Visit to children hospital

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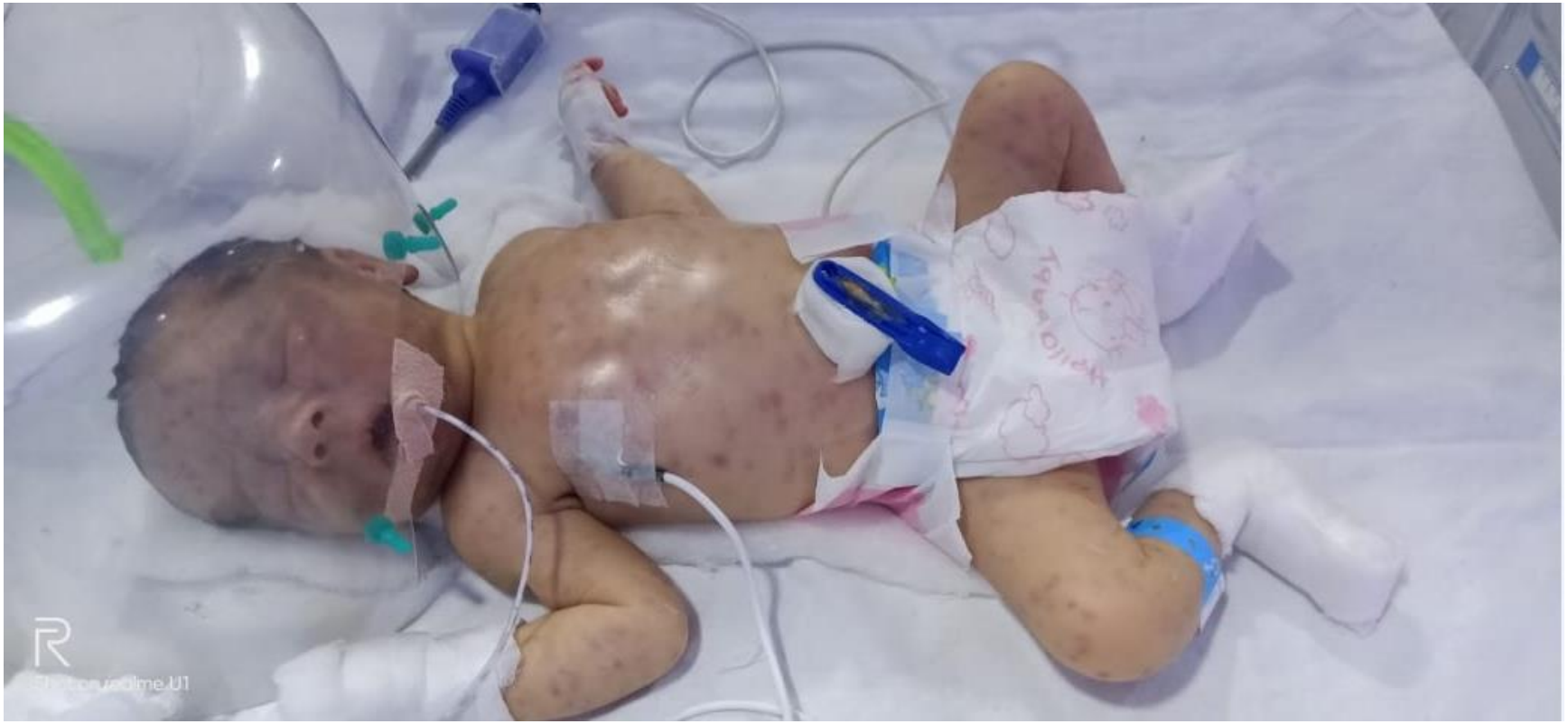
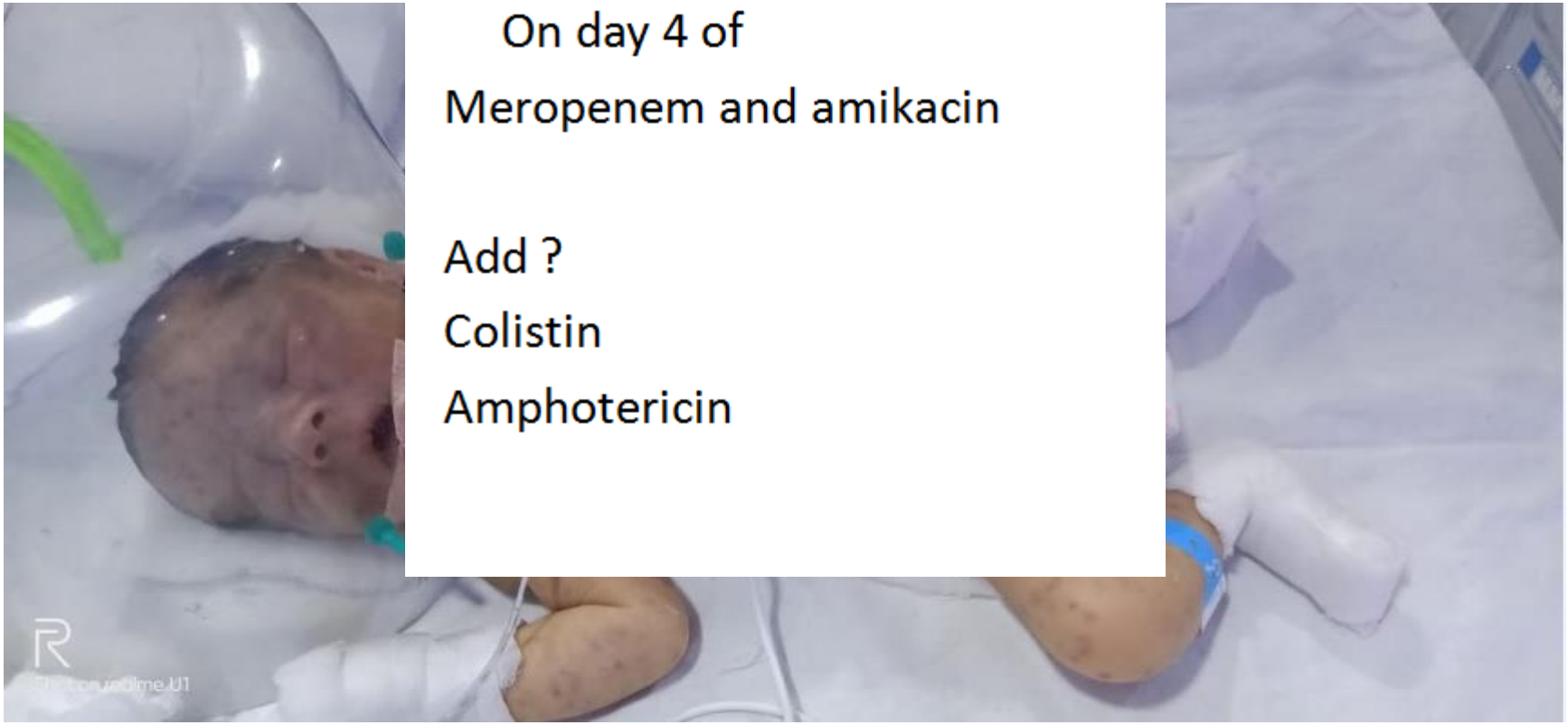
NEONATAL SEPSIS



