IAP Guidelines on Rickettsial Diseases in Children

NARENDRA RATHI, *ATUL KULKARNI AND #VIJAY YEWALE; FOR *INDIAN ACADEMY OF PEDIATRICS GUIDELINES ON RICKETTSIAL DISEASES IN CHILDREN COMMITTEE*

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Objective: To formulate practice guidelines on rickettsial diseases in children for pediatricians across India.

Justification: Rickettsial diseases are increasingly being reported from various parts of India. Due to low index of suspicion, nonspecific clinical features in early course of disease, and absence of easily available, sensitive and specific diagnostic tests, these infections are difficult to diagnose. With timely diagnosis, therapy is easy, affordable and often successful. On the other hand, in endemic areas, where healthcare workers have high index of suspicion for these infections, there is rampant and irrational use of doxycycline as a therapeutic trial in patients of undifferentiated fevers. Thus, there is a need to formulate practice guidelines regarding rickettsial diseases in children in Indian context.

Process: A committee was formed for preparing guidelines on rickettsial diseases in children in June 2016. A meeting of consultative committee was held in IAP office, Mumbai and scientific content was discussed. Methodology and results were scrutinized by all members and consensus was reached. Textbook references and published guidelines were also used in few instances to make recommendations. Various Indian and international publications pertinent to present study were collated and guidelines were approved by all committee members. Future updates in these guidelines will be dictated by new scientific data in the field of rickettsial diseases in children.

Recommendations: Indian tick typhus and scrub typhus are commonly seen rickettsial diseases in India. It is recommended that practicing pediatricians should be well conversant with compatible clinical scenario, suggestive epidemiological features, differential diagnoses and suggestive laboratory features to make diagnosis and avoid over diagnosis of these infections, as suggested in these guidelines. Doxycycline is the drug of choice and treatment should begin promptly without waiting for confirmatory laboratory results.

Keywords: *Doxycycline, Indian tick typhus, Management algorithm, Scrub typhus, Spotted fever*.

There is a surge in the number of publications on rickettsial diseases from India in recent years. These infections have been reported from various states and union territories like Maharashtra, Delhi, Karnataka, West Bengal, Pondicherry, Kerala, Tamil Nadu, Himachal Pradesh, Jammu and Kashmir, Rajasthan, Meghalaya, Manipur, Goa and Uttarakhand [1-4]. Once thought to be diseases of rural population, these infections are increasingly reported from urban areas of India.

Rickettsial diseases pose multiple problems to clinicians [5]. Treatment of these infections is inexpensive and highly effective in early course of the disease but it is extremely difficult to make a diagnosis at this stage due to low index of suspicion, non-specificity of signs and symptoms and absence of low cost, rapid and widely available diagnostic test. Even if suspected by clinician, therapy is empirical as serological tests for diagnosis become positive around a week after onset of fever and early diagnostic test like polymerase chain reaction (PCR) is not freely available. Public health impact of these infections is enormous in India, and it differs in areas with low and high index of suspicion [5]. In areas with low index of suspicion, there is underdiagnosis [6], and untreated cases have high morbidity (gangrene, Acute Respiratory Distress Syndrome, gastrointestinal bleed, neurological sequelae, disseminated intravascular coagulation etc), high mortality (death rate up to 30%) and financial burden on families towards investigations and empiric treatment [7]. In endemic areas with high index of suspicion, there is rampant and irrational use of empiric doxycycline therapy for cases with undifferentiated fevers, with high propensity for adverse effects and drug resistance.

Rickettsia are obligate intracellular proteobacteria spread by eukaryotic vectors like ticks, mites, fleas and lice. Epidemiology of these infections is based on geographic and temporal distribution of their vectors.

