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## Observational study on clinical profile and outcome of Rickettsial infections in children

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### Abstract

**Background:** Rickettsial diseases are one of the most re-emerging infections of the present time. They are generally incapacitating and difficult to diagnose. Untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treatable. Rickettsial infections are one of the important causes of pyrexia of unknown origin (PUO) and this needs to be differentiated from other febrile illnesses. Rickettsial infections are grossly under-diagnosed in India.

**Objectives of The Study:** To study the clinical profile and outcome of rickettsial infections in children aged less than 12 years

**Methods:** It is a time bound prospective hospital based observational study conducted from 2019 to 2020. All children aged less than 12 years admitted in paediatric ward with fever without an identifiable source of infection and one or more of the following clinical features: rash, oedema, hepatosplenomegaly, Lymphadenopathy, an Eschar and a tick bite or tick exposure were suspected to have rickettsial infection. The purpose of the study was explained to the parents or guardians of the child and an informed consent was taken from them enrolling the child in study group. All suspected cases were subjected to rickettsial IgM/IgG ELISA test and tests to exclude other diseases. All rickettsial IgM/IgG positive cases were followed up through hospital stay and outcomes were noted.

**Results:** The most common age group of presentation was between 1 and 5 yrs. The common symptoms in these children included fever (100%), rash (83.3%), edema of limbs (26.6%), puffiness of face (30%), generalised edema (23.3%), cough (23.3%), pain abdomen (16.6%), vomiting (13.3%), convulsions (10%), headache (3.33%) and arthralgia (3.33%). Signs like Hepatomegaly, facial puffiness, pedal edema, splenomegaly, ecchymosis present in 53.3%, 46.6%, 43.3%, 10% and 6.6% of the cases respectively, mimicking common illnesses. Thus warrants high index of suspicion. SCRUB Typhus and Indian Tick Typus Elisa Positive (mixed infection) noted in 14% of cases. Complications like meningoencephalitis (3.33%), shock (3.33%), DIC (3.33%) was observed in the study. There was good clinical response on initiation of doxycycline within 48hrs of initiation of treatment. Case fatality rate of rickettsial disease in this study was 6.66% (n=2).

**Conclusion:** Indian tick typhus is the most common rickettsial fever noted in this part of Telangana. Rickettsial diseases are difficult to diagnose, unless suspected but treatment is easy, affordable and often successful with dramatic response to antimicrobials.

**Keywords:** Rickettsial infection, ELISA, Childrens, Scrub Typhus, Hepatomegaly, Facial Puffiness.

### Introduction

Zinc is an essential trace element important for almost all biological systems. Zinc nutritive is likely to be suboptimal in many children of developing countries and may contribute to their impaired growth, increased susceptibility to infections and possibly to the high mortality. A large proportion of childhood deaths in developing countries are caused by diarrhea and pneumonia. Impaired zinc nutritive seems to play a role in the increased incidence and severity of these infections<sup>[1, 2]</sup>.

Acute lower respiratory infections (ALRI) predominantly pneumonia cause approximately 4 million deaths every year, accounting for one-third of all childhood deaths in developing countries<sup>[1]</sup>. Various factors have been associated with acute respiratory infections (ARI) in general and pneumonia in particular. These include, among others, nutritional status<sup>[2, 3, 4]</sup>, family characteristics<sup>[5]</sup> and environmental exposures<sup>[7, 8]</sup>. Most of environmental risk factors require multispectral coordination for modification. In contrast, some of the childhood risk factors can be modified by simple interventions like vitamin A or zinc supplementation<sup>[13]</sup>. Recent works have provided conflicting<sup>[9, 10, 11]</sup> evidence on the role of Rickettsial diseases are one of the most re-emerging infections of the present time, which are

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often failed to diagnose<sup>[1]</sup>. Untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treatable<sup>[2]</sup>. It is one of the most important causes of pyrexia of unknown origin (PUO) and this needs to be differentiated from other febrile illnesses like Enteric fever, Malaria, Dengue, Infectious mononucleosis, Kawasaki disease, Collagen vascular diseases<sup>[1]</sup>. Rickettsial infection is a zoonotic acute febrile illness caused by small, non-flagellated, obligate intracellular, pleomorphic gram-negative coccobacilli from the genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Neorickettsia* and *Anaplasma* and they are 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<sup>[3]</sup>.

