Congenital Infections: MARKED SINCE BIRTH

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OBJECTIVES

- **To present the differential diagnosis of infants presenting with clinical manifestations suggestive of congenital infection**
- **To discuss the practical approach to clinical recognition, diagnosis and management of common congenital infections**

Infections in the Newborn

Congenital infection

- infection acquired in-utero or during pregnancy
- organisms cross the placenta and infect the developing fetus

Perinatal infection

- Infection caused by organisms acquired by the newborn at the time of delivery

Neonatal infection

- Infection caused by organisms acquired by the newborn during the neonatal period (the first 28 days of life)

Congenital Infections

- **Significant cause of fetal and neonatal mortality and an important cause of early and later childhood morbidity (hearing loss, neurocognitive impairment)**
- **Variable incidence: greatest disease burden in low and middle-income countries and low socioeconomic status**
- **Evidence of infection may be seen at birth, in infancy, or years later**
- **The infected newborn infant may show growth retardation, CNS disorders, multiple clinical and laboratory abnormalities, sensorineural hearing loss, or neurodevelopmental disorders**

Neu et al. Clin Perinatol 2015; 42: 77–103

Infection during pregnancy that can affect the Fetus or Infant

Viruses	Bacteria, Parasite, Others
Cytomegalovirus (CMV) Rubella Herpes simplex virus (HSV) Varicella-zoster virus (VZV) Parvovirus B19 Hepatitis B virus Hepatitis C virus Enteroviruses Human papilloma virus Lymphocytic choriomeningitic virus Human immunodeficiency virus (HIV) Zika virus	Toxoplasmosis gondii Mycobacterium tuberculosis Plasmodium Listeria monocytogenes Group B streptococcus E. coli and other gram negative bacteria

Incidence of Congenital and Perinatal Infection

Infection	Incidence
Congenital CMV	Developed countries: 5-7 per 1000 live births Developing countries: 10-12 per 1000 live births
Neonatal HSV-2	1500 cases annually; 1 in 3200 to 1 in 10,000 live births
Congenital Toxoplasmosis	190,100 cases annually; 1.5 cases per 1000 live births
Congenital Rubella (CRS)	100,000 cases annually; 0.6–2.2 per 1000 live births (developing countries)
Congenital Syphilis	521,000–1,575,000 case annually: 212,000 stillbirths, 92,000 neonatal deaths, 65,00 preterm or LBW, 152,000 syphilis-infected newborns
Congenital Parvovirus B19	No available data
Congenital Varicella	No available data

Madrid L et al. Expert Review of Anti-infective Therapy 2016;1.4 (9): 845–861

IgG Seroprevalence of Women of Childbearing Age

Table 1 IgG seroprevalence of women of childbearing age for TORCH

	Toxoplasmosis (%)	Rubella (%)	Cytomegalovirus (%)	HSV (%)[35]
Europe	19.4–43.8[73–75]	96.5–97.7*[76–78]	41–69.4[79 80]	HSV-I: 68.7–79.4 HSV-II: 5.7–21.2[34 81 82]
Asia	8[83]	73.1–80.2[84]	100[85]	HSV-I: 90.3 HSV-II: 7.8–12.5[86 87]
USA	11[9]	91.5*[88]	70–90[89]	HSV-I: 56 HSV-II: 17[36 90]
Latin America	53[91]	62*[92]	100[93]	HSV-I: 80.7–75.8 HSV-II: 4–33.3[94 95]
Africa	72.5–88.8[11]	64.8–72.2[96 97]	72.2–100[96 98]	HSV-I: 92[99] HSV-II: 33.2–35[100 101]

*Indicates reference from a country/continent with national vaccination programme for rubella.
HSV, herpes simplex virus; IgG, immunoglobulin G.

de Jong EP, et al. Arch Dis Child Educ Pract Ed 2013;98:93–98.

Maternal Infection and Incidence of Congenital Infections

Primary Maternal Infection

- more likely to cause infection in fetus if acquired during pregnancy
- more likely to cause disease in the fetus and infant

Secondary Maternal Infection

- reactivation of old infection
- may result in infection in developing fetus
- less likely to cause disease
- asymptomatic disease more common

Clinical Manifestations of Congenital Infections

System	Abnormal Findings
General	IUGR, SGA, LBW, prematurity
CNS	hydrocephaly; microcephaly; intracranial calcifications; meningoencephalitis
Eye	chorioretinitis; keratoconjunctivitis; cataracts; glaucoma
Ears	sensorineural hearing loss
Respiratory	pneumonitis
CVS	myocarditis; congenital heart disease
GIT	hepatomegaly; splenomegaly; jaundice (conjugated)
Hematologic	hemolytic anemia; thrombocytopenia; bone marrow suppression
Skin	petechiae, intradermal erythropoeisis (blueberry muffin rash), maculopapular, vesicular, bullous
Bone	bone lucencies

Differential Diagnosis of Congenital Infections

Diagnosis	Examples
Genetic and metabolic disorders	Tuberous sclerosis complex; Sturge- Weber syndrome; Aicardi syndrome; Galactosemia; Urea cycle deficiencies; Lysosomal storage disorders; Inherited Leukodystrophies; G6PD deficiency
In utero exposure to drugs/ toxins	Alcohol, cocaine and other drugs, isotretinoin
Neonatal hyperbilirubinemia	Autoimmune hepatitis; Biliary atresia; Ischemic injury; thrombosis
Hematologic disease (neonatal thrombocytopenia)	Hemolytic disease of the NB; hereditary spherocytosis; autoimmune thrombocytopenia
Congenital heart Disease	PDA, PS; aortic valve stenosis; Tricuspid atresia; ASD; VSD; coarctation of the aorta
Other neonatal infection	Neonatal sepsis, meningitis, pneumonia; DIC
Other neonatal conditions	RDS; PPHN, meconium aspiration; pneumothorax

