fever, rash, eschar, headache and myalgia alongwith high index of suspicion are crucial factors for early diagnosis.

The National Centre for Disease Control has played an important role in providing serological evidence of Rickettsial diseases in India in various states like Jammu & Kashmir, Himachal Pradesh, Uttarakhand, Haryana, Rajasthan, Assam, West Bengal, Maharashtra, Tamil Nadu, Kerala, Karnataka, Sikkim, and Manipur in the last decade.¹⁸⁻²⁴ These reported cases are an underestimate as there are no community based studies and there is a lack of availability of confirmatory laboratory tests in most settings.

The rickettsial diseases once thought to have been eradicated from India are re-emerging in many parts of our country. Their presence has recently been documented in at least eleven states of our country. There are many reports of occurrence of rickettsial diseases from hills of north and eastern parts of India as well from southern plateau in last few years. Recently both scrub typhus and SFG rickettsioses have been reported from Haryana, which is situated in plains of north India. Batra has reported a high magnitude of scrub typhus, spotted fever and Indian tick typhus caused by *R. conorii*.¹⁸ An extensive study on tickborne rickettsiosis in Pune district of Maharashtra revealed that Indian tick

typhus exists as zoonosis.²⁵ These diseases are difficult to diagnose due to low index of suspicion, non-specific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests but they are easy and inexpensive to treat with rapid response to appropriate antimicrobial therapy if diagnosed early. Rickettsial diseases should be suspected in all cases of non-specific febrile illnesses with clinical, laboratory and epidemiological clues suggestive of this disease thereby preventing the high morbidity and mortality associated with undiagnosed and lately diagnosed cases. If diagnosed early they also help in reducing the financial strain on patients with fever without source (FWS) and pyrexia of unknown origin (PUO) by reducing the need of extensive investigations and starting multiple empiric therapies. Many cases of rickettsial diseases go undiagnosed due to lack of diagnostic tools. Greater clinical awareness, a higher index of suspicion, better use of available diagnostic tools would increase the frequency with which rickettsial diseases are diagnosed. Failure of early diagnosis is associated with significant mortality and morbidity and also leads to expensive PUO workup. Mittal et al²⁶ in the entomological study reported that poorly maintained kitchen gardens and long grass attracted rodent populations. At many places, vector mites were collected from the rodents caught from active rodent burrows in kitchen gardens. Presence of vector mites above the critical limit indicates that during monsoon season, these areas may act as potential sites for the transmission of Rickettsial diseases. Animal sheds near houses in rural areas, pet and stray dogs, cattle and long uncut grass are other factors favouring vectors.

Untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treated.²⁷ 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 the clinician is the difficult diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective.²⁷

Treatment: (S.B.)

Doxycycline is the first line treatment for adults and children of all ages. Dosage for children under 45 kg (100 lbs): 2.2 mg/kg/dose is given twice a day. Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Standard duration of treatment is 7-14 days.²⁸ Other drugs available are Chloramphenicol, macrolides like Azithromycin, Clarithromycin, Roxithromycin, and fluoroquinolones like Ciprofloxacin, Ofloxacin, Pefloxacin, Levofloxacin.

A Cochrane review published in 2010 indicates that most of the antibiotics tested worked; this includes Doxycycline, Tetracycline, Telithromycin and Azithromycin. Rifampicin seems to be more effective than Doxycycline in areas where scrub typhus appears to respond poorly to standard anti-rickettsial drugs.²⁹

Other supportive measures such as intravenous of fluids, oxygenation, correction of electrolyte imbalances, maintaining coagulation status are to be provided according to the patient's clinical situation.

Prevention: (A.J.)

Personal avoidance of ticks (wearing proper clothing and use of repellents) remains an integral part of protection against rickettsial infections. In case of bites, prompt removal of ticks might prove extremely beneficial in prevention of infection. Attempting to control the tick reservoir is not usually feasible. Use of

antibiotics following tick exposure is not currently indicated to prevent rickettsial infection.³

Rocky Mountain spotted fever: A recently developed improved killed chicken embryo vaccine has shown partial protection against RMSF.

Rickettsial-pox: Avoidance of contact with and control of house mouse infestations is important to prevent acquisition of infection.³

Boutonneuse fever: Natural immunity occurs following infection. Effective vaccines are not yet available.³

Louse-borne (epidemic) typhus: Delousing of individuals and use of insecticides to treat clothing are effective preventive measures against the spread of louse-borne typhus. Killed vaccines were shown to reduce mortality rates but were not effective in prevention of disease. Brill-Zinsser disease is analogous to primary louse-borne epidemic typhus.

Murine Typhus: Prevention is primarily by controlling the flea and rat populations. Insecticides should be used before rodenticides to prevent rat fleas from seeking alternate hosts if rats are no longer available.³

Scrub Typhus: The disease is best prevented by the use of personal protective measures including repellents. People entering an exposed area should wear closed footwear such as boots with socks, and long trousers. Exposed areas of skin and clothing itself should be treated with mite repellents. Those people working in infested areas should consider impregnating clothing with permethrin. Prophylactic treatment usually consists of oral Chloramphenicol or Tetracycline given once every 5 days for thirty-five days, or weekly doses of Doxycycline during and for 6 weeks after exposure have both been shown to be effective regimens. No effective vaccine has been developed for scrub typhus.³

In summary, prevention is possible if the following suggestions are followed:

1. Avoiding tick bites, by avoiding tick - infested areas, which is key to the prevention of Rickettsial diseases.
2. Limit exposure to tick habitats, including grassy and wooded areas.¹⁵
3. Avoid contact with vector reservoirs like dogs, cattle, sheep, goats and rodents.
4. Inspect the body carefully for ticks after being in a tick habitat.
5. Remove attached ticks immediately by grasping with tweezers close to skin and pulling gently with steady pressure
6. Antibiotic prophylaxis after tick bite is not beneficial.¹⁵

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