Congenital Infections
Beyond the Acronyms

Theunis Avenant

SAPA/SASPID
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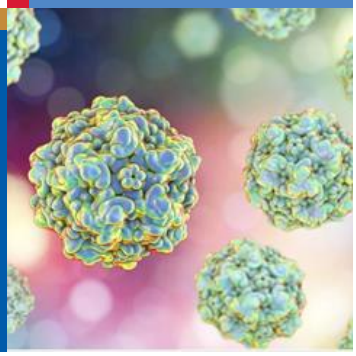
Faculty of
Health Sciences
Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo



ABSTRACTS

Meeting of the American Pediatric Society and the Society for Pediatric Research

Atlantic City, New Jersey, April 28–May 1, 1971

SPECIAL SESSIONS

The ToRCH complex——perinatal infections associated with toxoplasma and rubella, cytomegol- and herpes simplex viruses. ANDRÉ J. NAHMIAS, KENNETH W. WALLS, JOHN A. STEWART, KENNETH L. HERRMANN, and WILLIAM J. FLYNT, JR. *Emory Univ. Sch. of Med., and Ctr. for Disease Control (CDC), Atlanta, Ga.*

TORCH

TORCHeS

STORCH

CHEAPTORCHES

TORCH Serology in Neonates

- TORCH not an etiologic agent
- Screening with battery of "TORCH titers" expensive and has poor diagnostic yield
- Underestimate multiplicity of pathogens
- Inappropriate/indiscriminate use as a screening test
  - Wrong indications, e.g. isolated SGA
  - Wrong timing
  - Wrong interpretation of the single serum results
- TORCH titers should never be used as a single test to diagnose or rule out a congenital infection
- Is considered outdated

Gonzales LA, PIDSP 26th Annual Convention 21 Feb 2019
Arch Dis Child Educ Pract Ed 2013;0:1-9
Indian J Pediatr (2011) 78: 88-95

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IUGR

- Association with congenital infections based on limited data
- Several studies assessed association between SGA and TORCH
  - None showed cost effectiveness for complete “TORCH testing” if no other signs
  - SGA = less than 10th centile
  - One in ten babies would have to be tested

Clin Pediatr 1982;21:417-20
Early Hum Dev 2011;87:103-7

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Diagnosis of congenital/perinatal infections by neonatologists: a national survey

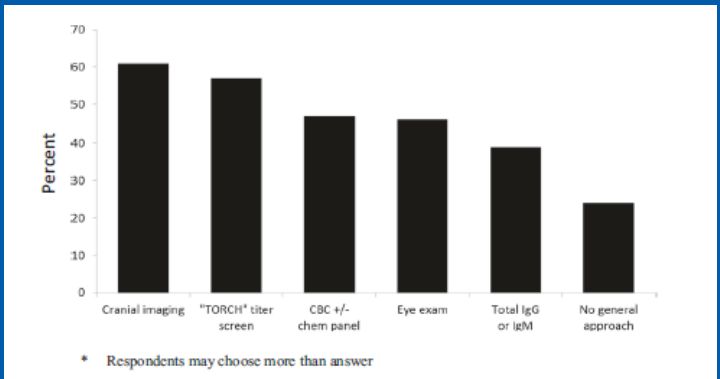

Fig. 1 General approach to diagnose congenital/perinatal infection if “seriously considering” diagnosis

Journal of Perinatology (2019) 39:690–696

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Diagnostic Principles

- Not starting with blank page for most babies
- Consider long list of pathogens in view of
  - Clinical symptoms
  - Epidemiology
  - Maternal vaccination status
  - Past and recent infections
  - Early pregnancy screening
  - Risk factors and exposures
    - Travel to endemic areas
    - Sexual behaviour
- TARGETED TESTING for specific pathogens in well-defined circumstances

Arch Dis Child Educ Pract Ed 2013;0:1-9
Paediatrics in Review, 32;12: 537-542

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Infections in the Newborn

Congenital Infection	Perinatal Infection	Neonatal Infection
• Infection acquired in – utero • Organisms cross the placenta	• Infection acquired by the newborn around delivery	• Infection acquired during first 28 days of life

