Overview of TORCH infections

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INTRODUCTION

Infections acquired in utero or during the birth process are a significant cause of fetal and neonatal mortality and an important contributor to early and later childhood morbidity. The infected newborn infant may show abnormal growth, developmental anomalies, or multiple clinical and laboratory abnormalities [1]. The TORCH acronym is well recognized in the field of neonatal/perinatal medicine [2]. It includes:

- Toxoplasmosis
- Others (syphilis, Zika virus, varicella-zoster virus)
- Rubella
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)

Other well-described causes of in utero infection include enteroviruses, parvovirus B19, and lymphocytic choriomeningitis virus. Thus, broadening the "other" category to include additional pathogens has been proposed [3,4].

An overview of the clinical features of specific TORCH infections and an approach to the infant with suspected intrauterine infection will be provided below. The individual TORCH infections are discussed in more detail separately:

- (See "Toxoplasmosis and pregnancy" and "Congenital toxoplasmosis: Clinical features and diagnosis" and "Congenital toxoplasmosis: Treatment, outcome, and prevention".)

- (See "Syphilis in pregnancy" and "Congenital syphilis: Clinical features and diagnosis" and "Congenital syphilis: Evaluation, management, and prevention".)
- (See "Varicella-zoster virus infection in pregnancy" and "Varicella-zoster infection in the newborn".)
- (See "Zika virus infection: Evaluation and management of pregnant women" and "Congenital Zika virus infection: Clinical features, evaluation, and management of the neonate".)
- (See "Rubella in pregnancy" and "Congenital rubella".)
- (See "Cytomegalovirus infection in pregnancy" and "Congenital cytomegalovirus infection: Clinical features and diagnosis" and "Congenital cytomegalovirus infection: Management and outcome".)
- (See "Genital herpes simplex virus infection and pregnancy" and "Neonatal herpes simplex virus infection: Clinical features and diagnosis" and "Neonatal herpes simplex virus infection: Management and prevention".)
- (See "Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention", section on 'Neonates'.)
- (See "Parvovirus B19 infection during pregnancy".)

SCREENING FOR TORCH INFECTIONS

Screening during pregnancy — The practice of screening pregnant women for TORCH infections varies geographically. In the United States, the American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women be screened for rubella and syphilis at the first prenatal visit. In other countries, pregnant women also may be screened for toxoplasmosis. Prenatal screening recommendations are discussed in greater detail separately. (See "Prenatal care: Initial assessment", section on 'Standard panel'.)

Newborn screening — Asymptomatic infants generally are not screened for congenital infections, with the following exceptions:

- Toxoplasmosis – Some European countries and a few select states in the United States have adopted universal newborn screening for toxoplasmosis [5-7]. This is discussed

separately. (See "Congenital toxoplasmosis: Clinical features and diagnosis", section on 'Newborn screening'.)

- Cytomegalovirus (CMV) – Targeted newborn screening for congenital CMV infection (ie, testing infants who fail the newborn hearing screen) is performed in some institutions. Universal screening has been proposed, but the most reliable and cost-effective method for screening has not been established, and this practice has not gained widespread adoption. This is discussed in greater detail separately. (See "Congenital cytomegalovirus infection: Clinical features and diagnosis", section on 'Newborn screening for congenital cytomegalovirus'.)

Although identification of immunoglobulin M (IgM) antibodies in the newborn is suggestive of congenital infection (because IgM antibodies do not cross the placenta), indiscriminate screening for TORCH infections with a battery of "TORCH titers" is costly and has a poor diagnostic yield [8-11]. Our preferred approach involves testing of infants with suspected congenital infections for specific pathogens based upon their clinical presentation [12]. (See 'Approach to the infant with suspected intrauterine infection' below.)

CLINICAL FEATURES OF TORCH INFECTIONS

Congenital toxoplasmosis — Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. Primary infection during pregnancy can result in congenital disease. (See "Toxoplasmosis and pregnancy".)

Most infants with congenital toxoplasmosis are asymptomatic or without apparent abnormalities at birth. Although subclinical disease is the rule, signs present at birth may include fever, maculopapular rash, hepatosplenomegaly, microcephaly, seizures, jaundice, thrombocytopenia, and, rarely, generalized lymphadenopathy (picture 1). The so-called classic triad of congenital toxoplasmosis consists of chorioretinitis, hydrocephalus, and intracranial calcifications (image 1).

Infants with subclinical congenital toxoplasmosis who do not receive treatment have an increased risk of long-term sequelae. The most common late finding is chorioretinitis (picture 2), which can result in vision loss. Intellectual disability, deafness, seizures, and spasticity also can be seen in a minority of untreated children.

The diagnosis, management, and prevention of congenital toxoplasmosis are discussed separately. (See "Congenital toxoplasmosis: Clinical features and diagnosis" and "Congenital toxoplasmosis: Treatment, outcome, and prevention".)

Congenital syphilis — Congenital syphilis occurs when the spirochete *Treponema pallidum* is transmitted from a pregnant woman to her fetus. Infection can result in stillbirth, hydrops fetalis, or prematurity and associated long-term morbidity. Because of this morbidity, great emphasis has been placed on routine syphilis screening of all pregnant women. (See "Syphilis in pregnancy", section on 'Maternal screening'.)

The incidence of congenital syphilis reflects the rate of syphilis in women of childbearing age. Many congenital cases develop because the mother received no prenatal care, no penicillin treatment, or inadequate treatment before or during pregnancy.

Most neonates with congenital syphilis are asymptomatic at birth. Overt infection can manifest in the fetus, the newborn, or later in childhood. Clinical manifestations after birth are divided arbitrarily into early (≤2 years of age (table 1)) and late (>2 years of age (table 2)).

The diagnosis, management, and prevention of congenital syphilis are discussed separately. (See "Congenital syphilis: Clinical features and diagnosis" and "Congenital syphilis: Evaluation, management, and prevention".)

Congenital varicella syndrome — Most cases of congenital varicella syndrome occur in infants whose mothers were infected between 8 and 20 weeks gestation. Characteristic findings in neonates may include:

- Cutaneous scars, which may be depressed and pigmented in a dermatomal distribution
- Cataracts, chorioretinitis, microphthalmos, nystagmus
- Hypoplastic limbs
- Cortical atrophy and seizures

The clinical manifestations and diagnosis of congenital varicella syndrome are discussed separately. (See "Varicella-zoster virus infection in pregnancy", section on 'Fetal effects of VZV infection' and "Varicella-zoster virus infection in pregnancy", section on 'Congenital varicella syndrome'.)

Congenital Zika syndrome — Congenital Zika virus infection is associated with severe congenital anomalies; the greatest risk of serious fetal sequelae is with first-trimester infection. The principal clinical features of congenital Zika syndrome (CZS) include (picture 3):

- Microcephaly
- Facial disproportion
- Hypertonia/spasticity and hyperreflexia
- Seizures

- Irritability
- Arthrogryposis
- Ocular abnormalities
- Sensorineural hearing loss
- Neuroradiologic abnormalities (eg, intracranial calcifications, ventriculomegaly (image 2A-B))

The features of CZS have been described in case reports and small case series. However, the full spectrum of the syndrome is still evolving. The clinical manifestations and diagnosis of congenital Zika virus infection are reviewed in greater detail separately. (See "Congenital Zika virus infection: Clinical features, evaluation, and management of the neonate".)