NEONATAL SEPSIS



Let’s go back…

- Full term male child wt 3.2 kg
- IVF- LSCS
- Liqour – miconium stained
- Tone – good
- Cry - good
- Apgar 1’-8 5’-9
- Activity good

Temp – wnl
HR- 152
RR-44
CRT<3
SYST EXAM WNL
UMBLICAL CORD NORMAL
ORFICES PATENT
CONGENIITAL ANOMALY NONE

Parents

Father

- G6PD deficiency

Mother

- Oligohydramnios
- Hypothyroidism

DAY 2

- Tacypnoea, intermittent grunting, minimal sub costal retractions
- CXR – bilateral hazy lung fields
- In Nicu found to have macular rash
- Tazotum iv
- Amikacin
- Oxygen and supportive care

- Hb 11
- Wbc 5400 (N44/L53/E2)
- Platelets-68000
- Blood goup B +
- PT INR 1.16
- CRP 5.8
- CREAT 0.9
- BILIRUBIN 9.6 (D-5.9)
- TSH 7.02

Phototherapy

Improving in nxt 48 hours

Shifted to mothers side

Spoon feeding

2 DAYS LATER – desaturation/seizure

Hypocalcemia
Hypomagnesemia

Non palpable
Purpura/petechie

Iv levitericitam
Iv calcium gluconate
Iv magnesium
Phototherapy
Vitamin K
phenobarbitone
Meropenem/amikacin/

- Hb – 12.9
- Wbc 7000(N35/L61/E2)
- Platelets- 71000
- Creat- 0.85
- Bilirubin 13.5 (D-9.1)
- OT/PT- 69/25
- SAP-233
- I-Ca- 0.9

Csf

- Wbc 20 (N4/L96)
- Sugar 29
- Protein 109

Usg brain and abdomen

- Tiny echogenic focus seen in bilateral caudo-thalamic groove-grade 1 germinal matrix hemorrhage – follow up suggested

- Gall bladder is partially distended and shows mild wall edema

Questions I had in mind !