Rickettsia are divided into four biogroups namely spotted fever group (SFG) comprising Rocky Mountain spotted fever, Rickettsial pox, Indian Tick Typhus or Mediterranean spotted fever or Boutonneuse fever; Typhus group comprising Epidemic louse borne typhus, Brill–Zinsser disease and Endemic/Murine flea borne typhus; Scrub typhus group and miscellaneous group comprising Ehrlichiosis, Anaplasmosis, TIBOLA (tick borne lymphadenopathy) and DEBONEL (dermacentor borne necrosis eschar lymphadenopathy). Diffuse endothelial infection (infective vasculitis) leading to microvascular leakage and vascular lumen obstruction are basic pathogenetic mechanisms, which explain various clinical features of these infections. The most abundant surface protein of the rickettsia is OmpB and antibodies to OmpB could be a novel treatment tool in future.

Given the increasing reports of rickettsial infections in recent times, diagnostic dilemma in the minds of practicing pediatricians, lack of freely available, rapid and cheap diagnostic tests and enormous public health impact of these infections, Indian Academy of Pediatrics (IAP) felt the need to form practice guidelines on this topic to help pediatricians across India in the management of rickettsial diseases.

RECOMMENDATIONS

Case Definitions

Suspected case: A patient having compatible clinical scenario, suggestive epidemiological features and absence of definite alternative diagnosis should be termed as a suspected case of rickettsia. Definition of 'compatible clinical scenario' and 'suggestive epidemiological features' and list of differential diagnosis is provided in ***Box* 1, 2** and **3**, respectively. Alternative diagnosis can be searched from (but not limited to) the list of differential diagnoses (***Box* 3**).

Probable case: Suspected case having either eschar, or having rapid (<48 hours) defervescence with anti-rickettsial therapy, or having suggestive laboratory features (***Box* 4**), or having Weil-Felix test positive with titre of 1:80 or more in OX2, OX19 or OXK or positive IgM ELISA for rickettsia (optical density >0.5).

BOX 1 COMPATIBLE CLINICAL SCENARIO FOR RICKETTSIAL INFECTION

One or more of the following:

- Undifferentiated fever of more than 5 days.
- Sepsis of unclear etiology.
- Fever with rash.
- Fever with edema.
- Dengue-like disease.
- Fever with headache and myalgia.
- Fever with hepatosplenomegaly and / or lymphadenopathy.
- Aseptic meningitis / meningoencephalitis / acute encephalitic syndrome.
- Fever with cough and pulmonary infiltrates or community acquired pneumonia.
- Fever with acute kidney injury.
- Fever with acute gastrointestinal or hepatic involvement.

BOX 2 SUGGESTIVE EPIDEMIOLOGICAL FEATURES FOR RICKETTSIAL INFECTIONS

One or more of the following within 14 days of illness onset:

- Tick bite.
- Ticks seen on clothes or in and around homes or in areas where children play
- Visit to areas which are common habitats of vectors like high uncut grass or weeds or bushes or rice fields or woodlands (where rodents share habitats with animals) or grassy lawns or river banks or poorly maintained kitchen gardens.
- Animal sheds in proximity of homes.
- Contact with pet or stray dog infested with ticks.
- Living in or travel to areas endemic for rickettsial diseases.
- Occurrence of similar clinical cases simultaneously or sequentially in family members, coworkers, neighbourhood or pets.
- Exposure to rodents.

BOX 3 DIFFERENTIAL DIAGNOSES FOR RICKETTSIAL INFECTIONS*

- *Viral diseases:* enteroviral diseases, measles, dengue fever, chikungunya, infectious mononucleosis.
- *Bacterial diseases:* meningococcemia, leptospirosis, typhoid fever, scarlet fever, secondary syphilis, infective endocarditis.
- *Protozoal diseases:* malaria.
- *Vasculitis:* Kawasaki disease, thrombotic thrombocytopenic purpura.
- Adverse drug reactions.
- Differential diagnoses pertaining to each systemic presentation.

** Not an exhaustive list.*

BOX 4 SUGGESTIVE LABORATORY FEATURES FOR RICKETTSIAL INFECTIONS

- Normal to low total leukocyte count with a shift to left in early stages and leukocytosis later on
- Thrombocytopenia
- Raised ESR and CRP
- Hyponatremia
- Hypoalbuminemia and
- Elevated hepatic transaminases.

