

NEONATAL SEPSIS AND CONGENITAL INFECTIONS

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Objectives

- At the end of the presentation, the participant will be able to:
 - List the pathogens that cause neonatal sepsis
 - Discuss the epidemiology of the common pathogens of sepsis
 - Know the agents that are responsible for congenital infections
 - Discuss the clinical features of the causes of congenital infections

NEONATAL INFECTIONS

- Bacterial neonatal sepsis
- Viral infections mimicking bacterial sepsis
- In-utero infections (congenital infections)

NEONATAL SEPSIS

- Bacterial vs viral
- Early-onset vs Late-onset
- Perinatal vs Nosocomial vs Community acquisition
- Clinical syndromes similar regardless of etiology

BACTERIAL NEONATAL SEPSIS

- Overall incidence 1-5 per 1000 live births
- Early-onset sepsis
 - symptom onset within 6 days of life
 - maternal complications common
 - vertical transmission of organisms colonizing genital tract

BACTERIAL NEONATAL SEPSIS

- Late-onset sepsis
 - symptom onset after 6th day of life
 - 2 distinct groups of neonates
 - healthy newborns who have been discharged to home
 - high-risk hospitalized neonates who develop hospital-associated infection

QUESTION #1

- Of the following, the organism **LEAST** likely to cause early-onset neonatal sepsis is:
 - A. *Listeria monocytogenes*
 - B. Group B Streptococci
 - C. *Streptococcus pneumoniae*
 - D. *E. coli*
 - E. *viridans streptococci*

ETIOLOGY OF EARLY-ONSET BACTERIAL SEPSIS

- Group B Streptococci
 - dramatic decline since implementation of intrapartum prophylaxis
- *Escherichia coli*
 - probably most common now
- *Listeria monocytogenes*
- Less Common
 - *viridans streptococci*
 - non-typeable *Haemophilus influenzae*

QUESTION #2

- All of the following are important causes of late-onset neonatal sepsis, **EXCEPT**:
 - A. *Streptococcus pyogenes*
 - B. Coagulase-negative Staphylococci
 - C. *Staphylococcus aureus*
 - D. Gram-negative bacilli
 - E. *Candida albicans*

ETIOLOGY OF LATE-ONSET NEONATAL SEPSIS

- Healthy newborns previously discharged from hospital
 - Group B Streptococci
 - *L. monocytogenes*
 - *E. coli*
 - *Salmonella* species
- Less frequent causes:
 - *H. influenzae*- nontypeable
 - *Neisseria meningitidis*
 - *Streptococcus pneumoniae*

ETIOLOGY OF LATE-ONSET SEPSIS*

- High risk newborns (VLBW infants in NICU)
 - Coagulase-negative Staphylococci—48%
 - Most common cause of late-onset sepsis in hospitalized high-risk neonates
 - Gram-negative bacilli (*E. coli*, *Klebsiella* sp, *Enterobacter* sp, *Pseudomonas* sp)—20%
 - *S. aureus*—8%
 - *Candida albicans*—12%
 - Enterococci—3%

*NICHD Neonatal Network, *Pediatrics* 2002;110:285

BACTERIAL NEONATAL SEPSIS: RISK FACTORS FOR VLBW INFANTS

- Invasive procedures
- Mechanical ventilation
- Indwelling intravascular catheters
- Total Parenteral Nutrition
- Widespread use of broad-spectrum antibiotics
- H₂ blockers

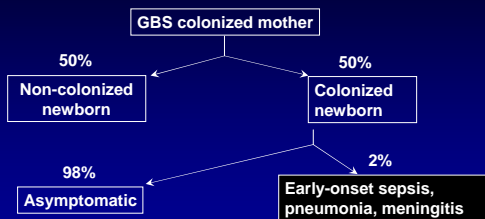
CLINICAL MANIFESTATIONS OF NEONATAL SEPSIS

- Signs and symptoms often subtle and nonspecific
- Features of neonatal meningitis often indistinguishable from sepsis
- Noninfectious illnesses have similar features
 - RDS; Congenital heart disease; Metabolic disorders
- Most neonatal pathogens produce similar symptoms