- Whats the syndrome ?

  Neonatal Sepsis – Meningitis /pnuemonia

  (GBS, ESBL, enterovirus)

- Differential's ?

  MAS, congenital infections

  leukemia & LCH – hematologist added

Requested

- Peripheral blood smear
- Blood culture
- Continue Meropenem , send blood culture
- Switch amikacin to vancomycin
- Biofire Meningitis panel on CSF
- CT brain , fundus examination, Usg abdomen
- Torch serology in neonate
- Mother s Torch serology not done earlier
- HIV elisa
- *Plan – skin biopsy*

- Normal Rbc, lymphocytosis, reduced platelets
  no atypical cells.

CT BRAIN - B/L symmetric periventricular calcifications

Fundus - RE – chorio retinal scar

LE - active chorio retinitis with vitritis

Rpt Usg abdomen – mild splenomegaly

Neonate

- Toxo ig M & igG +
- HSV IgM & IgG -
- CMV ig G +
- CMV Ig M –
- RUBELLA ig G +
- RUBELLA ig M -

mother

- Toxo ig M & igG +
- HSV IgM & IgG -
- CMV ig G +
- CMV Ig M –
- RUBELLA ig G +
- RUBELLA ig M –

- Toxo avidity - 85% (>35%)

- Toxoplasma PCR asked on csf but was differed by primary team (platelets)
- CMV viral load –urine – negative

- Sulphadiazine and pyrimithamine was started

Date	Age	W.T	H.B.	R.B.C.	W.B.C.	PLATELET
14-3-20	12 Day	3.400 kg.	7.9	2.37	3700	168000
15-3-20	13 Day	3.400 kg.	—	—	—	—
18-3-20	16 Day	—	7.1	2.20	4300	279000
20-3-20	18 Day	3.500 kg	10.9	3.56	9000	355000
26-3-20	24 Day	—	9.7	3.13	6490	271000
10-4-20	1 month 8 Day	3.820 kg.	8.7	2.83	6770	432000
5-5-20	2 month 30 Day	4.240 kg.	14.3	4.81	10620	201000
9-6-20	3 month 7 Day	5.120 kg.	12.8	4.45	7820	338000
3-7-20	4 month 1 Day	5.760 kg	—	—	—	—
1-8-20	5 month	6.600 kg.	11.6	4.20	9820	350000
17-9-20	6 month 15 Day	7.200 kg.	12.4	4.47	11730	384000
22-11-20	8 month 20 Day	7.500 kg.	12.9	4.72	12160	365000
20-02-21	11 month 18 Day	8.850 kg	11.4	4.13	13760	378000

Today

An approach to the diagnosis of congenital infections

E Lee Ford-Jones MD FRCPC, *Division of Infectious Diseases, The Hospital for Sick Children, Toronto, Ontario*

S-TORCH

- Toxoplasmosis
- Rubella
- CMV
- HSV

- Syphillis

CHEAP-TORCHES

- CHICKENPOX
- HEPATITIS(B,C,E)
- ENTEROVIRUS
- AIDS
- PARVOVIRUS B19

- Lcmv,tb,zika ….

An approach to the diagnosis of congenital infections. Paediatr Child Health. 1999

Maternal History suggestive of Congenital infection

History	Infection
Illness	
Rash	Syphilis, rubella, parvovirus B19, enterovirus
Arthritis	Parvovirus B19, rubella
Mononucleosis-like fatigue, lymphadenopathy	CMV, toxoplasmosis, HIV

E Lee Ford-Jones MD. An approach to the diagnosis of congenital infections; Paediatr Child Health Vol 4 No 2 March 1999

Index of Suspicion

In the absence of suggestive maternal laboratory results, suspect congenital infections in neonates with:

- Hydrops fetalis
- Microcephaly
- Seizures
- Cataract
- Hearing loss
- CHD
- Hepatosplenomegaly
- Jaundice
- Rash
- Thrombocytopenia
- IUGR

Majority clinically inapparent ("asymptomatic") at birth

Karen E Johnson et al. Overview of TORCH infections, Uptodate, Oct 11, 2012

What to suspect

- Anemia with hydrops - Rubella,cmv,toxo
- Bone lesions – rubella,syphillis
- IC calcification/hydrocephalus – Toxoplasmosis,CMV,HSV,Parvovirus B19, rubella, HIV,LCMV
- Congenital heart disease – Rubella
- Hearing loss – hydrops plus syphillis
- Jaundice/ low plt - CMV, toxo, rubella, HSV, syphilis, enterovirus