Congenital rubella — Rubella typically causes a mild, self-limited illness; its major impact occurs during pregnancy, when it can have devastating effects on the developing fetus.

Congenital rubella syndrome (CRS) is rare in developed countries with established rubella immunization programs. It is no longer endemic in the United States, although an average of five to six cases are reported to the National Congenital Rubella Registry each year, usually in infants whose mothers emigrated from countries without rubella immunization programs.

Clinical manifestations of CRS include sensorineural deafness, cataracts, cardiac malformations (eg, patent ductus arteriosus, pulmonary artery hypoplasia), and neurologic and endocrinologic sequelae (table 3). Neonatal manifestations may include growth retardation, radiolucent bone disease (not pathognomonic of congenital rubella), hepatosplenomegaly, thrombocytopenia, purpuric skin lesions (classically described as "blueberry muffin" lesions (picture 4) that represent extramedullary hematopoiesis), and hyperbilirubinemia.

The diagnosis, management, and prevention of CRS are discussed separately. (See "Congenital rubella".)

Congenital cytomegalovirus — Congenital cytomegalovirus (CMV) infection is the leading cause of nonhereditary sensorineural hearing loss and can cause other long-term neurodevelopmental disabilities, including cerebral palsy, intellectual disability, vision impairment, and seizures.

CMV infection is common worldwide. Despite its listing as the fourth infection in the TORCH designation, CMV has emerged as the most common congenital viral infection. Maternal CMV infection during pregnancy most often results from close contact with young children, particularly children attending daycare centers.

At birth, most infants with congenital CMV are asymptomatic, but approximately 10 percent have symptoms. Clinical manifestations include petechiae (picture 5), jaundice at birth, hepatosplenomegaly, thrombocytopenia, small size for gestational age, microcephaly, intracranial calcifications (image 3A-B), sensorineural hearing loss, chorioretinitis, and seizures.

Sensorineural hearing loss is the most common sequela of congenital CMV and is detected at birth in approximately one-third of infants with symptomatic disease. Many infants with congenital CMV infection are identified solely on the basis of a failed newborn hearing screen. Delayed-onset hearing loss also occurs, although the risk is lower if antiviral treatment is provided in infancy.

The diagnosis, management, and prevention of congenital CMV are discussed separately. (See "Congenital cytomegalovirus infection: Clinical features and diagnosis" and "Congenital cytomegalovirus infection: Management and outcome" and "Cytomegalovirus infection in pregnancy", section on 'Strategies for prevention of maternal and/or fetal infection'.)

Herpes simplex virus — Genital herpes simplex virus (HSV) infection during pregnancy poses a significant risk to the developing fetus and newborn.

- **Perinatally acquired infection** – Most cases of neonatal HSV infection are perinatally acquired. HSV is transmitted to an infant during birth, primarily through an infected maternal genital tract. The risk of transmission is greater with primary HSV infection acquired during pregnancy compared with reactivation of previous infection. Among mothers with primary infection, acquisition near the time of labor is the major risk factor for transmission to the neonate. (See "Genital herpes simplex virus infection and pregnancy".)

  Most newborns with perinatally acquired HSV appear normal at birth, although many are born prematurely. HSV infection in newborns usually develops in one of three patterns, which occur with roughly equal frequency (table 4):

  - Localized to the skin, eyes, and mouth
  - Localized central nervous system (CNS) disease
  - Disseminated disease involving multiple organs

  The initial manifestations of CNS disease frequently are nonspecific and include temperature instability, respiratory distress, poor feeding, and lethargy; they may progress quite rapidly to hypotension, jaundice, disseminated intravascular coagulation, apnea, and shock. Vesicular skin lesions (picture 6A-C) may or may not be present and

develop late in some patients; the absence of skin lesions complicates recognition of the infection. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis".)

- **Congenital (in utero) infection** – Intrauterine HSV infection is rare and usually results from maternal viremia associated with primary HSV infection during pregnancy. Live-born infants with congenital HSV infection may exhibit a characteristic triad of skin vesicles, ulcerations, or scarring (picture 7); eye damage; and severe CNS manifestations, including microcephaly or hydranencephaly. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Intrauterine HSV'.)

The diagnosis, management, and prevention of neonatal HSV infections are discussed separately. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Evaluation and diagnosis' and "Neonatal herpes simplex virus infection: Management and prevention".)

APPROACH TO THE INFANT WITH SUSPECTED INTRAUTERINE INFECTION

Overview — A high index of suspicion for congenital infection and awareness of the prominent features of the most common congenital infections can help to facilitate early diagnosis and tailor appropriate diagnostic evaluation (table 5). For many of the infections discussed in the previous sections, timely diagnosis is crucial to ensure that appropriate therapy is initiated. It also allows for family counseling regarding the prognosis, so that an appropriate care plan can be put in place.

Our preferred approach to testing infants suspected of having a congenital infection is to test only for select pathogens based upon specific clinical findings (table 5) [3,4]. We discourage the practice of indiscriminate screening of infants who have findings compatible with congenital infection with a battery of "TORCH titers" because such an approach is costly and has a poor diagnostic yield [8-13]. In addition, the number of pathogens responsible for in utero and perinatal infections continues to expand such that the approach of indiscriminate testing has become challenging. The optimal approach remains uncertain, and practice varies considerably [14].

Clinical suspicion — In some cases, intrauterine infection may be suspected on the basis of laboratory results obtained during pregnancy (eg, positive syphilis serology with increasing titers). In the absence of suggestive maternal laboratory results, intrauterine infection may be suspected in newborns with certain clinical manifestations or combinations of clinical manifestations including (but not limited to):

- Hydrops fetalis
- Microcephaly
- Seizures
- Cataract
- Hearing loss
- Congenital heart disease
- Hepatosplenomegaly
- Jaundice
- Rash
- Thrombocytopenia

These findings are not restricted to TORCH infections, and some of the features above may occur in other infections (eg, human parvovirus, Chagas disease) and in conditions other than intrauterine infection (eg, inborn errors of metabolism, Rh incompatibility, etc). Thus, the entire clinical constellation, including maternal history and exposures, must be taken into account when deciding to evaluate an infant for congenital infection.

Initial evaluation — The evaluation of a newborn with clinical findings compatible with intrauterine infection may include [15-17]:

- Review of maternal history (evidence of rubella immunity, syphilis serology, history of herpes simplex virus [HSV], exposure to cats, etc)
- Assessment of physical stigmata consistent with various intrauterine infections (table 5)
- Complete blood count and platelet count
- Liver function tests (particularly important in HSV infection)
- Radiographs of long bones
- Ophthalmologic evaluation
- Audiologic evaluation
- Neuroimaging
- Lumbar puncture

Specific evaluation — The results of the initial evaluation may help to determine whether evaluation for a specific pathogen (or pathogens) is warranted. Findings that are more prominent in particular infections, and may prompt evaluation for a specific pathogen, are listed in the table (table 5).