GROUP B STREPTOCOCCI: MATERNAL COLONIZATION

- 15-40% of all pregnant women are colonized with GBS
 - Genital and GI tracts
 - Highest: African-Americans, <20yo
 - Lowest: Asian, Mexican-Americans
- Colonization
 - Constant or intermittent
 - Colonization during one pregnancy does not predict colonization in subsequent pregnancy

Mother to Infant Transmission of GBS



CDC Prevention Guidelines, 2010

Additional Risk Factors for Early-onset GBS Disease

- Obstetric risk factors:
 - Preterm delivery
 - Prolonged rupture of membranes
 - Infection of the placental tissues or amniotic fluid / fever during labor
- GBS in the mother's urine during pregnancy (marker for heavy colonization)
- Previous infant with GBS disease
- Low maternal levels of anti-GBS antibodies
- Demographic risk factors
 - African American
 - Young maternal age

CDC Prevention Guidelines, 2010

Question #3: Which of the following is a TRUE statement concerning early-onset GBS neonatal sepsis?

- A. Pneumonia and apnea are the most common clinical features
- B. Meningitis is present in 80% of cases
- C. The case-fatality rate is lower than with late-onset GBS infection
- D. Septic shock occurs in 75% of patients
- E. The mean age of onset is 72 hours of life

GBS INFECTION: EARLY VS LATE ONSET

	Early-onset	Late-onset
Incidence	0.3/1000 (1-4/1000 before IAP)	0.3/1000
Mean age at onset	8 hours	27 days
Incidence of prematurity	Increased	Not increased
Obstetric complications	Common	Unusual
Manifestations	Pneumonia(40%) Meningitis(5-10%) Septic Shock(25%)	Bacteremia Meningitis Bone/joint/skin
Mortality rate	10-15%	2-6%

NEONATAL SEPSIS/MENINGITIS DUE TO *E. COLI* INFECTION

- Incidence approx 1 per 1000 live births
- Most cases early-onset
 - Ki capsular antigen present in 80% of cases of meningitis
- Vertical transmission major route of transmission
- Infants with Galactosemia particularly susceptible to *E. coli* infection
- CFR high(20%) and sequelae in 30-50%

NEONATAL LISTERIOSIS

	<u>Early-onset</u>	<u>Late-onset</u>
Age at onset	At birth	1-8 weeks
Birthweight	Often LBW	Usually term
Obstetric complications	Common (amnionitis, brown staining)	Infrequent
Source of isolate	Blood(75%)	CSF(90%)
Fatality rate	25%	5%

NEONATAL LISTERIOSIS

- Maternal prodromal illness common-65%
- Elevated monocyte count present in 50% of bacteremic infants
- Monocytes not typically found in CSF of infants with meningitis
- Erythematous rash with 1-2mm pale nodules on skin and pharynx occasionally seen (granulomas on path)
 - **granulomatosis infantisepticum**

NEONATAL BACTERIAL SEPSIS:DIAGNOSIS

- Isolation of organism from blood or CSF definitive
- Latex Particle agglutination for GBS and *E. coli* limited by poor sensitivity and specificity
- Hematologic abnormalities often accompanying sepsis
 - elevated ratio immature to total neutrophils (>0.2)
 - neutropenia
 - elevated neutrophil count
 - thrombocytopenia

EMPIRIC THERAPY FOR NEONATAL SEPSIS

- Early-onset sepsis
 - Ampicillin + Aminoglycoside
 - Cephalosporins should not be used empirically
- Late-onset sepsis
 - VLBW infants in the NICU
 - Oxacillin or Vancomycin + Aminoglycoside or 3rd gen cephalosporin
 - "Community" acquired
 - Ampicillin + 3rd gen cephalosporin

TREATMENT OF NEONATAL LISTERIOSIS

- Ampicillin and Gentamicin initially (bactericidal), then ampicillin alone
- Cephalosporins NOT active against *L. monocytogenes*
- 2-3 week duration