An approach to the diagnosis of congenital infections. Paediatr Child Health. 1999

- Maculopapular rash - Syphilis, measles, rubella, enterovirus
- Microcephaly - CMV, toxo, rubella, varicella, HSV
- Myocarditis/encephalomyocarditis - Echovirus, coxsackie B, other enterovirus
- Ocular findings - CMV, toxo, rubella, HSV, syphilis, enterovirus, parvovirus B19
- Progressive hepatic failure and clotting abnormalities - Echovirus, coxsackie B, other enterovirus, HSV, toxoplasmosis
- Purpura - CMV, toxo, syphilis, rubella, HSV, enterovirus, parvovirus B19
- Vesicles - HSV, syphilis, varicella, enterovirus

Top pathgens by sd

- CNS /ocular findings - CMV, Toxo,syphillis
- Myocarditis/encephalitis - enterovirus
- Skeletal issues - Syphillis, rubella
- Hydrops – rubella , CMV, Toxo
- Congenital heart disease – Rubella
- Hearing loss – hydrops plus syphillis
- Jaundice/ low plt - CMV, toxo,
- Rash – CMV, Toxo, syphillis, measels, rubella
- Vesicles – varicella,enterovirus,hsv,syphillis

An approach to the diagnosis of congenital infections. Paediatr Child Health. 1999

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Serologic Prevalence of *Toxoplasma gondii* in Indian Women of Child Bearing Age and Effects of Social and Environmental Factors

2014

Sarman Singh[1]*, Arshi Munawwar[1], Sugandhi Rao[2], Sanjay Mehta[3], Naba Kumar Hazarika[4]

