

## Congenital Infections of the Newborn — Definition and Treatment

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**Congenital infections are common and are associated with significant morbidities for the infant. Classically, congenital infections of the infant have been given the acronym TORCH which stands for toxoplasmosis, others (syphilis, varicella-zoster virus, parvovirus B19 and human immunodeficiency virus), rubella, cytomegalovirus and herpes simplex.**



### Definition

They are a set of specific congenital infections acquired either in utero or during delivery causing significant fetal and neonatal morbidity and mortality.

### Epidemiology of Congenital Infections of the Infant

The incidence and distribution of congenital infections in infants have changed over the last decade. Congenital toxoplasmosis and congenital syphilis are decreasing in incidence because of the introduction of **new treatments** and the **mandatory testing of mothers for syphilis**.

**Avoidance of cats and undercooked meats** has also been linked to the decreasing incidence of congenital toxoplasmosis.

Congenital **varicella and rubella** are also becoming less common since the introduction of **vaccination** against these two viruses. The most common cause of congenital infections nowadays is **cytomegalovirus**, but this might change soon as **Ganciclovir** has been shown to be an effective treatment against the virus.

The use of **antiviral therapy** and **cesarean delivery** has lowered the incidence of congenital herpes and has improved the clinical outcome of the infants.

## Pathophysiology of Congenital Infections of the Infant

Most of the above mentioned infectious agents are known to **cross the placental barrier** and to spread to the fetus in utero which can cause **fetal loss**, the emergence of certain **congenital malformations**, **prematurity** or **chronic postnatal infection**. Maternal illness is usually mild, but the consequences to the fetus are usually severe.

Maternal infections very early in pregnancy can cause **fetal loss** which is believed to be **underestimated** because at this stage most women are not aware that they are pregnant.

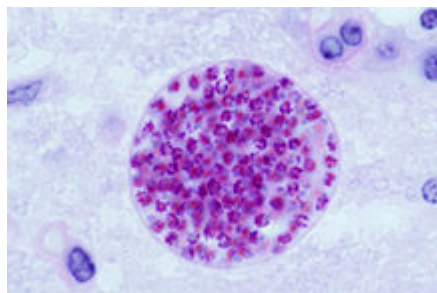
The **transplacental spread** of these organisms to the fetus might be associated with **chronic infection** because of the immaturity of the fetus' immune system. These organisms are usually not very virulent and the immune system of the developing fetus can develop tolerance to them. If this happens, the fetal immune system will fail to eliminate the infecting organisms and chronic infection might occur.

The clinical presentation of these congenital infections can be seen soon after birth, during infancy, childhood or later in adulthood.

## Congenital Toxoplasmosis

### Definition

Congenital toxoplasmosis is caused by the protozoan **toxoplasma gondii** which is transmitted from the infected mother to the developing fetus transplacentally. The causative organism can be acquired by exposure to contaminated cat feces or by eating raw meat.



Microscopic cysts containing *Toxoplasma gondii* develop in the tissues of many vertebrates. Here, in mouse brain tissue,

thousands of resting parasites (stained red) are enveloped by a thin parasite cyst wall.

Congenital toxoplasmosis is usually **unrecognized at birth**, and women in the United States are not routinely screened for toxoplasmosis. Unfortunately, the clinical consequences of congenital toxoplasmosis are usually present in most affected individuals by early adulthood.

## Clinical features

The most common findings of congenital toxoplasmosis in infants are **chorioretinitis** which can lead to blindness, obstructive [hydrocephalus](#) and intracranial calcification. Unfortunately, mental retardation is commonly seen in infants who develop intracranial calcifications. Seizures and motor deficits are also commonly seen in affected infants.

## Diagnosis

The **early detection of maternal toxoplasmosis** is essential to prevent the spread of the infection to the fetus. In Europe, monthly screening for toxoplasmosis has become the standard of care as it is useful in the detection of early seroconversion.

A polymerase chain reaction test for toxoplasmosis in the amniotic fluid is also an option and can help in establishing the diagnosis at an early stage. Once the diagnosis is confirmed, the mother should receive **spiramycin** 1.5 grams two times a day to prevent fetal infection.

If the polymerase chain reaction test comes back positive, then the possibility of fetal infection is high. In that case, the use of **pyrimethamine and sulfadiazine plus folinic acid** is recommended.

Maternal symptoms of toxoplasmosis are not specific and can be easily missed even by an experienced physician. Therefore, whenever in doubt, it is recommended to order a serology test or a polymerase chain reaction test to confirm the diagnosis.