Approach to the Diagnosis of Congenital Infection

- Obtain a thorough maternal history, including immunization status, past and recent infections, and exposures
- Perform a careful physical examination of the neonate; different clinical findings may indicate a specific diagnosis
- Evaluate for the presence of ophthalmologic, neurologic, and other manifestations not detected on physical examination
- Conduct targeted diagnostic testing directed only toward those infections that fit the clinical and historical picture

"TORCH Infection"

- **TORCH - acronym originally grouped 4 pathogens causing infections with similar presentations e.g. rash & ocular findings (*Nahmias 1971*).**
- **Proposed to simplify diagnostic procedures in severely ill neonates suspected to have congenital infections**
- **Since then the acronym has been expanded, with the addition of syphilis, Parvovirus B19, Enterovirus, Hepatitis B, HIV, etc. as 'Others' (TORCHeS, STORCH, CHEAPTORCHES)**
- **Use of the acronym may aid clinician remember the causative organisms**

Nahmias AJ, Walls KW, Steward J, et al. The ToRCH complex-perinatal infections associated with toxoplasma and rubella, cytomegalo- and herpes simplex viruses. Pediatr Res 1971;5:405–6.

Problems with TORCH test

- TORCH is not an etiologic agent
- Increasing numbers of pathogens responsible for in utero and perinatal infections listed in the “Other category”
- TORCH titers should never be used as a single test to diagnose or rule out a congenital infection
- Inappropriate/indiscriminate use as a screening test
  - wrong indications, e.g. isolated SGA
  - wrong timing
  - wrong interpretation of the single serum results
  - wrong specimens
- Indiscriminate screening for TORCH infections with the battery of "TORCH titers" is expensive and has a poor diagnostic yield

Shedding new light on the old "TORCH"

Performing a 'TORCH' test, without consideration of each component, should now be considered outdated and replaced by TARGETED TESTING for specific pathogens in well-defined circumstances.

- **An alternate approach involves testing of infants with suspected congenital infections for *specific* pathogens based upon their clinical presentation**
- **Awareness of the prominent features of the most common congenital infections help to facilitate early diagnosis of congenital infection**

Clinical Diagnosis of Congenital Infection

- **Clinical syndromes for many viral infections in the neonatal period overlap and share characteristics**
- **Awareness of the classic physical stigmata and distinct features of common congenital infections can help to facilitate early diagnosis**
- **Appropriate diagnostic evaluation should be tailored to the most likely diagnosis, taking into consideration epidemiologic, clinical and physical examination findings**

Congenital Toxoplasmosis

- Infection acquired by exposure to contaminated cat feces or by eating undercooked meat containing pseudocysts
- Congenital toxoplasmosis occurs in mothers with primary infection during or shortly before pregnancy or from reactivation of latent infection in immunocompromised pregnant women
- Higher risk of vertical transmission during later stages of pregnancy, but infection is usually mild or subclinical
- Maternal infection in first trimester less likely to infect fetus but fetal damage is more severe

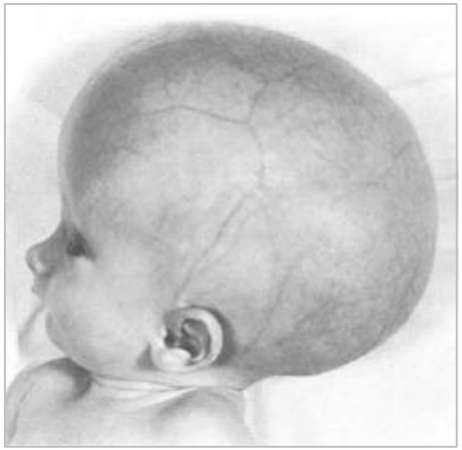
Risk of Transmission

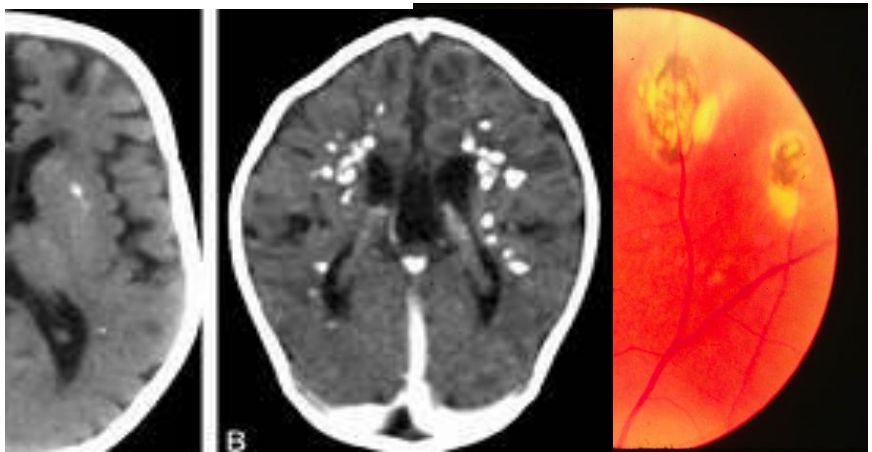
Maternal Infection	Neonatal Infection	
Trimester	Infected	Symptomatic Disease
1st	5-15%	50%
2nd	25-40%	25%
3rd	30-80%	3%

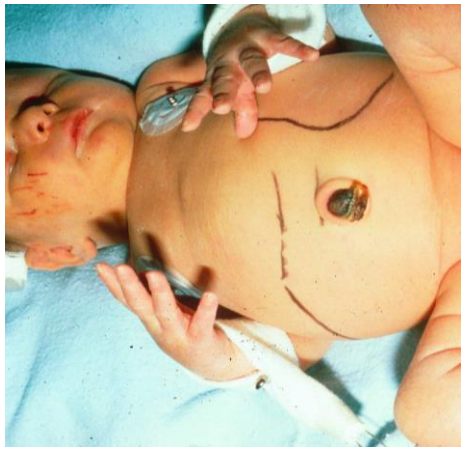
Tian C et al. NeoReviews 2010;.11 (8); e436; ; Guerina N. Congenital toxoplasmosis: Clinical features and diagnosis. UptoDate 2018