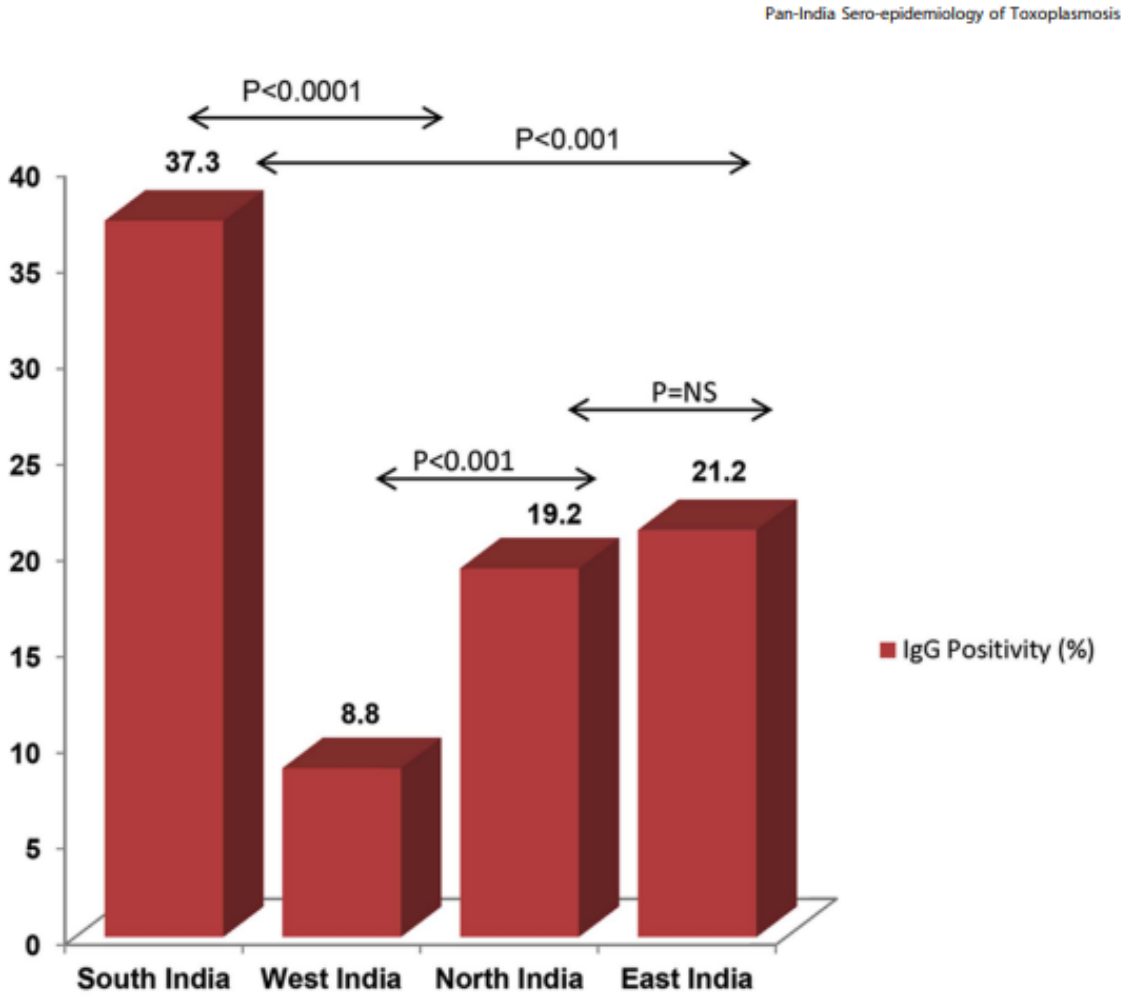
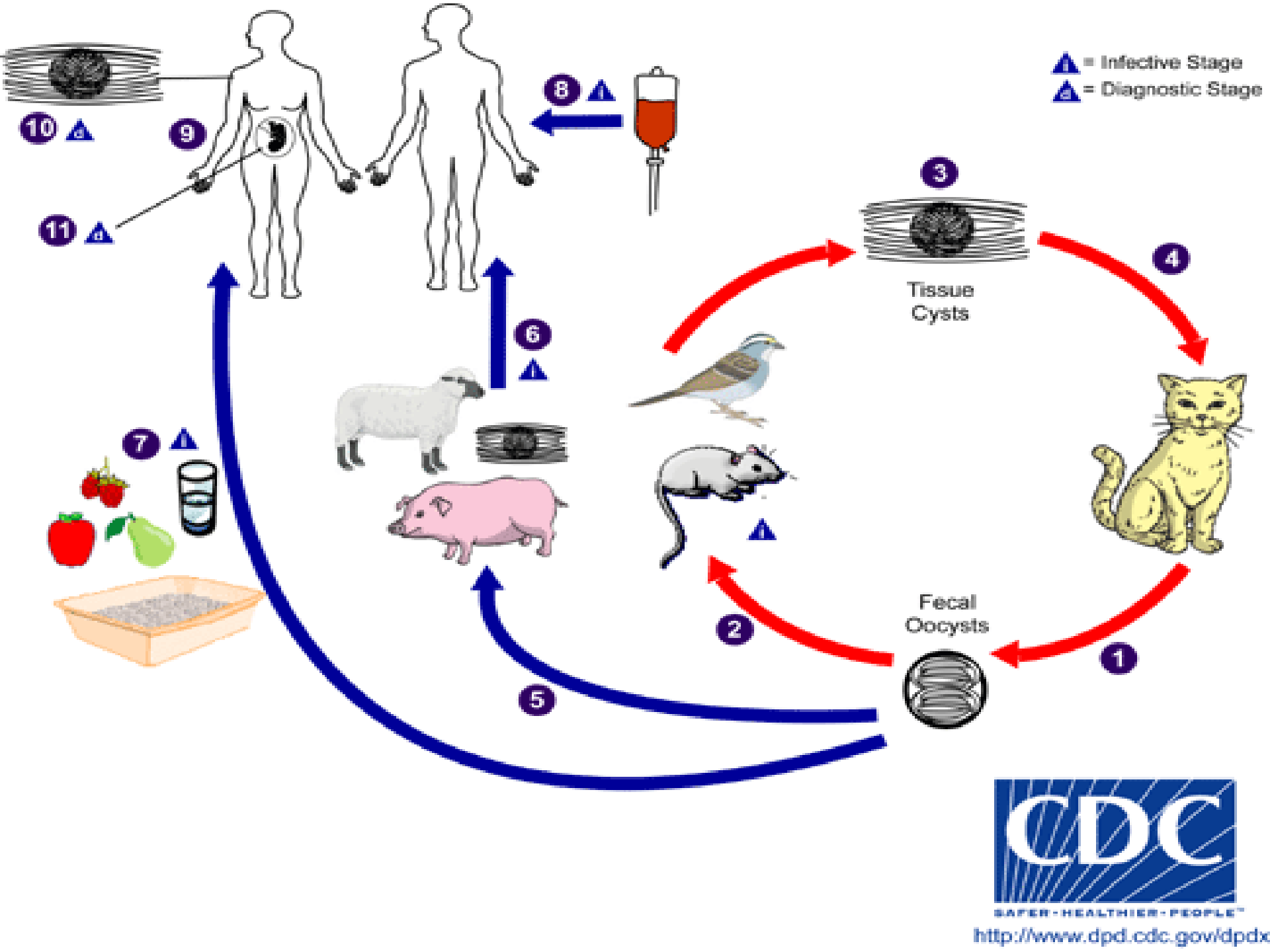


Figure 3. Prevalence of toxoplasmosis in women from 4 regional study centers. The prevalence rates varied from one region to another but the most significant difference was between South India and the other three regions.