Adapted from Gonzales LA, PIDSP 26th Annual Convention 21 Feb 2019

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Organisms Causing Infections in Neonate

- **Cytomegalovirus (CMV)**
- **Rubella**
- **Herpes simplex virus (HSV)**
- **Varicella-zoster virus (VZV)**
- **Parvovirus B19**
- Hepatitis B and C viruses
- Enteroviruses
- Human papilloma virus
- Lymphocytic choriomeningitic virus
- Human immunodeficiency virus (HIV)
- Zika virus

Syphilis
Toxoplasmosis gondii
Mycobacterium tuberculosis
Plasmodium
Listeria monocytogenes Group B streptococcus
E. coli and other gram negative bacteria

Awareness of the prominent features of the most common congenital infections help to facilitate early diagnosis of congenital infection

Varicella

Varicella

- Transmission risk approximately 2% before 20 weeks and <1%percent before 13 weeks
- Characteristic findings
  - Intrauterine growth restriction
  - Cicatricial (scarring) skin lesions, which may be depressed and pigmented in a dermatomal distribution
  - Ocular defects, such as cataracts, chorioretinitis, Horner syndrome, microphthalmos and nystagmus
  - Limb abnormalities, which often include hypoplasia of bone and muscle
  - Central nervous system abnormalities (cortical atrophy, seizures, and intellectual disability)

- Congenital varicella syndrome - mortality rate of 30 percent in the first few months of life
- 15% risk of developing herpes zoster in the first four years of life (later intrauterine infection)

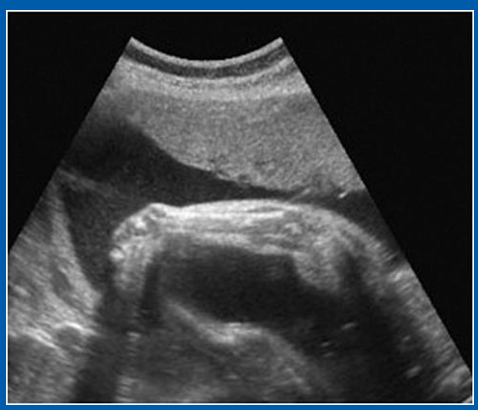
Laura E Riley, Varicella-zoster virus infection in pregnancy, UpToDate@

Diagnosis of Congenital Varicella

Antenatal

- PCR testing on fetal blood or amniotic fluid for VZV

- Ultrasonography for detection of fetal abnormalities



Dr Catherine Noel
Prenatal Diagnosis, Volume: 32, Issue: 6, Pages: 511-518

Lamont RF et al. BJOG 2011; 118:1155

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Diagnosis of Congenital Varicella

Postnatal

- History of maternal varicella during first or second trimester
- Presence of foetal abnormalities compatible with congenital varicella syndrome
- Evidence of intrauterine VZV infection
  - Detection of VZV DNA in the newborn
  - IgM antibodies in cord blood
  - Persistence of VZV IgG beyond seven months
  - Appearance of clinical zoster infection during early infancy

Vinayak V Kodur and Deeparaj G Hegde
Indian Pediatr 2016;53: 269

Lamont RF et al. BJOG 2011; 118:1155

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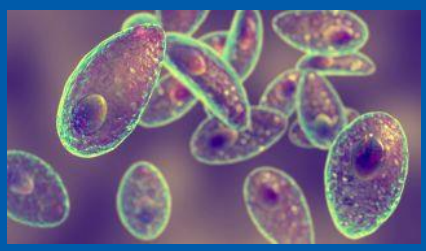

Toxoplasma

Clinical features

- 70 to 90 percent of newborns - **no manifestations on routine physical examination**
- Additional evaluation recommended when there is a high index of suspicion

Clinical features

- Systemic signs
  - Preterm birth, small for gestational age, rash (petechial, blueberry muffin), sepsis like illness, hepato/splenomegaly, myocarditis, hepatitis, hepatic calcifications
- 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
- Laboratory abnormalities
  - Anemia, thrombocytopenia, CSF abnormalities like pleocytosis

Bollani et al Frontiers in Pediatrics 1 July 2022 | Volume 10

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Prenatal Diagnosis

Scenario	IgG antibodies	IgM antibodies	Interpretation	Comment
1	Negative	Negative	Absence of immunity	Monthly serologic follow-up and 1 month after delivery
2	Positive	Negative	Infection acquired before pregnancy	- Repeat tests after 1 month to confirm previous infection - Stop follow-up if only IgG antibodies are positive
3	Negative	Positive	Initial seroconversion or IgM falsely positive	- Repeat test weekly - Second level tests - Eventual prenatal diagnosis - Neonatal follow-up
4	Positive	Positive	Acute infection or Persistence of IgM	- Date infection - Second level tests - Eventual prenatal diagnosis - Neonatal follow-up

- PCR for *T. gondii* DNA in amniotic fluid has revolutionized prenatal diagnosis
- Specificity and positive predictive value of 100%, negative predictive value is 98,1%

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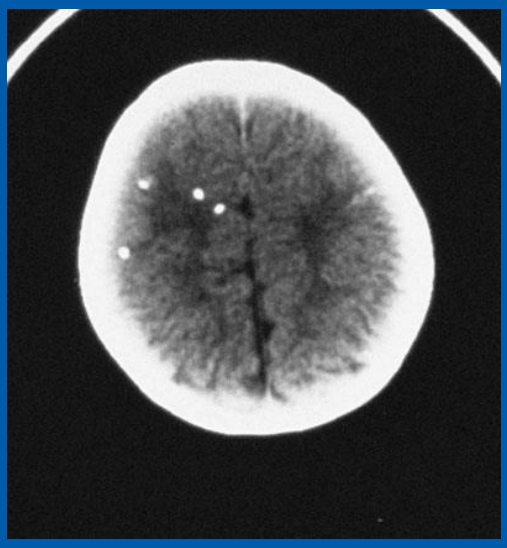
Clinical evaluation

- Lumbar puncture
  - PCR on CSF
- Neuroimaging
- Eye examination
- Hearing evaluation
- Serology



Atlas of Infectious Diseases: Pediatric Infectious Diseases. Edited by CM Wilfert. Philadelphia, Current Medicine, 1998

Diagnosis in Newborn

- Presence of Toxoplasma - specific IgM or IgA
  or
- Molecular detection of *T . gondii* DNA in the cerebrospinal fluid

Confirmed congenital Toxoplasma infection

- Positive PCR on CSF
- Positive IgG with positive IgM and/or IgA
  - A positive Toxoplasma IgM (after five days of life) and/or IgA (after 10 days of life) with compatible maternal serology
- Infants who have positive initial serology but lack clinical abnormalities require repeat testing
- Increase in anti-Toxoplasma IgG titer during the first year of life
- **Positive IgG beyond 12 months of age - Gold standard**

Pesch M, BMJ 2021; 373

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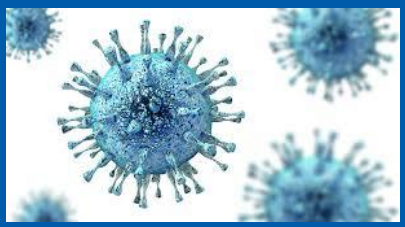
Diagnosis

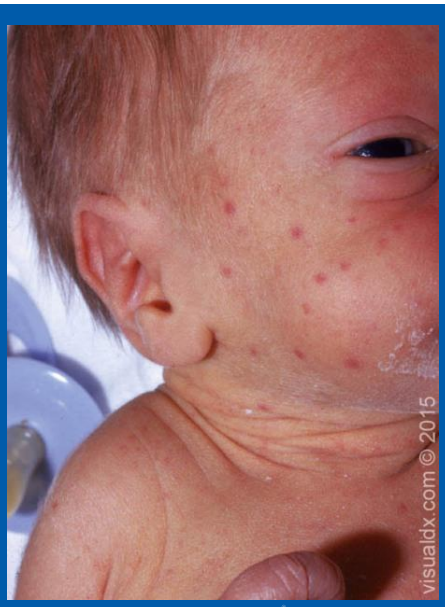
- Presumed congenital Toxoplasma infection
  - Characteristic clinical findings, positive IgG, but negative IgM and IgA
  - Negative IgM and IgA titres do not exclude infection - delayed antibody production
  - PCR testing and repeat serologic testing can help establish the diagnosis
- Excluded congenital Toxoplasma infection
  - Negative IgG, IgM and IgA
  - Negative IgM and IgA with positive IgG titre that declines over time