Confirmed case: Suspected case having rickettsial DNA detected in whole blood or tissue samples, or fourfold rise in antibody titres on acute and convalescent sera detected by immunofluorescence assay (IFA) or immuno-peroxidase assay (IPA) [8]. In countries like India, where PCR and IFA are not commonly available, properly performed paired serological tests like ELISA have high positive predictive value.

ETIOLOGICAL AGENTS

Rickettsia conorii causing Indian tick typhus and *Orientia tsutsugamushi* causing Scrub typhus are common etiological agents in India. *Rickettsia kellyi candidiatus* like species are also reported [10]. Rarely murine flea borne typhus is reported [8]. Though there are differences in geographical distribution, vectors, host and clinical features, antibiotic treatment is same for both these groups.

EPIDEMIOLOGY AND PATHOGENESIS

- SFG is reported from Maharashtra, Karnataka and Tamil Nadu while scrub typhus is reported from almost all states and union territories of India.
- Rickettsial diseases can occur throughout the year, but more commonly seen from from May to February [1].
- Due to low prevalence of rickettsial organisms in vectors, there is no role of doxycycline prophylaxis after tick bite [11].
- Rickettsial diseases occur at all ages including neonates [12,13].

CLINICAL FEATURES

Incubation period is 1 to 2 weeks. There is marked differences in disease severity and mortality due to remarkable genetic heterogeneity of rickettsial strains.

Fever: It is abrupt onset, high grade, may be associated with headache, myalgia and arthralgia.

Rash: Though rash is considered as a hallmark of these infections, it may be absent. Rash of SFG appears on day 2 to 5 of illness [13], can be pruritic, is evolving (initially macular, becoming maculopapular, petechial, purpuric or gangrenous), has centripetal spread, and can involve palms and soles (considered typical of rickettsial diseases). Rash in these locations can also be seen in meningococcemia, infective endocarditis, adverse drug reactions, enteroviral diseases and syphilis. Rash in scrub typhus is maculopapular, uncommon than SFG, seen in 30 to 43% cases. The rash in typhus group is quite atypical, initially appearing on trunk, spreading centrifugally and usually sparing palms and soles.

Eschar: It is a crusty necrotic lesion with or without surrounding erythematous halo, which suggest the location of the vector bite. It is painless, nonpruritic and about 1 cm in diameter. Eschar is usually single but multiple eschars do occur. It resembles the skin burn of cigarette butt and is associated with regional lymphadenopathy. In fact, one should search for eschar in the draining area of regional lymphadenopathy, if the later is discovered, as regional lymphadenopathy is a marker of hidden or developing eschar [14]. It is recommended that eschars be carefully looked for, as those in intertriginous area may be missed. Eschar is considered as pathognomonic of rickettsial diseases, though it can be seen in anthrax, bacterial ecthyma, spider bite and rat bite fever. It is uncommon in SFG while more commonly seen in scrub typhus (7-97%).

Hepatosplenomegaly and lymphadenopathy.

Edema: periorbital or pedal edema or anasarca.

Conjunctival injection.

Systemic presentations: Apart from above mentioned clinical features, rickettsial infections have various systemic clinical features. Of particular importance is to realise that rickettsial infections can have initial presentations with these systemic features. It is recommended that clinicians should be aware of 4 systemic presentations of rickettsial diseases: central nervous system, respiratory, gastrointestinal and renal. Rickettsial diseases should be considered in the differential diagnosis of every patient with aseptic meningitis or meningoencephalitis or acute encephalitic syndrome with compatible epidemiological history [15-18]. Cough associated with pulmonary infiltrates or pneumonia is another common presentation of rickettsial diseases [19]. It is recommended to add empiric treatment for scrub typhus in addition to recommended regimen for the management of community acquired pneumonia, in regions where scrub typhus is likely to

occur [8]. Gastrointestinal and hepatic presentation in the form of nausea, vomiting, diarrhea, abdominal pain, and hepatitis, severe enough to suggest diagnosis of acute gastroenteritis or surgical abdomen, is known in children with rickettsial infections, especially in the early part of the clinical course [20, 21]. Acute renal failure (ARF) can be a presenting feature of rickettsial disease and is associated with a bad prognosis. The possibility of scrub typhus should be borne in mind, whenever a patient of fever presents with varying degrees of renal insufficiency, particularly if eschar exists along with the history of environmental exposure [13,22,23].