Prenatal ultrasonographic features of [intrauterine growth restriction](#), fetal hydrocephalus, intracranial calcifications and ascites are suggestive of fetal toxoplasmosis. Again, combination therapy of **pyrimethamine, sulfadiazine** and **folinic acid** should be commenced.

## Toxoplasmosis prevention

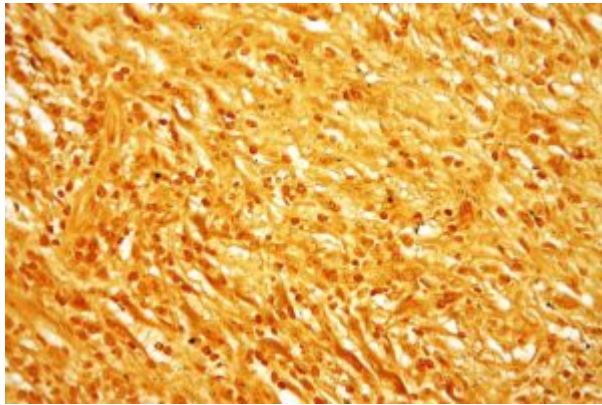
- Pregnant women should be tested if there is concern for risk.
- Pregnant women should avoid uncooked meat.
- Pregnant women should change cat litter daily or have someone else do it.

## Congenital Syphilis

### Stages

All mothers who have [syphilis](#) will transmit the causative organism, ***Treponema pallidum***, to the developing fetus by the transplacental route. Syphilis can be classified into three stages.

- The **primary stage** is characterized by the presence of a syphilitic chancre and lymphadenitis.
- The **secondary stage** is characterized by the hematogenous dissemination of the organisms and is the stage seen in infants with congenital syphilis. These infants can then go into a latent asymptomatic stage or a symptomatic tertiary stage.
- **The symptomatic tertiary stage** of congenital syphilis is characterized by neurological and cardiovascular disease, in addition to skin [granulomatous disease](#).



**Image:** "Micrograph showing Treponema pallidum, the spirochete that causes syphilis. Dieterle stain," by Nephron - Own work. License: [CC BY-SA 3.0](#)

## Epidemiology

The incidence of congenital syphilis has declined since the introduction of **mandatory serologic screening during pregnancy**. Fetal infection is more common to happen in mothers who are in the primary or secondary stage of syphilis.

## Clinical features

Congenital syphilis can be symptomatic before the age of two years, i.e., early disease or the symptoms might emerge after two years, i.e., late disease. Without effective treatment, **perinatal death** occurs in one-third of the cases. The remaining two-thirds are usually born asymptomatic, but if left untreated, symptoms will emerge within the first few months of life.

The **early manifestations** of congenital syphilis include bloody nasal discharge, hepatosplenomegaly, [jaundice](#), elevated hepatic enzymes, lymphadenopathy, hemolytic anemia, osteochondritis, and [thrombocytopenia](#). Mucocutaneous rash, [failure to thrive](#), nephritis, blindness due to chorioretinitis and central nervous system abnormalities are also commonly observed in early disease. Late features of congenital syphilis include chronic inflammation of the bones, teeth and the central nervous system.

## Diagnosis

The diagnosis of congenital syphilis can be confirmed by using **dark-field microscopy** on specimens obtained from the placenta or the umbilicus, or by **serologic testing**. The most commonly used serologic tests are the **Venereal Disease Research Laboratory test** and the **Rapid Plasma Reagin test**. These two tests detect antibodies against

cardiolipin, and they are not specific for syphilis but are useful in the prediction of the disease activity and severity.

*T. pallidum* immobilization test, the fluorescent treponemal antibody absorption test and the microhemagglutination assays for *T. pallidum* are specific for syphilis. Polymerase chain reaction testing for *T. pallidum* is still not available for clinical practice.

## Treatment

Symptomatic infants who are confirmed to have syphilis by one of the non-specific quantitative tests or the specific tests should receive treatment. Additionally, asymptomatic infants of mothers who have a positive serology test should be evaluated and if found to have congenital syphilis should be treated.

Whenever the documented history of maternal treatment is not available, maternal treatment against syphilis was less than one month before delivery or the mother did not receive a penicillin drug, the infant should be evaluated and treated.