The diagnostic evaluation for specific infections is discussed separately:

- Congenital toxoplasmosis (see "Congenital toxoplasmosis: Clinical features and diagnosis", section on 'Evaluation')

- Congenital syphilis (see "Congenital syphilis: Clinical features and diagnosis")
- Congenital rubella (see "Congenital rubella", section on 'Evaluation')
- Congenital cytomegalovirus (CMV) (see "Congenital cytomegalovirus infection: Clinical features and diagnosis", section on 'Diagnostic approach')
- Congenital HSV (see "Neonatal herpes simplex virus infection: Clinical features and diagnosis", section on 'Evaluation and diagnosis')
- Congenital varicella (see "Varicella-zoster infection in the newborn", section on 'Diagnosis')
- Congenital enterovirus infection (see "Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention", section on 'Laboratory diagnosis')
- Congenital Zika virus infection (see "Congenital Zika virus infection: Clinical features, evaluation, and management of the neonate", section on 'Evaluation')

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: TORCH infections".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Avoiding infections in pregnancy (The Basics)")

- Beyond the Basics topic (see "Patient education: Avoiding infections in pregnancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **TORCH infections** – The TORCH acronym (which stands for **t**oxoplasmosis, **o**ther [syphilis, varicella, Zika virus], **r**ubella, **c**ytomegalovirus, and **h**erpes simplex virus) is well recognized in the field of neonatal and perinatal medicine. These intrauterine and perinatal infections contribute to fetal and infant mortality, and they are important causes of childhood morbidity. Infected newborns may show abnormal growth and development in conjunction with multiple clinical and laboratory abnormalities (table 5) (see 'Overview' above):

  - **Congenital toxoplasmosis** – The classic triad of congenital toxoplasmosis consists of chorioretinitis (picture 2), hydrocephalus, and intracranial calcifications (image 1); signs present at birth may include fever, maculopapular rash, hepatosplenomegaly, microcephaly, seizures, jaundice, thrombocytopenia, and, rarely, generalized lymphadenopathy (picture 1). However, most infants with congenital toxoplasmosis are asymptomatic or without apparent abnormalities at birth. (See "Congenital toxoplasmosis: Clinical features and diagnosis" and "Congenital toxoplasmosis: Treatment, outcome, and prevention".)

  - **Congenital syphilis** – Most neonates with congenital syphilis are asymptomatic at birth. Clinical manifestations after birth are divided arbitrarily into early (≤2 years of age (table 1)) and late (>2 years of age (table 2)). (See "Congenital syphilis: Clinical features and diagnosis" and "Congenital syphilis: Evaluation, management, and prevention".)

  - **Congenital varicella** – Characteristic features of congenital varicella infection include cutaneous scars, cataracts, chorioretinitis, microphthalmos, nystagmus, hypoplastic limbs, cortical atrophy, and seizures. (See "Varicella-zoster virus infection in pregnancy", section on 'Fetal effects of VZV infection' and "Varicella-zoster virus infection in pregnancy", section on 'Congenital varicella syndrome'.)

  - **Congenital Zika syndrome (CZS)** – Congenital Zika virus infection is associated with severe congenital anomalies; the greatest risk of serious fetal sequelae is with first-trimester infection. The principal clinical features of CZS include (picture 3) microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures,

irritability, arthrogryposis, ocular abnormalities, sensorineural hearing loss, and neuroradiologic abnormalities (eg, intracranial calcifications, ventriculomegaly (image 2A-B)). (See "Congenital Zika virus infection: Clinical features, evaluation, and management of the neonate".)

- **Congenital rubella syndrome (CRS)** – Clinical manifestations of CRS include sensorineural deafness, cataracts, cardiac malformations (eg, patent ductus arteriosus, pulmonary artery hypoplasia), and neurologic and endocrinologic sequelae. Neonatal manifestations may include growth retardation, radiolucent bone disease (not pathognomonic of congenital rubella), hepatosplenomegaly, thrombocytopenia, purpuric skin lesions (classically described as "blueberry muffin" lesions that represent extramedullary hematopoiesis), and hyperbilirubinemia. (See "Congenital rubella".)

- **Congenital cytomegalovirus (CMV)** – Most infants with congenital CMV infection are asymptomatic at birth. Among symptomatic infants, clinical manifestations include petechiae, jaundice, hepatosplenomegaly, chorioretinitis, and neurologic involvement (eg, microcephaly, motor disability, sensorineural hearing loss, cerebral calcifications (image 4), lethargy, seizures). Both asymptomatic and symptomatic infants with congenital CMV are at risk of developing late complications including hearing loss, vision impairment, intellectual disability, and delay in psychomotor development. (See "Congenital cytomegalovirus infection: Clinical features and diagnosis" and "Congenital cytomegalovirus infection: Management and outcome".)

- **Neonatal herpes simplex virus (HSV)** – Most cases of neonatal HSV infection are perinatally acquired. Affected newborns typically appear normal at birth, although many are born prematurely. Neonatal HSV infection usually develops in one of three patterns: localized to the skin, eyes, and mouth; localized central nervous system (CNS) disease; and disseminated disease (table 4). The initial manifestations of CNS disease frequently are nonspecific and include temperature instability, respiratory distress, poor feeding, and lethargy; they may progress quite rapidly to hypotension, jaundice, disseminated intravascular coagulation, apnea, and shock. Vesicular skin lesions may or may not be present. (See "Neonatal herpes simplex virus infection: Clinical features and diagnosis" and "Neonatal herpes simplex virus infection: Management and prevention".)

- **Others** – Other well-described causes of in utero infection include enteroviruses, varicella-zoster virus, parvovirus B19, and lymphocytic choriomeningitis virus. Thus, broadening the "other" category to include additional pathogens has been proposed.

- **Diagnostic approach** – Timely diagnosis of congenital and perinatally acquired infections is crucial to the initiation of appropriate therapy. Intrauterine infection may be suspected based upon maternal laboratory results and/or clinical findings or combinations of clinical findings in the fetus or newborn (eg, hydrops fetalis, microcephaly, seizures, cataract, hearing loss, congenital heart disease, hepatosplenomegaly, jaundice, and/or rash (table 5)).

  Our preferred approach to testing infants with suspected congenital infection is to test only for select pathogens based upon specific clinical findings. We discourage the practice of indiscriminate screening with a battery of "TORCH titers" because such an approach is costly and has a poor diagnostic yield. (See 'Approach to the infant with suspected intrauterine infection' above.)

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Topic 6011 Version 35.0

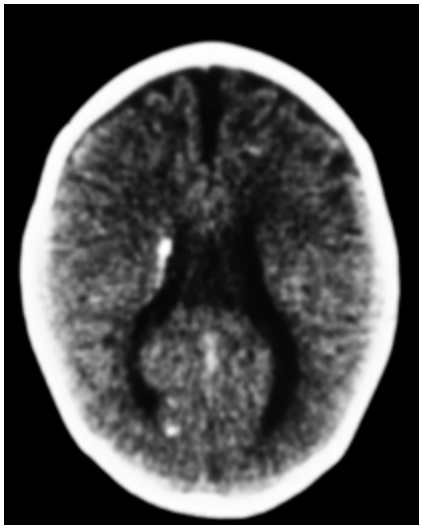
GRAPHICS

Generalized clinical manifestations of congenital toxoplasmosis

Clinical manifestations of congenital toxoplasmosis in this infant include hepatosplenomegaly, jaundice, and thrombocytopenic purpura.