Review > Parasitology. 2011 Dec;138(14):1829-31. doi: 10.1017/S0031182011001478.
Epub 2011 Sep 9.

Toxoplasma gondii: the changing paradigm of congenital toxoplasmosis

- 3 genotypes identified so far
- Difference in reactivation and disease severity



CDC
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http://www.dpd.cdc.gov/dpdx

Toxoplasmosis-acquisition

- Ingestion of undercooked contaminated meat
- Ingestion of oocysts from hands, food, soil, or contaminated water
- Organ transplantation
- Blood transfusion
- Transplacental transmission;
- Transmission through breast milk has not been described.
- Prevention:
  - avoid raw vegetables/boil water/hand wash after cat contact/cook meat thoroughly
- Optimal way to prevent is by systematic screening monthly with serology on all pregnant women as in France
  - associated with a significant reduction in the rate of congenital infection and a better outcome at 3 years of age in infected children

McAuley JB. Congenital Toxoplasmosis. *J Pediatric Infect Dis Soc*. 2014

Risk of congenital toxoplasmosis

Gestational Age at the Time of Maternal Infection			
	6 WG	18 WG	30 WG
Pre-test probability of congenital toxoplasmosis (%)	2.2	23.0	56
Positive likelihood ratio	79 (29->1000)	69 (34->1000)	43 (20->1000)
Probability of fœtal infection (%)	64.0 (39.0–100)	95.4 (91.0–100)	98.2 (96.2–100)
Negative likelikhood ratio	0.43 (0.10–0.78)	0.37 (0.25–0.48)	0.23 (0.12–0.36)
Probability of fetal infection (%)	1.0 (0.2–1.7)	10.0 (7.0–12.5)	22.6 (13.2–31.4)

WG: weeks of gestation.

severe disease in fetus

Subclinical/chorioretinitis

Peyron F, L'ollivier C, Mandelbrot L, et al. Maternal and Congenital Toxoplasmosis: Diagnosis and Treatment Recommendations of a French Multidisciplinary Working Group. *Pathogens*. 2019.

Toxoplasmosis syndrome's

- 1) acquired – immuno-competent patient
- 2) acquired or reactivated- immuno-deficient patient
- 3) ocular
- 4) congenital.

McAuley JB. Congenital Toxoplasmosis. *J Pediatric Infect Dis Soc*. 2014

Congenital Toxoplasmosis

TABLE 1 | Clinical features reported to be associated with congenital toxoplasmosis (14, 21, 22).

Systemic signs	Preterm birth*, small for gestational age*, rash* (petechial, blueberry muffin), sepsis like illness*, hepato/splenomegaly*, myocarditis*, hepatitis*, hepatic calcifications* jaundice, temperature instability, pneumonitis, lymphadenopathy
Laboratory abnormalities	Anemia*, thrombocytopenia*, CSF abnormalities like pleocytosis, elevated protein, eosinophilia, hypoglycorrhachia* increased level of liver enzymes or bilirubin level
Neurological signs	Macro or microcephaly*, hydrocephalus*, hypotonia*, palsies*, seizures*, psychomotor retardation*, spasticity*, SNHL*, intracranial calcifications*
Ocular signs	Amblyopia*, cataract*, chorioretinitis*, nystagmus*, optic nerve atrophy*, strabismus*, retinal scarring*, visual impairment*, microphthalmia, microcornea

Toxoplasma antibodies In general

- IgG appears within 1-2 weeks, peaks at 1-2 months and remains elevated at low titers lifelong
- Avidity test positivity means infection was 3-5 months earlier
- IgM appears earlier than IgG
  - may persist for up to 5 years after the acute infection
  - never use as sole basis for diagnosis as only 40% of positive tests indicate true recent infection

Toxoplasmosis-diagnosis

- Causes cervical lymphadenopathy or a mononucleosis like infection
- Diagnosed by rising titer of IgG antibodies, done 3 weeks apart
- Single elevated IgM titer unreliable as levels remain elevated for months
- In pregnancy, Elevated IgG levels indicate a past infection, robust immunity and no risk to fetus

