Leptospirosis and Scrub Typhus

Often Missed Diagnosis of FUO
Case-1

16 yr boy from rural background

- Fever with chills
- Cough and severe myalgia x 4 to 5 days

Antimalarial taken for 3 days

- T-101°F
- Conjunctiva and throat: congested
- Mild icterus
- S/E: clinically normal

Clinical diagnosis:

- Viral fever
  - Hepatitis
  - Influenza
  - Dengue
- Malaria
- Enteric Fever

IV antibiotic and IV fluids started and investigation and blood culture sent.
Investigations

- HB- 12 g/dL, WBC -7000, P65L35 plt: 2 lacs
- S. bilirubin-1.5(D1.0,ID 0.5) SGPT:80, SGOT:70
- Typhi dot IgM, Dengue IgG /IgM and rapid malarial ag-negative
- Urine: protein +, Bile salt+, Bile pigments+
- X ray chest and USG abdomen: normal
- CPK-300 IU/L, S.creatinine-1 mg/dl

Same treatment continued
Course

- 3rd hospitalize day fever continued
- Rpt investigations:
  - CBC (inconclusive)
  - Typhi dot IgM, Dengue IgG/IgM and rapid malarial ag-negative
  - USG abdomen: normal

Thought of Lepto →
- Rapid leptospirosis test: positive,
- ELISA IgM; +ve (>15)
- MAT: +ve (1:400),
- PCR: +ve
- Culture for lepto sent
- Diagnosis: Icteric Leptospirosis

Treated with CP x 7 days.
10th day Pt became afebrile, LFT: normal
When should one suspect Leptospirosis

Epidemiological setting

Abrupt onset of fever, chills, conjunctival suffusion, headache, myalgia and jaundice

(May cause acute renal failure, bleeding including pulmonary hemorrhage syndrome, meningitis, myocarditis and uveitis)

Conjunctival suffusion and muscle tenderness, most notable in the calf and lumbar areas, are the most distinguishing physical findings

The diagnosis is more difficult when patients present with symptoms of cough, dyspnea, nausea, vomiting, abdominal pain, diarrhea, arthralgia and a skin rash
Environmental factors

- **Soil pH**: Survival of leptospira prolonged for months in alkaline pH
- Water logging, flood
- Rare in young children & infants
Mode of transmission

Animal Source → Environment → Human

Direct contact with urine or tissue of infected animal
- Through skin abrasions, intact mucus membrane

Indirect contact
- Broken skin with infected soil, water or vegetation
- Ingestion of contaminated food & water

Droplet infection
- Inhalation of droplets of infected urine
Natural History

Animal source - Exposure - Infection

Overt Clinical Illness  Inapparent

Anicteric  Icteric  No carrier

Recovery  Fatality  Dead end
When to Suspect

3 symptoms
- Chills & Fever
- Myalgia
- Fatigue

3 signs
- Conjunctival suffusion
- Calf muscle tenderness
- Enlarged LN
Fever
- Viral fever, Malaria, Typhus

Jaundice
- Malaria, Viral hepatitis, Sepsis

Renal Failure
- Malaria, Hanta virus, Sepsis

Meningitis

Bacterial / Viral causes
- Hemorrhagic Fever

Dengue, Hanta virus, Typhus

Differential Diagnosis
- Typhoid fever
- Pulmonary Hemorrhage
- Icterohemorrhage
- Renal failure
- Meningoencephalitis

Leptospira
- Pathogenesis
  - Vasculitis
  - Immunologic and cytotoxic injury
Clinical Presentation

- **Anicteric**
  - Common, mild
  - < 2% Mortality

- **Icteric**
  - Rare, Severe
  - 15% Mortality

90% of Cases

10% of Cases
Comparison of Anicteric and Icteric type

<table>
<thead>
<tr>
<th></th>
<th>Anicteric leptospirosis</th>
<th>Icteric leptospirosis (Weil's syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td>First stage 3-7 days</td>
<td>First stage 3-7 days</td>
</tr>
<tr>
<td></td>
<td>(Septicemic)</td>
<td>(Septicemic)</td>
</tr>
<tr>
<td></td>
<td>Second stage 0 days-1</td>
<td>Second stage 10-30 days</td>
</tr>
<tr>
<td></td>
<td>month</td>
<td>(Immune)</td>
</tr>
<tr>
<td></td>
<td>(Immune)</td>
<td></td>
</tr>
<tr>
<td><strong>Important clinical</strong></td>
<td>Myalgia, headache,</td>
<td>Jaundice, hemorrhage, renal failure</td>
</tr>
<tr>
<td>findings</td>
<td>abdominal pain,</td>
<td>myocarditis</td>
</tr>
<tr>
<td></td>
<td>vomiting, conjunctival</td>
<td></td>
</tr>
<tr>
<td></td>
<td>suffusion, fever</td>
<td></td>
</tr>
<tr>
<td><strong>Leptospires</strong></td>
<td>Blood</td>
<td>Blood</td>
</tr>
<tr>
<td>present</td>
<td>CSF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>Urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lab Tests

