

TORCH INFECTIONS, PATHOGENICITY & MORTALITY ASSESSMENTS

By

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Abstract

A TORCH infection, also known as TORCH syndrome, is an infection of the developing fetus or newborn that can occur in utero, during delivery, or after birth. TORCH syndrome is a cluster of symptoms caused by congenital infection with toxoplasmosis, rubella, cytomegalovirus, *Herpes simplex*, and other organisms including syphilis, parvovirus, and Varicella zoster as well as Zika virus and others. TORCH syndrome is caused by in-utero infection with one of the TORCH agents, disrupting fetal development. Early diagnosis by specific IgM and persistence of IgG beyond 6-9 months is diagnostic. TORCH syndrome may develop before birth, causing still-birth, in the neonatal period, or later in life, refers very broadly pathogens that cause perinatal infection and contribute to neonatal morbidity and mortality. They can cause non-specific signs and symptoms in the fetus or infant, such as microcephaly, lethargy, cataracts, hearing loss, and congenital heart diseases. Other signs include hepatosplenomegaly, petechiae or purpura, jaundice, vision loss, intellectual disability, deafness, and seizures. Treatment of pregnancy women is supportive and depends on symptoms present and thereby preventing the infection from affecting the fetus.

Key words: Toxoplasmosis, Other agents, Rubella Cytomegalovirus, Herpes simplex, Overview

Introduction

Original of TORCH perinatal infections was a group five pathogens with similar presentations including rash and ocular infection (Epps *et al*, 1995). TORCH is an acronym for Toxoplasmosis, Others, Rubella, Cytomegalovirus, & *Herpes simplex* (Stegmann and Carey, 2002). These are: 1-Toxoplasmosis, 2- Others (Syphilis, *Varicella zoster*, HBV, HIV, & Parvovirus B19), 3-Rubella, 4- Cytomegalovirus, & 5- *Herpes simplex* (Doménech *et al*, 1997). It is known in neonatal/perinatal medicine with others including enteroviruses, Varicella zoster virus, & Parvovirus B19, broadening another category to include amore pathogens was proposed (Maldonado *et al*, 2011).

Given increasing pathogens numbers were responsible for in utero and perinatal infections, the validity of indiscriminate screening of neonates or infants with data compatible with congenital TORCH infection questioned titers (Stamos and Rowley, 1994). An approach involves testing of infants with

suspected congenital infections for specific pathogens based upon clinical presentation (Kinney and Kumar, 1988). Now diagnosis of perinatal acquired infections is crucial to the initiation of appropriate therapy. A high suspicion index for congenital infection and awareness of the prominent features of the commonest congenital infections facilitate early diagnosis of congenital infection.

Screening: Pregnant women screening for TORCH infections varies geographically, pregnant women may reduce adverse pregnancy incidence and prevent birth defects. American College of Obstetricians & Gynecologists (ACOG) recommended that pregnant women must be screened for rubella and syphilis at the first prenatal visit. In other countries, pregnant women were screened for toxoplasmosis (Khan and Kazzi, 2000). Asymptomatic infants generally were not tested for congenital infections, but some European countries and some of United States provide universal toxoplasmosis screening (Garland and Gilbert, 1993). IgM antibodies

in newborn were suggestive of congenital infection (IgM not cross placenta), indiscriminate screening for TORCH infections with battery of its titers was expensive without good diagnostic yield (Cullen *et al*, 1998). An alternate approach involves infants testing for suspected congenital infections for specific pathogens based upon clinical presentation (Leland *et al*, 1983).

Review and General discussion

1- Congenital toxoplasmosis: Toxoplasmosis is caused by a protozoan parasite *T. gondii*, primary during pregnancy caused congenital disease. Also, infection is acquired during childhood and adolescence (Welton and Ades, 2005). *Toxoplasma gondii* is an obligate intracellular exists in 3 forms: the oocyst, which is shed only in cat feces; tachyzoite (a rapidly dividing form observed in the acute infection phase); and bradyzoite (a slow growing form within the tissue cysts (Remington *et al*, 2006). During a primary infection, a cat can shed millions of oocysts daily from its alimentary canal for a period of 1 to 3 weeks. Oocysts become infective 1 to 5 days later and may remain infectious for over a year, especially in warm, humid environments (Wendte *et al*, 2010). Cats typically develop immunity after a primary infection; and recurrent infection with passage of oocysts was unlikely (Cook *et al*, 2000). In developed temperate climate countries, the main source of maternal infection is by ingestion of bradyzoites contained in undercooked or cured meat or meat products (de Moura *et al*, 2006). Ingestion of oocysts, from contaminated soil or water, or eating soil-contaminated fruit or vegetables is also a major infective source (Boyer *et al*, 2011). Infection rates declined over the last 30 years, with 10 to 50% of adults aged 15 to 45 years showed serological evidence of past infection (Gilbert, 2000). Much higher infection rates (up to 80%) were found in tropics in communities exposed to contaminated soil, undercooked meat, or unfiltered water (Bahia-Oliveira *et al*, 2003). Also, needle-stick injury and blood transfusion as noso-

comial was reported (Saleh *et al*, 2016)

Acute toxoplasmosis infection in a mother is usually asymptomatic, but when occurs, are nonspecific, such as fatigue, fever, headache, malaise, & myalgia, but lymphadenopathy being a more specific sign (Gilbert and Gras, 2003). Immunocompetent women infected prior to conception never transmit toxoplasmosis to fetus, although rare exceptions (Chemla *et al*, 2002), but immunocompromised ones (e.g., with AIDS or on immunosuppressive drugs) may have parasitemia during pregnancy despite preconception infection; infants were at congenital risk (Boumahni *et al*, 2004). Fatality increased with advancing gestational age at time of maternal seroconversion; transmission risk 15% if a mother seroconverted at 13 weeks, 44% at 26 weeks, & 71% at 36 weeks (Thiébaud *et al*, 2007).

Clinically: About 80 to 90% of acute toxoplasmosis in immunocompetent hosts was asymptomatic (Remington, 1974). If occurred, commonest one was bilateral, symmetrical, non-tender cervical adenopathy; with lymph nodes were usually < 3cm in size and non-fluctuant (McCabe *et al*, 1987). But, 20 to 30% of symptomatic ones showed generalized lymphadenopathy, constitutional ones, as fever, chills, and sweats were mild.

Headaches, myalgias, pharyngitis, diffuse non-pruritic maculopapular rash, or hepatosplenomegaly may also occur. Most immunocompetent patients showed a benign, self-limited course from weeks to months, or rarely more (O'Connell *et al*, 1993), rare pneumonitis, acute respiratory distress, myocarditis, pericarditis (Leal *et al*, 2007), polymyositis (Calore *et al*, 2000), hepatitis, or encephalitis (Montoya *et al*, 2005).

Toxoplasmosis is one of the commonest causes of chorioretinitis (posterior uveitis) in immunocompetent hosts, occurred congenital or postnatal. Adults with acquired disease in infancy or childhood can show bilateral eye involvement, scarring, and recurrences secondary to reactivation disease. Patients > 40 years of age are at risk of recur-

ce than younger ones; clusters of episodes can occur after prolonged disease-free intervals. Acute adult patients suffered from unilateral ocular disease without prior scarring (Gilbert and Stanford, 2000).

A small proportion of women terminated pregnancies because of toxoplasmosis, but termination is discouraged unless there was risk fetal infection based on PCR result and ultrasound intracranial abnormalities (Binguet *et al*, 2004). Rationale for this approach is that the infected babies have a good prognosis and, on average, do not differ in their development at 3 to 4 years from uninfected children (Freeman *et al*, 2005). Fetuses with ultrasound intracranial lesions were at high risk of neurological sequelae or postnatal death. It was not clear whether prenatal treatment reduced risk of intracranial lesions (McLeod *et al*, 2006). In France about 1.4% of 1208 infected women underwent termination, and majority had fetal infection (Thalib *et al*, 2005). Generally, if a woman was infected before becoming pregnant, the unborn child would be protected by mother's developed immunity. If a woman becomes newly infected during or just before pregnancy, she can pass infection to unborn baby (congenital transmission). Damage to unborn child is often more severe in earlier pregnancy transmission.

Potential results can be: a- miscarriage, b- stillborn child, or c- child born with signs of congenital toxoplasmosis as abnormal enlarged or small head (CDC, 2018). Infants infected before birth showed no symptoms, but develop later in life with potential vision loss, mental disability, and seizures. Although subclinical disease is rule; signs present at birth may be fever, maculopapular rash, hepatosplenomegaly, microcephaly, jaundice, seizures, thrombocytopenia, and rarely, generalized lymphadenopathy. Classic congenital toxoplasmosis triad was chorioretinitis, hydrocephalus, and intracranial calcifications (Abdulla *et al*, 1994). Symptoms and signs in infancy and later were: abnormal spinal fluid, anemia, chorioretinitis, convu-

lsions, deafness, fever, growth and mental retardations, hepatomegaly, hydrocephalus, intracranial calcifications, jaundice, learning disabilities, lymphadenopathy, maculopapular rash, microcephaly, spasticity and palsies, splenomegaly, thrombocytopenia or visual impairment (Jones *et al*, 2003).

In Egypt, some many authors dealt with toxoplasmosis (references Saleh *et al*, 2014)

2- Congenital syphilis: Spirochete *Treponema palladium* is transmitted from a pregnant mother to her fetus, causing stillbirth, hydrops fetalis, or prematurity and associated long-term morbidity, associated with several adverse outcomes (CDC, 2010) including: perinatal death, premature delivery, low birth weight, congenital anomalies, active congenital syphilis in neonate and long-term sequelae; as deafness and neurologic impairment. Because of morbidity, great emphasis was done on routine syphilis screening of all pregnant women (Golden *et al*, 2003). Early syphilis was referred to as primary, secondary, & early latent syphilis, which typically occurred within the first year after infection, classically associated with sexual transmission (Fiumara, 1951). Ricci *et al*. (1989) reported vertical transmission at any stage and perinatal one in 50% of patients with primary or secondary syphilis, with fewer congenital infections in women with early latent (40%), late (10%), & tertiary disease (10%).

Diagnosis: Serological testing was carried out on mother and infant. If neonatal IgG antibody titers were significantly high than the mother's then congenital syphilis can be confirmed. Specific IgM in infant was test of confirmation; pleocytosis raised protein level and positive CSF serology suggested neurosyphilis (Michael and Isaacs, 2012). Follow-up of treated children with congenital syphilis, serial nontreponemal (VDRL or RPR) serology must be repeated at 1, 2, 4, 6 & 12 months. Nontreponemal titer must be nonreactive by a year of age when appropriately treated. Children with persistent positive titers, even at a low level, must have a second treatment course. Treated neuro-syp-

hilis infants (positive CSF VDRL, or abnormal cell count or protein) must have a repeat CSF examination at 6 month intervals until normal (Arnold and Ford-Jones, 2000).

Signs and symptoms: Most babies infected before birth appeared normal. By time, symptoms may develop. In babies less than 2 years old, symptoms may include: enlarged liver and/or spleen (mass in belly), failure to gain weight or failure to thrive (including prior to birth, with low birth-weight), fever, irritability, irritation and cracking of skin around the mouth, genitals, and anus, rash starting as small blisters, especially on the palms and soles, and later changing to copper-colored, flat or bumpy rash, skeletal (bone) abnormalities, unable to move a painful arm or leg, watery fluid from nose.

Symptoms in older infants and young children may include: abnormal notched & peg-shaped teeth (Hutchinson teeth), bone pain, blindness, cornea clouding (covering of eyeball), decreased hearing or deafness, nose deformity with flattened nasal bridge (saddle nose), gray, mucus-like patches around anus and vagina, joint swelling, saber shins (lower leg bone), skin scarring around mouth, genitals and anus (Kollman and Dobson, 2016)

Treatment: For proven or probable syphilis in the first four weeks of life, treatment is aqueous crystalline penicillin G: 50.000 units/kg/dose I.V. every 12hr in first week, and increased to every 8hr after seven days of life, for 10 to 14 days. An alternative treatment is aqueous procaine penicillin G: 50.000units/kg /day I. M. for 10 to 14 days. Infants at least 4 weeks old or older were treated with aqueous penicillin G: 50.000units/kg/dose every 6hr I.V. for 10 to 14 days due to difficulty to exclude neuro-syphilis (CDC, 1998). CDC (1998) added that for the asymptomatic treatment, exposed infant was controversial. Some experts gave a full penicillin course to asymptomatic ones (with normal CSF & radiographic examination) and have an inadequate maternal treatment history, includes no maternal treatment; in-

sufficient penicillin treatment (single dose of benzathine penicillin G for late latent syphilis); failed penicillin therapy (inadequately response to treatment); adequate one must be given less than a month before delivery; or treatment with a non-penicillin regimen. Alternative to immediate treatment was close follow-up with initiation of therapy if there were signs or symptoms, or if non-treponemal titers increase or fail to decline, a single dose of benzathine penicillin G was recommended for this scenario, especially when follow-up was not assured, but treatment failures occurred (Beck-Sague and Alexander, 1987). Arnold and Ford-Jones (2000) reported that if adequate follow-up of an exposed, asymptomatic infant cannot be guaranteed, consideration must be given to a therapy full course for the child before hospital discharging. Infant born to mothers who were HIV co-infected and in whom follow-up cannot be assured must be treated for 10 to 14 days, regardless of maternal treatment history and symptomatology as response to maternal treatment was unpredictable. Children born to mothers with signs or symptoms of secondary or early latent syphilis within a year after delivery must be tested and treated if serology is reactive. Congenital syphilis incidence reflected the syphilis rate in women childbearing age. Many congenital cases developed as a mother neither received prenatal care, nor penicillin, or inadequate treatment before or during pregnancy (Chakraborty and Luck, 2008).

In Egypt, WHO (2018) reported that deaths was 324 (0.0.6% of total deaths and the age adjusted death rate was 0.23/100.000 with rank of#82 in the world populations

3- Congenital rubella: (CRS) can develop in fetus of a pregnant woman who has contracted rubella, usually in first trimester. If infection occurred 0-28 days before conception, infant is affected with 43% risk, if 0-12 weeks after conception; risk increased to 81% if 13-26 weeks after conception, risk was 54% being affected by the disease but,

infants are not generally affected if rubella was contracted during third trimester, or 26 to 40 weeks after conception. Problems rarely occur when rubella is contracted by mother after 20 weeks of gestation, and continues to disseminate virus after birth (William, 2011). Rubella is very dangerous for a pregnant woman and her developing baby. Also, postnatal rubella (German measles) is a generally mild, self-limited illness characterized by rash, lymphadenopathy, and low-grade fever (Heggie and Robbins, 1969). But, congenital rubella may cause many anomalies, depending on the organ system involved and gestational age. Anyone who was not vaccinated against rubella would be at risk of getting the disease. Oster *et al.* (2010) reported that the classic triad for congenital rubella syndrome in patients was sensorineural deafness (58%), eye abnormalities, especially retinopathy, cataract, glaucoma, and microphthalmia (43%), and congenital heart disease, mainly pulmonary artery stenosis and patent ductus arteriosus (50%). Other CRS manifestations may include spleen, liver, or bone marrow problems (some of which may disappear shortly after birth), intellectual disability, microcephaly, low birth weight, thrombocytopenic purpura, extramedullary hematopoiesis (presents as a blueberry muffin rash), enlarged liver, small jaw size, & skin lesions (Muhle *et al.*, 2004). Also, children must be closely watched on their development for any indication of autism, developmental delay, growth retardation, learning disabilities, or schizophrenia (Brown, 2006), and diabetes mellitus (Forrest *et al.*, 1971).

Prevention: vaccinating majority of population is effective to prevent congenital rubella syndrome, and is a must for women who plan to be pregnant & measles mumps, rubella (MMR) vaccination must be, at least 28 days prior to conception (CDC, 2020)

Gadallah *et al.* (2014) in Egypt adopted a comprehensive strategy to eliminate measles and rubella by conducting a catch up campaign (2008) targeting children & young ad-

ults in age to explore rubella seroprevalence as well as among females aged 20 to 30 years. They reported relatively low seroprevalence rate of rubella antibodies

4- Congenital cytomegalovirus: Cytomegalovirus (CMV) is a ubiquitous virus worldwide. Despite its listing as the fourth infection in TORCH designation, CMV emerged as the commonest congenital viral one (Mussi-Pinhata *et al.*, 2009), with birth prevalence of 0.48 to 1.30% in last decades (van der Weiden *et al.*, 2011). Most infants with congenital CMV were asymptomatic, but about 10 to 15% of infected infants experience symptomatic infection that can be severe and fatal (Davis *et al.*, 2017). Both asymptomatic and symptomatic newborns were at risk to develop long-term neurodevelopmental morbidity, particularly sensorineural hearing loss (Fowler *et al.*, 2018).