Graphic 71515 Version 1.0

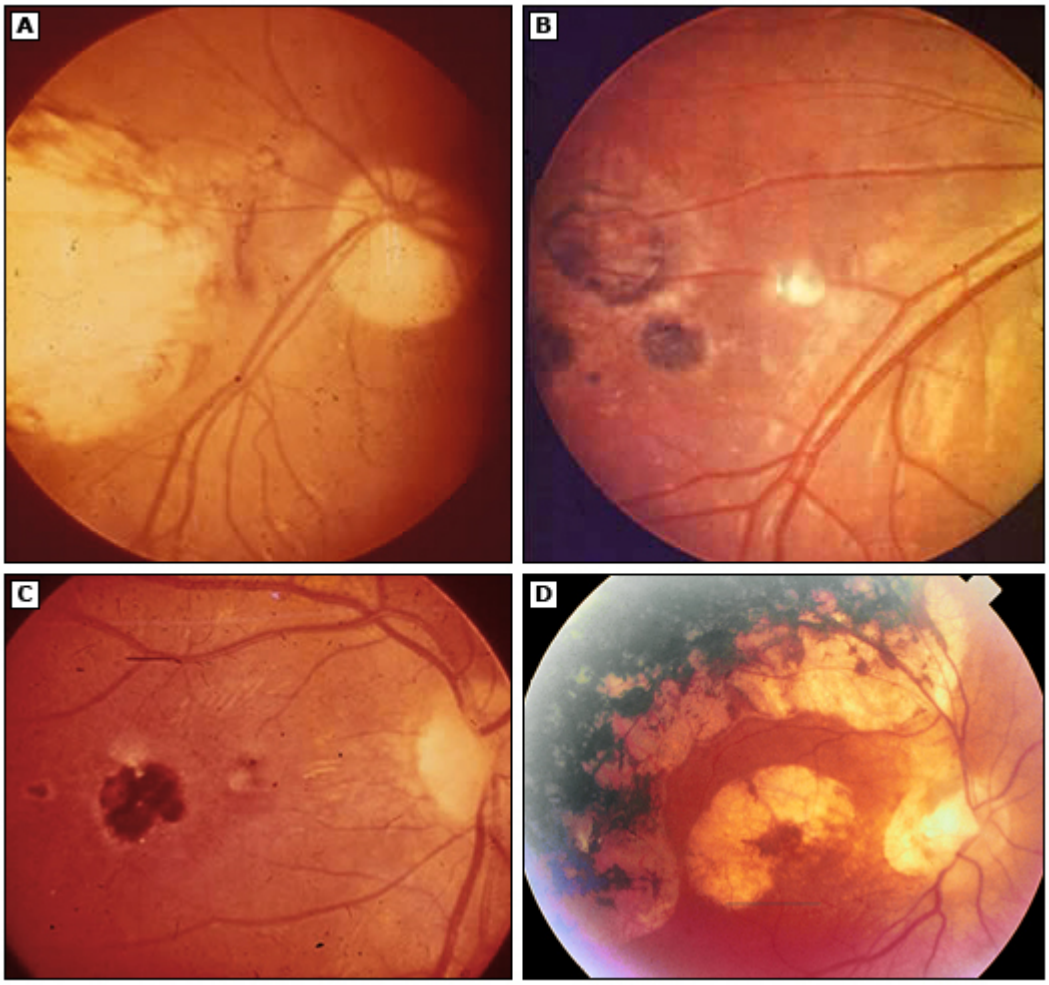
Congenital toxoplasmosis intracranial calcifications



Brain computed tomographic scan showing small, calcified lesions.

Graphic 60804 Version 17.0

Congenital toxoplasmosis chorioretinitis



(A) Severe, active retinochoroiditis.

(B) Peripheral retinochoroiditis.

(C) Central, healed retinochoroiditis.

(D) Multiple chorioretinal scars.

Panels A, B, and C reproduced from: Centers for Disease Control and Prevention. Parasite Image Library. Available at: www.cdc.gov/dpdx. Accessed on December 15, 2010.

Panel D reproduced from: Gold DH, Weingeist TA. Color Atlas of the Eye in Systemic Disease. Baltimore: Lippincott Williams & Wilkins, 2001. Copyright © 2001 Lippincott Williams & Wilkins.

Graphic 80549 Version 2.0

Clinical manifestations of early congenital syphilis*

Gestational/perinatal	
Stillbirth	
Prematurity	
Birth weight <2500 g	
Nonimmune hydrops fetalis	
Placenta	Large, thick, pale (send for pathologic/histologic evaluation)
Umbilical cord	Inflamed with abscess-like foci of necrosis within Wharton's jelly, centered around the umbilical vessels (necrotizing funisitis); barber-pole appearance (send for pathologic/histologic evaluation)
Systemic	
Fever	May be more prominent in infants born to mothers who are affected late in pregnancy and whose serology is negative at delivery
Hepatomegaly	Splenomegaly occurs in approximately one-half of patients with hepatomegaly—isolated splenomegaly does not occur
Generalized lymphadenopathy	May be as large as 1 cm; generally nontender and firm
Failure to thrive	
Edema	Due to anemia/hydrops fetalis, nephrotic syndrome, malnutrition
Mucocutaneous	
Syphilitic rhinitis ("snuffles")	Can be an early feature, developing after the first week of life; **contains spirochetes and is infectious (use contact precautions)**
Maculopapular rash	Usually appears one to two weeks after rhinitis. Oval lesions, initially red or pink and then coppery brown; may be associated with superficial desquamation or scaling, particularly on the palms or soles; more common on the buttocks, back, posterior thighs, and soles; **contains spirochetes and is infectious (use contact precautions)**.
Vesicular rash (pemphigus syphiliticus)	May be present at birth, most often develops in first four weeks; widely disseminated; vesicular fluid **contains spirochetes and is infectious (use contact precautions)**
Condylomata lata	Single or multiple, flat, wartlike, moist lesions around the

	mouth, nares, and anus and other areas of the skin where there is moisture or friction; **lesions contain spirochetes and are infectious (use contact precautions)**; frequently present without other signs of infection
Jaundice	Hyperbilirubinemia secondary to syphilitic hepatitis and/or hemolysis
Hematologic	
Anemia	Newborn period: Hemolytic (Coomb's test [direct antiglobulin test] negative); may persist after effective treatment After one month of age: May be chronic and nonhemolytic
Thrombocytopenia	May be associated with bleeding or petechiae; can be the only manifestation of congenital infection
Leukopenia	
Leukocytosis	
Musculoskeletal	
Pseudoparalysis of Parrot	Lack of movement of an extremity because of pain associated with bone lesion; affects upper extremities more often than lower; usually unilateral; rarely present at birth; poorly correlated with radiographic abnormalities
Radiographic abnormalities:	Most frequent abnormality in untreated early congenital syphilis; not usually clinically discernible; typically multiple and symmetric
Periostitis	Irregular periosteal thickening; usually present at birth, but may appear in the first few weeks of life
Wegner sign	Metaphyseal serration or "sawtooth metaphysis"
Wimberger sign	Demineralization and osseous destruction of the upper medial tibial
Neurologic	
CSF abnormalities	Reactive CSF VDRL; elevated CSF white blood cell count; elevated CSF protein
Acute syphilitic leptomeningitis	Onset during the first year of life, usually between 3 and 6 months; presentation similar to bacterial meningitis but CSF findings more consistent with aseptic meningitis (mononuclear predominance); responds to penicillin therapy
Chronic meningovascular syphilis	Onset toward the end of the first year; hydrocephalus; cranial nerve palsies; intellectual/neurodevelopmental

	deterioration; cerebral infarction; protracted course
Miscellaneous	
Pneumonia/pneumonitis/respiratory distress	Complete opacification of both lung fields on chest radiograph
Nephrotic syndrome	Usually occurs at two to three months of age and manifests with generalized edema and ascites

CSF: cerebrospinal fluid; VDRL: Venereal Disease Research Laboratory test.