Clinical Manifestations of Congenital Toxoplamosis

Classic TRIAD:	• Microcephaly
• Hydrocephalus	• Hepatosplenomegaly
• Diffuse cerebral calcifications	• Anemia
	• Thrombocytopenia
• Chorioretinitis	• Jaundice







Diagnosis of Congenital Toxoplasmosis

Diagnostic Test	Prenatal	Postnatal
Serology	T. gondii specific IgM or IgA in fetal blood; IgG avidity test in combination with IgM (more sensitive)	T. gondii specific IgM or IgA within 1st 6 mos of life; increasing T. gondii IgG during 1st yr of life and persisting >1 yr of age
Nucleic Acid Test (PCR)	T. gondii DNA in amniotic fluid	T gondii DNA detection in CSF
Isolation in tissue or blood	Detection of parasite in amniotic fluid or fetal blood	Isolation of parasite from placenta, umbilical cord, blood

Tian C et al. NeoReviews 2010;.11 (8); e436; del Pizzo J. Pediatrics in Review 2011;32;537

Treatment of Congenital Toxoplasmosis

Drug of choice	Alternative
PYRIMETHAMINE 2 mg/kg (max 50 mg) once daily for 2 days; then 1 mg/kg (max 25 mg) once daily for six mos; then 1 mg/kg (maximum 25 mg) 3 times per week to complete one year of therapy	four 21-day cycles of PYRIMETHAMINE-SULFADIAZINE interrupted with 30 days of SPIRAMYCIN
PLUS SULFADIAZINE 100 mg/kg per day divided in 2 doses daily for one year	For infants with sulfadiazine allergy or G6PD deficiency: Clindamycin 20 to 30 mg/kg per day divided in 4 doses (in combInation with PYRIMETHAMINE)
PLUS FOLINIC ACID supplement 10 mg 3 times per week during and for one week after pyrimethamine therapy	

Guerina N. Congenital toxoplasmosis: Treatment, outcome, and prevention. UptoDate 2018

Meta-analysis on Efficacy of Anti-Toxoplasma Medicines in Humans

Drug	OUTCOME		
	Pooled Negative Conversion Rate	Pooled Cure Rate in Toxo enceph	Vertical transmission rate
Spiramycin ± Pyrimethamine-Sulfadiazine	83.4%		9.9%
Azithromycin	82.5%		
Traditional Chinese medicine (TCM)	85.5%		
Pyrimethamine- Sulfadiazine		49.8%	
TMP/SMX		59.9%	
Sulfonamide ± other drugs		49.4%	
Pyrimethamine-Clindamycin		47.6%	

Wei HX et al. A Systematic Review and Meta-Analysis of the Efficacy of Anti-Toxoplasma gondii Medicines in Humans. PLoS ONE 2015; 10(9): e0138204..

Congenital CMV Infection

- **Most likely sources of infection for pregnant women are young children and infected sexual partners; viral shedding persists for years**
- **Primary infection results in greater risk of viral transmission and greater fetal damage infection**
- **Symptomatic infection may also result from reactivation during pregnancy or reinfection by a new CMV strain**

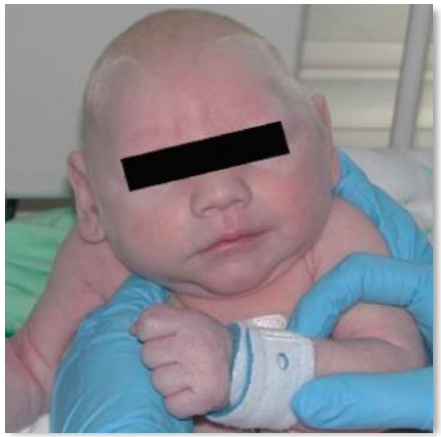
Risk of Transmission

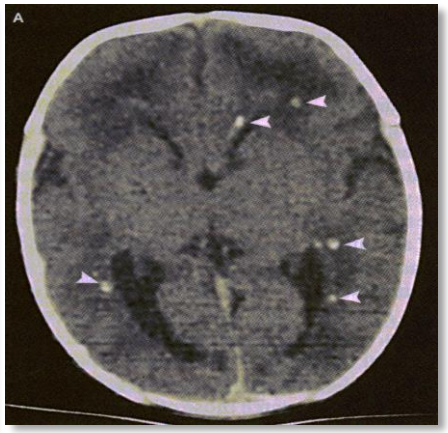
Maternal Infection	Neonatal Infection		
	Infected	Symptomatic Disease	Asymptomatic but develop Subsequent sequelae
Primary	30-40%	10-15%	5-15%
Recurrent/Reinfection	0.2-2.2%	0-1%	8%

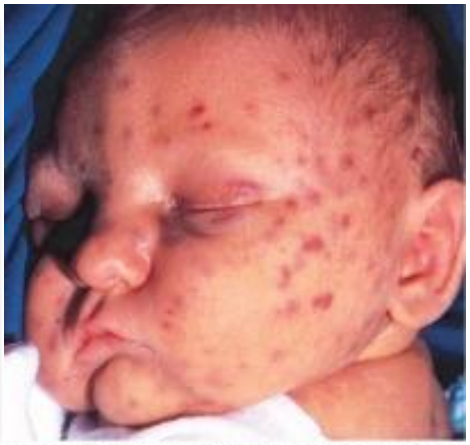
Emery VC and the neonate. F1000 Research 2017; Fowler K et al. Seminars Perinatology 2018;
Ravello MG et al. Clinical Microbiology ReviewSs 2002: 680–715