TREATMENT OF GRAM-NEGATIVE SEPSIS AND MENINGITIS

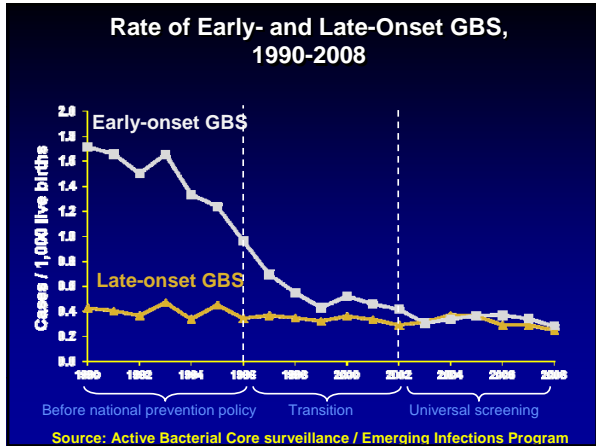
- Ampicillin and Gentamicin
 - initial empiric therapy
- Cefotaxime safe and effective alternative and often used in combo with aminoglycoside for meningitis
- Even with appropriate therapy, CSF cultures remain positive for at least 2-3 days after initiation of therapy
- Failure to sterilize CSF should prompt search for brain abscess or other complication
- 3-week course recommended for meningitis

BRAIN ABSCESS AND GRAM-NEGATIVE MENINGITIS

- Propensity to cause Brain Abscess
 - *Citrobacter koseri* (formerly *diversus*)
 - *Enterobacter sakazakii*
 - *Serratia marcescens*

PREVENTION OF EARLY-ONSET GBS SEPSIS

- 2002 and 2010 CDC guidelines
 - Based on data showing that the screening method was >50% more effective than the risk-factor strategy



- ### Key Prevention Strategies Remain Unchanged in 2010
- Universal screening of pregnant women for GBS at 35-37 weeks gestational age
 - Intrapartum antibiotic prophylaxis for:
 - GBS positive screening test
 - GBS colonization status unknown with
 - Delivery <37 weeks
 - Temperature during labor $\geq 100.4^{\circ} \text{F}$ ($\geq 38.0^{\circ} \text{C}$)
 - Rupture of membranes ≥ 18 hours
 - Previous infant with GBS disease
 - GBS in the mother's urine during current pregnancy
- CDC Prevention Guidelines, 2010

- ### Key Prevention Strategies Remain Unchanged in 2010
- Penicillin preferred drug for IAP
 - Ampicillin acceptable alternative
 - Cefazolin preferred for penicillin-allergic at low risk of anaphylaxis
- CDC Prevention Guidelines, 2010

Intrapartum GBS Prophylaxis Not Indicated

- Colonization with GBS during a previous pregnancy
 - Unless another indication during the current pregnancy
- GBS bacteriuria during a previous pregnancy
 - Unless another indication during the current pregnancy
- Negative vaginal and rectal GBS screening test during the current pregnancy
 - Regardless of intrapartum risk factors
- Cesarean delivery performed before labor onset on a woman with intact amniotic membranes
 - Regardless of maternal GBS test status
 - Regardless of gestational age

CDC Prevention Guidelines, 2010

QUESTION #4

Of the following, the virus *least* likely to cause symptoms at birth that mimic bacterial neonatal sepsis is:

- A. Herpes simplex virus
- B. Human immunodeficiency virus (HIV)
- C. Cytomegalovirus
- D. Enterovirus
- E. Adenovirus

ETIOLOGY OF NEONATAL VIRAL SEPSIS

- Herpes simplex virus types I and II
- Enteroviruses
 - Echoviruses
 - Coxsackie
- Cytomegalovirus
- Respiratory viruses
 - RSV
 - Influenza
 - Adenovirus

Neonatal HSV Infections

- Most occur from infected maternal genital tract at delivery
- Signs of infection by 4-5 weeks of age
- Risk largely influenced by maternal antibody status
 - 50% transmission with primary infection
 - 5% transmission with recurrent infection

Neonatal HSV Infections

- High prevalence of asymptomatic maternal infection
- