NEONATAL SCRUB TYPHUS – CASE SERIES

Newborn Unit
Kanchi Kamakoti Childs Trust Hospital, Chennai
1. Case Presentations (Chronological Order)
2. Rickettsial infection
3. Diagnostic Dilemmas
4. Carry Home Messages
Case- 1

• Baby “A”, **Day 28**, Male, R/O **Tirunelveli**

• Term, B Wt 3.4 kg

• Oligohydramnios, Em L.S.C.S. (Indic: PROM)

• D 1-3: Mild resp distress. Improved.

• **D 10-12**: Mother febrile. Managed as ? Viral

• **D 21**: Admitted for fever. IV antibiotics. Referred due to Persistent fever, increasing respiratory distress, & positivity of all titers of TORCH panel
• Admitted on **Day 28**
• **Wt: 2.6 kg** (Birth weight 3.4 kg).
• **Febrile** (T-101), dehydrated, **Hepatomegaly** (4 cm) & **splenomegaly** (4 cm)
• TLC: 15400, P84L15Band2, **Plt: 15,000 (Clumps+)**, **CRP: 132, PCT 0.95**, ↑ SGOT & SGPT
• PT 18/14, PTT 37/30
• CSF: WNL
INV & COURSE

- Blood, urine, CSF culture: NG
- TORCH: HSV2 IgM positive
- CSF HSV PCR and urine CMV PCR negative
- CXR & CT Chest: Pneumonitis, Bil Pleural Effusion
- CT Brain NAD
- USG Abdo: Hepatosplenomegaly & ascites
- ECHO: PERICARDIAL EFFUSION
- Managed with Antibiotics, Acyclovir, IVF, PRBCs
- Inotropes for shock, AED for seizures
• IgM for **SCRUB TYPHUS: HIGHLY REACTIVE**
  (Maternal IgM scrub typhus highly positive)
• PCR for eubacterial genome positive (DNA sequencing: Orientia tsutsugamushi)
• Rx: oral **Doxycycline**
• Baby improved & became afebrile after day 4 of **doxycycline** (Course: 10 days)
• At discharge (9.2.12), wt 3.02 kg, HSM regressed, plt 3.7 lac
• “Well” on follow-up
Case 2

- B/o “P”, Term, Female, R/O Nellore
- Mother 20 yr, uneventful antenatal period
- NVD. Cried at Birth. B Wt 3.38 kg
- Apparently well till D8: Lethargy, ↓ Feed
- **D9: Abdo distension, Thrombocytopenia → Referred**
- KKCTH Admission (**D10**): Wt 3.2 kg, Hypoxic, Resp distress, **Shock, Fever, down-rolling of eyes, Posturing**
- Abdo distension, **Hepatomegaly 3cms, Splenomegaly 3cms**
Course

- **Investigations**: TLC 9,900, P75,L21,M4, Toxic granules+
- **Plt**: 75,000, CRP 133.9, PCT 1.24
- **PT >1min/14sec, PTT 1.12 min/30 sec**
- **CSF**: WNL, Bld, CSF culture: NG
- **CT Brain**: NAD
- **Echo**: Raised PASP, Small OS ASD,
- **Scrub Typhus Elisa**: Negative
• Resp Distress: \( \text{O}_2 \)
• Bleed PR: FFP, Plt, Vit K
• Inotropes, Antibiotics, Phenobarbitone, PRBCs
• Plt 25,000, Doxycycline wef D9(H): Good response
• PCR based DNA sequencing targeting the 16rRNA region of Eubacterial genome revealed the presence of **Orienta tsutsugamushi** [Report: D13(H)]
• Plt [D14(H)]1.75 lakh
• Disch on D16(H) on Doxycycline
Case 3

- B/o “M”, D7, Term, R/O Thanjavur
- Mother: **Fever (With Hypotension)** for 5 days in 7th mth requiring ICU admission. ↓ fetal movements in the last week of pregnancy.
- LSCS at term(Indic: previous LSCS with fetal distress). MSL
- CIAB. Bwt: 2.9 kg
- **At birth**: Respiratory distress, lethargy, staring, squint, petechiae (Plt – 50,000)
- Developed **fever**. Antibiotics given.
- **Persistent thrombocytopenia** - Given platelet transfusion and steroid → **Referred**
At Admission