Rickettsial infections are grossly under-diagnosed in India. As no single laboratory test is specific for early diagnosis, treatment needs to be started empirically on clinical and epidemiological suspicion. In view of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic test, these infections are extremely difficult to diagnose but treatment is easy, affordable and often successful with dramatic response to antimicrobials<sup>[1]</sup>.

The National Centre for Disease Control (NCDC, formerly National Institute of Communicable Disease) has played 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<sup>[4]</sup>. Batra has reported high magnitude of scrub typhus, spotted fever Indian tick typhus<sup>[2]</sup>.

Weil-Felix antibody testing should not be performed, because it lacks both sensitivity and specificity. Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titre is not seen until after the first week of illness. *Orientia tsutsugamushi* serologic tests such as indirect fluorescent antibody assay are approximately 90% sensitive with 11 or more days of fever. Infections from Indian tick typhus can be confirmed by immunohistologic or immunofluorescent or demonstration of seroconversion by 4 fold rise in serum antibody titres<sup>[4]</sup>.

IgM and IgG ELISA: ELISA techniques, particularly immunoglobulin M (IgM) capture assays are probably the most sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies, indicates recent infection with rickettsia. Immunofluorescence assay (IFA) is a gold standard for diagnosis of rickettsial infection<sup>[5]</sup>.

The majority of studies regarding rickettsial infections in India and other parts of the world are based on adult populations and on scrub typhus. There is a paucity of studies regarding the incidence and clinical profile of rickettsial disease in children from the Indian subcontinent and majority of published studies are retrospective or sporadic case reports<sup>[6]</sup>. Hence this study aims to study the clinical features and outcomes of paediatric rickettsial disease.

### Objectives

To study the clinical profile and outcome of rickettsial infections in children aged less than 12 years.

### Methodology

#### Source of data

All children less than 12 years of age with clinical features of Rickettsial infection and serology positive for Rickettsial

IgM/IgG ELISA admitted to Govt Medical College & General Hospital Nalgonda, Telangana, India.

### Method of collection of data

**Study design:** Prospective time bound observational study.

### Inclusion criteria

- All children up to 12 years of age will be considered.
- All children aged less than 12 years admitted in pediatric ward with fever without an identifiable source of infection and one or more of the following clinical features: rash, edema, hepatosplenomegaly, lymphadenopathy, an eschar and a tick bite or tick exposure were suspected to have rickettsial infection along with positive serology test for Rickettsial IgM/IgG ELISA

### Exclusion criteria

- Cases with other established causes of infection

### Method of Study

It is a time bound prospective hospital based observational study conducted from 2019 to 2020. All children aged less than 12 years admitted in pediatric ward with fever without an identifiable source of infection and one or more of the following clinical features: rash, edema, hepatosplenomegaly, lymphadenopathy, an eschar and a tick bite or tick exposure were suspected to have rickettsial infection. The purpose of the study was explained to the parents or guardians of the child and an informed consent was taken from them enrolling the child in study group. All suspected cases were subjected to rickettsial IgM/IgG ELISA test and tests to exclude malaria- thick and thin peripheral smear, WIDAL for enteric fever and NS 1 and IgM Mac ELISA for dengue fever. Patients were treated according to the hospital protocol. All rickettsial IgM/IgG positive cases were followed up through hospital stay and outcomes were noted. The ELISA kit used in this study was Scrub typhus IgM/IgG from INBIOS international from USA and *Rickettsia Conorii* ELISA IgM/IgG VIRCELL from Spain.

Chest X-rays, tests for renal and liver function, serum electrolyte, ultrasonography (USG), neuroimaging, cerebrospinal fluid analysis (CSF) were done as and when required.

### Data Collection

A predesigned proforma was used to collect data regarding age, gender, residential area, exposure to animals. Clinical data, including the duration of the fever, associated symptoms, vital signs, general and systemic examination. findings, complications, investigations, treatment and defervescence time were recorded.

### Scrub Typhus IGM Elisa System

The Scrub Typhus IgM ELISA test for exposure to *Orientia tsutsugamushi* (OT) is an ELISA assay system for the detection of IgM antibodies in human serum to OT derived recombinant antigen. This test is to aid in the diagnosis of human exposure to OT species.

### Kit performance and quality

It has got a sensitivity of 91% and Specificity of 100%.

### Data analysis

Results are determined by strength of average OD values for a given sample. Cut-off value in our study was 0.2652.