Approach to toxoplasmosis serology in pregnancy

- IgG -, IgM - : excludes current or past infection, counsel patient about future risk
- IgG +, IgM - :
  - 1st and 2nd trimesters: past infection, no risk to fetus, no further testing
  - 3rd trimester: infection could have been either remote or in early pregnancy, further testing required
- IgG -, IgM + : may have current infection
  - repeat serology in 3 weeks or do confirmatory testing
  - if IgG turns positive, recent infection confirmed
- IgG +, IgM + : recent infection possible, confirmatory testing eg IgG avidity test needed

Management of *Toxoplasma gondii* Infection during Pregnancy, *Clinical Infectious Diseases*, Volume 47, Issue 4, 15 August 2008

Diagnosis of Congenital Toxoplasmosis

TABLE 1 Principles and methods used for the diagnosis of congenital toxoplasmosis

Principle	Detection	Platform	Diagnostic of congenital toxoplasmosis
Toxoplasma-specific humoral responses	IgG, IgM, IgA	Dye test, ELISA, and ELISA-like assays, ISAGA, immunofluorescence, agglutination	Positive IgM after 5 days of life and in the absence of blood transfusions. Positive IgA after 10 days of life. Persistence of *Toxoplasma* IgG beyond 1 year of age
	IgG, IgM, and IgA to specific *Toxoplasma* antigens	Western blots	Presence of specific bands only seen in the newborn or bands with higher intensity than maternal ones for IgG and/or IgM and/or IgA in a reference laboratory
Toxoplasma nucleic acid amplification	DNA	PCR	Positive result in any body fluid (e.g., amniotic fluid, cerebrospinal fluid[a], peripheral blood, urine)

Pomares C, Montoya JG. Laboratory Diagnosis of Congenital Toxoplasmosis. J Clin Microbiol. 2016.

Immunohistochemistry of *Toxoplasma*-specific antigens in tissue	Antigens	Immunoperoxidase	Positive result in any tissue (e.g., brain or other fetal tissue)
Visualization by microscopy	Visual identification of tachyzoites and/or cysts	Stains such as hematoxylin/eosin, Giemsa	Positive identification in a reference laboratory
Isolation of *Toxoplasma*	Whole live parasite	Inoculation in peritoneal cavity of mice	Detection of live cysts from any body fluid or tissue that has been inoculated in mice in a reference laboratory
Brain imaging	Brain calcifications, hydrocephaly, microcephaly	Ultrasound, computed tomography, brain magnetic resonance imaging	Findings can be suggestive but are not diagnostic of CT since other etiologies may result in similar findings
Retinal exam	Inflammation in choroidal and retinal layers	Ophthalmological exam	Retinochoroidal lesions can be highly suggestive or, at times, diagnostic of CT