Cytomegalovirus

Transmission

- Primary infection just before or during pregnancy
  - 30-35% risk of transmission
- Non-primary infections - exposed to a different strain, or has a reactivation of a latent infection
  - 1-2% risk of transmission
- Infections that occur earlier associated with poorer foetal outcomes
- Overall birth prevalence of congenital CMV infection is 0.64%
  - Rates vary considerably among different study populations



Marsico C, Ital J Pediatr 2017;43:38
Reviews in Medical Virology 2007, 17 (4): 253-76

1000 Infants with Congenital CMV Infection

100 symptomatic disease

AT BIRTH

- Petechiae/purpura: 72
- Jaundice: 39
- Hepatosplenomegaly: 50
- Seizures: 7
- Small for gestational age: 58
- Microcephaly: 51
- Thrombocytopenia: 70
- Elevated ALT: 17
- CNS involvement: 59
- SNHL at birth: 58
- Chorioretinitis: 25

LONG TERM SEQUELAE

- Any neurodevelopmental impairment: 40-60
- Intellectual disability: 43
- Borderline intelligence: 17
- Delayed onset SNHL: 16
- Any SNHL: 74
- Ophthalmic abnormality: 51
- Vision impairment: 33
- Legal blindness: 15

Pesch M, BMJ 2021; 373

1000 Infants with Congenital CMV Infection

Pesch M, BMJ 2021; 373

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Diagnosis

- Requires identification of the virus **before age 3 weeks**
- Perinatally acquired infections may begin to manifest at this time
- The standard laboratory test for diagnosing congenital CMV infection is PCR on saliva, with urine usually collected and tested for confirmation (or blood)

- The reason for the confirmatory test on urine is that most CMV seropositive mothers shed CMV in their breast milk.
- False-positive CMV result on saliva if collected shortly after breastfeeding

- Immunoglobulin M (IgM) assays are unfortunately too nonspecific to reliably diagnose congenital CMV infection
- False-positive results are common; therefore, making the diagnosis of congenital infection outside of the immediate perinatal period is very difficult

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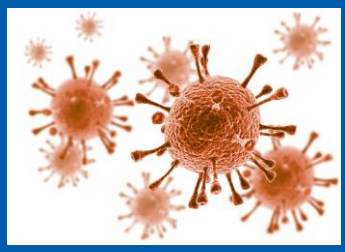
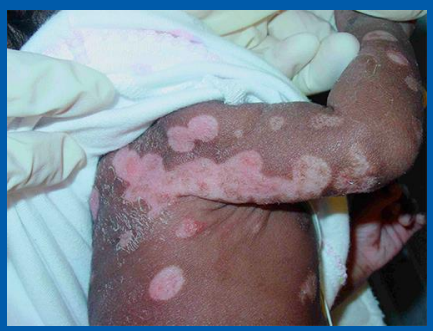


Herpes Simplex

Transmission

- Intrauterine HSV
  - **Very rare**
  - Primary HSV infection with viraemia during pregnancy or ascending infection
- Perinatal
  - The majority (85 percent) of neonatal HSV infections are acquired perinatally
- Postnatal
  - Approximately 10 percent



Gonzales LA, PIDSP 26th Annual Convention 21 Feb 2019

CLINICAL MANIFESTATIONS

- Intrauterine infection due to maternal primary infection
  - Placental infarcts; necrotizing, calcifying funisitis, hydrops fetalis; and fetal demise
  - Survivors of in utero HSV infection may exhibit a characteristic triad (<1/3rd of patients)
    - **Skin vesicles, ulcerations, scarring**
    - **Eye damage**
    - **Severe central nervous system manifestations**, including microcephaly or hydranencephaly
  - Intrauterine infection due to ascending infection
    - Vary from mild e.g. scarring to disseminated disease