Complications: Disseminated intravascular coagulation, Acute Respiratory Distress syndrome, Hemophagocytic Lymphohistiocytosis, purpura fulminans, gangrene [24] and myocarditis are various complications seen.

SCORING SYSTEM

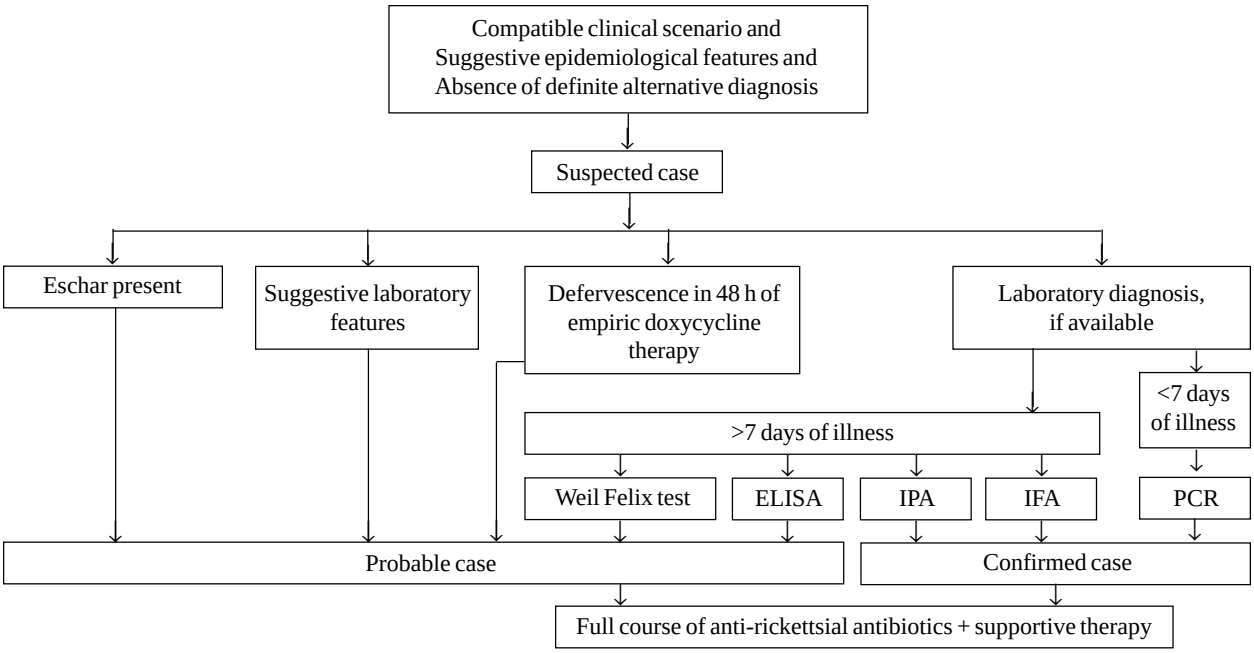
The scoring system proposed by Rathi, *et al*. [13] for diagnosis of SFG rickettsioses using clinical, laboratory, and epidemiological features with a diagnostic cutoff score of 14 has high sensitivity (96.1%) and specificity (98.8%), similar to detection of specific IgM antibody by ELISA but needs revalidation in multicentric, prospective trials with larger sample size including both hospitalized and outpatient children.

LABORATORY DIAGNOSIS (***Fig*. 1**)

Suggestive laboratory features: Presence of these features support the diagnosis and help to rule out some differential diagnoses. These are enumerated in ***Box* 4**. In fact, clinicians must look for rash and eschar in all cases of fever and should collect serum sample for suggestive laboratory features before administration of empirical antibiotics.