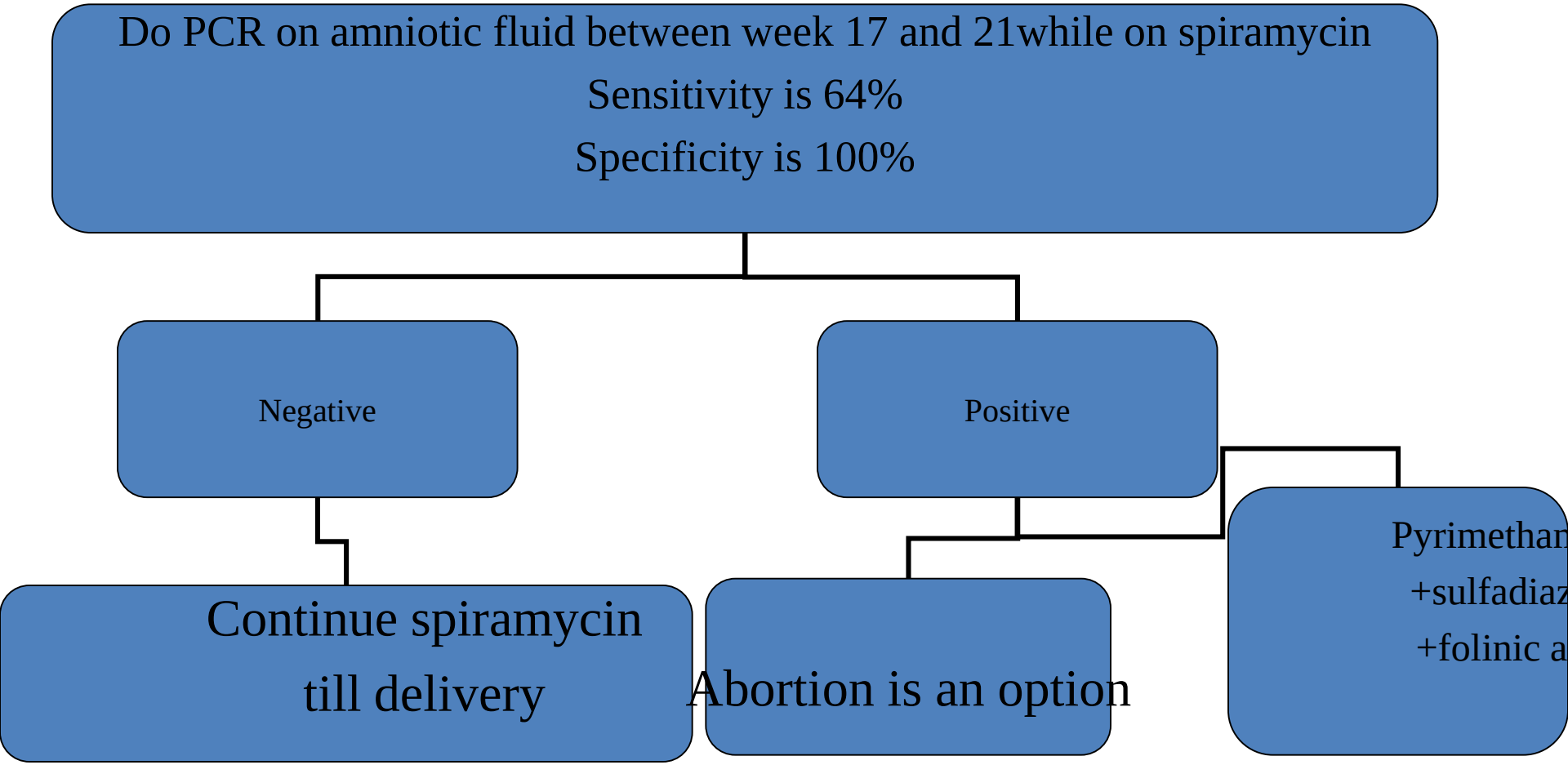
Pomares C, Montoya JG. Laboratory Diagnosis of Congenital Toxoplasmosis. J Clin Microbiol. 2016.

Treatment of acute toxoplasmosis in pregnancy

- Need to start treatment within 3 weeks for favorable outcome
- Diagnosed prior to 18 weeks:
  - start spiramycin 1g q8h
  - reduces risk by 60%
  - does not cross the placenta, not teratogenic
  - Use of spiramycin until week 16, followed by pyrimethamine, sulfadiazine, and folinic acid for at least 4 weeks reduces transmission to 4.5%
- Diagnosed after 18 weeks:
  - start pyrimethamine-sulfadiazine
  - Pyrimethamine potentially teratogenic in first trimester

German protocol Clin Infect Dis 2012 54: 1545-1552)

Diagnosed prior to 18 weeks



Management of *Toxoplasma gondii* Infection during Pregnancy, *Clinical Infectious Diseases*, Volume 47, Issue 4, 15 August 2008

Treatment congenital Toxoplasmosis

- No RCT for this combination therapy in infants.
- Large cohort studies from North america suggest lower rates of reccurence and ocular disease reactivation with 1 year combination therapy
- A French RCT is currently comparing the efficacy of triple therapy for 3 vs 12 months on the development of chorioretinitis over a 2-year period in infants with *non-severe* CT (ClinicalTrials.gov NCT01202500).
- Current therapy targets tachyzoites and not slower-growing, latent bradyzoites

new-onset chorioretinitis

- Up to 1/3 rd of treated patients
- Regular follow up fundus exam (annually)
- Same combination therapy, stop 2 wks after inflammation settles
- Prednisolone if vision threatening

Take home

- Congenital Toxoplasmosis can lead to long term sequel along with severe disease specially if infection acquired in 1st trimester.
- Females planning to conceive should undergo serological evaluation before pregnancy and subsequently in each trimester and follow precautions to prevent acquisition of toxoplasma through out pregnancy if non-immune.
- If Toxoplasma acquired during pregnancy, early initiation of therapy can prevent long term sequel
- Congenital Infections like CMV should be carefully ruled out.
- Currently No RCT for treatment of Congenital Toxoplasmosis is available but best outcomes with 12 month therapy with pyrimethamine and sulfadiazine combination from observational studies.
- Annual retinal evaluation in patients with Congenital Toxoplasmosis mandatory to rule out relapsing Chorio-retinitis for early initiation of therapy.

Thank you