Epidemiology: Primary infection and reactivation of virus can occur during pregnancy, and both can result in congenital CMV, the commonest congenital viral infection. About 40,000 infants were born with congenital CMV infection annually in the USA. Although majority of congenital infections were asymptomatic, about 5 to 20% of infants born to mothers with primary CMV infection may be overtly symptomatic. Such children have a mortality rate of 30%, and severe neurologic morbidity in 80% of survivors (Coles, 1988). CMV seroconversion during pregnancy was 2.0 to 2.5% (Lazzarotto *et al.*, 1999). Intrauterine infection was in 0.5 to 2% of all live births. Congenital infection from seropositive women ranged from 0.2 to 1.5%, but primary maternal infection during pregnancy gave infection to 40% fetuses (Stagno and Whitley, 1985). Lamarre *et al.* (2016) in Canada found that 40.4% of pregnant women were CMV seropositive, but CMV infection was associated with working as a daycare educator, lower education and income, having had children, mother language neither French nor English, and not born in Canada or USA. They added that of initially seronegative women,

24/1122 (2.1%) seroconverted between first & third trimesters, and 60% pregnant women were CMV infection susceptible and seroconversion rate. Torii *et al.* (2019) in Japan reported that seroconversion of CMV IgG and high IgM during early pregnancy were cCMV predictors, and high IgM titer (> 7.28 index) was a predictor despite relative low sensitivity. IgG levels had already plateaued at first evaluation in mothers with cCMV. Maternal screening offered insufficient positive predictive value for diagnosing cCMV, but identified asymptomatic cCMV cases in early stages. General, little risk of CMV related complications in children of infected mothers at least 6 months before conception, comprised 50 to 80% of women of child-bearing ages, newborn CMV was 1% (Boppana *et al.*, 1999). These infants had little significant illness or sequels, but severe fetal cytomegalic inclusion disease after CMV maternal reactivation during first trimester (Rousseau *et al.*, 2000).

Factors that can influence CMV infection during pregnancy include maternal age, parity, and gestational age (Gratacap-Cavallier *et al.*, 1998). Gestational age didn't influence transmission risk of CMV in utero (Demmler, 1991), but risk increase was in late gestation in a retrospective study (36, 45, & 78%, for first, second, & third trimesters, respectively), more severe sequelae were acquired in earlier pregnancy (Bodéus *et al.*, 1999a).

Transmission: By contact with the patient passing virus in saliva, urine, or body fluids. Congenital CMV infection resulted from virus transplacental transmission, also sexually, via organ transplants, by breast milk, and, rarely, blood transfusion. Transmission was higher in households with young children or in daycare centers were up to 70% in children 1 to 3 years old (Raynor, 1993).

Clinical manifestations: Congenital CMV has a wide constellation of clinical symptoms, ranging from none to fulminant end-organ dysfunction. About 90% of the infants with congenital CMV infection are asym-

ptomatic at birth. But, 0.5 to 15% of these children were at risk of developing psychomotor, hearing, neurologic, ocular, or dental abnormalities within the first few years of life (Casteels *et al.*, 1999). Some asymptomatic infants with congenital CMV infection were identified by newborn hearing screening (Stehel *et al.*, 2008). Sensorineural hearing loss was in 5 to 10% of cases and interfered with learning abilities (Kumar *et al.*, 1984). Hearing loss was associated with increased CMV concentrations in peripheral blood and urine (Boppana *et al.*, 2005). About 10% of congenital CMV infection infants were symptomatic (Britt, 2011). Symptomatic congenital infection correlated with virus amount in amniotic fluid; infants born to mothers with $\geq 10^3$ genome equivalents in amniotic fluid by PCR had a 100% probability of acquiring CMV, and with $\geq 10^5$ genome equivalents, which was symptomatic (Guerra *et al.*, 2000).

Symptomatic infants (50%) were presented with an attenuated form of congenital infection, usually consisting of isolated splenomegaly, jaundice, and/or petechiae (Kylat *et al.*, 2006). Others 50% were present with the syndrome of cytomegalic inclusion disease, consisting of jaundice; 67%, hepatosplenomegaly; 60% & petechial rash; 76% (Boppana *et al.*, 1992). Multiorgan involvement as microcephaly, motor disability, chorioretinitis, cerebral calcifications, lethargy, respiratory distress, and seizures were reported (Saigal *et al.*, 1982). Laboratory abnormalities were abnormal CBC (mainly thrombocytopenia), hemolytic anemia, elevated transaminases, and direct & indirect bilirubin. In this fulminant presentation, mortality was up to 30% within a few days or weeks. In survivors, jaundice and hepatosplenomegaly may subside, but neurologic sequelae (as microcephaly, intellectual disability or mental retardation, hearing disorders) persist (Istas *et al.*, 1995). About 80% of symptomatic infants at birth developed late complications as hearing loss, vision impairment, and varying degrees of intellectual disability and

delay in psychomotor development. Acquired infections in late pregnancy gave less prominent signs, but severe problems associated with CNS calcification, microcephaly, & hearing loss were reported (Steinlin *et al*, 1996). Many brain abnormalities were reported on cranial imaging (as unenhanced computed tomographic scan or CTS). Abnormalities include periventricular leukomalacia and cystic abnormalities, periventricular calcifications (linear or punctate), ventriculomegaly, vasculitis, neuronal migration abnormalities, and hydranencephaly (Noyola *et al*, 2001).

Sensorineural hearing loss was > 65% of symptomatic congenital CMV infected newborns (Boppana *et al*, 1997). Like that associated with asymptomatic infection, hearing loss always progressive, eventually producing severe to profound hearing loss in the affected ear. The infants with hearing loss caused by congenital CMV infection or disease may be cognitively normal, or they may experience cognitive delays, depending upon degree of brain involvement in utero (Williamson *et al*, 1992). Ocular abnormalities, including chorioretinitis (a posterior uveitis), retinal scars, optic atrophy, & central vision loss, also may occur. Among 125 infants with congenital CMV, 42 were symptomatic, visual impairment was significantly commonest in symptomatic patients; 22 vs. 2.4% (Fowler *et al*, 1997). Moderate to severe involvement was frequently bilaterally included optic atrophy, macular scars, and cortical visual impairment. Strabismus was more frequent in those with symptomatic compared to asymptomatic CMV; 29 vs. 1.2% (Coats *et al*, 2000). Microcephaly, intracranial calcifications, or other CT scan abnormalities & chorioretinitis correlated with a poor neurodevelopmental outcome, but without such factors predict a normal or near-normal cognitive outcome. Symptomatic congenital CMV infants must undergo regular screening of hearing, vision, & development, with follow-up testing and referred as indicated.