Diagnosis

- HSV PCR
  - Surface swabs of the conjunctivae, mouth, nasopharynx, and rectum
  - Swabs/scrapings of any skin and mucous membrane lesions
  - CSF
  - Whole blood or plasma
  - Tracheal aspirate, if intubated

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Rubella

Transmission

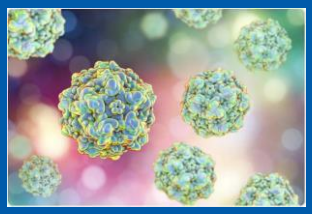
- Incidence of defects 80 to 85 percent if maternal rubella acquired during **first trimester**
- Highest risk in the first 10 weeks of gestation
- Structural cardiac and eye defects
  - Maternal infection before eight weeks
- Hearing loss until 18 weeks
- Congenital defects unlikely if infection after 18 to 20 weeks gestation

Gandhi N, Indian J Dermatol 2015;60:521

Early Manifestations	Late Manifestations
Foetal growth restriction	Hearing loss
Central nervous system involvement	Endocrine disorders
Sensorineural hearing loss	Eye problems
Congenital heart disease	Vascular disease
Eye disease	Panencephalitis
Petechiae and purpura	Immune defects
Other	Prolonged viral shedding

Laboratory Diagnosis

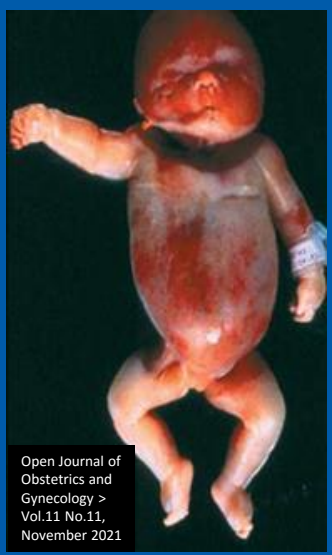
- Rubella-specific IgM antibodies
- Demonstration of rubella-specific IgG antibodies that persist
- Detection of **rubella virus RNA by PCR** from nasopharyngeal swab, blood sample(including cord blood), urine, or cerebrospinal fluid
- Laboratory evaluation before one year of age, after which it is difficult to establish a diagnosis of CRI



Parvovirus

Maternal Infection

- **Foetal deaths**
  - Limited to B19 infections first half of pregnancy
  - 6.3 percent of affected pregnancies
- **Transient effusions**
  - Isolated foetal pleural or pericardial effusions that resolve spontaneously before term
  - Direct pleural or myocardial inflammation
- **Foetal hydrops**
  - B19 is cytotoxic to foetal red blood cell precursors
  - Anaemia and hydrops foetalis
  - Risk of anaemia and foetal hydrops greater when women infected earlier in pregnancy



Open Journal of Obstetrics and Gynecology > Vol.11 No.11, November 2021

Enders M. Prenat Diagn 2004; 24:513.

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Diagnosis

Foetal parvovirus infection

- Polymerase chain reaction on amniotic fluid
- Another option is to obtain foetal blood for B19 IgM
  - Percutaneous foetal blood sampling carries a 1% foetal loss rate

Neonatal infection

- IgM
- B19 DNA can be detected in neonatal blood
- Possibility of false-negatives, even in severe infections

Journal of Clinical Virology 129 (2020) 104482

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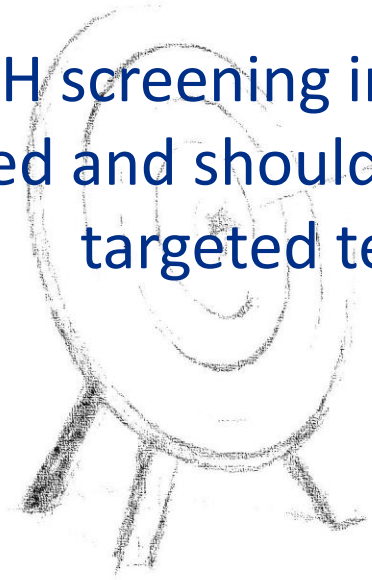
TORCH screening in the neonate outdated and should be replaced by targeted testing



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Thank you