Clinical Manifestations of Congenital CMV Infection

• Classic TRIAD:	• Low birth weight
• Microcephaly	• Rash : petechiae, purpura, ecchymoses; "Blueberry muffin rash"
• Intracranial calcifications	
• Chorioretinitis	• Thrombocytopenia
• Neurodevelopmental delay	• Pneumonia
• Cognitive impairment	• Hepatosplenomegaly
• Sensorineural hearing loss	• Jaundice







Diagnosis of Congenital CMV Infection

Diagnostic Test	Prenatal	Postnatal
Viral Culture	Viral isolation from amniotic fluid	Viral isolation from urine or saliva obtained w/in 3 wks of age
Rapid culture (shell vial assay or shell vial culture)		Enhanced culture method for early antigen production in urine or saliva obtained w/in 3 wks of life
Nucleic Acid Test (PCR)	CMV-DNA in amniotic fluid and fetal blood	CMV DNA in blood or urine or saliva w/in 3 wks of age
Serology	CMV IgM and IgG avidity index (low= recent infection; high = past infection)	Serum for CMV-specific IgM (+ in 20-70%); Fourfold rise in CMV-specific IgG

1.Saldan A et al.. J Clin Microbiol 2017; 55:693–702.; 2. Gail J Demmler-Harrison,Congenital cytomegalovirus infection: Clinical features and diagnosis. UpToDate 2018. .

Treatment of Congenital CMV Infection

- **Indications:**
  - **Severe symptomatic infants with disseminated disease or CNS involvement**
  - **32 weeks gestation and < 1 month of age**
- **Antiviral therapy - should be started w/in first month of life**
  - **Ganciclovir 6 mg/kg every 12h IV x 6 weeks, followed by oral Valganciclovir 16mg/kg every 12h**
  - **Total duration: 6 months therapy more beneficial for long- term hearing and neurodevelopmental outcomes than 6 weeks treatment**
  - **Consider prolonging treatment until 12 month for those with persistent viremia, retinitis, or liver disease**

Kimberlin DW et al. N Engl J Med. 2015; 372(10): 933–43;

Alternative treatment for Congenital CMV Infection

- **For suspected or confirmed ganciclovir-resistant CMV strains or toxicity to gancyclovir:**
  - **Foscarnet 60 mg/kg per dose IV every 8 hours for 2-3 weeks, followed by maintenance therapy at 90 mg/kg per dose once daily for 2-3 weeks.**
  - **Cidofovir 5 mg/kg per dose IV every 7 days for 2 weeks, then every other week for an additional 4 weeks or 1 mg/kg per dose 3 times per week**

Treatment for Congenital CMV

- **Unclear benefit of Antiviral Treatment [1]**
  - **Asymptomatic infants**
  - **Children with isolated sensorineural hearing loss (≥20 dB in one or both ears)**
  - **Infants up to 12 weeks of age with congenital CMV infection**
  - **In-utero treatment with high-dose valacyclovir (8 g/day)**
- **New antiviral drug: [2]**
  - **Letermovir - first US-FDA-approved CMV DNA terminase complex inhibitor for post-transplantation CMV or resistance to standard antiviral**

1. Kimberlin DW et al.. N Engl J Med. 2015; 372(10): 933–43; 2. Amir J et al. Eur J Pediatr. 2010. Epub ahead of print)

Prevention of Congenital CMV Infection

- **Universal precautions: [1,2]**
  - **infected infants excrete virus in the urine for first 2-3 years of life**
  - **counseling women about CMV prevention during pregnancy: Avoid contact with the saliva and urine of young children**
- **Investigational :**
  - **CMV hyper- immune globulin(HIG) to prevent intrauterine CMV transmission in women with primary CMV infection during pregnancy [3]**
  - **CMV vaccine – recombinant CMV glycoprotein B (gB) vaccine administered in seronegative women showed an approximately 50% reduction in maternal infection[4]**

1. Kimberlin DW et al. N Engl J Med. 2015; 372(10): 933–43; .2. Fowler K et al. Seminars Perinatology 2 018 3. Pass RF et al. nN Engl J Med. 2009; 360(12): 1191–9; 4. Revello MG et al. N Engl J Med. 2014; 370(14): 1316–26

Congenital Rubella Syndrome

- **Incidence of CRS depends on the prevalence of rubella susceptible women of childbearing age in the population (≈10-20%)**
- **Nonimmune mother with primary rubella infection in the first trimester of pregnancy has higher risk of vertical transmission or rubella infection (80%–90%)**
- **Rubella infection during first trimester is associated with the most severe birth defects (CRS)**

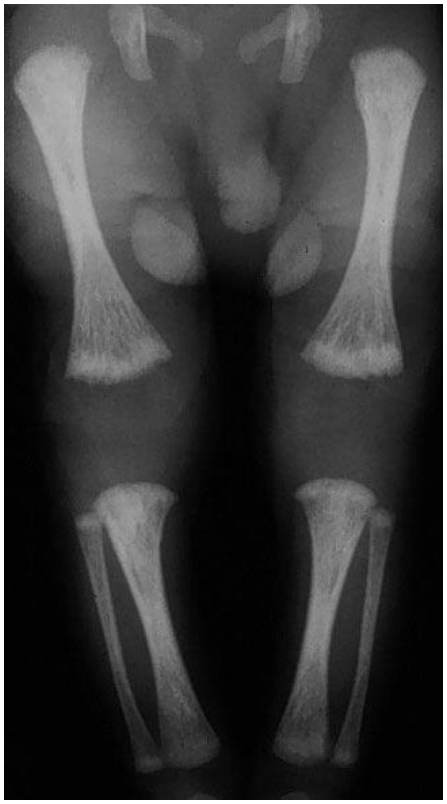
Risk of Transmission

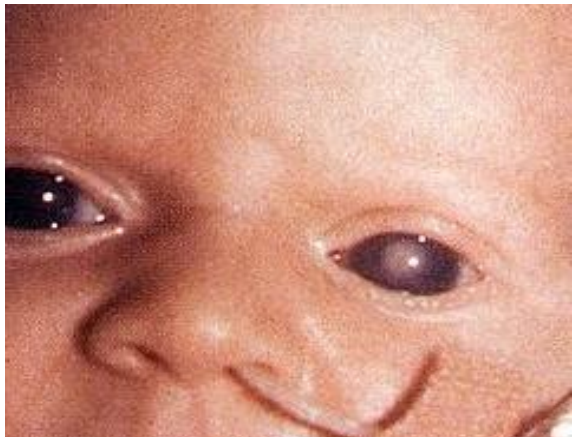
Maternal Infection	Neonatal Infection	
Trimester	Infection	Symptomatic (CRS)
1st	90%	85%
2nd	50%	20-30%
3rd	low	5%

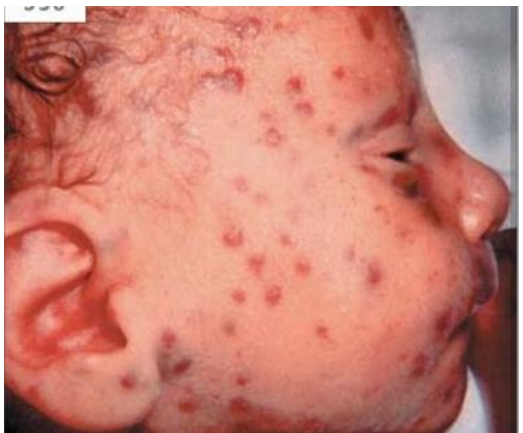
Miller E et al.. Lancet 1982; 2:781. 13; Cooper LZ. Rev Infect Dis 1985; 7 Suppl 1:S2; Grillner Lvet al.. Scand J In fect Dis 1983; 15:321. 53; Enders G et al. Lancet 1988; 1:1445.

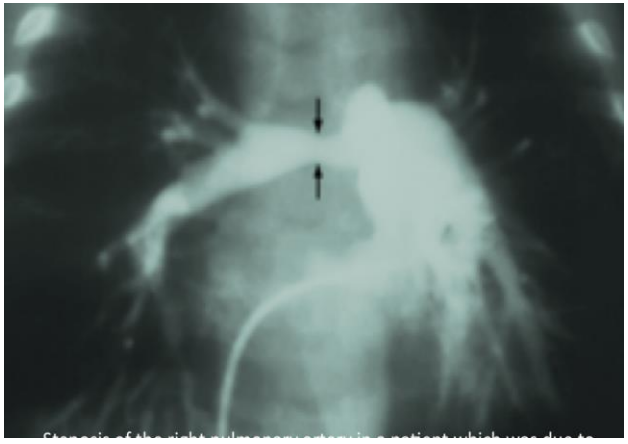
Clinical Manifestations of Congenital Rubella

• Eye abnormalities:	• Microcephaly
• Cataracts	• Meningoencephalitis
• Retinopathy (pigmentary)	• Radiolucent Bone lesions (osteitis)
• Glaucoma	• Blueberry muffin rash; purpura
• Microphthalmia	
• Congenital Heart Disease: PDA, PS	• Hepatosplenomegaly
• Sensorineural hearing loss	• Thrombocytopenia









Sequelae of Congenital Rubella Infection

Organ system	Late/Delayed Manifestations
CNS	Progressive sensorineural hearing loss; panencephalitis, learning problems, ataxia
Endocrine disorders	Diabetes, thyroid disease, growth hormone deficiency
Eye problems	Pigmentary retinopathy, cataract, glaucoma, keratic precipitates, keratoconus, corneal hydrops, microphthalmos
Vascular effects	Coronary, cerebral, and peripheral vascular disease in adulthood
Immune defects	Repeated infections, defective T-cell response with associated autoimmune phenomena

Dobson SR. Congenital rubella syndrome: Clinical features and diagnosis. UpToDate. 2018

Diagnosis of Congenital Rubella

Diagnostic Test	Procedure and Specimen
Serology	Rubella specific IgM in serum, up to 3 mos of age; Rising or stable rubella specific IgG serum levels between 6 -12 mos of age
Viral culture	Rubella virus isolation from throat or nasopharyngeal swab, urine, CSF, lens, blood
Nucleic Acid Test (PCR)	Rubella RNA on throat or nasopharyngeal swab, urine, CSF, lens, blood

de Jong EP, et al. Arch Dis Child Educ Pract Ed 2013;98:93–98.

Prevention of Congenital Rubella

- **No specific treatment available**
- **MMR Vaccination in childhood**
  - **Antibody induced in 95% after 1 dose if given at 12 mos; 2 dose MMR schedule captures primary vaccine failures**
- **All infants with CRS are considered contagious until at least 1 year of age, unless 2 cultures of clinical specimens obtained 1 month apart are negative for rubella virus after 3 months of age**

Congenital Syphilis

- **Risk for congenital syphilis is dependent on the stage of maternal infection at the time of exposure during pregnancy**
- **Untreated maternal syphilis: 40% of pregnancies result in stillbirths, abortions, perinatal deaths**
- **Untreated congenital SY: 50% of infected infants will develop sequelae or complications**