Diagnosis: Congenital CMV infection is by virus isolation in urine, or saliva samples within the first 3 weeks of life. They often have very high virus titers, and culture frequently becomes positive within one to three days of incubation. The use of culture enhancement centrifugation systems, such as the shell vial assay (staining for early antigen production), was substituted for traditional cell monolayer culture in many laboratories. Detection of CMV/DNA in urine and serum of newborns also by PCR was used to diagnose congenital CMV infection, but these methods were less available, more expensive, and often less reliable than was traditional cell culture or shell vial culture of urine (Nelson *et al*, 1995). CMV-IgM antibodies in cord serum or as part of a TORCH titer panel were highly suggestive of congenital infection but must be confirmed by viral culture. CMV-IgG antibody was not helpful as most of general population had CMV antibody, and positivity reflected a passive transfer of maternal antibody to infant. The CMV-IgM itself cannot diagnose primary CMV infection because IgM can be present during secondary CMV infection IgM positive in combination with low IgG avidity results are considered reliable evidence for primary infection (CDC, 2020).

Different approaches were evaluated to identify women at risk of transmitting CMV during pregnancy. Amniocentesis for PCR or culture is the preferred method of diagnosis, but negative results didn't exclude intrauterine infection. Ultrasonographic markers, including microcephaly, hepatosplenomegaly, and intracranial calcification, may suggest fetal CMV infection, but normal ultrasonography does not exclude the diagnosis. Measurement of IgM, & IgG avidity determination, and combined application of the microneutralization and avidity assays are additional approaches to making a prenatal diagnosis (Bodéus *et al*, 1999b).

Differential diagnoses: CMV must be differentiated (Emery, 2001): 1- autoimmune hepatitis, 2- enteroviruses, 3- fever of unkn-

own origin (FUO), 4- HIV & AIDS, 5- human herpes virus 6 (HHV-6), 6- Epstein-Barr virus (EBV) infectious mononucleosis, 7- toxoplasmosis & 8-viral hepatitis. But, in immunocompromised host it must be differentiated from 1- Aspergillosis, 2- Brain abscess (Patel and Clifford, 2014), 3- Chagas disease 4- Chickenpox, 5- Cryptococcosis, 6- CNS lymphoma, 7- Disseminated tuberculosis, 8- HSV infection and 9- Progressive multifocal leukoencephalopathy (Bustamante and Wade, 1991).

Treatment: In a phase II randomized, controlled multicenter clinical trial evaluating use of ganciclovir[®] for infants with symptomatic congenital CMV infection and evidence of CNS involvement, 47 infants given ganciclovir as 8 to 12mg/kg daily in 2 divided doses for up to 6 weeks (Whitley *et al*, 1997). Ganciclovir was discontinued in 8 patients because of side effects, but was well tolerated in other newborns. Decreased virus excretion was noted with ganciclovir administration, although virus returned promptly after therapy cessation. Infants 16% had stabilization or hearing improvement at 6 months of follow-up and similar success was in a smaller trial (Nigro *et al*, 1994).

A phase III randomized clinical trial of ganciclovir (6mg/kg/dose IV every 12hrs) for 6 weeks in neonates with virologically confirmed congenital CMV disease and neurologic involvement suggested that treatment with ganciclovir prevents hearing deterioration at six months and possibly beyond. Conclusion was limited as only 42/100 enrolled subjects were evaluated for primary outcome; hearing assessment at 6months (Kimberlin *et al*, 2003). Besides, neutropenia (absolute neutrophil count \leq 1250/ microL) was more common among ganciclovir recipients than controls (63 vs. 21%). It was unknown whether this early and intensive administration of ganciclovir would hasten disease resolution, beneficially influence growth and development, decrease auditory and visual impairment, or improve intellectual outcome in these infants. Ganciclovir

must not be routinely used for fear of unforeseen long-term effects, such as testicular atrophy and bone marrow suppression. But, it may be reasonable to consider in selected cases. However, anecdotal evidence does suggest that critically ill newborns, especially those who are premature and have CMV pneumonia, may benefit acutely from ganciclovir treatment. Compassionate use also may be appropriate for patients with life- or little threatening congenital CMV. Thus, its use only with careful consideration in selected cases (Prober and Enright, 2003).

Treatment of asymptomatic newborns with congenital infection was not indicated. Even though the infants were at some risk for hearing loss, side effects of therapy with available antiviral agents and lack of established benefit argue against routine use. CMV hyperimmune globulin was not evaluated extensively to treat congenital CMV. But, one anecdotal reported some benefit. CMV immune globulin and alpha interferon for congenital CMV treatment, and development of vaccines was underway (Nigro *et al*, 1999).

In Egypt, Kamel *et al*. (2014) in a cross-sectional study of 546 pregnant at Suez Canal University Hospital, reported that IgM positive women had no primary CMV infection in the index pregnancy as evidenced by the high CMV IgG avidity testing.

5- Herpes simplex virus: Genital *Herpes simplex* virus (HSV) infection during pregnancy poses a significant risk to develop fetus and newborn commonly cause recurrent infection affecting the skin, mouth, lips, eyes, and genitals (Plotkin, 2001). HSV is transmitted to an infant during birth, primarily through an infected maternal genital tract, and genital herpes during pregnancy led to spontaneous abortion, intrauterine retardation growth, preterm labor, and congenital & neonatal herpes infection (Ciavattini *et al*, 2007). In childbirth HSV-1 & HSV-2 are vertically transmitted (Corey and Wald, 2009), and called non-genital HSV (Usatine and Tinitigan, 2010).