Serology: These tests are usually positive after first week of illness. These are biogroup-specific and not species-specific. Four-fold rise in titers in two serum samples, 2-4 weeks apart, favours diagnosis. Weil Felix test is used if other tests are not available. It has advantages of being inexpensive, easily available, not requiring expertise and sophisticated instruments. It has lower sensitivity but better specificity. A single titre above 1:80 may indicate possibility of infection, but at a high cut-off titre (1:320) positive predictive value and specificity is better [25]. IgM ELISA has high sensitivity and specificity and hence preferred. IFA is gold standard test but has disadvantages of being expensive, not easily available and needing a lot of expertise and sophisticated instruments. Other tests like western blot and IPA are not routinely available.

RICT: Rapid immunochromatographic test is not recommended at present for diagnosis.



ELISA: Enzyme-linked Immunosorbant Assay, IPA: Immunoperoxidase assay, IFA: Immunoflorescent assay, PCR: Polymerase chain reaction.

FIG. 1 *Management Algorithm for Rickettsial Infections*.

PCR: It is useful for diagnosis in the first week of illness and unlike serology, it is species specific. It also has an advantage in endemic areas with high background level of antibodies in the population. It can be done on whole blood, eschar or skin biopsy and eschar scrapings. Specificity of PCR is almost 100%, while sensitivity is 22.5%- 36.1% (for nested PCR) and 45%-82% (for Real-time PCR) [26]. Sensitivity is more in tissue specimen than blood and is decreased by doxycycline therapy [27].

Isolation of organisms by cell culture and laboratory animals and immunostaining of skin rash or eschar biopsy are not useful for clinical purpose.

TREATMENT (*Fig.* 1)

Treatment must be initiated empirically in suspected cases without awaiting laboratory confirmation, as morbidity and mortality escalate rapidly with each day of treatment delay. Also treatment should not be discontinued solely on the basis of a negative test result [27].

Patients with organ dysfunction, severe thrombocytopenia, mental status changes, need for supportive therapy, inability to take oral medications or unreliable caregiver and follow up should be hospitalized.

Concomitant empiric treatment for other conditions which are life threatening and cannot be reliably ruled out may need to be administered (*e.g.*, meningococcemia) while awaiting laboratory results.

Doxycycline is the drug of choice. Use of doxycycline for treatment of rickettsial diseases in children of any age is no longer a matter of controversy. Doxycycline used at the dose and duration for these infections, even with multiple courses, do not result into teeth staining or enamel hypoplasia [28, 29]. It should be used orally or intravenously in the dose of 2.2 mg/ kg twice daily for children <40 kg and 100 mg twice daily for children above 40 kg, for 3 days after subsidence of fever or total 7 days. Severe or complicated cases may need 10 days therapy. The response to doxycycline is dramatic and fever persisting beyond 48 hours of initiation of doxycycline should prompt consideration of alternative or additional diagnosis, including coinfection [27]. Alternative effective drugs are macrolides (oral clarirthromycin or oral/ intravenous azithromycin), chloramphenicol and rifampicin. Azithromycin is used in the dose of 10 mg/kg/ day for 5 days.

Rickettsial strains with reduced susceptibility to doxycycline are reported [30, 31], and alternative drugs can be used in such a situation [32]. It is recommended that rifampicin should not be routinely used for treatment of rickettsial diseases in India. Clinicians should monitor the progress of patients in the light of reports of drug resistance. Fluoroquinolones are not recommended for treatment [33]. Sulfonamides are contraindicated.

Supportive management: Severely ill patients may need other supportive measures as dictated by clinical situation.

POOR PROGNOSTIC FACTORS

G6PD deficiency, sulfonamide therapy, younger age, shorter incubation period, absence of rash, diabetes mellitus and delayed institution of anti-rickettsial drugs is associated with poorer outcome.

PREVENTION

Vaccine and post-exposure prophylaxis is not available for clinical use. Vector control, prevention of vector bite, prompt removal of attached ticks and pre-exposure chemoprophylaxis are useful strategies to prevent rickettsial diseases.