### Rickettsia Conorii Elisa IgG/IgM

#### Principle of the test

The ELISA method is based upon the reaction of antibodies in the sample tested with the antigen adsorbed on the polystyrene surface. Unbound immunoglobulins are washed off. An enzyme-labeled anti-human globulin binds the antigen-antibody complex in a second step. After a new washing step, bound conjugate is developed with the aid of a substrate solution (TMB) to render a blue colored soluble product which turns into yellow after adding the acid stopping solution.

#### Interpretation of results

Calculated the mean O.D. for cut off serum.

Antibody index = (sample O.D./ cut off serum mean O.D.) x 10.

**Table 1:** Kit Performance and Quality

	Sensitivity	Specificity
Ig M	94%	95%
Ig G	85%	100%

**Table 2:** Interpretation of the Result

Index	Interpretation of the Result
<9	Negative
9-11	Equivocal
>11	Positive

- Meningoencephalitis was diagnosed when the following conditions were observed-
  - i). Encephalopathy features like altered sensorium, seizures, meningismus
  - ii). CSF analysis suggestive of aseptic meningitis
  - iii). Neuroimaging findings suggestive of meningoencephalitis<sup>4</sup>
- Hypotension was defined as a Systolic blood pressure below the 5th percentile for the corresponding age, sex and height.
- Hepatitis was diagnosed when liver transaminases were found to be elevated (twice the normal range)<sup>7</sup>
- Thrombocytopenia was defined as a platelet count of less than 150,000/cumm<sup>7</sup>
- Vasculitis was diagnosed when gangrene of the extremities or purpura fulminans present.
- Bronchopneumonia was diagnosed with streaky opacities or parenchymal lung lesions on a chest radiograph and presence of cough or dyspnea.
- Disseminated intravascular coagulation was diagnosed; spontaneous bleeding, thrombocytopenia, prolonged PT/aPTT.

#### Statistical Analysis

Data was analysed in Microsoft Office Excel 2007 version. Descriptive statistics are presented in terms of counts, percentages, mean and standard deviation values.

### Results

**Table 3:** Elisa for Rickettsial IGM/igg (n=30)

Elisa	Positive	Percentage
Scrub typhus	5	16.6%
Indian tick typhus	20	66.6%
Scrub typhus and indian tick ty-Pus (mixed)	5	16.6%

Out of 30 cases positive for rickettsial IgM/IgG 5(16.6%) were positive for scrub typhus, 20(66.66%) and 5(16.6%) were positive for both scrub and Indian tick ty- phus.

**Table 4:** Gender Distribution (n=30)

Gender	No. of Patients	Percentage (%)
Male	12	40
Female	18	60
Total	30	100

Out of 30 children diagnosed with rickettsial disease, 40% (12) were boys and 60% (18) were girls.

**Table 5:** Age Group Wise Distribution of Cases (n=30)

Age in years	No. of Patients	Percentage (%)
<1 year	2	6.66
1-5 years	15	50
6-10 years	8	26.6
11-12 years	5	16.6
Total	30	100.0

Most common age group of occurrence of rickettsial infection was between 1 to 5 years (50%) followed by the age group of 6 to 10 years with 8 cases (26.6%).

**Table 6:** Monthwise Distribution of Cases (n=30)

Month	No. of Patients	Percentage (%)
January	1	3.33
February	1	3.33
March	1	3.33
May	2	6.66
June	2	6.66
July	3	10
August	6	20
September	4	13.3
October	3	10
November	4	13.3
December	3	10

More cases presented during second half of the year. Maximum number of cases were in the month of August (n=6, 20%), followed by September (n=4, 13.3%).

**Table 7: Clinical Symptoms (n=30)**

Symptoms		No. of patients (n=34)	%
Fever		30	100
Duration of fever	Duration < 5 days	2	6.66
	5-7 days	18	60
	8-10 days	10	33.3
Rash	Generalized rash	25	83.3
	Rash with involvement of palms and soles	15/25	60
Edema of legs		8	26.66
Facial puffiness		9	30
Generalized edema		7	23.33
Cough		7	23.33
Pain abdomen		5	16.66
Vomiting		4	13.33
Convulsion/ Seizures		3	10
Contact with pets or exposure to animals		10	33.3
Headache		1	3.33
Arthralgia		1	3.33

Fever was present in all cases (n=30, 100%). Duration of fever ranged from 2 days to 10 days, of which 2 cases (6.66%) presented within 4 days of illness. 60% (n=18) presented in the second half of first week. 33.3% (n=10) presented in the first half of second week. Rash was seen in 83.3% (n=25) of cases. Out of those 27 cases 17 had involvement of palms and soles (60%). The

other common presentation was symptoms were periorbital puffiness in 30% (n=9), edema of legs in 26.6% (n=8), generalized edema in 20.6% (n=7).

**Contact with pets or animal exposure:** was seen in 12(35.2%) cases.

**Table 8: Clinical Signs (n=30)**

		No. of patients (n=30)	%	
Rashes	Macular	28	5	17.8
	Maculo-papular		13	46.4
	Petechiae		10	35.7
Hepatomegaly		16	53.3	
Facial Puffiness		14	46.66	
Pedal Edema		13	43.33	
Conjunctival congestion		9	30	
Pallor		7	23.33	
Ascites		5	16.6	
Generalized Edema		4	13.33	
Hepatosplenomegaly		3	10	
Echymosis		2	6.66	

Out of 34 cases, rash was present in 28 cases (82.3%). 53.3% (n=16) cases presented with hepatomegaly. Facial Puffiness was present in 46.6% (n=14). 43.3% (n=13) cases were present with pedal Edema and 29.4% (n=10) cases were present with petechiae. Conjunctival congestion was

present in 30% (n=9) of children and pallor in 23.3% (n=7). Signs of ascites were present in 5 children (16.6%). Generalized Edema was present in 23.3% (n=7) of children. Hepatosplenomegaly was seen in 10% (n=3). Signs of Echymosis were present in 2 children (6.66%).

**Laboratory Parameters**

**Table 9: Blood Parametres**

Parameters	No. of patients (n)	%
<b>Hemoglobin(g/dl)</b>		
• <9	7/30	23.3
• >9	25/30	83.3
<b>TLC (cumm)</b>		
• Normal	25/30	83.3
• Leucopenia	3/30	10
• Leukocytosis	4/30	13.3
<b>Platelet counts</b>		
• <1.5 lakh/cumm	10/30	33.3
• >1.5 lakh/cumm	20/30	66.6
<b>S. Sodium (mEq/L)</b>		
• Normal	8/30	26.6

• Hyponatremia	20/30	66.6
<b>S. AST(U/L)</b>		
• Normal	10/15	66.6
• Elevated	4/15	26.6
<b>S. ALT(U/L)</b>		
• Normal	12/15	80
• Elevated	4/15	26.6
<b>Total Bilirubin (mg/dl)</b>		
• Normal	15/15	100
• Elevated	1/15	6.66
<b>Total protein (gm/dl)</b>		
• Normal	11/15	73.33
• Decreased	5/15	33.3
<b>Albumin (gm/dl)</b>		
• Normal	14/15	93.33
• Decreased	2/15	13.33
<b>S. Creatinine(mg/dl)</b>		
• Normal	30/30	100

Considering hematological parameters, 23.3% (n=7) had hemoglobin<9g%, 10% (n=3) had leucopenia and 13.3% (n=4) had leukocytosis. Thrombo- cytopenia (<1.5 lakh/cumm) was present in 10 cases (33.3%).

Renal function test, liver function tests, were done as and when required. Out of 30 cases, 8 cases had normal serum sodium levels. Hyponatremia (S. Sodium <135mEq/L) was present in 20 cases (66.6%). 4 out of 15 cases had elevated serum transaminase level (AST and ALT elevated twice the normal value).

Elevated bilirubin (>2mg/dl) was present in 1 out of 15 cases. Hypoalbuminemia was seen in 2 out of 15 cases. 25 out of 30 cases had renal function test done, all had normal serum creatinine levels.

**Imaging**

Two cases had neuroimaging (CT Brain) done, both reported normal. USG was done on 18 children. One children enlarged hypoechoic liver with splenome- galy and one children had hepatosplenomegaly. Sixteen children USG Abdomen scanning was normal.

CSF analysis was done in only one patient, which showed features of aseptic meningitis (Cell count 20 cells, Cell type 70% lymphocytes 30% neutro- phils, glucose-59, protein-22 and chloride-98. ZN stain-Neg, Gram stain-Neg, C/S -no growth)

**Complications**

- Out of 30 cases, 3 cases had complications.
- One patient had meningoen- cephalitis with Shock.
  - Rickettsial vasculitis with DIC with Shock was seen in one case and
  - Meningoen- cephalitis was seen in one case.

**Table 10:** Duration of Hospitalization (n=30)

Duration	No. of Patients	%
≤ 5 days	15	50
6-10 days	14	46.6
≥11 days	1	3.33
Total	30	100.0

Out of 30 cases, 15 cases (50%) had duration of hospitalization for less than or equal to 5 days, 14 cases

(46.6%) were hospitalized for 6-10 days and 1 cases (3.33%) for 21 days as child had meningoen- cephalitis.