• Admitted on **day 7** of life. Weight: 2.78 kg (B wt: 2.9 Kg)
• Resp: **Tachypnea, SCR**
• CVS: **Pale, Cutis, Cold periph, prolonged CFT, BP 66/48/52**
• CNS: **Encephalopathy, seizures, intermittent convergent squint,**
• Abdo: **Liver 3 cm, spleen 3 cm**
• Skin: **petechiae** present
Investigations

- Hb 16.7, TLC 26,814, P80, L20, NRBC 35, Plt 25,000, CRP 82.8, PCT 6.12
- Bld culture: NG, CSF: WNL
- Dengue & IgM scrub typhus –ve
- iCa 0.87, BUN 178, Cr 1.4, Bili 6.8 (2.4)
- AST: 84, ALT: 34, SAP 709, GGT 262, Alb 3
- CXray: Haziness R lung
- Echo: Small PDA
- CT Brain: NAD
Management

• Baby managed with antibiotics, Inotropes, Phenobarbitone, O2 and supportive treatment.
• In view of irregular respiration, baby intubated and **ventilated**.
• Umbilical venous catheterization done.
• Baby had recurrent episodes of **fever**.
• D2(H): Edema ↑
• D3(H): **Eubacterial genome positive**, CSF HSV PCR -ve, Urine CMV PCR -ve
• D4(H): **Rpt Echo: pericardial effusion**, PDA
  USG Abdo: Gr 1 RMD, minimal ascites
  Clinical suspicion of scrub typhus: **Doxycycline**, **DVET** done for sepsis.
  Resp acidosis: CMV → **HFOV**
• D5(H): **Pericardiocentesis** done on for pericardial effusion.
  Asp: 8 Lymp, numerous RBCs
  Persistent shock: Steroids
• D6(H): ↓ urine Output
  **Eubacterial genome positive for scrub typhus** and **Azithromycin** added
## Investigations

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<td>2</td>
<td>158</td>
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<tr>
<td>8</td>
<td>197</td>
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<td>9</td>
<td>195</td>
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<td>10</td>
<td>144</td>
<td>1.9</td>
<td>60,000</td>
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Course

• D9: Baby underwent peritoneal dialysis for ARF (Urea 195, Cr 2.4, K 6.3). Managed for severe acidosis

• D10: Managed for ET bleed, Hyperkalemia, Shock and acidosis. Expired.

• **Cause of Death:** SCRUB TYPHUS WITH SEPTIC SHOCK, SEVERE ENCEPHALOPATHY, MULTIORGAN DYSFUNCTION AND ACUTE RENAL FAILURE
Case 4

- **B/O “R”, R/O Nellore**
- 21 Yrs. Old, G2 P1 L1 A1, Oligohydramnios, Leucorrhea
- Delivered vaginally, DNClAB, MSL, BWt 3kg
- Baby birth weight: 3 kgs
- D1: Resp Distress, Seizure. Mx in NICU
- Improved and disch on day 5.
- **D20: Febrile**, Admitted
  - Thrombocytopenia, USG Abdo: HSM
  → Referred
Admission

- **Wt 2.8kg (B.Wt 3kg)**
- Tachycardia, Cutis, **Shock**, Jerky breathing
- Liver 5 cm, Spleen 2 cm, CVS: ESM
- Hb 11.5, **Plt 1,00,000**, TLC 17,200, P44,L52,Band 2, **Toxic Granules+**, MP -ve, **CRP 113.8, PCT 7.87**, Bili 3.3 (1.6), **SGOT 276, SGPT 184**
- Dengue IgM, NS1Ag negative
- Cxray: Bil UZ haziness, Echo: Mild PS
• Managed with Antibiotics, IV fluids, Inotropes
• **Arching**, Hypertonia
• CSF study WNL
• CSF & Bld culture was sterile
• Plt: 1lac→40K→30K
• High suspicion of Rickettsial inf: oral **Doxycycline**
Course

