Certain groups of congenital infection of the newborn are known by the name: TORCH by the acronym:

- Toxoplasmosis.
- Others (syphilis, HIV, coxsackie virus, hepatitis B, varicella-zoster).
- Rubella.
- Cytomegalovirus disease & Herpes simplex disease.

The overall incidence of these infections is about 2.5% at live newborns. The diagnosis from birth of these infections is very important because long term prognosis is affected.
CONGENITAL INFECTIONS

- Intrauterine infections can generate:
  - Abortion;
  - Stillbirth child;
  - Prematurity;
  - IUGR;
  - Congenital malformations;

  **Transmission:**
  - Transplacental - the most frequent.
  - Infected amniotic fluid;
  - During delivery;

The severity or the clinical manifestation of these infections at fetus or newborn depends on:

1. Gestational age - abortions and stillbirth child appear at early time of gestation.
2. The virulence of pathogen agent;
3. Primary or recurrent infections of the mother;
4. If fetus or newborn received transfer of antibodies from the mother;
CONGENITAL INFECTIONS

The mechanism by TORCH infections can produce congenital malformation may be explain by:
- The pertubance of embriogenesis;
- Tissular destruction of already formed organs;

Clinical manifestations of these infections may be:
- Absent;
- Subtle;
- Non-specific;
- Common with others diseases: RDS, sepsis.

CONGENITAL INFECTIONS

- These congenital are grouped together because of similar clinical presentation in many patients:
  1. Premature delivery;
  2. IUGR or intrauterine death;
  3. Jaundice, petechia or purpura;
  4. Hepatosplenomegaly, anemia, trombocytopenia;
  5. Hydrocephaly, microcephaly, intracranial calcification;
  6. Chorioretinitis;
  7. Myocarditis & cardiac abnormalities.
CONGENITAL INFECTIONS. Diagnosis approach.

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CONGENITAL INFECTIONS

- Mental retardation, deafness, visual sequel can be diagnosed later, hence the importance of correct diagnosis and management of a newborn under suspicion with TORCH infection. For each disease of this group there are specific signs and laboratory tests.
CONGENITAL INFECTIONS

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| **RUBELLA**             |                             |
|                        | Hidrocephaly                |
|                        | Cataracts or glaucoma       |
|                        | Hearing loss                |
|                        | Congenital heart disease    |

| **CYTOMEGALOVIRUS**     |                             |
|                        | Microcephaly with periventric calcification |
|                        | Petechiae                   |

| **HERPES SIMPLEX**      |                             |
|                        | Skin lesions                |
|                        | Keratoconjunctivitis        |
|                        | CNS involvement             |

CONGENITAL INFECTIONS - TOXOPLASMOSIS

Toxoplasma gondii is a protozoan parasite capable of causing intrauterine infection.

**Incidence**-varies from 12,5-1,5%, as primary infection for pregnant women and approximately 0,5-6,5%; as congenital infection.

The transmission of toxoplasmosis in human being, may be:

- Digestive-ingestion of unpasteurized milk, undercooked meat;
- Contact with cats feces;
- Hematogenous route-transplacental;
- Via blood products transfusion.
CONGENITAL INFECTIONS - TOXOPLASMOsis

- Infections transmitted earlier in gestation are likely to cause more severe fetal effects (abortion, stillbirth, or severe disease with teratogenesis). Those transmitted later are more apt to be subclinical. Rarely, a parasite may be transmitted via an infected placenta during parturition. Infections in the fetus or neonate usually involve disease in one or two forms: infection of the CNS or eyes, or infection of the CNS and eyes with disseminated infection. 70-90% of infants with congenital infection is asymptomatic at birth. However, visual impairment, learning disabilities, or mental impairment becomes apparent in a large percentage of children months to several years later.

CONGENITAL INFECTIONS - TOXOPLASMOSIS

If the mother is infected, the infection may or not be transmitted to the fetus. The later in pregnancy that infection is acquired, the more likely is transmission to the fetus:

- 14% in first trimester;
- 29% in second trimester;
- 59% in third trimester;
TOXOPLASMOSIS - Clinical presentation

Congenital toxoplasmosis may be manifested as clinical neonatal disease, disease in the first few months of life, late sequel or subclinical disease.

- Clinical disease → those who present with evident clinical disease may have disseminated illness or isolated CNS or ocular disease. Late sequel is primarily related to ocular or CNS disease.
- Obstructive hydrocephalus¹, chorioretinitis² and intracranial calcifications³ form the classic triad of toxoplasmosis.

TOXOPLASMOSIS - Clinical presentation

Signs and symptoms in infants with congenital toxoplasmosis include:

- chorioretinitis
- abnormalities of CNS (high protein value);
- anemia;
- seizures;
- intracranial calcification;
- direct hyperbilirubinemia;
- fever;
- hepatosplenomegaly;
- lymphadenophaty;
- vomiting;
- microcephaly or hidrocephaly;
- cataracts/glaucoma/optic atrophy;
- eosinophilia/bleeding diathesis;
- rash;
- pneumonitis.
TOXOPLASMOSIS - Clinical presentation

- Toxoplasmosis has been associated with congenital nephrosis, myocarditis and isolated mental retardation.
- Subclinical infection is believed to be the most common. Studies of this infant (in whom infection is identified by serologic testing or documented maternal infection) indicate that a large percentage may have minor CSF abnormalities at birth and later develop visual or neurological sequel or learning disabilities.

TOXOPLASMOSIS - Diagnosis

**Prenatal diagnosis** - can be made by detecting the parasite in fetal blood or amniotic fluid, or by documenting toxo IgM and IgA antibodies in fetal blood.

**Direct isolation of the organism from body fluids or tissues** - requires inoculating bloods, body fluids, or placental tissue into mice or tissue culture and is not already available.

**Serologic tests** - toxoplasma specific IgM antibodies can be measured by indirect fluorescent antibody (IFA) test, enzyme-linked immunosorbent assay (ELISA), or IgM immunosorbent agglutination assay (IgM-ISAGA); usually become positive within 1-2 weeks of infection. If IgM titters are high and accompanied by high specific IgG titters, as measured by IFA or Sabin-Feldman dye test, this suggests acute infection. IgA antibodies are found in more than 95% of patient with acute infections. Toxoplasma-specific Ig-E antibodies are found in almost all women who seroconvert during pregnancy.

**CSF** - examination should be performed in suspected cases. The most characteristic abnormalities are xantochromia, mononuclear pleocytosis and a very high protein level.

**Skull film or CT scan** of the head may demonstrate characteristic intracranial calcifications.

**Ophtalmologic exam** characteristically shows chorioretinitis.
TOXOPLASMOSIS – management & treatment

Management. Prevention of toxoplasmosis in pregnancy includes advising pregnant women to avoid eating raw meat or raw eggs and to avoid exposure to cat feces.

Treatment of symptomatic infants during the first 6 months of life consists of a combination of:

- **Pyrimethamine** - 1 mg/kg orally in 1 or 2 divided doses daily after an initial loading dose of 2 mg/kg day for two days.
- **Sulfadiazine** - 100 mg/kg/day orally, in two divided doses.
- **Leucovorin** (folinic acid) is given 5-10 mg every 3 days. After a 6-month regimen, treatment can be continued or modified to include 1-month courses of spiramycin alternating with 1-month courses of pyrimethamine, sulfadiazine, and leucovorin for an additional 6 months. Spiramycin is a macrolide antibiotic; it is given daily at a dose of 100 mg/kg/day in two divided oral doses.
- Corticosteroids are somewhat controversial; prednisone is given 1.5 mg/kg/day orally in two divided doses, in infants with chorioretinitis or elevations in spinal fluid protein, in order to decrease the inflammatory response.

Infants with symptomatic congenital toxoplasmosis are also treated for one year. They receive an initial 6 weeks course of pyrimethamine, sulfadiazine, and leucovorin followed by alternating courses of spiramycin for 6 weeks and the other three drugs repeated for 4 weeks.

Healthy infants born to mothers with gestational toxoplasmosis can be treated with a 4-weeks course of pyrimethamine, sulfadiazine, and leucovorin.

If diagnosis of congenital toxoplasmosis is established later, chemotherapy is continued as delineated for infants with subclinical infections.

Infants treated with pyrimethamine and sulfadiazine require weekly blood counts, platelet counts and urine microscopy to detect any adverse drug effects.
RUBELLA

- **Definition**: Viral infection capable of causing chronic intrauterine infection and damage to the developing fetus.
- **Incidence**: Varies from 0.1% to 2% of birth with higher incidence after rubella epidemics. The fetal infection rate varies according to the timing of maternal infection during pregnancy:
  - 1 - 12 weeks, there is an 81% risk of fetal infection;
  - 17 - 22w. = 36% risk;
  - 23 - 30w. = 30% risk;
  - 31 - 36w. = 60% risk;
  - Last month of pregnancy = 100%.
- **Pathophysiology**
  - Rubella virus is an RNA virus. Human are the only known hosts, with an incubation period of ~18 days following contact. Virus is spread by respiratory secretions, and is also spread from stool, urine and cervical secretions. Maternal viremia is a prerequisite for placental infection, which may or may not spread to the fetus (there is a high incidence of subclinical infections). Most cases occur following primary disease. Maternal antibodies to previous infection are protective for the fetus.
  - The disease involves angiopathy as well as cytolytic changes. Other viral effects include chromosome breakage, decreased cell multiplication time, and mitotic arrest in certain cell types. There is a little inflammatory reaction.
  - **Risk factors**: Women of childbearing age who are rubella nonimmune.
Clinical presentation

Rubella has a wide spectrum of presentations, ranging from acute disseminated infection to deficit and defects not evident at birth. Clinical manifestation can be categorized in three groups:

1. Transitory phenomena:
   - Trombocytopenia
   - Hepatitis;
2. Permanent structural defects:
   - Congenital heart malformation;
   - Cataracts;
3. Later presenting defects:
   - Sensorineural hearing loss;
   - Diabetes mellitus;

Congenital rubella syndrome presents a classic triad:

1. **Cataracts** (in 1/3 of cases);
2. **Sensorineural hearing loss** is the most frequent sequelae - 80% of infected children;
3. **Congenital malformation** in ~ 50% of children infected in first 8 w. of gestation and consist in PDA, pulmonary artery stenosis);
RUBELLA

- Clinical signs at birth:
  1. IUGR;
  2. Splenomegaly;
  3. Trombocytopenia;
  4. Signs of meningoencephalitis;
  5. Signs of interstitial pneumonia;
  6. Adenophaty.

- Other signs, less common:
  1. Prematurity;
  2. Hepatitis;
  3. Anemia;
  4. Purpura, rash, petechiae.

RUBELLA

- Later presentation defects:
  1. Diabetes mellitus & thyroid disease;
  2. Hearing deficit;
  3. Glaucoma;
  4. Arterial hypertension;
  5. Progressive mental retardation;
  6. Autism;
  7. Subacute sclerosing panencephalitis, due to meningoencephalitis.
RUBELLA

Diagnosis
- **Open cultures** - the virus can be cultured from:
  - Nasopharyngeal swabs, conjunctival scrapings, urine, CSF.
- **CSF examination** - may reveal encephalitis with an increased protein cellular ratio in some cases.
- **Serologic studies** - may be helpful, but the disease itself may cause immunology aberration and delay the infant's ability to mount IgM or IgG responses.
- **Radiological studies** - may show metaphyseal radiolucencies that correlate with metaphyseal osteoporosis.
- **Unspecific test** - hematological exploration, bilirubin determination, ECHO exams.

Treatment
- Prophylaxis anti-rubella vaccine of the susceptible population, especially young children. Vaccine should not be given to pregnant women. Passive immunization does not prevent fetal infection when maternal infection occurs.
- There is no specific treatment for rubella. Long term follow-up is needed secondary to late-onset symptoms.

CYTOMEGALOVIRUS (CMV)

Definition:
- CMV is a DNA virus and a member of the "herpesvirus group".

Incidence:
- CMV is the most frequent cause for IUGR, with a 1-2% incidence in newborn population.

Pathophysiology
CMV is a ubiquitous virus that may be transmitted in secretions, blood, and urine and perhaps by sexual contact. More than 90% of primary CMV infections are asymptomatic. CMV is capable of penetrating the placental barrier as well as the blood brain barrier. Both primary and recurrent maternal CMV can lead to transmission of virus to the fetus.
CYTOMEGALOVIRUS

- The period for the greatest fetal risk for disease and subsequent neurologic impairment is the first 22 weeks of gestation. Fetal viremia is spread by hematogenous route.
- The primary target organs are CNS, eyes, liver, lungs and kidneys.
- Characteristic histopathological features of CMV include focal necrosis, inflammatory response, the formation of enlarged cells with intranuclear inclusions (cytomegalic cells), and the production of multinucleated gigantic cells.
- CMV may also be transmitted to the infant at delivery (with cervical colonization), via breast milk, and via transfusion of seropositive blood to an infant whose mother is seronegative.

Risk factors:
- Lower social -economic status;
- Drug abuse;
- Sexual promiscuity in the mother

CYTOMEGALOVIRUS

Clinical presentation
- Subclinical infection is 10 times more frequent than clinical illness.

The most frequent signs:
1. Hepatosplenomegaly;
2. Thrombocytopenia with or without purpura;
3. Petechiae;
4. Jaundice with high direct bilirubin level;

Rare signs:
- Inguinal hernia at male;
- Chorioretinitis;
- Optic atrophy;

Sign of severity:
- Microcephaly;
- Intracerebral calcifications;
- IUGR;
- Prematurity.
By 2 years of age 5-15% of infants who are asymptomatic at birth, may develop serious sequel such as hearing loss and ocular abnormalities.

Late sequel with subclinical infection, such as:
- Mental retardation;
- Learning disabilities;
- Sensorineural hearing loss

Studies have now shown for children with asymptomatic congenital CMV infection a prevalence of sensorial hearing loss of 7.2%.

Approximately one half had bilateral loss, and 50% of affected children had progressive deteriration. Repeated auditory evaluation during the first 3 years is strongly recommended.

**Diagnosis**
- The standard diagnostic for CMV infection is urine or saliva culture. Most urine specimens from infants with congenital CMV are positive within 48-72h.
- Serologic tests - are available, but not specific complement fixation test that measures IgG will detect more than 75% of positive cases but also has a significant false-positive rate.
- Radiological studies - skull films or CT scans of the head may demonstrate characteristic intracranian calcifications.