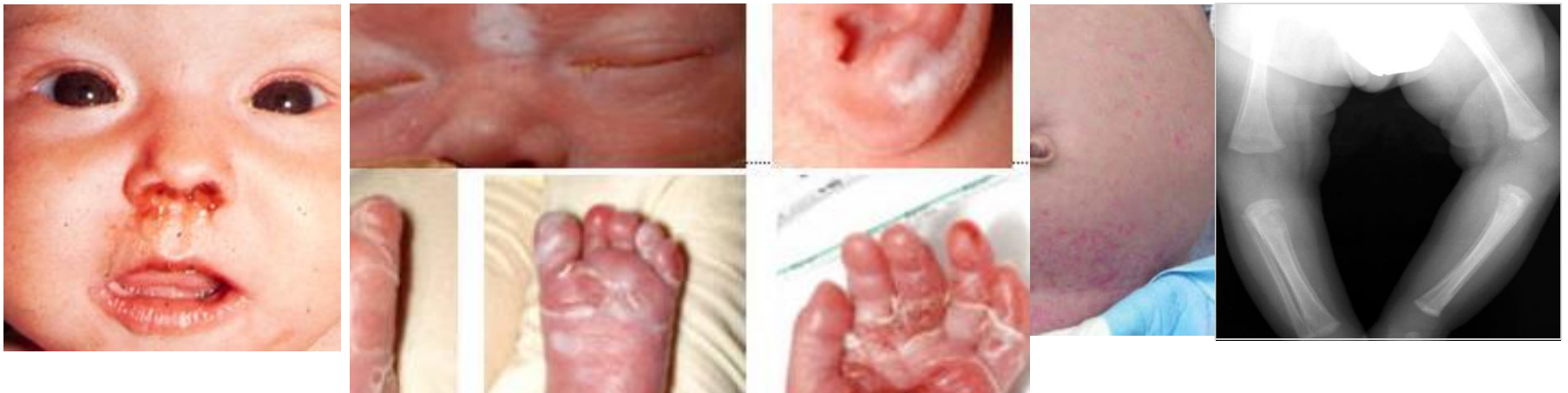
Risk of Transmission

Maternal Infection	Neonatal Infection
Primary	70-100%
Secondary	60-100%
Latent	30%

Ravello MG et al. Clinical Microbiology ReviewS, 2002: 680–715

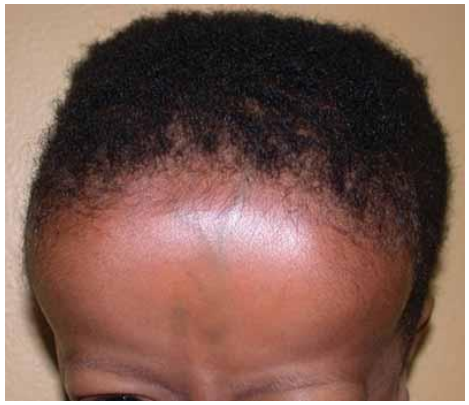
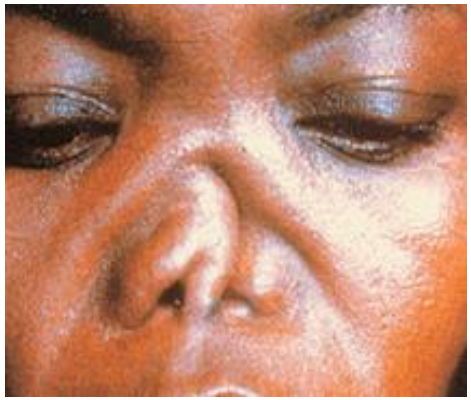
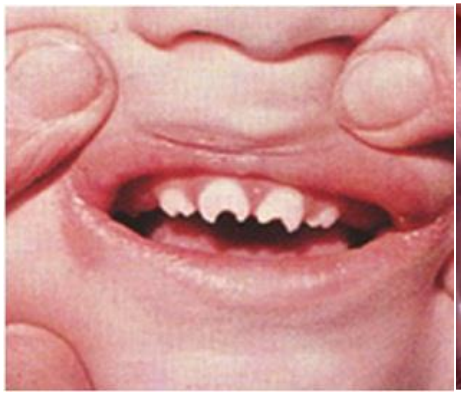
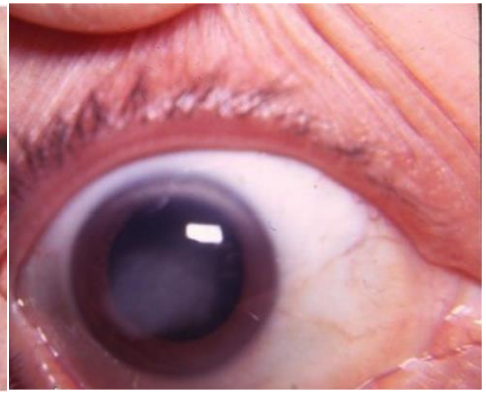
Early Clinical Manifestations of Congenital Syphilis

Low birth weight	Pseudoparalysis
Pneumonitis	Lymphadenopathy
Hepatosplenomegaly	Anemia (hemolytic)
Jaundice	Thrombocytopenia
Persistent rhinitis (snuffles)	Hemorrhage
Maculopapular or bullous rash (palms, soles, diaper area)	Skeletal abnormalities (osteochondritis, periostitis)



Late Clinical Manifestations of Congenital Syphilis

Hydrocephalus	Hutchinson' teeth
Frontal bossing	Sensorineural Hearing loss
Saddle shape nose	Keratitis
High arched palate	Glaucoma
Short maxilla	Perioral fissures

Diagnosis of Congenital Syphilis

Diagnostic Test	Specimen
Serology	NON-TREPONEMAL TEST : RPR (rapid plasma reagin) ; VDRL (Veneral Disease Research Laboratory) • Highly sensitive; low specificity • false positives in collagen vascular disease
	SPECIFIC TREPONEMAL TEST: FTA-ABS (Fluorescent Treponemal Antibody Absorption; TP-PA (Treponemal pallidum particle agglutination) • Treponemal tests remain positive for life • FTA ABS is not 100% specific • false positives in other spirochetal diseases
Microscopy	Dark-field microscopy or direct fluorescent antibody (DFA) test to identify T. pallidum in the umbilical cord, placenta, nasal discharge, or skin lesion material