The **most effective therapy** for congenital syphilis is a 10-day course of aqueous penicillin G 100,000 to 150,000 units/kg/24 every twelve hours for the first week and every eight hours thereafter, or Procaine Penicillin G 50,000 units/kg IM once a day for ten days. The success of the treatment is confirmed by reversion to a negative serology test result from one of the non-specific tests mentioned above.

Early findings	Later findings
Hepatosplenomegaly	Hutchinson teeth (notched teeth)
Adenopathy	Hearing loss
Rash	Saddle nose
Rhinitis (snuffles)	Saber shins
Metaphyseal lucencies on radiography	Developmental delay

## Varicella-Zoster Infection

### Definition

**Primary maternal varicella-zoster infection** can cause congenital varicella syndrome or neonatal varicella depending on the time of the onset of the maternal infection. Congenital varicella syndrome occurs when transplacental spread occurs during early fetal development, whereas neonatal varicella happens if transplacental infection occurs during delivery.

### Epidemiology

Approximately 25 % of the fetuses of infected mothers will acquire the infection, but only 2 % will be clinically affected. When infection occurs within the sixth to 12<sup>th</sup> week of gestation, limb development can be affected. Fetal infection at 16 to 20 weeks of gestation is associated with eye and brain disease. Fetal infection during the third trimester is believed to result in less severe disease.

### Clinical features

The most common presentation of congenital varicella syndrome is that of cicatricial skin

scars, atrophy of extremities, the presence of a neurogenic bladder,+ and hydronephrosis. The presence of these last three features is suggestive of **autonomic nervous system involvement**. Microcephaly, cortical atrophy, seizures and mental retardation can also be seen in congenital varicella syndrome. Eye disease is characterized by microphthalmia, cataracts and chorioretinitis.

## Diagnosis

The diagnosis of varicella-zoster virus fetal infection can be confirmed by a **documented maternal history of chickenpox during pregnancy** along with a typical clinical picture of congenital varicella syndrome in the neonate.

**Polymerase chain reaction testing** for the virus DNA is available and can also help in establishing the diagnosis. Polymerase chain reaction testing can be confirmed on cord blood, chorionic villi sampling or fetal blood sampling. Varicella-zoster virus immunoglobulin-M and immunoglobulin-G are positive in congenital varicella syndrome.

## Treatment

Women who are exposed to varicella-zoster virus but have not yet developed the infection might benefit from the administration of varicella-zoster immune globulin.

Pregnant women with severe varicella might benefit from the administration of **acyclovir** but it is not known if this has any effect on the risk of fetal infection. Antiviral treatment of congenital varicella syndrome is not indicated because the virus does not replicate in the newborn.

If the mother develops chickenpox within the last few days of her pregnancy, the risk of neonatal varicella is very high. The mortality of this condition can be as high as 30 %, and the use of **varicella-zoster immune globulin** in the newborn has been shown to be life-saving.

## Parvovirus B19

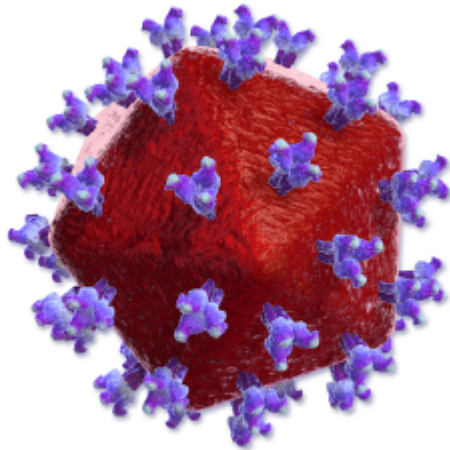
### Definition

**Parvovirus B19 infection** in adults is usually asymptomatic or goes undetected. Parvovirus B19 infection during the second trimester can be associated with **hydrops fetalis** or **fetal loss**. If the fetus does not develop any of these acute complications, or if intrauterine blood transfusion is successful in saving the fetus, the risk of chronic parvovirus B19 infection in the fetus is negligible.

## Human Immunodeficiency Virus

### Pathophysiology

The **human immunodeficiency virus (HIV)** has been shown to be able to spread via the transplacental route to the developing fetus. Pregnant women who are confirmed to have HIV can transmit the virus to their fetuses in up to 40 % of the cases.



## Human Immunodeficiency Virus (HIV)

Picture: "HIV" by BruceBlaus. License: [CC BY-SA 4.0](#)

In almost all newborns of HIV positive mothers, HIV specific antibodies are positive at birth. This, however, does not mean that these infants have been infected as serologic reversion has been reported to occur in a considerable number of children by age of 18 months. **Breastfeeding** has also been linked to an increased risk of postnatal transmission of HIV to the infant.