* All of these findings may occur in other congenital infections; none is specific for congenital syphilis.

Data from:

1. *Ingall D, Sanchez PJ, Baker CH. Syphilis. In: Infectious Diseases of the Fetus and Newborn infant, 6th edition, Remington JS, Klein JO, Wilson CB, Baker CJ (Eds), Elsevier Saunders, Philadelphia 2006. p.545.*
2. *Dobson SR, Sanchez PJ. Syphilis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th, Cherry JD, Harrison GJ, Kaplan SL, et al. (Eds), Elsevier Saunders, Philadelphia 2014. p.1761.*
3. *Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis 2005; 16:245.*
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Graphic 67809 Version 8.0

Stigmata of late congenital syphilis

Facial features	Frontal bossing, saddle nose, short maxilla, protuberant mandible
Ophthalmologic	Interstitial keratitis, chorioretinitis, secondary glaucoma, corneal scarring, optic atrophy
Ears	Sensorineural hearing loss
Oropharynx	Hutchinson teeth, mulberry molars, perforation of hard palate
Cutaneous	Rhagades, gummas
Central nervous system	Intellectual disability, arrested hydrocephalus, seizures, optic atrophy, juvenile general paresis
Skeletal	Saber shins (anterior bowing of the tibia), Higoumenakis sign (enlargement of the sternoclavicular portion of the clavicle), Clutton joints (painless arthritis), scaphoid scapula

Data from:

1. *Ingall D, Sanchez PJ, Baker CH. Syphilis. In: Infectious Diseases of the Fetus and Newborn infant, 6th edition, Remington JS, Klein JO, Wilson CB, Baker CJ (Eds), Elsevier Saunders, Philadelphia 2006. p.545.*
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3. *Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis 2005; 16:245.*
4. *Chakraborty R, Luck S. Syphilis is on the increase: the implications for child health. Arch Dis Child 2008; 93:105.*

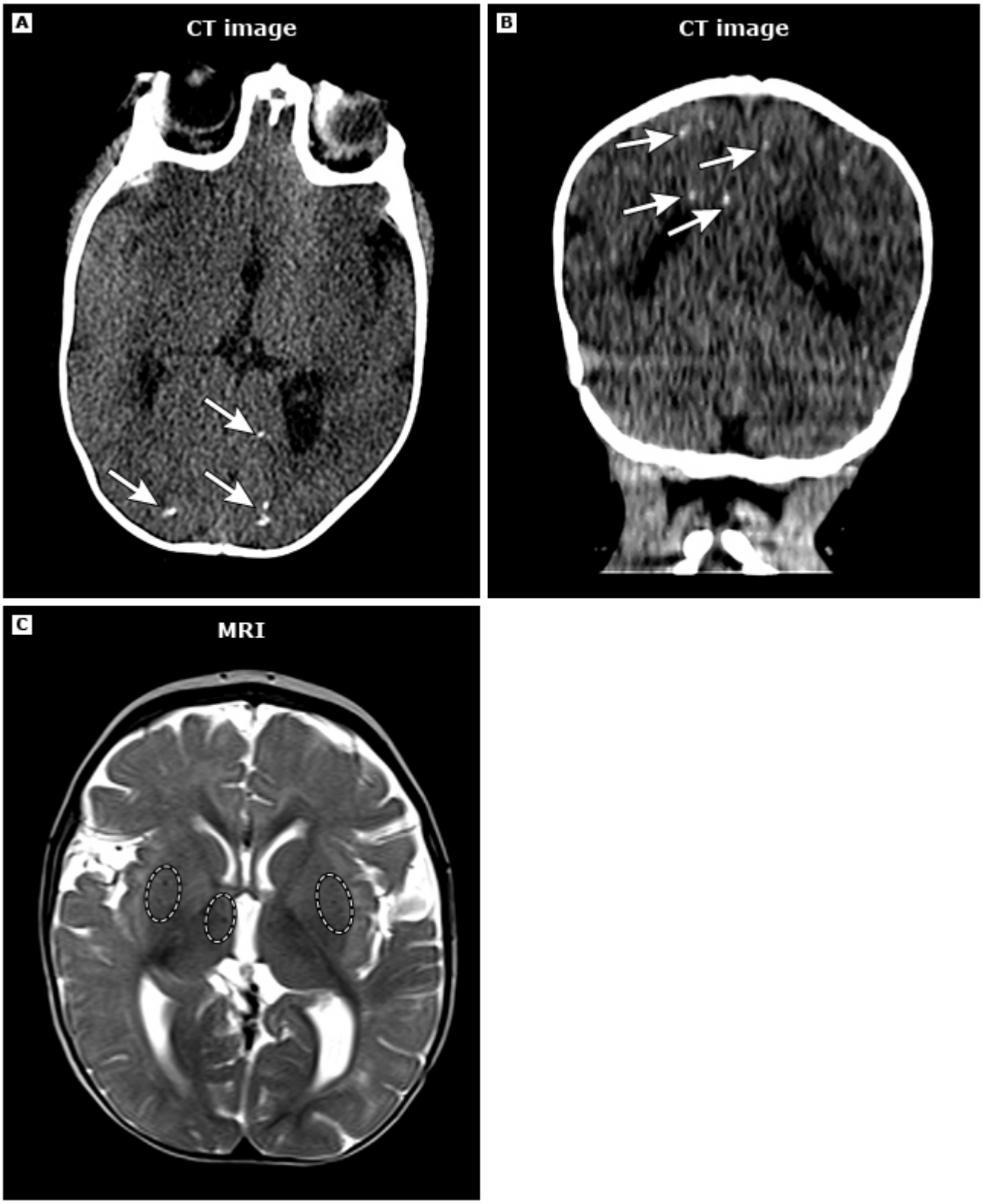
Graphic 81529 Version 3.0

Newborn with congenital Zika syndrome

Newborn infant congenitally infected with Zika virus. Clinical features of congenital Zika syndrome include microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures, irritability, arthrogryposis, club feet, ocular abnormalities, and hearing loss.

Graphic 109690 Version 2.0

Intracranial calcifications in congenital Zika virus infection



Neuroimaging with CT and MRI showing intracranial calcifications in infants with CZS.