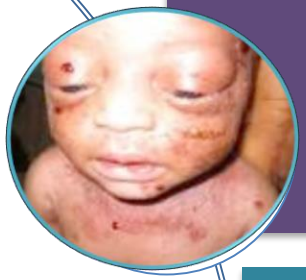
WHO guidelines for the treatment of Treponema pallidum (syphilis).2016

Treatment of Congenital Syphilis

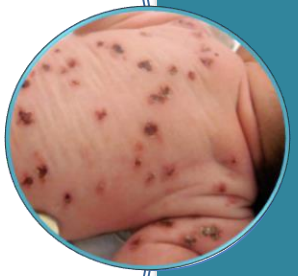
Indication	Recommended Drug
Infants with confirmed congenital syphilis OR clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimen	AQUEOUS CRYSTALLINE PENICILLIN ≤ 7days: 50,000 U/Kg every 12 hrs > 1 week : 50,000 U/Kg every 8 hrs >2yrs old: 200 000–300 000 U/kg/day Duration: 10 days * Plus Benzathine penicillin 50,000 U/kg IM after 10 days course of Aqueous crystalline penicillin Alternative: Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days
Infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection	BENZATHINE PENICILLIN G 50 000 U/kg/day single dose intramuscularly

AAP Red Book 2015 30th ed 2015; Doson SR. Congenital syphilis: Evaluation, management, and prevention. UpToDate 2018

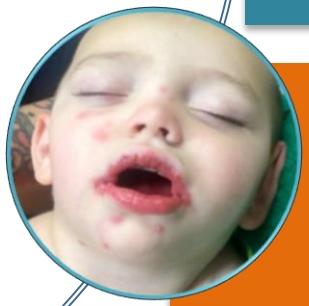
HSV Infection in the Newborn: Periods of Acquisition



Congenital (≈ 5%) : transmitted in-utero from maternal viremia associated with primary HSV infection during pregnancy



Perinatal (≈ 85%) : acquired intrapartum from infected genital secretions or after prolonged rupture of membranes in mothers with active HSV infection at or near the time of delivery.



Postnatal (≈ 10-15%) : acquired from breastfeeding or non-maternal sources after delivery, e.g. caretaker with active HSV-1 infection

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Congenital HSV Infection

- **Risk of infection is greater in infants born to mothers with Primary 1st episode genital HSV infection at delivery compared to those who have antibodies to a different HSV type (Nonprimary first episode), and less in cases of recurrent infections with the same type**
- **60%– 80% of mothers of children born with neonatal HSV infection are asymptomatic with no history of genital herpes**

Risk of Transmission

Maternal Infection at delivery	Neonatal Infection
Primary Infection	25-60%
Nonprimary HSV	24-31%
Recurrent Infection	<2%

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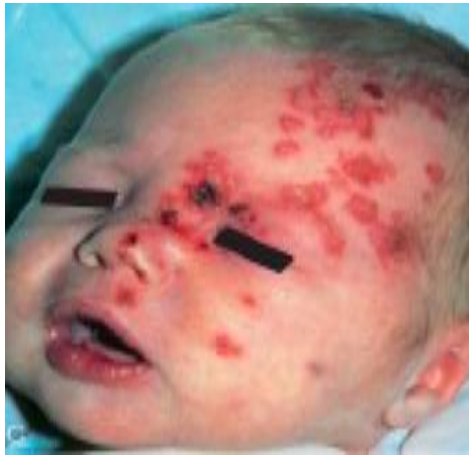
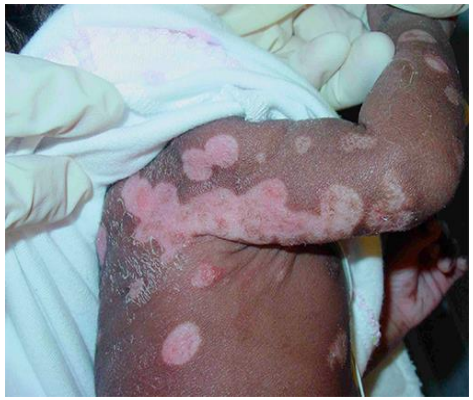
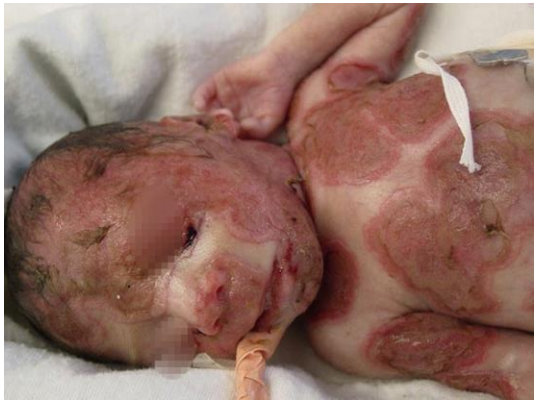
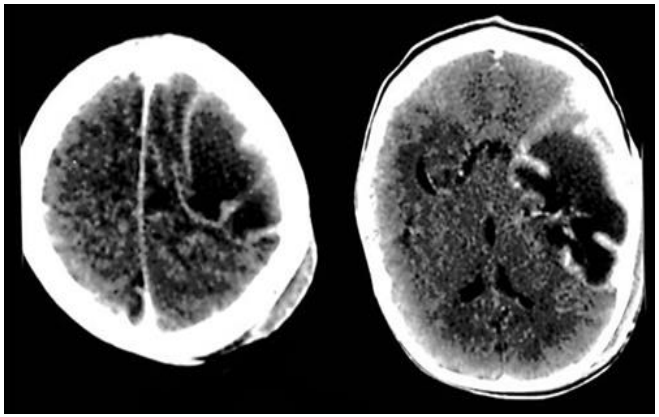
Intrauterine (Congenital) HSV Infection