**Management**
- Prevention - standard precautions, especially good hand washing.
- Control of blood products;
- Antiviral agents - ganciclovir has been show to be partially effective in the treatment of newborn with symptomatic infection, but this drug is mutagenic, teratogenic and carcinogenic.
HERPES SIMPLEX VIRUS

Definition:
- Herpes simplex virus (HSV) is a DNA virus related to CMV, Epstein-Barr virus, and varicella virus, and is among the most prevalent of all viral infections encountered by humans.

Incidence:
- The estimated rate of occurrence of neonatal HVS is 1/1000 to 1/5000 deliveries per year.

Pathophysiology:
- There are two serologic subtypes of HSV: HSV-1 (orolabial) and HSV-2 (genital). Three quarters of neonatal herpes infections are secondary to HSV-2, with the remainder caused by HSV-1.
- HSV infection of the neonate can be acquired intrauterine, intrapartum, or postnatal. Most infections are acquired in the intrapartum period as ascending infections with rupture of membranes or by delivery through an infected cervix or vagina.

Clinical aspects:
Intrauterine infection is different from acquired infection.

- Intrauterine infection:
  - Skin lesions;
  - Chorioretinitis;
  - Micro/hydrocephaly;
  - These cases may have a fatal evolution. The survivors may present neurological sequel, growth retard, ocular and hearing deficits.

Perinatal infection:
1. Localized infections - involving the skin, eyes or oral cavity (42% of cases)
2. CNS localization (35% of cases)
3. Disseminated disease (23% of cases) - which mimic very well bacterial sepsis:
   - Irritability;
   - Termic instability;
   - Apnea spells;
   - Jaundice;
   - Shock;
   - Hepatomegaly;
   - Seizures.
**HERPES SIMPLEX VIRUS**

Clinical manifestation of infection with HSV appear in about:
- 16,2+9 days for CNS involvement;
- 11+0,5 days for localized infection;

Neurologic signs may appear in any type of localization and consist in:
- Microcephaly;
- Spastic tetraplegy;
- Treatment resistant seizures;
- Blindness;
- Growth retardation.

**HERPES SIMPLEX VIRUS**

**Diagnosis:**
- **Viral cultures** - cultures obtained from conjunctiva, throat, feces, urine, nasal pharynx, and CSF. The virus grows readily, with preliminary results available in 24-72 h.
- **Immunologic assays** - to detect HSV antigen in lesion scrapings, usually using monoclonal anti-HSV antibodies in either an ELISA or fluorescent microscopy assay, are very specific and 80-90% sensitive,
- **Tzanck smear** – cytological examination of the base of skin vesicles, looking for characteristic but nonspecific giant cells is only about 50% sensitive.
- **Serologic tests** - are not helpful in diagnosis of neonatal infection.
- **Lumbar punction** - should be performed in all suspected cases. Evidence of hemorrhagic CSF with increased white blood cells and protein may be found.
**HERPES SIMPLEX VIRUS**

- **Management**
  - **Antepartum** - correct and prompt diagnosis of herpes genital infection; in case of clinically apparent HSV infection → C-section.
  - **Neonatal treatment:**
    - Isolation of infants with known infection and careful hand-washing;
    - The infant may not be breast-fed as long as breast lesion are present on the mother, and the mother should be instructed in good hand-washing technique.
    - Pharmacological therapy - the first-line drug of choice is acyclovir, the second choice being vidarabine.

**VIRAL HEPATITIS. HEPATITIS A.**

- **HEPATITIS A.**
  - **Definition** - Hepatitis A is caused by RNA virus transmitted by fecal-oral route.
  - **Pathophysiology** - the risk of intrauterine transmission is limited because the period of viremia is short and fecal contamination does not occur at the time of delivery.
  - **Clinical presentation** - most infants are asymptomatic, with mild anomalies of liver function.
  - **Diagnosis** - IgM antibodies to hepatitis A virus is present during the acute or early convalescent phase of disease.
  - Characteristically, the transaminases and serum bilirubin levels are elevated.
  - **Management** - the infant should be isolated with enteric precaution.
  - Immunoglobulin 0.02 ml/kg, i.m. should be given to the newborn whose mother’s symptoms began between 2 weeks before and one week after delivery.
VIRAL HEPATITIS. HEPATITIS B.

Definition - hepatitis B is caused by a DNA virus. It has a long incubation period (45-160 days) after exposure.

Pathophysiology:
- If the mother is a chronic carrier, there is a 3-50% vertical transmission to the infant. In the fetus and the neonate, transmission has been suggested by the following mechanism:
  - Transplacental transmission either during pregnancy or at the time of delivery secondary to placental leaks.
  - Natal transmission by exposure to hepatitis B surface antigen in amniotic fluid, vaginal secretions, or maternal blood.
  - Postnatal transmission, by fecal-oral spread, blood transfusion.

Clinical presentation
- Maternal hepatitis B infection has not been associated with abortion, stillbirth, or congenital malformations. Prematurity has occurred, especially with acute hepatitis during pregnancy. Fetuses or newborns exposed to HVB present a wide spectrum of disease:
  - Mild transient acute infection;
  - Chronic active hepatitis with or without cirrhosis;
  - Chronic persistent hepatitis;
  - Chronic asymptomatic HbsAg carriage;
  - Fulminant fatal hepatitis (rare)
VIRAL HEPATITIS. HEPATITIS B.

Diagnosis
- Differential diagnosis - acute biliary atresia and acute hepatitis secondary to other viruses (CMV, rubella).
- Transaminases - levels may be markedly increased before the rise in bilirubin levels.
- Bilirubin direct and indirect may be elevated.
- Test for: HbsAg and antiHBc-Ig M. Most infant demonstrate antigenemia by 6 month of age, with peak at 3-4 month.

Management:
- Immunization program. WHO has recommended that all countries add HVB vaccine to their routine childhood immunization program by 1997.
- Isolation-precaution in handling blood and secretion;
- HbsAg-positive mother-the infant should be given hepatitis B immune globulin 0,5 ml, within 12 h after delivery. If HbsAg status of mother is unknown, test the mother as soon as possible.
CONGENITAL INFECTIONS

SYPHILIS

Definition:
- Syphilis is a sexually transmitted disease caused by *Treponema pallidum*. Early congenital syphilis is when clinical manifestation occurs before 2 years of age; late congenital syphilis is when manifestation occurs at more than 2 years of life.
- Incidence has increased in the late years. An estimated 2-5 infants are affected with congenital syphilis for every 100 women diagnosed with primary or secondary syphilis.
SYPHILIS

Pathophysiology
- Treponemas appear able to cross the placenta at any during pregnancy, thereby infecting the fetus. Syphilis can cause:
  - Preterm delivery,
  - Stillbirth,
  - Congenital infection,
  - Neonatal death.
- That depends on the stage of maternal infection and duration of fetal infection prior to delivery. Untreated infection in the first and second trimesters often leads to significant fetal morbidity, while with third trimester infection many infants are asymptomatic.
- Infection can also be acquired via contact of infectious lesions during passage to birth canal.

SYPHILIS

Clinical presentation
- Generally, neonates do not have signs of primary syphilis from in utero-acquired infection. There is a 40-60% possibility of CNS involvement. The most common findings in the neonatal period include:
  - Hepatosplenomegaly;
  - Jaundice;
  - Osteochondritis;
- Other signs may be:
  - Generalized lymphadenopathy;
  - Pneumonitis;
  - Myocarditis;
  - Nephrosis;
  - Rash, vesiculobullous, especially on the palms and soles;
  - Hemolytic anemia;
  - Hemorrhagic rinitis.
- Late congenital syphilis manifests by: Hutchinson's teeth healed retinitis, eight-nerve deafness, mental retardation, and hydrocephalus
SYPHILIS

Diagnosis
1. NonSPECIFIC REAGIN ANTIBODY TESTS:
   A. Venereal disease research laboratory (VDRL).
      - a titer least 2 dilutions higher in the infant than in the mother signifies probable active infection.
   B. Rapid plasma reagin is a screening test for syphilis
2. SPECIFIC TREPONEMAL TEST
   A. FTA-ABS test may be positive in the infant secondary to maternal transfer of IgG. If positivity persist after 6-12 month, the infant is probably infected.
   B. IgM FTA-ABS measures antibody to the treponeme developed by the infant.
3. MICROSCOPIC DARK-FIELD EXAMINATION - should be performed on appropriate lesions for spirochetes.
4. COMPLETE BLOOD CELL COUNT - monocytosis is typically seen; look for hemolytic anemia or a leukemoid reaction.
5. LUMBAR PUNCTURE CNS disease may be detected by positive serologic reaction.
6. X-RAY studies of the long bones may show sclerotic changes of the metaphysis and diaphysis, with wide spread osteitis and periostitis

SYPHILIS

Management:
Infants born to mothers who received adequate penicillin treatment for syphilis during pregnancy are at minimal risk. VDRL-positive infant will receive treatment: penicillin G, 100.000-150.000ui/kg/24h, i.v. or procaine penicillin 50000 U/kg/day i.m. The duration of therapy is 10-14 days in both cases. Asymptomatic infant born to mothers whose treatment for syphilis may have been inadequate should be fully evaluated, including CSF examination. The infant should repeated rapid plasma reagin test at 3, 6 and 12 month (most infants will develop a negative titer).
HIV

Definition
- HIV is an enveloped RNA virus that is a member of lentivirus, a subfamily of retroviruses. Infection is most commonly secondary to HIV1.

Incidence
- The WHO estimates that 18 millions adults and 1.5 million children have been infected with HIV. By the year 2000, women are expected to account for 30% of all cases of AIDS.

Pathophysiology
- HIV-1 is particularly tropic for CD-4 T cells and monocyte or macrophage lineage. Following the infection of the cell, viral RNA is uncoated as a double-strand DNA transcript is made. The DNA is transported to the nucleus and integrated into the host genome DNA. There is eventual destruction of both the cellular and humoral arms of the immune system. As well, HIV1 gene products of cytokines elaborated by the infected cells may affect macrophage, B-lymphocyte, and T-lymphocyte function.

HIV Transmission
- About 90% of pediatric cases are by vertical transmission. Transmission mother-fetus-newborn varies between 16-40%.
- Transplacental transmission - HIV may infect placenta in any moment of pregnancy. The mechanism of transplacental transfer is unknown, but HIV may infect the trophoblast and the placenta macrophages. Increased risk of vertical transmission has been correlated with increased duration of membrane rupture before delivery.
- Intrapartum - due to exposure to contaminated blood;
- Breast milk - is the predominant way of postnatal HIV transmission to infants and accounts for approximately an additional 14% transmission risk among breastfed population;
- Blood transfusion
- Pediatric HIV infection: 50% of cases appear in the first year of life and 80% in first 3 years of life.
HIV

- **Clinical signs:**
  1. Asymptomatic;
  2. Minor signs:
     - Limphadenophathy;
     - Hepatomegaly;
     - Dermatitis;
     - Recurrent / persistent respiratory infections;

- **Moderate signs:**
  - Anemia, neutropenia less than 1000/mm³;
  - Persistent trombocitopenia;
  - Bacterial meningitis, pneumonia, sepsis;
  - Persistent candida infection, 2 month, after 6 month of life;
  - Chronic diarrhea, hepatitis;
  - Fever more than 1 month;
  - Infection with CMV;

- **Severe signs:**
  - Severe bacterial infection, multiple or recurrent: sepsis, pneumonia, meningitis, osteomielitis, caused by Pneumocystis carinii, Candida, Salmonella, B.K., Toxoplasma.
HIV

SUGESTIVE signs for HIV may be:

- Persistent weight loss, more than 10% of birth weight;
- Decreased with least 2 percentile on weight curves at one year of life;
- Chronic diarrhea;
- Persistent fever (more than one month).

HIV

Diagnosis

- Positive test for HIV antibodies; diagnosis of HIV infection in children more than 18 month of age is similar to the adults, based on detection of anti-HIV IgG antibodies in serum using Elisa&Westernblot analysis;
- Recently available virology test permitting early diagnosis of HIV in infants in the first month of life include:HIV culture, PCR and P24 antigen detection;
- Surrogate markers for disease: immunology abnormalities, including hypergammaglobulinemia, a low CD4 T lymphocyte count, decreased CD4 percentage.
HIV

Management
- In present, there is no cure for HIV infection.
- It may be useful:
  - close nutritional monitoring;
  - prophylaxis for infections with opportunist agents (P. carinii)
  - treatment of complications;
  - routine immunization schedules should be followed for DTP, MMR, and HVB.
- **Zidovudine** is the most efficacy drug in children, especially in those with CNS anomalies. (2mg/kg at every 6 hour - syrup 10mg/ml).

NEONATAL SEPSIS

Definition = septicemia represents the immune response at infection whose constitution takes part in a constant succession:
- Etiologic factors;
- Contamination;
- Septic primary focar;
- Migration of pathogen agent in systemic circulation;
- Apparition of secondary septic determinations;
- **Bacteriemia** represents transient germ discharge in systemic circulation, proved by positive cultures.
- Incidence-1-8% of live newborns (depend on statistics).
NEONATAL SEPSIS

Risk factors:

- **Neonatal:**
  - prematurity;
  - male sex;

- **Maternal:**
  - maternal peripartum fever or infection-chorioamnionitis;
  - urinary tract infection;
  - vaginal colonization with GBS;
  - perineal colonization with E.coli;
  - obstetric complication;
  - rupture of membranes more than 18-24 h
  - amniotic fluid problems-meconium stained;

NEONATAL SEPSIS

Maneuvers of newborn:

- Resuscitation at birth;
- Invasive procedures;
- Excessive use of antibiotics;
- Overcrowded newborn units;
- Inadequate condition of transport;
NEONATAL SEPSIS

Pathophysiology:
A. Antenatal and perinatal infection:
   - Hematogenous transmission - Listeria;
   - Ascendent transmission - GBS, E.Coli
B. Delivery contamination - while natural delivery - E.Coli
C. Postpartum:
   - Nosocomial infection;
   - Invasive procedures in NICU.

The primary sites of colonization tend to be:
- Nasopharynx;
- Oropharynx;
- Conjunctiva;
- Skin;
- Umbilical cord.
NEONATAL SEPSIS

Etiological agents:
The principal pathogens involved in neonatal sepsis have tended to change in time. The agents associated with primary sepsis are usually the vaginal flora. Most centers report **group B streptococci** as the most common, followed by **Gram negative enteric organism**, especially **E.coli**. Other pathogens include:

- Listeria monocytogenes;
- S.aureus;
- Streptococci
- Anaerobes;
- H.influenzae;
- Fungal organism;
- Viruses;

The flora causing neonatal sepsis varies in each nursery.
Clinical presentation.

The initial diagnosis of sepsis is a clinical one, because it is imperative to begin treatment before the results of culture are available.

Clinical signs and symptoms of sepsis are non specific, and the differential diagnosis is broad, including RDS, metabolic disease, CNS diseases, cardiac diseases, and other infection process (TORCH infections for ex.).

"ALARM" SIGNS:
- Change in behavior (the nurse doesn't like the kid);
- Weight loss/stationary weight;
- Feeding problems
- Vomiting;
- Grunting, flaring;
- Thermoregulation problems;
- Grey colour of the skin;
- In these situation is imperative to give antibiotics and to take cultures.
NEONATAL SEPSIS

IN EVOLUTIVE PHASE (severe infections syndrome)
- Bad general state;
- Hypotension;
- Hypo/hypertermia (hypothermia rather than fever);
- Skin: petechiae, rashes, pustula, omphalitis, precocious jaundice;

VISCERAL SIGNS:
1. Cardiovascular:
   - Cardiovascular collapse and hypotension
   - Long refill capillary time; poor peripheral perfusion, cold extremities;
2. Digestive:
   - Abdominal distension + edema of abdominal wall (EUN)
   - Vomiting;
   - Hepatosplenomegaly;
3. Meningitis and meningoencephalitis (25-50%).
4. Rare: osteoarticular perturbances, hepatic and ocular.

NEONATAL SEPSIS

| General signs | Bad general state; Temperature instability |
| Neurologic signs | Apathy, irritability, strident cry; Hypotonia, hyporeactivity, seizures, coma; |
| Respiratory signs | Apnea, tachypnea; Cyanosis, grunting; costal retractions |
| Digestive and abdominal | Feeding difficulties, poor sucking reflex; Abdominal distension; hepatosplenomegaly Vomiting, diarrhea; |
| Cardiovascular signs | Pallor, cyanosis; prolonged capillary refill time; Tachycardia/bradycardia; arrhythmia; Cold extremities; hypotension, edema; |
| Skin | Purpura, petechiae, omphalitis, cellulite; scleredema |
| Hematological | Jaundice, hemorrhage, purpura; |
| Musculoskeletal system | Palsy, abnormal position of limbs; pain. |
NEONATAL SEPSIS

**Laboratory diagnosis**
- It doesn't exist any laboratory test that has an acceptable value for infection prediction.
- **Diagnosis = risk factors + clinical signs + laboratory exams**

  In case of suspicion of sepsis, blood and other normally sterile body fluids should be obtained.

  Hematological signs which indicates high risk of bacterial sepsis:
  - WBC more than 33.000/mmc or less than 5000/mmc;
  - Neutrophiles less than 1000/mmc;
  - Immature/total neutrophiles ratio more than 0,2.

  **OTHER signs of sepsis suspicion:**
  - Anemia+trombopenia association; Perturbances of clotting factors
  - CRP more than 2 mg% and fibrinogen more than 3,5 g% in first 2 days.
  - IgM in blood umbilical cord more than 20mg% indicates intrauterine infection;
  - Hyper/hypoglycemia; persistent metabolic acidosis; mixed hiperbilirubinemia;

**CONFIRMED SEPTICAEMIA:**
- Positive blood culture(20% of cases negative hemocultures)
- Positive CSF cultures;
- Antigen detection test-available for GBS, Neisseria, H.influenzae, S.pneumoniae.
- ChestX-ray.

**Management:**
- Prophylaxis - screening program at all pregnant women for detection GBS and E.coli. Dosage of 4 g of ampicillin during labor decrease the risk of infection with GBS.
- Postnatal - in case of sepsis suspicion, before obtain the cultures result, initiate treatment wit antibiotics of broad spectrum: -Ampicillin=150 mg/kg/day-12 h.q. and Gentamicin=2, 5 mg/kg/dose at 12,18 h.q.
- Third generation cephalosporin are reserved to infection with Gram negative germs.
- In nosocomial sepsis the suspected agent is S.aureus, so is preferred Vancomycine as drug.
NEONATAL SEPSIS

Antibiotherapy must be adjusted according with antibiogram:
1. **GBS** → ampicillin,
2. **Lysteria** → ampicillin,
3. **Staph. aureus coagulase-positive** → oxacillin
4. **Staph. aureus coagulase-negative** → vancomycin
5. **Enterobacteriaceae** → ampicillin + aminoglicoside + cephalosporin,
6. **anaerobes** → clindamicin + metronidazole

The length of treatment varies from 10 to 21 days.

Other measures:
- Thermal confort;
- Correct TPN;
- Monitorization of vital signs;
- Treatment of septic shock;
- Immunotherapy (Ig, granulocytes transfusion, blood transfusion exchange transfusion)

Evolution and prognosis depend on:
- **The host** - preterm or term newborn;
- **The causing agent**;
- **The complications and sequel** may be severe due to:
  - CNS involvement
  - Septic shock
  - Secondary hypoxemia
  - PHT

The mortality remains high, septicaemia representing the **third cause** of mortality in NICU, after HMD and congenital malformations.
Jaundice is generally defined as yellowish discoloration of the skin secondary to hyperbilirubinemia. Hyperbilirubinemia is defined as a total serum bilirubin level greater than 50 mg%/o(5 mg/dl).

65% of newborns are clinically jaundiced - physiological jaundice, considered to be secondary to the immaturity of hepatic enzyme systems at birth.

Bilirubin is the end product of the catabolism of hem and is produced mainly by the breakdown of red blood cells hemoglobin. Other sources of hem include myoglobin and certain liver enzymes. Bilirubin exists in several forms in the blood but is predominantly bound to serum albumin. Free conjugated bilirubin and possibly other forms, may enter central nervous system and become toxic to the cells. The precise mechanism is unknown.

In the liver cells, unconjugated bilirubin is bound to ligandin, Z-protein and others proteins; it is conjugated by uridine diphosphate glucuronyl transferase(UDP-t). Conjugated bilirubin is water-soluble and can be excreted by urine, but most of it is rapidly excreted into the intestine.
JAUNDICE

Hyperbilirubinemia presents in one of two forms in the neonate: unconjugated hyperbilirubinemia or conjugated hyperbilirubinemia, with different causes and potential complications.

JAUNDICE

Causes of unconjugated hyperbilirubinemia:

1. Physiological jaundice
2. Hemolytic anemia
   - ABO or Rh incompatibility;
   - Infection, drugs;
   - Congenital: hereditary spherocytosis, infantile pyknocytosis, pyruvate kinase deficiency (PK), G6PD deficiency.
3. Polycythemia
   - Placental hypertransfusion: twin-twin transfusion, maternal-fetal transfusion, delayed cord clamping;
   - Endocrine disorders: maternal diabetes, conjugated adrenal hyperplasia;
   - Other disorders: Down syndrome, Beckwith-Wiedeman syndr.
JAUNDICE

Physiologic jaundice
- In almost every newborn infant, elevation of serum unconjugated bilirubin develops during the first week of life and resolves spontaneously.
- Frequency=50-80% in full term infants and about 90% in prematures. Physiologic jaundice must, first of all be differentiating from pathologic one, using exclusive criteria:
  - Unconjugated bilirubin level more than 12,5 mg/dl in term infant;
  - Unconjugated bilirubin level more than 15 mg/dl in prematures;
  - Bilirubin rate increasing at a rate more than 0,5 mg/kg/h;
  - Jaundice in the first hour of life;
  - Conjugated bilirubin level more than 2 mg/dl;
  - Clinical jaundice persisting for more than one week in full term infants or two weeks in premature infants;

JAUNDICE

Physiology
- Full term infant-serum unconjugated bilirubin progressively rises to mean peak of 5-6 mg/dl by the third day of life in both white and black babies and a peak of 10-14 mg/dl at 3-4 days in Asian babies.
- Preterm neonate-liver function is less mature, and jaundice is more frequent and pronounced. A peak concentration of 10-12 mg/dl is reached by the fifth day of life.

Mechanism - a number of mechanisms have been suggested:
1. Increased bilirubin load because of larger red blood cell volume, the shorter life span of red blood cells and increased entero-hepatic circulation in newborn infants.
2. Defective uptake of bilirubin by the liver.
3. Defective conjugation.
4. Impaired excretion into bile.
5. Overall impaired of liver function.
JAUNDICE

Clinical aspects:

- Clinical jaundice is visible when the serum bilirubin level approaches 5-7 mg/dl. Jaundice is often apparent first in the face, than descending to the torso and lower extremities as the degree of jaundice increases. Jaundice can be demonstrated in some infants by pressing lightly on the skin with a finger. These signs should not appear within the first 24 hours after birth in healthy infants.

- Besides confirming the presence of jaundice, physical examination, may also be helpful in determining the cause of hyperbilirubinemia (cephalhematoma, hepatosplenomegaly etc).

JAUNDICE

BILIRUBIN LEVEL

More than 12 mg/dl

Less than 12 mg/dl

Coombs test

POSITIVE

NEGATIVE

Rh or ABO incompatibility

Monitor mother’s & infant’s group & Rh

RBC counts

1. Hepatitis
2. Infections
3. Obstruction of bile ducts

ABO incomp
RBC enz.def.
CID, drugs

Hemorrhage
Breastfeeding
Hypothyroidism
Diabetic mother

Asses BILIRUBIN

Abnormal

Normal
THANK YOU!