**Table 11:** Outcome (n=30):

Outcome	No. of patients	%
Died	1	3.33
Improved	29	96.3
Total	30	100.0

Out of 30 cases 1 case died accounting for a case fatality rate of 3.33%. Cause of death was

1. Meningoen- cephalitis with Shock.
2. Rickettsial vasculitis with DIC with Shock.

**Discussion**

Rickettsial diseases are reported from various parts of India [1], However, the reported cases underestimate the burden of rickettsial diseases in India due to the lack of both community based studies and availability of specific laboratory tests. Present study describes the clinical profile of rickettsial infection in children.

**Demographic data**

The mean age of occurrence of rickettsial infection in present study was 5.4 years with maximum incidence in the age group of 1 to 5 yrs (50%). Similar observations of age predilection for less than 5 years was made by Patil D *et al.*, [8].

In this study females (60%) outnumbered males, with male to female ratio of 0.9:1 (16:18). This differs from the studies by other authors like Kumar M *et al.*, [12]. who reported male preponderance.

The majority of the cases were observed during second half of the year, from July to December around 79.5%. Similar observations have been recorded by Krishna MR *et al.* [9] (June to November).

In this study all the cases were from rural areas and most of them belonged to lower socioeconomic status. This might be attributable to more chances of over- crowding, poor hygiene, tick infestation and louse infestation in these patients.

**Clinical profile****Clinical symptoms**

In the present study all patients presented with fever (100%), similar finding was noted in other studies <sup>[10]</sup>, approximately 60% (n=18) of the patients presented with 5-7 days of acute febrile illness with no foci of infection. Rash was seen in 83.3% of which 60% (n=15/25) had involvement of palms and soles. Facial puffiness was seen in 30%, swelling of limbs seen in 26.6% and generalized edema in 23.3%.

A history of tick/mite bite was not available in any of the cases. Similar findings have been reported by Sirisanthana V *et al.* <sup>[11]</sup> None of the cases in the present study had eschar unlike other studies <sup>[12]</sup>. Mahajan SK *et al.* <sup>[6]</sup> did not find eschar in any of their cases. Though presence of eschar confirms and is pathognomonic of scrub typhus group of rickettsial diseases, but its absence does not exclude the possibility of scrub typhus.

**Laboratory parameters**

In our study 10% (n=3) had leucopenia. Similar findings was noted in other studies like Takhar *et al.* <sup>[13]</sup> (15%).

Out of 30 cases, 8 cases had normal serum sodium levels. Hyponatremia (S.Sodium <135mEq/L) was present in 20 cases (66.6%). Similar findings were noted by Ratageri VH *et al.* <sup>[10]</sup> (71.4%)

**Complications**

The most common complication observed in this study was meningoencephalitis in 3.3% (1) of cases. Similar findings were noted in studies by Rathi NB *et al.* <sup>[14]</sup> and Palanivel S *et al.* <sup>[15]</sup> reporting meningoencephalitis in 5% and 6% of patients respectively.

There were no renal or cardiac complication seen in this study, unlike study done by Kumar M *et al.* <sup>[12]</sup> where in myocarditis with cardiogenic shock in 34%, acute kidney injury in 20% of cases noted which was attributed to late referrals.

**Treatment**

All the 30 cases in our study received treatment with Doxycycline, of which 28 cases(93.3%) was improved. 80% responded to the treatment within 48 hrs and 15% of cases responded after 48 hrs. Kumar M *et al.* <sup>[12]</sup> has demonstrated that good response to Doxycycline (97%).

**Outcome**

Rickettsial disease is known to produce serious complications and has a mortality rate of 30% <sup>[2, 4]</sup>. Deaths were attributable to late presentation, delayed diagnosis and drug resistance.

**Conclusion**

Rickettsial diseases are one of the important causes of pyrexia of unknown origin, which are grossly under diagnosed in India.

It is most commonly seen in younger age group. Children presenting with fever, rash, edema of legs or facial puffiness should be suspected of rickettsial fever. Hepatosplenomegaly, rash and third space fluid loss are the most common clinical signs noted. Rickettsial diseases are difficult to diagnose, unless suspected but treatment is easy, affordable and often successful with dramatic response to antimicrobials.

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**Conflict of Interest**

None

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Nil

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