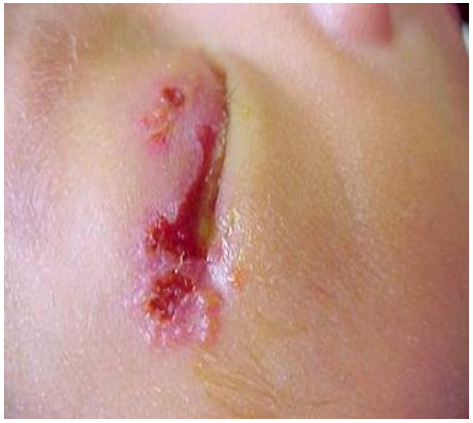
Skin lesions	**skin vesicles, ulcerations, or scarring**
Eye damage	**periorbital skin vesicles, keratoconjunctivitis, cataracts, chorioretinitis, retinal dysplacia**
CNS manifestations	**microcephaly or hydranencephaly; aseptic meningitis, meningoencephalitis**











Clinical Categories of Neonatal HSV Infection

Category	Manifestations
Localized skin, eye, mouth (≈ 45%)	Muco-cutaneous vesicular lesions of the skin, eye, mucous membrane; other skin manifestations (pustules, erythema, or ulcerations); 50-60% may progress to CNS or disseminated disease if not treated early.
CNS disease (≈ 30%)	Brain abnormalities (microcephaly; hydranencephaly) w/ or w/o SEM; aseptic meningitis, meningoencephalitis
Disseminated disease (≈ 25%)	Sepsis-like presentation, multiple organs involvement (liver, pneumonia, blood, multiple organ system); may have SEM and/or CNS involvement

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Diagnosis of Congenital or Neonatal HSV

Diagnostic Test	Procedure and Specimen
HSV Culture	Isolation of HSV in surface cultures or skin lesion swabs/scraping mouth, NP, eyes, urine, blood, stool, rectum, CSF
Nucleic Acid Test	HSV DNA PCR in the blood, amniotic fluid, CSF, body fluids
Direct fluorescent antibody assay(DFA)	rapid detection of HSV antigens in skin vesicle scrapings and mucous membrane lesions
Serology	HSV IgM serology
Histopathology (Tzank smear)	Skin tissue scraping - Multinucleate giant cells with intranuclear inclusions

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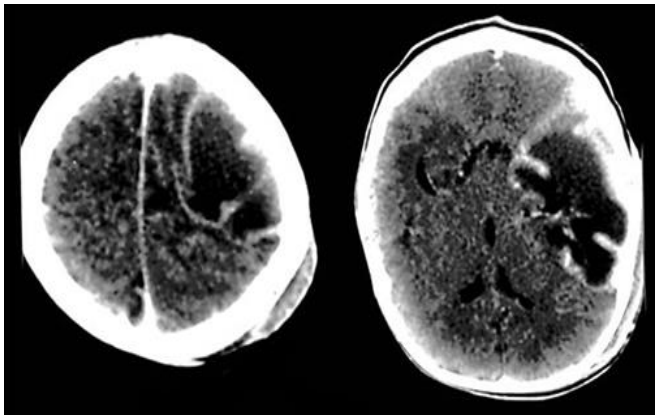
Ancillary Diagnostic tests for HSV Meningoencephalitis

- **Electroencephalogram (EEG)**
  - **periodic or quasiperiodic epileptiform discharges**
  - **Foci are predominantly temporal, frontal, or central in distribution.**
  - **In older infants, hemispheric, monomorphic slow waves appear interspersed on a low-voltage or suppressed background.**

- **Neuroimaging studies**
  - **CT scan : parenchymal brain edema or abnormal attenuation, hemorrhage, or destructive lesions**
  - **Classic temporal lobe destructive lesions, multifocal lesions or limited to the brainstem or cerebellum**



Treatment of Congenital or Neonatal HSV Infection

Antiviral of Choice	Alternative
Acyclovir 20 mg/kg/dose q 8hrs IV	Ganciclovir 6 mg/kg q 12hrs IV for infants ≤90 days of age; 5 mg/kg every 12 hours IV for infants >90 days
	Foscarnet 60 mg/kg every 12 hours IV
For ocular involvement: Topical ophthalmic solution (eg, 1% trifluridine, 0.1% idoxuridine, or 0.15% ganciclovir)	

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Duration of Treatment of Congenital or Neonatal HSV

- **Localized Skin-Eyes-Mouth: 14 days**
- **CNS or Disseminated: ≥ 21 days**
  - **Repeat blood and CSF HSV PCR at the end of the 21-day**
  - **Continue IV acyclovir until negative HSV PCR; evaluate for primary immune disorder**
- **Acyclovir therapy should be administered for infants with negative virologic studies in whom neonatal HSV is strongly suspected, until results of HSV workup are known**
- **Asymptomatic infants delivered vaginally to women with active genital HSV:**
  - **First episode genital HSV: Acyclovir for 10 days**
  - **Recurrent maternal HSV : discontinue acyclovir at 48 to 72 hours if HSV PCR and viral studies are negative.**

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Oral suppressive therapy following HSV Treatment

- **Following parenteral treatment for all forms of neonatal HSV disease (SEM, CNS, and disseminated disease)**
- **Suppressive therapy reduces cutaneous recurrences and is associated with improved neurologic outcomes in infants with CNS disease**
- **Acyclovir 300 mg/m^2 per dose orally 3 times per day for 6 months**

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Key Points: Congenital Infections

- **Congenital infections account for significant fetal and neonatal mortality and morbidity, including long term sequelae and permanent disability**
- **Clinical presentation of congenital infections can be seen soon after birth, during infancy, childhood or later in adulthood**
- **A high index of suspicion for congenital infection and awareness of the prominent features can help to facilitate early diagnosis and tailor appropriate diagnostic evaluation**
- **For many of these pathogens, prevention strategies are available, including treating infected pregnant women to prevent vertical transmission to their offspring**
- **In equivocal cases, decisions regarding treatment must weigh the risks and benefits of initiating treatment**