Serological Test:
- Ig M based immune assay (Rapid test)
- Slide agglutination latex agglutination
- Immunochromatographic
- ELISA
- Microscopic agglutination test (MAT)

Microscopic Demonstration: (Dark field and silver impregnation)

Isolation of organism: Culture

Molecular Diagnosis: PCR
### MAT (Microscopic agglutination test)

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serovar specific</td>
<td>14-21 strains</td>
</tr>
<tr>
<td>Complex, Time consuming,</td>
<td>IgM-IgG differentiation not possible</td>
</tr>
</tbody>
</table>

- **Serovar specific antibody test** - *gold standard*
- Significant titer to diagnose = 1:100 in non endemic
- = 1:400 in endemic area
- May be negative during first two weeks
- Rising titer confirmatory (after 14 days)

*Note: IgM-IgG differentiation not possible*
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Headache</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Fever</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Temp &gt; 39 F</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Conj. suffusion</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>Meningism</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>Muscle pain</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>Jaundice</td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>Alb, ↑ creatinine</td>
<td>Definite</td>
</tr>
<tr>
<td></td>
<td>Rain fall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contaminate H₂O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal contact</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ELISA IgM + ve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAT positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAT high titer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAT rising titer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture positive</td>
<td></td>
</tr>
</tbody>
</table>

Score of 25 or more – Presumptive Diagnosis
Score of 20 to 25 – Possible case of leptospirosis
Treatment

Suspected/probable/confirmed case

(1) No organ involvement
Doxycycline 100mg BD for 7 days (> then 8 years)
Amoxicillin/Ampicillin- 30-50mg/kg/day – for 7 days ( for < then 8 years)

(2) With Organ involvement
Inj. Crystalline penicillin 2-4lac IU/kg/day- 4hourly
If allergic to penicillin, give
Inj. Ceftriaxone 50-75mg/kg/day I.V for 7days or
Inj. Cefotaxime 50-100MG/kg/day I.V for 7 days.

Management of Organ involvement : as per any case of organ involvement.
Prognosis and Mortality

- Cardiac
- Bleeding
- Pulmonary
- Renal
- Meningitis
- Fatality
Fever without focus is a common presentation.

In epidemiological setting consider Leptospirosis as one of the differential diagnosis.

Confirmative diagnosis: difficult, takes long time

Microscopic agglutination test is the gold standard (rising titer)
Small, Gram Negative Obligatory Intracellular CoccoBacilli

RICKETSSIAL INFECTIONS
<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>Disease</th>
<th>Rickettsial agent</th>
<th>Insect vector</th>
<th>Mammalian reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I Typhus group</strong></td>
<td>a Epidemic typhus</td>
<td>R. prowazeki</td>
<td>louse</td>
<td>humans</td>
</tr>
<tr>
<td></td>
<td>b Murine typhus</td>
<td>R. typhi</td>
<td>flea</td>
<td>Rodent</td>
</tr>
<tr>
<td><strong>II Scrub typhus</strong></td>
<td></td>
<td>O. tusugamushi</td>
<td>mite</td>
<td>rodent</td>
</tr>
<tr>
<td><strong>III Spotted fever group</strong></td>
<td>a Indian tick typhus</td>
<td>R. conorii</td>
<td>Tick</td>
<td>Dog/rodents</td>
</tr>
<tr>
<td></td>
<td>b Rocky mountain spotted fever</td>
<td>R. rickettsii</td>
<td>Tick</td>
<td>Dogs/rodents</td>
</tr>
<tr>
<td><strong>IV Others</strong></td>
<td>a Rickettsial pox</td>
<td>R. akari</td>
<td>Mite</td>
<td>Mice</td>
</tr>
<tr>
<td></td>
<td>b Q fever</td>
<td>C. burnettii</td>
<td>Nil</td>
<td>Cattle sheep goat</td>
</tr>
<tr>
<td></td>
<td>c Trench fever</td>
<td>Rochalimaea quintana</td>
<td>Louse</td>
<td>Humans</td>
</tr>
<tr>
<td></td>
<td>d Ehrlichiosis</td>
<td>Ehrlichia</td>
<td>Tick</td>
<td>Deer/dog</td>
</tr>
<tr>
<td></td>
<td>e Anaplasmosis</td>
<td>Anaplastmaphagocytophilium</td>
<td>Tick</td>
<td>Deer/dog</td>
</tr>
</tbody>
</table>