Herpes viruses (Herpesviridae family) are

eight types, 2 of which are HSV-1 & 2 infect man. Both HSV-1 & HSV-2 cause oral or genital infection. HSV-1 causes gingivostomatitis, herpes labialis, & herpes keratitis. HSV-2 causes genital lesions (Ryan and Ray, 2004). Lafferty (2002) in USA reported increased prevalence of genital HSV infection worldwide, and with high prevalence of HSV-2 in Europe among antenatal persons that the commonest cause of genital ulceration in the developing world. He added that people with a high standard of life may escape oral HSV-1 infection in childhood, as asymptomatic oral shedding HSV-1 was common, adults without immunity to HSV-1 who practice oral sex mainly at risk for genital HSV-1 infection. Suligoj *et al.* (2002) in Italy reported that HSV-2 seroprevalence was higher among patients' attended clinics for sexually transmitted diseases (STD) than among general population, with ages increase, and suggested seroscreening for HSV-2 for STD patients. Weiss (2004) in U.K. reported that HSV-2 was a common infection in many countries, with high prevalence in sub-Saharan Africa, than in USA. He added that in sub-Saharan Africa adult infection ranged from 30% to 80% in women, & from 10% to 50% in men, with HSV-2 the major causes of morbidity and increases HIV risk acquisition, due to mucosal membranes disruption. Malkin (2004) in France found that prevalence of HSV-2 infection varied between developed countries. In healthy adults, HSV-2 seroprevalence was higher in USA than in Europe and that the proportion of genital herpes infections caused by HSV-1 increased in the developed world, possibly due to changes in oral-genital sexual behavior and lower rates of HSV-1 acquisition in childhood. Marchi *et al.* (2017) in Italy reported that HSV-2 was one of the commonest causes of genital disease, but HSV-1 is associated primarily with orolabial ulceration; but, HSV epidemiology changes gave increase in genital and neonatal herpes especially caused by HSV-1. Reg-ezi *et al.* (2017) reported that HSV affected

areas of skin exposed to contact with a patient (shaking hands with an infected one didn't transmit disease). Many patients never develop symptoms and signs, but if occurred may include watery blisters in skin or mucous membranes of mouth, lips, nose, or genitals caused by HSV-1, but HSV-2 causes genital lesions (Ryan and Ray, 2004) or ocular herpes (Farooq and Shukla, 2012).

Other symptoms include pain, itching, and burning. Less frequent, but common symptoms include discharge from penis or vagina, fever, headache, muscle pain, swollen and enlarged lymph nodes and malaise, also women in addition suffered from painful urination, and cervicitis as well as herpetic proctitis (inflammation of anus & rectum) common in individuals participating in anal intercourse (Gupta *et al.*, 2007). Lesions in males were on glans penis, shaft of penis or other genital parts, on inner thigh, buttocks, or anus, and in females were on or near pubis, clitoris or other parts of vulva, buttocks or anus (Hofstetter *et al.*, 2014).

Diagnosis: Usually based on a physical exam and certain laboratory tests: 1- Viral culture involves taking a tissue sample or sores scraping for laboratory examination. 2- PCR to copy patient DNA from a sample of his blood, tissue from a sore or spinal fluid. DNA can be tested for HSV to determine its type. 3- Blood for HSV antibodies to detect a past herpes infection.

Ocular herpes by a specific clinical diagnosis of HSV as the cause of dendritic keratitis can be made by ophthalmologists based on the characteristic clinical features (Barker, 2008). Corneal smears or impression cytology specimens can be analyzed by culture, antigen detection, or fluorescent antibody testing. Serologic tests may show a rising antibody titer during primary infection but are of no diagnostic assistance during recurrent episodes.

Treatment usually involves general-purpose antiviral drugs that interfere with viral replication, reduce physical severity of outbreak-associated lesions, and lower trans-

mission chance to others. Daily use of antivirals valaciclovir Kimberlin *et al*, 2011), which can reduce reactivation rates (Koelle and Corey, 2008). Extensive use of anti-herpetic drugs led to drug resistance development, which in turn led to treatment failure. Pyrithione; a zinc ionophore have anti-HSV activity (Qiu *et al*, 2013). Treatment of eye herpes was based on presentation of epithelial keratitis caused by live virus while stromal disease is an immune response and metaherptic ulcer results from inability of corneal epithelium to heal (Wilhelmus, 2015). Antiviral treatment may reduce HSV keratitis risk recurring in people having a graft due to HSV infection and improve chances of graft survival

Neonatal conjunctivitis: Intravenous Acyclovir 60mg/kg/day every 8hrs for 14 days for SEM (Skin-Eye-Mouth) disease. Extend the treatment for 21 days for central nervous system involvement and the disseminated disease. Oral suppressive acyclovir therapy (300mg 2 or 3/day) to pregnant women with active, recurrent genital HSV infection from 36 weeks of gestation & elective Caesarean surgery before membranes breakage gave best prevention for birth-HSV transmission (Kimberlin *et al*, 2001).

Other HSV complications: a possible link between HSV-1 and Alzheimer's disease in people with epsilon4 allele of gene APOE (Middleton *et al*, 1980). Sevilla *et al*. (2004) in Spain reported an adolescent with Hodgkin disease that developed fatal hepatic failure secondary to acute HSV. Looker *et al*. (2017) in U K reported that of HSV-2 infection increased risk of acquiring HIV. Boukhalova *et al*. (2019) in USA reported an association between HSV-1 infection a ubiquitous human pathogen generally associated with facial cold sores, and multifocal brain demyelination in an otherwise normal host, cotton rat *Sigmodon hispidus*. Kirkland *et al*. (2020) in Germany reported a 30-year-old female with recurrent septic meningitis (Mollaret meningitis) from HSV-2.

Nasrallah *et al*. (2018) in Qatar found that

HSV-1 seroprevalence among immigrant Egyptians (97.5%), Yemenis (92.6%), Sudanese (90.7%), Syrians (88.5%), Jordanians (86.5%), Qataris (82.3%), Iranians (81.4%), Lebanese (81.4%), Palestinians (80.5%) and Pakistanis (77.0%).

6- Congenital varicella syndrome: Human alphaherpesvirus 3 (HHV-3), usually referred to as varicella-zoster virus (VZV), is one of the herpesviruses infecting man. It causes chickenpox (varicella), which commonly affecting children, teens, and young adults, and shingles (herpes zoster) in adults, but rare in children. Infections were species-specific to man, but can survive in external environments for a few hours (Nagel and Gildea, 2007). VZV infection in children is generally a mild, but infection in adults can lead to significant morbidity and mortality. During pregnancy, varicella pneumonia can be severe and maternal infection led to congenital abnormalities with devastating consequences (Lamont *et al*, 2011). Most congenital varicella syndrome occurred in infants whose mothers were infected between 8 & 20 weeks gestation. Characteristic findings in neonates include: 1- Cutaneous scars, which may be depressed & pigmented in a dermatomal distribution, 2- Cataracts, chorioretinitis, microphthalmos, nystagmus, 3- Hypoplastic limbs, & 4- Cortical atrophy & seizures (Gardella and Brown, 2007). If a mother acquired varicella during the early gestational period (weeks 8 to 20), fetus was at risk to develop congenital varicella syndrome as limb hypoplasia, skin lesions, neurologic abnormalities, and structural eye damage, but mother infected before or after delivery, baby was at risk for neonatal varicella, present with mild rash to disseminated infection (Enders *et al*, 1994).

Risky people for severe varicella include: 1-Immunocompromised people without evidence of immunity to varicella, 2- Newborns whose mothers have varicella from five days before to two days after delivery, 3- Premature babies exposed to varicella or herpes zoster, specifically, & 4- Pregn-

ant women without evidence of immunity to varicella. Diagnosis: 1- Maternal if doubted clinically infection may be confirmed by viral DNA detection by PCR testing of skin scrapings from vesicle base or by VZV antigen by immunofluorescence. Also, VZV can be cultured from vesicular fluid, although the virus replicates slowly and culture is less sensitive than direct detection techniques. 2- Prenatal diagnosis by PCR testing of fetal blood or amniotic fluid for VZV DNA in conjunction and with ultrasonography to detect fetal abnormalities (Mazzella *et al*, 2003). 3- Postnatal diagnosis required the following criteria (Alkalay *et al*, 1987): History of maternal varicella infection during first or second trimester, presence of compatible fetal abnormalities consistent with congenital varicella, & evidence of intrauterine infection. Watson *et al*. (2007) reported that intrauterine infection were diagnosed by detection of VZV/DNA in newborn; VZV-specific IgM antibodies in cord blood; VZV-IgG beyond 7 months of age or appearance of clinical zoster infection in early infancy. In 30% of cases, VZV reactivated later, causing shingles or herpes zoster (Harpaz *et al*, 2008).

Transmission: Varicella is highly contagious, as virus can be spread from person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster, and possibly via infected respiratory secretions that also may be aerosolized (CDC, 2011). A person with varicella is considered contagious beginning 1 to 2 days before rash onset until all the chickenpox lesions have crusted, and average incubation period for varicella is 14 to 16 days after exposure to a varicella or a herpes zoster rash, with a range of 10 to 21 days. A mild prodrome of fever and malaise may occur 1 to 2 days before rash onset, particularly in adults. In children, the rash is often the first sign of disease.

1- Person to person: Varicella is highly communicable with secondary attack rates in susceptible household contacts approach

90% in the pre-vaccination era, as patients are infectious from 1 to 2 days (nasopharyngeal mucosa or conjunctival or nasal/oral mucosa droplets) until lesions were crusted over (Marin *et al*, 2007).

2- Mother to infant: Maternal varicella infection not only has important implications for the mother's health, but also for her fetus (Harger *et al*, 2002). Transmission can occur in utero, perinatally, or postnatally, but postnatal varicella is transmitted through respiratory droplets or direct contact with varicella patient (Enright and Prober, 2004). Passage of varicella zoster virus to fetus during zoster is rare, low rates of transmission may be due to preexisting maternal antibody to VZV or lower levels of viremia that accompany VZV reactivation as shingles compared with primary infection to chickenpox (Gnann, 2002).

4- Nosocomial transmission of VZV is well-recognized and can be life threatening to certain groups of patients. Reports of nosocomial transmission are uncommon in the United States since introduction of varicella vaccine (CDC, 2013).

Treatment: By some drug agents included acyclovir[®] for chickenpox, famciclovir[®], valaciclovir[®] for shingles, zoster-immune globulin (ZIG), & vidarabine[®] (CDC, 2012). Acyclovir is frequently used as drug of choice in primary VZV infections when given early can significantly shorten duration of any symptoms. However, reaching an effective serum concentration of acyclovir typically requires intravenous administration, making its use more difficult outside of a hospital (Cornelissen, 2013)

Conclusion

1. TORCH infections are a group of perinatal infections with similar clinical presentations, including rash and ocular findings. Other important causes of intrauterine/perinatal infection include enteroviruses, varicella zoster virus, and parvovirus B19.

2. Intrauterine and perinatal infections are a significant cause of fetal and neonatal mortality and an important contributor to child-

hood morbidity. Awareness of the prominent clinical features of TORCH and other intrauterine/perinatal infections is crucial to timely diagnosis and initiation of treatment.

3. Classic triad of congenital toxoplasmosis is chorioretinitis, hydrocephalus, and intracranial calcifications; signs present at birth may include fever, maculopapular rash, hepatosplenomegaly, microcephaly, seizures, jaundice, thrombocytopenia, and, rarely, generalized lymphadenopathy. But, most congenital toxoplasmosis infants are asymptomatic or normalities at birth.

4. Most neonates with congenital syphilis are asymptomatic at birth. Clinical manifestations after birth are divided arbitrarily into early (≤ 2 years) & late (> 2 years of age). Clinical manifestations of congenital rubella syndrome include sensorineural deafness, cataracts, cardiac malformations (e.g., patent ductus arteriosus, pulmonary artery hypoplasia), and neurologic and endocrinologic sequelae. Neonatal manifestations include growth retardation, radiolucent bone disease (non-pathognomonic congenital rubella), hepatosplenomegaly, thrombocytopenia, purpuric skin lesions (classically described as blueberry muffin lesions that represent extramedullary hematopoiesis), and hyperbilirubinemia.

5. Most congenital cytomegalovirus (CMV) infants are asymptomatic at birth. Symptomatic infants, clinical manifestations include hepatosplenomegaly, jaundice, petechiae, & multiorgan involvement (e.g., microcephaly, motor disability, chorioretinitis, cerebral calcifications, lethargy, respiratory distress, seizures). Asymptomatic and symptomatic infants with congenital CMV are at risk to develop late complications including hearing loss, vision impairment, intellectual disability, and delay in psychomotor development.

6. Most newborns with perinatally acquired *H. simplex* virus appear normal at birth, although many are born prematurely. HSV infection in newborns usually develops in one of three patterns: localized to the skin, eyes, and mouth; localized CNS disease; and dis-

seminated disease. Initial CNS manifestations are frequently nonspecific and include temperature instability, respiratory distress, poor feeding, and lethargy; progress quite rapidly to hypotension, jaundice, disseminated intravascular coagulation apnea, & shock, with or without vesicular skin lesions.

7. Characteristic features of congenital varicella infection include cutaneous scars, cataracts, chorioretinitis, microphthalmos, nystagmus; hypoplastic limbs; cortical atrophy, and seizures.

8. Diagnosis of perinatally acquired infections is crucial to initiation of appropriate therapy. A high index of suspicion for congenital infection and awareness of prominent features of commonest congenital infections facilitate early diagnosis and tailor good diagnostic evaluation. Lack of maternal laboratory results compatible with intrauterine infection, intrauterine infection may be suspected in newborns with clinical, or combinations of clinical manifestations; as hydrops fetalis, microcephaly, seizures, cataract, hearing loss, congenital heart disease, hepatosplenomegaly, jaundice, or rash.

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Table 1: Clinical manifestations suggestive of specific neonatal congenital infections (Maldonado *et al*, 2011).

Cytomegalovirus	Periventricular intracranial calcifications
	Microcephaly
	Thrombocytopenia
Herpes simplex virus	Mucocutaneous vesicles or scarring
	CSF pleocytosis
	Thrombocytopenia
	Elevated liver transaminases
Rubella	Conjunctivitis or keratoconjunctivitis
	Cataracts, congenital glaucoma, pigmentary retinopathy
	Heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis)
	Radiolucent bone disease
Syphilis	Sensorineural hearing loss
	Skeletal abnormalities (osteochondritis and periostitis)
	Pseudoparalysis
	Persistent rhinitis
Toxoplasmosis	Maculopapular rash (particularly on palms and soles or in diaper area)
	Intracranial calcifications (diffuse)
	Hydrocephalus and/or microcephaly
	Chorioretinitis
Congenital varicella	Otherwise unexplained mononuclear CSF pleocytosis or elevated CSF protein
	Cicatricial or vesicular skin lesions
	Limb hypoplasia

Table 2: Clinical manifestations of early congenital syphilis (Chakraborty and Luck, 2008).

Gestational/perinatal	Stillbirth, Prematurity, Birth weight <2500g, Non-immune 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 umbilical vessels (necrotizing funisitis); barber-pole appearance (send for pathologic/histologic evaluation)
Systemic	Fever: More prominent in infants born to mothers affected late in pregnancy and with negative serology at delivery
	Hepatomegaly: Splenomegaly about 50% of patients with hepatomegaly, not only splenomegaly.
	Generalized lymphadenopathy: May be as large as 1 cm; generally non-tender and firm or Failure to thrive
	Edema: Due to anemia/hydrops fetalis, nephrotic syndrome, malnutrition
Mucocutaneous	Syphilitic rhinitis (snuffles): An early feature, developing after first week of life with infectious spirochetes (contact)
	Maculopapular rash: 1 to 2 weeks after rhinitis. Oval lesions, initially red or pink, then coppery brown; associated with superficial desquamation or scaling, mainly on palms or soles; commonest on buttocks, back, posterior thighs, and soles with infectious spirochetes (contact precautions).
	Vesicular rash (pemphigus syphiliticus): May be at birth, mostly develops in first 4 weeks; widely disseminated; vesicular fluid with infectious spirochetes (contact precautions)
	Condyloma lata: Single or multiple, flat, wart-like, moist lesions around mouth, nares, and anus and other skin areas with moisture or friction; lesions with infectious spirochetes (precautions); frequently present without other infection signs
	Jaundice: Hyperbilirubinemia secondary to syphilitic hepatitis and/or hemolysis
Hematologic	Anemia: Newborn period, hemolytic (Coomb's test, with negative direct antiglobulin test); may persist after effective treatment, After a month of age: chronic and/or nonhemolytic
	Thrombocytopenia: Associated? with bleeding or petechial; only congenital infection manifestation
	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; 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, may appear in 1 st few weeks.
	Wegner sign: Metaphyseal serration or "sawtooth metaphysis"
Neurologic	Weinberger sign: Demineralization and osseous destruction of upper medial tibial
	CSF abnormalities: Reactive CSF VDRL; elevated CSF white blood cell count; elevated CSF protein
	Acute syphilitic leptomenigitis: Onset in 1 st year of life, 3 to 6 months; as bacterial meningitis, CSF more consistent with aseptic meningitis (mononuclear predominance); treated by penicillin
Miscellaneous	Chronic meningovascular syphilis: Onset end of 1 st year; hydrocephalus; cranial nerve palsies; intellectual/ neurodevelopmental deterioration; cerebral infarction; protracted course
	Pneumonia/pneumonitis/respiratory distress: Complete pacification of lungs on chest radiograph
	Nephrotic syndrome: Usually at 2 to 3 months of age, with generalized edema and ascites

Table 3: Stigmata of late congenital syphilis (Dobson and Sanchez, 2009).

Face	Frontal bossing, saddle nose, short maxilla, protuberant mandible
Ocular	Interstitial keratitis, chorioretinitis, secondary glaucoma, corneal scarring, optic atrophy
Ears	Sensor neural hearing loss
Oropharynx	Hutchinson teeth, mulberry molars, perforation of hard palate
Cutaneous	Rhagades, gummas
CN system	Intellectual disability, arrested hydrocephalus, seizures, optic atrophy, juvenile general paresis
Skeletal	Saber shins (tibia anterior bowing), higoumenakis (sternoclavicular enlarge, clavicle portion), painless clutter joints,