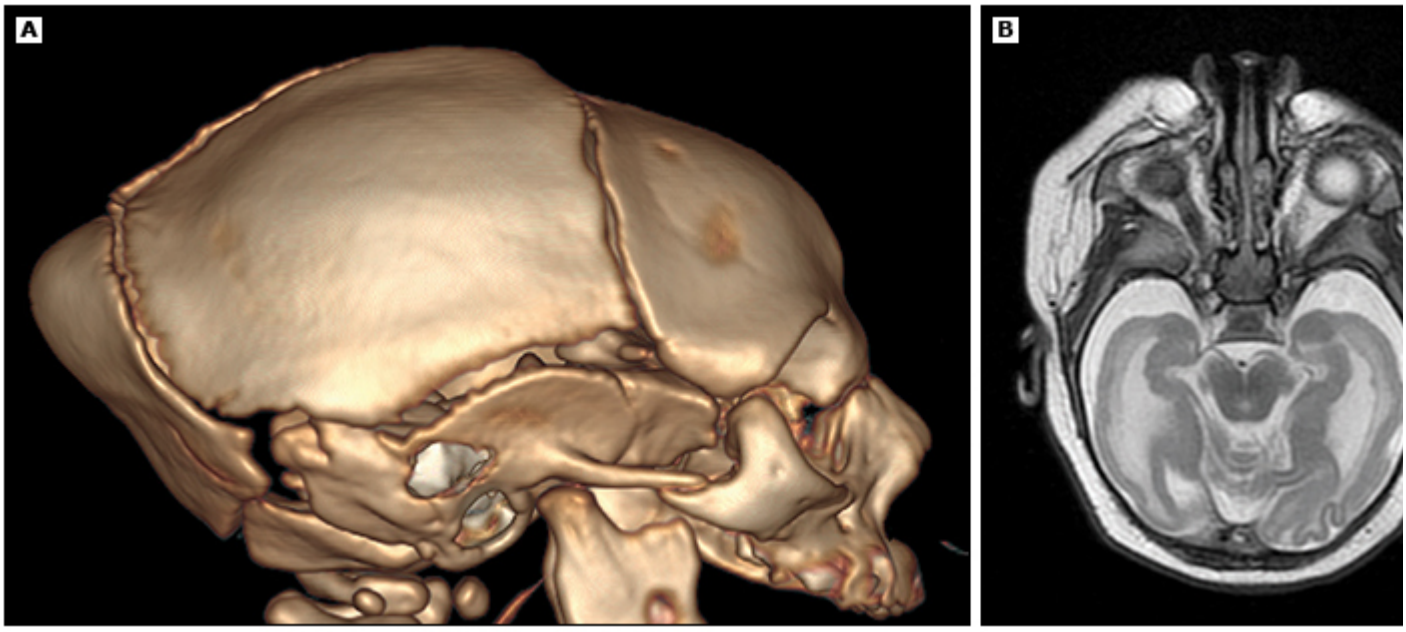
(Panels A and B) Axial (A) and coronal (B) noncontrast CT images showing punctate subcortical hyperdense (bright) lesions (arrows), consistent with calcification.

(Panel C) Axial T2-weighted MRI showing multiple punctate hypointense (dark) lesions in the basal ganglia bilaterally (dashed circles), consistent with calcification.

CT: computed tomography; MRI: magnetic resonance imaging; CZS: congenital Zika syndrome.

Graphic 109691 Version 2.0

Cranial imaging in an infant with severe congenital Zika syndrome



Imaging findings of an infant with severe CZS.

(A) Three-dimensional CT reconstruction showing classic phenotypic pattern of fetal skull collapse with over cranial sutures and prominent occipital protrusion.

(B) T2-weighted MRI showing simplified gyral pattern with a lissencephalic appearance of the brain.

CZS: congenital Zika syndrome; CT: computed tomography; MRI: magnetic resonance imaging.

Graphic 109692 Version 2.0

Frequency and clinical course of selected clinical findings following intrauterine rubella infection

Manifestations in infancy			
Clinical manifestation	**Frequency**	**Typical time of onset**	**Course**
Hearing impairment	60%	Early infancy	Permanent
Heart defect	45%		
Patent ductus arteriosus	20%	Early infancy	Permanent
Peripheral pulmonic stenosis*	12%	Early infancy	Permanent
Microcephaly	27%	Neonatal	Permanent
Cataracts	25%	Early infancy	Permanent
Low birth weight (<2500 g)	23%	Neonatal	Poor weight gain may persist
Hepatosplenomegaly	19%	Neonatal	Transient
Purpura	17%	Neonatal	Transient
Intellectual disability (mental retardation)	13%	Variable	Permanent
Meningoencephalitis	10%	Neonatal	Transient
Radiolucent bone lesions	7%	Neonatal	Transient
Retinopathy	5%	Early infancy	Permanent
Late-onset manifestations¶			
Hearing loss			Permanent
Intellectual disability			Permanent
Diabetes mellitus			Permanent
Thyroid dysfunctionΔ			Permanent
Progressive panencephalitis			Permanent

* Includes pulmonary arterial hypoplasia, supravalvular stenosis, valvular stenosis, and peripheral branch stenosis.

¶ The frequency of these manifestations is not known, given the difficulty of establishing a diagnosis of congenital rubella infection in individuals older than 1 year of age.

Δ Includes hyperthyroidism, hypothyroidism, and thyroiditis.

Adapted from:

1. *Reef SE, Plotkin S, Cordero JF, et al. Preparing for elimination of congenital Rubella syndrome (CRS): summary of a workshop on CRS elimination in the United States. Clin Infect Dis 2000; 31:85.*
2. *Banatvala JE, Brown DW. Rubella. Lancet 2004; 363:1127.*

Graphic 75721 Version 5.0

Blueberry muffin lesions

This infant with congenital rubella syndrome presented with "blueberry muffin" skin lesions. These lesions indicate cutaneous hematopoiesis and may occur in other intrauterine infections and hematologic disorders.

Courtesy of Centers for Disease Control and Prevention Public Health Image Library.