*More than 19 types of spotted fever varieties are described depending upon the geographical area where these are prevalent*
EPIDEMIOLOGY

Scrub Typhus in India

- Jammu & Kashmir
- Himachal Pradesh
- Uttarakhand
- Uttar Pradesh
- Haryana
- Rajasthan
- Assam
- West Bengal
- Maharashtra
- Karnataka
- Tamil Nadu
- Kerala
- Pondicherry

*Mahajan S. K. 2012
MODE OF TRANSMISSION

Primary parasites of arthropods such as Lice, Fleas, Ticks, chiggers and Mite in which they are found in the alimentary canal.
PATHOGENESIS

BACTEREMIA

Proliferation in the endothelium of small blood vessels

→

Release of cytokines

→

Damage to endothelial integrity

→

Fluid leakage, platelet aggregation, polymorph, monocytic infiltration

→

Focal occlusive end arteritis (Microvasculitis)

→

Microinfract
Confirmation of rickettsiosis requires consideration of clinical, epidemiological and laboratory data.
COMPLICATIONS

- Meningoencephalitis
- Pneumonia
- ARDS
- Myocarditis
- Nephritis
- Hepatospleenomegaly
- Skin Rash, Necrosis, Gangrene
CLINICAL PRESENTATION

INCUBATION PERIOD

• 12 TO 15 DAYS
• MAY EXTEND UP TO 28 DAYS.

Rash

✓ Rose-red Blanching macules

✓ Spreads rapidly to involve entire body including Soles and Palms

✓ may become petechial or hemorrhagic some times palpable purpura.

✓ Purpura may enlarge into Ecchymoses, may become Necrotic
CLINICAL PRESENTATION

In Severe Disease

- Severe vascular obstruction may result in gangrene of
  - Digits
  - Earlobes
  - Scrotum
  - Entire limb
CLINICAL PRESENTATION

Eschar

At the initial site of tick attachment and regional lymphadenopathy
Distribution of eschars

Front:
- Chest, Abdomen (11.9%)

Back:
- Head, face, neck (19%)
- Axillae (21%)
- Upper extremities (7.4%)
- Genitalia, inguinal region, buttocks (33%)
- Back (4.5%)
- Lower extremities (2.8%)
CLINICAL PRESENTATION

• Anorexia, Myalgia, Restlessness, Arthralgia

• Splenomegaly And Hepatomegaly

• GI symptoms
  ✓ Nausea, Vomiting, Diarrhea, Pain Abdomen.

  • CNS SYMPTOMS
    ✓ Altered Sensorium, Delirium, Coma
    ✓ Convulsions
    ✓ Ataxia
    ✓ Meningism

Complications
Edema, Myocarditis, Hepatitis, Acute renal failure, Vascular collapse, Pneumonitis, ARDS, DIC
Diagnostic procedures for rickettsioses

- Biopsy
- Eschar or ticks
- Molecular Biology

Reference Lab

- IFA
- ELISA
- Weil – Felix Test

PCR

Western Blot Test

2nd Week
# Diagnostic procedures for rickettsioses

<table>
<thead>
<tr>
<th>Principle</th>
<th>Weil Felix</th>
<th>IgM and IgG ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heterophile antibody test</td>
<td>• Basis: sharing of the antigens between rickettsia and proteus</td>
<td>• Immunoglobulin capture Assays</td>
</tr>
<tr>
<td>• Demonstrates agglutinins to proteus vulgaris strain ox19, ox2 and proteus mirabilis oxk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When to do?</th>
<th>5-7 days after onset of fever</th>
<th>IgM at the end of 1\textsuperscript{st} week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IgG at the end of 2\textsuperscript{nd} week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When to consider Significant</th>
<th>Titre of &gt; 1:80</th>
<th>Optical Density of 0.5.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity &amp; specificity</th>
<th>low</th>
<th>High</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cost</th>
<th>inexpensive</th>
<th>Higher than weil felix</th>
</tr>
</thead>
</table>