- Scrub typhus IgM: **highly positive**
- PCR eubacterial genome: for *Orientia tsutsugamushi*.
- Baby became afebrile, arching & shock improved and feeding was established.
- Plt 75K → 1.3 lac
- CRP 85.5 → 9 → 3
- PCT 0.68 → 0.08
- Discharged on D10. Received 10 days Doxycycline
- Review at 1 week: WNL
CASE 5

• b/o “V”, R/O Nellore
• 23 yr Primi, Term, GDM, PIH
• LSCS (GDM, Oligohydramnios, Cord around neck)
• 2.5 kg, CIAB, DBF
• Phototherapy for NNH
• Apparently well till D14
Admission

- **D15**: Fever, **D18**: Abdominal distension
- Plt: 16,000, CRP 9.6, USG: Minimal free fluid
- Piperacillin-Tazobactam, Amikacin
- **D20**: Admitted KKCTH (6.2.13)
- Admission:
  - Wt 3.4kg (Bwt 2.5kg)
  - Moaning, Cutis, **Shock+**
  - Abdo distension, **HSM**
Investigations

- Hb 11.5gm, TLC 12100, P51L49, Plt 30,000
- CRP 115.6, PCT 8.2, MP Negative
- PT 25/14, PTT 57/30, SGOT 217, SGPT 86,
- CXray: RUZ haziness
- USG: Collapsed Bowel loops, Minimal free fluid, Mild HSM
- Antibiotics, Azithromycin
- Management: IV fluids, Inotropes, PRBCs, FFP
- Surgical consult
Course

- Worsening Shock, Resp Distress & Abdo distension. Developed Seizures, NG Bleed
- Hb 8.4, Plt 30K
- Intubated & Ventilated
- Elisa for scrub typhus IgM: Highly reactive
- Azithromycin contd
- USG guided aspirate: 110ml of ascitic fluid removed [1100 WBC (P10, L90), 3200 RBCs]
Course

- Echo: LV systolic dyfn, Rt pleural effusion
- Seizures $\rightarrow$ Cardiac arrest
- Resuscitated $\rightarrow$ Bradycardia
- Managed for septic shock, Hyperkalemia
- Baby succumbed & Died
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<td>Improved</td>
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<td>Death</td>
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RICKETTSIAL INFECTIONS IN NEONATES
Rickettsial infections

• Important re-emerging infections
• **India**: Maharashtra, Tamil Nadu, Karnataka, Kerala, J&K, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and WBengal.

• **Difficult to diagnose**: low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests.

• **Failure of timely diagnosis** → significant morbidity and mortality.

• With **timely diagnosis**, treatment “easy” & often successful with dramatic response to antimicrobials.
MICROBIOLOGICAL ASPECTS

• **Family Rickettsiaceae**: phylogenetically occupy a position between bacteria and viruses.

• Small, nonflagellate, gram negative pleomorphic cocco-bacilli adapted to obligate intracellular parasitism and transmitted by arthropod vectors.

• They are primary parasites of arthropods like lice, fleas, ticks and mites, in which they are found in the alimentary canal.

• In humans, they infect **vascular endothelium and reticuloendothelial cells**.

• *Coxiella burnetii* and *Rochalimaea quintana* have been excluded
Scrub Typhus

- **Scrub typhus** caused by *Orientia tsutsugamushi* (formerly: *Rickettsia tsutsugamushi*)
- Most prevalent human rickettsial infection
- Very Few Neonate reports.
- **Vector**: chigger, **Host**: rodents
- **Transovarial** transmission
- Regurgitation of infected saliva occurs during feeding.
- Not transmissible directly from person to person
PATHOLOGY

• Organisms enter human body → multiply locally → enter the bloodstream → invade their target cells (endothelium, RE cells)
• Inside host cells, organisms multiply → Cell lysis
• Vasculitis is the basic pathogenetic mechanism responsible for skin rash, microvascular leakage, edema, tissue hypoperfusion and end-organ ischemic injury.
PATHOGENESIS

• Formation of thrombi → tissue infarction and hemorrhagic necrosis.

• Inflammation & vascular leakage → interstitial pneumonitis, non-cardiogenic pulmonary edema, cerebral edema and meningoencephalitis

• Serositis

• Infection of endothelial cells → procoagulant activity → coagulation factor consumption, platelet adhesion and leukocyte emigration → (DIC like picture)
CLINICAL FEATURES

- Early CF nonspecific. Later: Mild to severe.
- Incubation period: 2-21 days.
- **FUO** most common presentation
- **Rash**: “Hallmark” of rickettsial disease
  - Pink, blanching, discrete macules → maculopapular, petechial or hemorrhagic.
  - Rash on palms and soles
  - Palpable purpura may be seen.
  - Occasionally petechiae → ecchymosis → gangrenous patches
• Necrotic **Eschar** at the inoculating site

• Generalised lymphadenopathy and hepatosplenoomegaly seen in majority of scrub typhus patients

• **CNS**: drowsiness, disorientation, photophobia, delirium, meningismus, etc

• (‘**typhus**’ refers to cloudy state of consciousness)
COMPLICATIONS

• **Respiratory:** Interstitial pneumonitis and noncardiogenic pulmonary edema secondary to pulmonary microvascular leakage.
• **Neurological:** Meningoencephalitic syndrome
• **Renal:** Acute Renal Insufficiency
• **CVS:** Pericardial Effusion, myocarditis
• **Other:** DIC like syn, hepatic failure, gangrene.
LAB FINDINGS

• **TLC- Early**: normal to low normal with marked shift to left. **Later**: leucocytosis in 30% of cases

• **Thrombocytopenia**: present in about 60% cases, **Platelet Clumps**

• **Biochemistry**: Hyponatremia, hypoalbuminemia, elevated hepatic transaminases, elevated blood urea
Serology

• **Serological Methods:**
  Microimmunoflorescence, immunoperoxidase assay, latex agglutination, indirect hemagglutination, ELISA, dot blot immunoassay (including dipstick test) and Weil-Felix test

• As all these tests detect antibodies, they would be able to make diagnosis only after **5-7** days of onset of disease.
- **Weil Felix Test**: OX-19, OX-2 and *P. mirabilis OX-K strains*) titer 1: ≥ 80 considered as positive

- **Microimmunofluorescence (MIF)**: serum specimens tested using a panel of 11 rickettsial antigens. Considered positive at cut off Ab titers of 1/128 for IgG and 1/64 for IgM.

- **IgM ELISA**: Qualitative ELISA Test for exposure to Orienta Tsutsugamushi (OT) Detection of IgM Ab in human serum to OT derived recombinant Ag

  Sensitivity and Specificity not established
Other Inv

- Immunohistochemistry
- Isolation of organism
- PCR: detects rickettsial DNA in whole blood, buffy coat fraction or tissue specimen. Most rapid assay for the diagnosis.

Disadvantages: varying levels of sensitivity, high cost and “nonavailability”.
EUBACTERIAL GENOME TEST

• It is a Bacterial DNA testing
• Based on the fact that each strain of bacteria has a specific "fingerprint" of genetic material (Which can be analyzed by PCR with universal eubacterial primers, possessing broad specificity for all Gram +ve & -ve bacteria)
• List of sequenced eubacterial genomes contains all the bacteria known to have publicly available complete genome sequences.
• Most of these sequences have been placed in the INTERNATIONAL NUCLEOTIDE SEQUENCE DATABASE COLLABORATION, a public database
Dendrogram representing the genetic relatedness of *Orientia tsutsugamushi*
PCR based DNA in Case 1

VRF 388 : Identified as Orientia tsutsugamushi by PCR Based DNA sequencing Phylogenetic tree constructed with the 16SrRNA sequence of VRF 388 revealed a close genetic relatedness with Orientia tsutsugamushi strain TH1817 (GenBank accession no:AF479300.1) and two other strains of Orientia tsutsugamushi GenBank accession nos (AF062074.1 and AF478127.1)
PCR based DNA sequencing in Neonatal Sepsis

• Dutta et al have emphasized the role of PCR based DNA sequencing targeting the 16SrRNA region in detection of aetiological agents causing neonatal sepsis.