## Clinical features

The congenital infection with HIV usually does not cause any symptoms at birth. The early manifestations of congenital HIV Infection are lymphadenopathy, hepatosplenomegaly, oral [candidiasis](#), and invasive bacterial infections. Recurrent [pneumonia](#) and failure to thrive can also be seen.

## Diagnosis

The diagnosis of congenital HIV infection can be confirmed by a positive **polymerase chain reaction test**. A negative polymerase chain reaction test at birth, one month and four months of age is sufficient in the exclusion of congenital HIV infection.

The use of **zidovudine** (ZDV) by the HIV positive mother prenatally and during delivery, and the administration of ZDV to the newborn have significantly lowered the risk of vertical transmission of HIV to the infant. The use of ZDV during delivery, when combined with nevirapine, has also lowered the risk of infant infection.

## Management of HIV in mothers and newborns



- **HAART** therapy for confirmed infected infants
- **AZT** during delivery for mothers

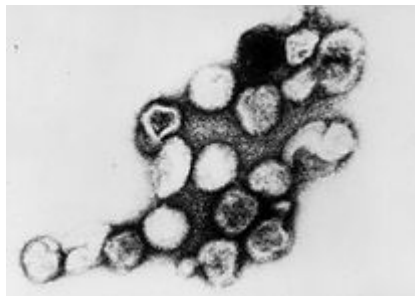


- C-section if mother is > 1,000 copies/cc
- **Exposed infant gets:**
  - AZT orally for 6 weeks after birth
  - TMP/SMX prophylaxis until known HIV negative.

## Congenital Rubella

### Epidemiology

The currently estimated incidence of congenital rubella is around 30 to 60 cases per year, a huge drop compared to the previously reported number of 57,686 cases in 1969. The main cause of this considerable drop in the incidence of congenital [rubella](#) is the introduction of [immunization](#) against the causative organism.



Transmission electron micrograph of rubella virus.

The severity of fetal involvement is dependent on the time of maternal infection. Maternal infection within the first eight weeks of gestation is usually associated with [miscarriage](#), spontaneous abortion or fetal loss. Fetuses infected before 11 weeks of gestation usually have multiple affected organs whereas those infected after 12 weeks of gestation only have deafness or retinopathy.

### Clinical features

Newborns with congenital rubella are usually asymptomatic at birth. The **early clinical features** of congenital rubella include generalized lymphadenopathy, hepatosplenomegaly, hepatitis, [jaundice](#), and [thrombocytopenia](#). These features usually resolve within weeks.

### Complications

The **long-term complications** of congenital rubella are sensorineural deafness, cataracts, mental retardation, and diabetes mellitus type 1. Affected infants should be presumed as infective until the age of 1 year.

### Diagnosis

**Isolation of the rubella virus** is successful up to one year after birth. Samples from the nasopharynx, cerebrospinal fluid or the urine can help in the isolation of the virus and establishing the diagnosis. The presence of rubella-specific hemagglutination inhibition after nine months of age is specific and diagnostic of congenital rubella.



## Treatment

Treatment of congenital rubella is not available and the focus should be on the **immunization of children and adults** to prevent acquiring the infection during pregnancy.

**Primary infection presents as:**



- Low-grade fever
- **Headache**
- Conjunctivitis
- **Cough**, congestion
- **Rash.**

**If a mother acquires the disease while pregnant, the infant can be stillborn or have the “triad”:**

- **I** - Cataracts
- **II** - Deafness
- **II** - Cardiac defects

## Congenital Cytomegalovirus Infection

### Definition

Congenital cytomegalovirus infection is the most common cause of congenital infection in the United States. Up to 20 % of infected infants develop sensorineural hearing loss, ocular damage and cognitive or motor dysfunction. Young, single, non-white mothers are at the highest risk of acquiring cytomegalovirus during pregnancy.

### Pathophysiology

Cytomegalovirus can spread to the fetus via the **transplacental route, during delivery** or by **breastfeeding**. Approximately 40 % of maternal primary infections cause congenital cytomegalovirus fetal infection. First-trimester primary maternal infection usually causes a more severe picture of congenital cytomegalovirus in the neonate at birth.

### Clinical features

The clinical manifestations of congenital cytomegalovirus infection can happen early during the neonatal period or late during childhood. The early presentation usually includes **intrauterine growth restriction**, microcephaly, lethargy, optic neuropathy, and intracranial calcifications. The mortality rate is high and can reach 12 % within the first six months of life. Mental retardation and hearing loss can occur during childhood and are usually progressive.