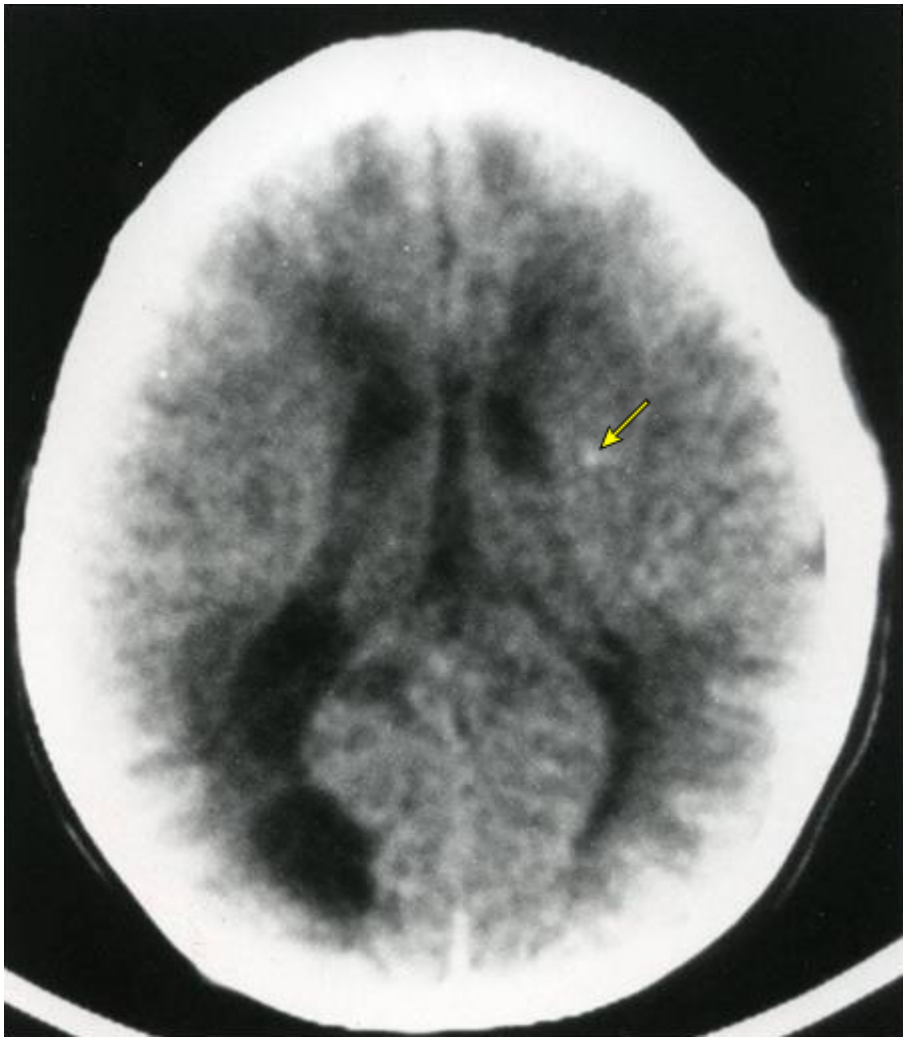
Graphic 69581 Version 3.0

Symptomatic congenital cytomegalovirus infection

Term neonate born with symptomatic congenital cytomegalovirus infection involving many organ systems. At birth the infant was jaundiced and had diffuse petechiae and purpura.

Graphic 98822 Version 2.0

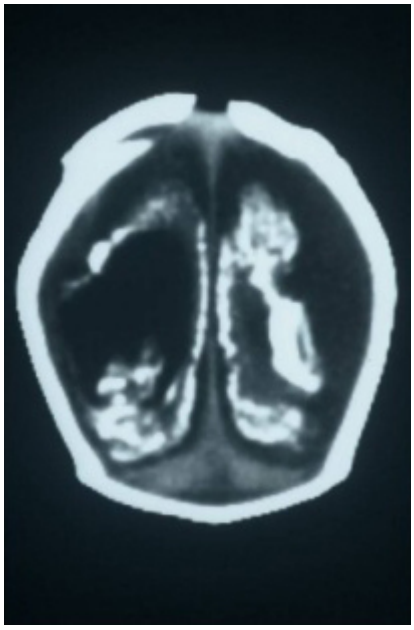
Unenhanced cranial computed tomography in infant with asymptomatic congenital cytomegalovirus infection



Unenhanced cranial computed tomography scan in an infant born with asymptomatic congenital cytomegalovirus infection. There is a unilateral enlarged lateral ventricle, periventricular leukomalacia, and one punctate periventricular calcification (arrow).

Graphic 98838 Version 1.0

Unenhanced cranial computed tomography in infant with symptomatic congenital cytomegalovirus infection



Unenhanced cranial computed tomography scan of a newborn with congenital cytomegalovirus disease, and severe central nervous system involvement. The infant was born with severe microcephaly with overriding sutures. He also had neonatal seizures and progressive chorioretinitis.

Graphic 98839 Version 1.0

Summary of clinical, laboratory, radiographic findings, and treatment of neonatal herpes simplex virus (HSV) infection

	Proportion of cases	Clinical manifestations	Diagnostic testing for HSV*			
			Viral culture of surface specimens¶	Viral culture of skin lesion scrapings$^{\Delta}$	Blood or plasma HSV PCR	
SEM disease	45%	▪ Characteristic vesicular lesions ▪ Conjunctivitis, excessive tearing ▪ Ulcerative lesions of the mouth, palate, and tongue	Positive in >90%	Positive in >90%	Positive in approximately 75%	N
CNS disease	30%	▪ Seizures ▪ Lethargy ▪ Irritability ▪ Tremors ▪ Poor feeding ▪ Skin lesions are present in 60 to 70%	Positive in >90%	Positive in >90% if lesions are present; however, skin lesions are often not present at the onset of disease	Positive in approximately 65%	P ir 1(

Disseminated disease	25%	▪ Sepsis syndrome ▪ Fever or hypothermia ▪ Hepatitis ▪ Respiratory distress ▪ DIC ▪ Skin lesions are present in 60 to 80% ▪ CNS involvement occurs in 60 to 75%	Positive in >90%	Positive in >90% if lesions are present; however, skin lesions are often not present at the onset of disease	Positive in 100%	P in

HSV: herpes simplex virus; PCR: polymerase chain reaction; CSF: cerebrospinal fluid; SEM: skin, eyes, mouth; CNS: central nervous system; EEG: electroencephalogram; DIC: disseminated intravascular coagulopathy; DFA: direct immunofluorescence assay; BSA: body surface area.

* All of these diagnostic tests should be performed in any neonate with suspected HSV infection.

¶ Surface cultures are performed on swab specimens collected from the conjunctivae, mouth, nasopharynx, and rectum. Some experts suggest these be obtained with a single swab, starting with eyes and ending with the rectum, and placed in one viral transport media tube. Alternatively, they may be collected with multiple swabs, which are then placed in a single viral transport media tube.

Δ DFA permits rapid detection of HSV antigens in skin lesion scrapings; however, DFA is not as sensitive as culture and therefore viral culture should also be performed.

◇ The dose of acyclovir must be adjusted for neonates with renal impairment and/or weight <1kg. Refer to Lexicomp for additional dosing information. If IV acyclovir is not available, ganciclovir as an alternative. Refer to the UpToDate topic on management of neonatal HSV infection for additional information. Oral acyclovir dosing is based on BSA, which is calculated as follows: square root (Height [cm] * Weight [kg] / 3600). The oral suppressive acyclovir dose should be adjusted each month to account for growth.

§ Idoxuridine (iododeoxyuridine) is not available in the United States.

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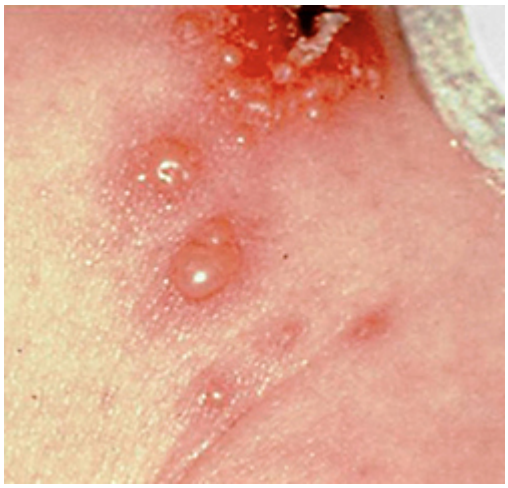
1. *1. American Academy of Pediatrics. Herpes simplex. In: Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed, Kimberlin DW (Ed), American Academy of Pediatrics, Elk Grove Village, IL 2015. p.432.*
2. *2. Kimberlin DW, Gutierrez KM. Herpes simplex virus infections. In: Remington and Klein's infectious diseases of the fetus and newborn infant, 8th ed, Wilson CB, Nizet V, Maldonado YA, et al. (Eds), Saunders, Phildelphia, PA 2016. p.843.*