• In clinical situations, the use of universal primer PCR has been shown to significantly reduce the time for initiation of suitable antibiotic therapy and the hospital stay.

Diagnosis

• **History:** Family history, animal contact
• **Presentation:** PUO, fever with rash, eschar, meningoencephalitis or aseptic meningitis, acute renal insufficiency and infective vasculitidis
• **Tick** bite or tick exposure
• **Epidemiological data**
• **Lab:** N/low TLC with left shift, thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases
• Rapid **defervescence** with appropriate antibiotics
DIFFERENTIAL DIAGNOSIS

- **Viral** (measles, enterovirus, dengue, infectious mononucleosis)
- **Protozoal** (malaria)
- **Bacterial** (meningococcemia, typhoid, leptospirosis, TSS)
- **Collagen vascular** (Kawasaki disease, other vasculitis)
- **Adverse drug reactions**
TREATMENT

• **Antibiotics:** tetracyclines, chloramphenicol, macrolides, fluroquinolones

• **Doxycycline** is the drug of choice. Oral unless patient vomiting/obtunded. Dose 5mg/kg/day (BD) for therapy should be at least 3 days after defervescence or minimum 5-7 days.

• **Doxycycline resistance:** macrolides or rifampicin

• Sulfonamides contraindicated

• **Good supportive therapy**

• Judicious use of **corticosteroids**
The antibiotics tested appear to cure the condition, and there seem to be little to choose between the broad spectrum antibiotics tested, but trials are small.

Rifampicin seem to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to conventional antibiotics (tetracycline and chloramphenical), and where doxycycline-resistant strain is suspected.

Severe, life threatening scrub typhus has been reported in neonates as a result of the infection being transmitted from their mothers (Wang 1992; Suntharasaj 1997).
Scrub Typhus in Pregnancy

• 5 patients with scrub typhus during pregnancy who were seen in India between October 2001 and February 2002. Four of the 5 women were treated initially with ciprofloxacin. Three women had stillbirths, 1 an abortion and 1 a low birthweight baby, which suggests that ciprofloxacin should not be used for treating pregnant women and that scrub typhus leads to severe adverse effects during pregnancy.

Scrub Typhus in Pregnancy

• Eight pregnant women with scrub typhus were treated successfully with a single 500-mg dose of azithromycin, and no relapses were reported. They all delivered healthy babies at term, without congenital or neonatal complications. In the reviews, azithromycin was effective against scrub typhus and had favorable pregnancy outcomes. Ciprofloxacin and cefuroxime failed to treat scrub typhus and fetal loss resulted.

VERTICAL TRANSMISSION

A 31-year-old, 34 weeks pregnant woman presented with fever, chill and cough for 6 weeks. Fetal jeopardy was found then a cesarean section was performed to deliver a 2,200 g male with hepatosplenomegaly. The mother's diagnosis was confirmed by positive Weil-Felix (OXK titer 1:320) and scrub typhus (titer 1:1600) tests. Vertical transmission was also demonstrated by a positive scrub typhus IgM in her child.

Controversies

• “Gold Standard” in Diagnosis?
• Reliability of PCR?
• Safety of Doxycycline (Neonates, Renal Failure)?
• ? Vertical Transmission of Rickettsia
Take Home Message

• **Suspect** Rickettsial infection in neonates with: Fever, Respiratory Distress, Hepatosplenomegaly, Pericardial Effusion, Ascites, Thrombocytopenia (Plt clumps) +/- Shock

• **Diagnosis:** IgM Scrub Typhus, PCR for Eubacterial Genome

• Treatment with **Doxycycline** effective & Safe

• **Potentially Fatal Disease**

• **Supportive treatment** important