## Diagnosis

Isolation and culturing of the virus from oral secretions or the urine of the newborn can help in establishing the diagnosis. Additionally, the detection of viral DNA by **polymerase chain reaction testing** can be very helpful in the early recognition of the disease.

## Treatment

Severe congenital cytomegalovirus infection is currently being treated in experimental studies by **intravenous ganciclovir**. **Valganciclovir** is available in an oral formulation and might be effective in cases of moderate to severe congenital cytomegalovirus infection. A **cytomegalovirus vaccine** is under development.

Symptoms at birth (10 %)	Late symptoms (50 %)
Premature	Hearing
Hepatosplenomegaly	Vision loss
Small for gestational age	Developmental delay
Microcephaly	Seizure disorder
Seizure	

## Congenital Herpes Simplex

### Epidemiology

In contrast to the previously discussed congenital infections, congenital herpes simplex is usually **acquired during delivery**. The estimated prevalence of congenital herpes simplex in the United States is 30 cases per 100,000 live births. The infant attack rate in primary maternal herpes can be as high as 50 % whereas the infection rate in the infant of a woman with disease reactivation is usually around 15 to 20 %.

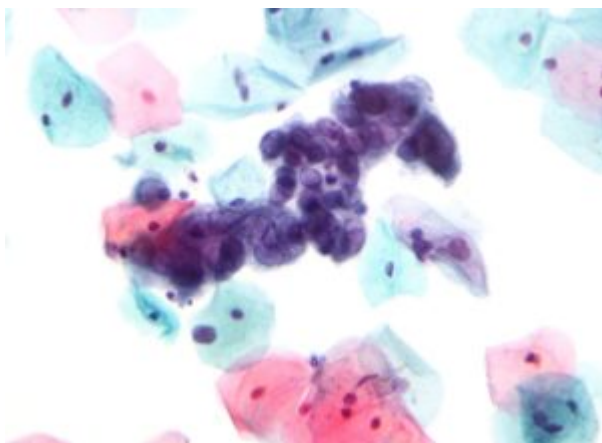


Image: "Micrograph showing the changes of herpes simplex virus (HSV). Pap test. Pap stain," by Nephron – Own work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

### Clinical features

The symptoms of congenital herpes simplex usually start within the first day of life but can be delayed up to one week after birth. Congenital herpes simplex might cause

localized skin, eye and mouth disease, encephalitis with or without skin, eye and mouth disease, or disseminated infection in the neonate.

**Encephalitis** usually happens between days 8 and 12 postpartum. Severe disseminated infection can cause irritability, seizures, [respiratory distress syndrome](#), jaundice, bleeding abnormalities, and [shock](#).

The clinical picture of disseminated congenital herpes simplex resemble bacterial sepsis and might be **difficult to recognize**. While localized skin disease seems to be benign, treatment should still be initiated as early as possible to prevent progression into a more severe disease with central nervous system involvement.

### Disseminated



- Severe encephalitis
- Chorioretinitis
- Skin lesions
- Hepatitis
- Coagulopathy/DIC
- Pneumonitis

## Diagnosis

**Viral cultures** and the detection of the viral DNA by **polymerase chain reaction testing** are the mainstay tools to confirm the diagnosis of congenital herpes simplex. Serology testing is not useful in the diagnosis of congenital herpes simplex.

Blood PCR	CSF PCR	Eye/mouth/rectal viral culture
The best test for disseminated disease	The best test for meningitis	The best test for skin/eye/mouth disease
<b>Ophthalmology consult for a comprehensive eye exam</b>		

## Treatment

Treatment of congenital herpes simplex includes **intravenous acyclovir** 20 mg/kg/dose three times a day for two to three weeks. **Neutropenia** is commonly seen in treated infants and **repeated complete blood counts** should be performed.

Neonates with congenital herpes simplex should be placed in the **intensive care** unit. Primary or recurrent active genital herpes in a pregnant woman at time of labor is an indication for **cesarean delivery**.

## References

Sue G. Boyer, Kenneth M. Boyer, [Update on TORCH infections in the newborn infant](#), Newborn and Infant Nursing Reviews, Volume 4, Issue 1, March 2004, Pages 70-80, ISSN 1527-3369, <https://doi.org/10.1053/j.nainr.2004.01.001> (<http://www.sciencedirect.com/science/article/pii/S1527336904000029>)

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