Vector control: Short term vector control could be achieved by controlling rodents and cutting, burning and bulldozing vegetations with heavy spraying of insecticides such as lindane.

Preventing vector bite: This is the most effective strategy.

- Avoid exposure to vector infested habitats (described under suggestive epidemiological features in *Box* 2).
- Closed toe shoes and light coloured (for tick visibility) long pants and long sleeves cloths should be worn with shirt tucked into pants and pants tucked into socks or boots.
- Permethrin based (on cloths) and 20-50% DEET (N, N-diethyl-m-toluamide) based (on skin) insect repellants should be used.
- Hot water washing and hot drying effectively kills ticks on cloths.
- Pets should be protected with medications or tick collars and periodic de-ticking be done.
- Regular tick checks should be performed after spending time with tick infested animals or in tick infested habitats.

Prompt removal of attached ticks: This is a useful strategy as ticks need minimum 4-6 hours of attachment before they transmit infection [11]. Bathing soon after exposure is effective. It is recommended that proper technique of tick removal be used. Use tweezers, grasp ticks head as close to skin surface as possible and gently pull upwards with constant pressure. Attachment area should be immediately cleaned with soap and water or

alcohol or an iodine scrub. Ticks should neither be removed nor be crushed with bare fingers. Gasoline, nail polish, kerosene, petroleum jelly or lit matchsticks should not be used for tick removal. Incineration of ticks after removal, rather than flushing down the sewer system is recommended [27].

Pre-exposure chemoprophylaxis: It is recommended for short period, high- risk exposure. Weekly doxycycline started before and for 6 weeks after exposure is recommended.

FUTURE PROSPECTS

It is recommended that research and development should focus on following issues: (*i*) Vaccines for rickettsial diseases; (*ii*) Rapid diagnostic card test combining antigen and antibody; (*iii*) Intravenous preparation of doxycycline; and (*iv*) Robust surveillance and reporting system.