*Baseline titres need to be standardized for each region*
<table>
<thead>
<tr>
<th><strong>SCRUB TYPHUS</strong></th>
<th><strong>INDIAN TICK TYPHUS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORGANISM</strong></td>
<td>O. tsutsugamushi</td>
</tr>
<tr>
<td><strong>AGENT</strong></td>
<td>Trombiculid mites</td>
</tr>
<tr>
<td><strong>VECTOR</strong></td>
<td>Rodents</td>
</tr>
<tr>
<td><strong>EPIDEMIOLOGY</strong></td>
<td>Endemic India Nepal China Tibet Pakistan Afghanistan</td>
</tr>
<tr>
<td><strong>RASH</strong></td>
<td>Transient</td>
</tr>
<tr>
<td></td>
<td>Seen in 40-60% cases</td>
</tr>
<tr>
<td><strong>ESCHAR</strong></td>
<td>5-60% pathognomonic</td>
</tr>
<tr>
<td><strong>DIAGNOSIS</strong></td>
<td>ELISA FOR SCRUB TYPHUS OX K</td>
</tr>
</tbody>
</table>
GUIDELINES

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
From Smile Healthcare, Rehabilitation and Research Foundation, Smile Institute of Child Health, Ramdaspeth, Akola; *Department of Pediatrics, Ashwini Medical College, Solapur; and #Dr Yewale Multispeciality Hospital for Children, Navi Mumbai; for Indian Academy of Pediatrics “Guidelines on Rickettsial Diseases in Children” Committee.
Correspondence to: Dr Narendra Rathii, Consultant Pediatrician, Smile Healthcare, Rehabilitation & Research Foundation, Smile Institute of Child Health, Ramdaspeth, Akola, Maharashtra, India. drnbrathi@hotmail.com.

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.
Clues for Clinical Diagnosis of Rickettsial Infections

- Patient hailing from an area which is endemic to Rickettsial infections.
- A definitive history of a tick-bite and/or contact with animals like dogs, rodents and cattle.
- Clinical triad of fever, rash and headache (irritability in younger children).
- Maculopapular rash extending over palms and soles, purpuric and necrotic rash, presence of eschar.
- Gangrene of digits, toes, ear-lobes.
- Edematous swelling of the body, hands and feet associated with hepatosplenomegaly, lymphadenopathy.
- Fever and rash associated with convulsions and change in sensorium.
- Fever which is unresponsive to usual antibiotics.
Case Definitions (ICMR 2015)

**Suspected Case**
- Any undifferentiated fever without focus more than 5 days should be suspected as case of rickettsial infection. Presence of eschar suggests scrub typhus even if duration of fever is less than 5 days.
- Differential diagnosis of Dengue, Malaria, Pneumonia, Leptospirosis, Enteric fever, meningococcemia, measles, enteroviral exanthems & uncommon causes like toxic shock syndrome, rubella, parvoviral infection, ITP, TTP, HUS, and Hepatitis should be considered.

**Probable Case**
Positive Weil Felix test with titers > 80 or four fold rise in titers or Positive Elisa test with OD > 0.5 for IgM antibodies.

**Confirmed Case**
Positive Rickettsial DNA detection in blood or eschar, by PCR or Rising antibody titer in sera by Indirect Fluorescent Assay (IFA) / Indirect Immunoperoxidase Assay (IPA).
TREATMENT

- Doxycycline
- Chloramphenicol

Time tested drugs to effectively treat rickettsial infections in patients of all ages including children.

Recommended treatment regimens

- **Doxycycline**: 2.2 mg / kg /dose bid po, max 200mg /day
- **Azithromycin** in the single dose of 10 mg/kg body weight for 5 days

Other drugs – Azithromycin, Clarithromycin, Fluroquinolones, Rifampicin.

Duration of treatment 5-7 days or at least 3 days until the patient is afebrile.
TREATMENT

• RESPONSE THERAPY:

• Most patients respond quickly with rapid improvement in signs and symptoms.

• Mortality is uncommon if treatment is started within 5 days of symptoms.

• Patients with mild illness: defervesce within 48 to 72 hours.

  • Patients with severe illness: critically ill and febrile for up to 5 days.

• No relapse in patients appropriately treated with either DOXYCYCLIN and CHLORAMPHENICOL.

• Response to Doxycycline is dramatic, and fever persisting beyond 48 hours of initiation of doxycycline should prompt consideration of alternative/additional diagnosis or infection.
Compatible clinical scenario and Suggestive epidemiological features and absence of definite alternative diagnosis

Suspected case

Eschar +

lab features +

Afebrile within 48 h of empiric doxy

Lab diagnosis, if available

>7 days of illness

<7 days of illness

Weil Felix test

ELISA

IPA

IF

PCR

Probable case

Confirmed case

Full course of anti-rickettsial antibiotics + supportive therapy

Management Algorithm for Rickettsial Infections

Rickettsia are dangerous pathogens and specific serological tests are available only in a few specialized laboratories, and these tests are positive in 2nd wk of the illness, so it is advisable to make a clinical diagnosis of the rickettsial fever based on detailed history, epidemiology and the physical findings.
Thank You