Graphic 106132 Version 2.0

Neck vesicles in neonate with herpes simplex virus infection



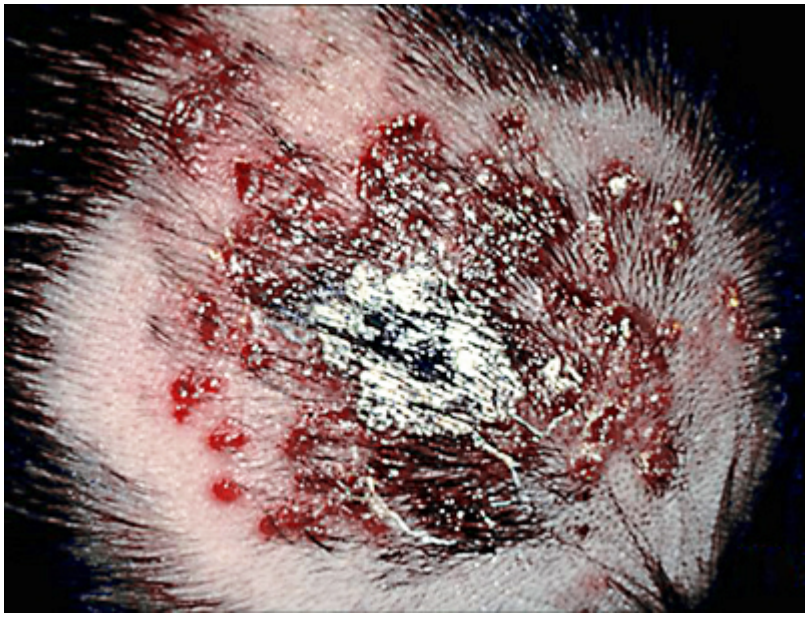
The early untreated skin lesions associated with neonatal HSV infection are characteristically clear vesicles on an erythematous base, often touching or "kissing," or coalesced in groups of vesicles. Culture of the clear fluid aspirated or swabbed from the vesicles will readily grow HSV in 24 to 48 hours, and slides made from cells scraped from the base of the lesion will show HSV viral antigens by DFA.

HSV: herpes simplex virus; DFA: direct immunofluorescence assay.

Courtesy of Gail J Demmler-Harrison, MD, Texas Children's Hospital.

Graphic 75059 Version 4.0

Neonatal herpes simplex virus scalp vesicles



Scalp lesions of neonate with skin, eye, and mouth neonatal HSV infection associated with fetal scalp monitor. Gram-stained smear and bacterial cultures were negative, and the lesions did not respond to topical and systemic antibiotics. Viral cultures grew HSV type 2, and the lesions responded to intravenous acyclovir.

HSV: herpes simplex virus

Courtesy of Jane Troendle-Atkins, MD, and Gail J Demmler-Harrison, MD, Texas Children's Hospital.

Graphic 56041 Version 3.0

Eye vesicles in neonate with herpes simplex virus infection

Neonate with HSV infection of the eye, showing characteristic coalescing vesicles on an erythematous base on eyelid and surrounding skin. Ophthalmologic evaluation of the eye should also be performed to determine if keratitis or keratoconjunctivitis is present.

HSV: herpes simplex virus.

Courtesy of Jenny Ravenscroft, MD, and Gail J Demmler-Harrison, MD, Texas Children's Hospital.

Graphic 78598 Version 4.0

Intrauterine herpes simplex virus

Hypopigmented, scaling, and crusted erosions of the trunk and extremities in a neonate with intrauterine herpes simplex virus infection.

Graphic 55645 Version 6.0

Clinical manifestations that are suggestive of specific congenital infections in the neonate

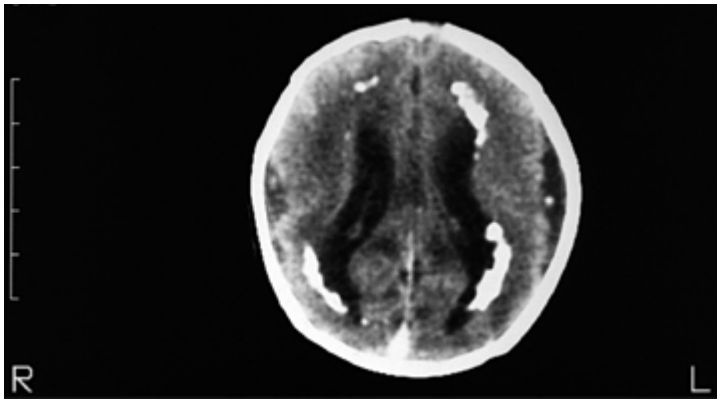
Congenital toxoplasmosis
▪ Intracranial calcifications (diffuse)
▪ Hydrocephalus
▪ Chorioretinitis
▪ Otherwise unexplained mononuclear CSF pleocytosis or elevated CSF protein
Congenital syphilis
▪ Skeletal abnormalities (osteochondritis and periostitis)
▪ Pseudoparalysis
▪ Persistent rhinitis
▪ Maculopapular rash (particularly on palms and soles or in diaper area)
Congenital rubella
▪ Cataracts, congenital glaucoma, pigmentary retinopathy
▪ Congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis)
▪ Radiolucent bone disease
▪ Sensorineural hearing loss
Congenital cytomegalovirus
▪ Thrombocytopenia
▪ Periventricular intracranial calcifications
▪ Microcephaly
▪ Hepatosplenomegaly
▪ Sensorineural hearing loss
Herpes simplex virus
Perinatally acquired HSV infection
• Mucocutaneous vesicles

• CSF pleocytosis
• Thrombocytopenia
• Elevated liver transaminases
• Conjunctivitis or keratoconjunctivitis
Congenital (in utero) HSV infection (rare)
• Skin vesicles, ulcerations, or scarring
• Eye abnormalities (eg, micro-ophthalmia)
• Brain abnormalities (eg, hydranencephaly, microcephaly)
Congenital varicella
▪ Cicatricial or vesicular skin lesions
▪ Microcephaly
Congenital Zika syndrome
▪ Microcephaly
▪ Intracranial calcifications
▪ Arthrogryposis
▪ Hypertonia/spasticity
▪ Ocular abnormalities
▪ Sensorineural hearing loss

CSF: cerebrospinal fluid; HSV: herpes simplex virus.

Graphic 76743 Version 10.0

Computed tomography scan of intracranial calcifications in congenital cytomegalovirus infection



Intracranial computed tomography scan of an infant born with congenital cytomegalovirus disease and central nervous system involvement. The scan shows classic linear periventricular calcifications and cortical atrophy. The infant had microcephaly at birth and developmental disabilities and major motor impairment at 8 years of age.

Graphic 69239 Version 4.0

Contributor Disclosures

Karen E Johnson, MD No relevant financial relationship(s) with ineligible companies to disclose. **Leonard E Weisman, MD** Equity Ownership/Stock Options: Vax-Immune [Ureaplasma diagnosis, vaccines, antibodies, other medical diagnostics and pre-analytical devices]. Patent Holder: Baylor College of Medicine [Ureaplasma diagnosis, vaccines, antibodies, process for preparing biological samples]. All of the relevant financial relationships listed have been mitigated. **Morven S Edwards, MD** Grant/Research/Clinical Trial Support: Pfizer [Group B Streptococcus]. Other Financial Interest: Texas State University personal services agreement [Chagas disease]. All of the relevant financial relationships listed have been mitigated. **Carrie Armsby, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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