REFERENCES

1. Dasari V, Kaur P, Murhekar MV. Rickettsial disease outbreaks in India: A Review. Ann Trop Med Public Health. 2014;7:249-54.
2. Kamarasu K, Malathi M, Rajagopal V, Subramani K, Jagadeesh Ramasamy D, Mathai E. Serological evidence for wide distribution of spotted fevers and typhus fever in Tamil Nadu. Indian J Med Res. 2007;126:128-30.
3. Bithu R, Kanodia V, Maheshwari RK. Possibility of scrub typhus in FUO cases: An experience from Rajasthan. Indian J Med Microbiol. 2014;32:387-90.
4. Narvencar KPS, Rodrigues S, Nevrekar RP, Dias L, Dias A, Vaz M, *et al*. Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa. Indian J Med Res. 2012;136:1020-4.
5. Rathi N. Rickettsial Diseases in India- A long way ahead. Pediatr Infect Dis. 2015;7: 61-3.
6. Kulkarni A. Childhood Rickettsiosis. Indian J Pediatr. 2011;78:81-7.
7. Rathi N, Rathi A. Rickettsial infections: Indian perspective. Indian Pediatr. 2010;47:157-64.
8. DHR-ICMR. Guidelines for Diagnosis and Management of Rickettsial Diseases in India. ICMR; 2015, February.
9. Mittal V, Gupta N, Bhattacharya D, Kumar K, Ichhpujani RL Singh S, *et al*. Serological evidence of rickettsial infections in Delhi. Indian J Med Res. 2012; 135:538-41.
10. Prakash JA, Sohan Lal T, Rosemol V, Verghese VP, Pulimood SA, Reller M, Molecular detection and analysis of spotted fever group *Rickettsia* in patients with fever and rash at a tertiary care centre in Tamil Nadu, India. Pathog Glob Health. 2012;106:40-5.
11. Paul ML, Ross MJ. Rickettsial and Ehrlichial Diseases. In: Cherry J, Demmler-Harrison GJ, Kaplan SL. Steinbach W, Hotez P. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed. New York: Saunders Elsevier; 2013. p. 2647-2666.e4.
12. Arthi P, Bagyalakshmi R, Krishna M, Krishna M, Nitin M, Madhavan HN, *et al*. First case series of emerging Rickettsial neonatal sepsis identified by PCR based DNA sequencing. Indian J Med Microbiol. 2013;31:343-8.
13. Rathi N, Rathi A, Goodman MH, Aghai ZH. Rickettsial diseases in Central India: proposed clinical scoring system for early detection of spotted fever. Indian Pediatr. 2011;48 :867-72.
14. Narayanasamy DK, Arunagirinathan AK, Kumar RK, Raghavendran VD. Clinico - laboratory profile of scrub typhus - An emerging rickettsiosis in India. Indian J Pediatr. 2016 Jun 29. (Epub ahead of print).
15. Sood AK, Chauhan L, Gupta H. CNS manifestations in Orientia tsutsugamushi Disease in North India. Indian J Pediatr. 2016;83:634.
16. Rathi N, Maheshwari M, Khandelwal R. Neurological manifestations of rickettsial infections in children. Pediatric Infectious Disease. 2016;7:64-6.
17. Tikare NV, Shahapur PR, Bidari LH, Mantur BG. Rickettsial meningoencephalitis in a child—a case report, J Trop Pediatr. 2010;56:198-200.
18. Baldwin K, Rathi N. Rickettsial Disease. *In*: Editors: Robert L, Daniel T, William M. International Neurology, second edition. Wiley Blackwell: UK, 2016. p. 291-5.
19. Watt G, Parola P. Scrub typhus and tropical rickettsiosis. Curr Opin Infect Dis. 2003;16:429-36.
20. Mahajan SK. Rickettsial diseases. J Assoc Physicians India. 2012;60:37-43.
21. Syed AZ, Carol S. Gastrointestinal and hepatic manifestations of tickborne diseases in US. Clin Infect Dis. 2002;34:1206-12.
22. Yen TH, Chang CT, Lin JL, Jiang JR, Lee KF. Scrub typhus: a frequently overlooked cause of acute renal failure. Ren Fail. 2003;25:397-410.
23. Kumar V, Kumar V, Yadav AK, Iyengar S, Bhalla A, Sharma N, *et al*. Scrub Typhus Is an Under-recognized Cause of Acute Febrile Illness with Acute Kidney Injury in India. PLoS Negl Trop Dis. 2014;8:e2605.
24. Kulkarni A, Vaidya S, Kulkarni P, Bidri LH, Padwal S. Rickettsial disease-an experience. Pediatr Infect Dis. 2009;1:118-24.
25. Batra HV. Spotted fevers & typhus fever in Tamil Nadu. Indian J Med Res. 2007;126:101-3.
26. Kim DM, Park G, Kim HS, Lee JY, Neupane GP, Graves S, Stenos J. Comparison of conventional, nested, and real-time quantitative PCR for diagnosis of scrub typhus. J Clin Microbiol. 2011;49:607-12.
27. Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, *et al*. Diagnosis and Management of Tickborne Rickettsial Diseases, CDC. MMWR Recomm Rep 2016;65:1-44.
28. Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. Clin Pediatr (Phila). 2007;46:121-6.
29. Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, *et al*. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. J Pediatr. 2015;166: 1246-51.

30. Kim YS, Yun HJ, Shim SK, Koo SH, Kim SY, Kim S. A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. Clin Infect Dis. 2004;39:1329-35.
31. Watt G, Chouriyagune C, Ruangweerayud R, Watcharapichat P, Phulsuksombati D, Jongsakul K, *et al*. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. Lancet. 1996;348:86-9.
32. Liu Q, Panpanich R. Antibiotics for treating scrub typhus. Cochrane Database Syst Rev. 2002;3:CD002150.
33. Elisabeth BN, Cristina S, Didier R, Philippe P. treatment of Rickettsial spp. infections: a review. Expert Rev Anti Infect Ther. 2012:10;1425-37.

ANNEXURE

"Guidelines on Rickettsial Diseases in Children" committee of IAP

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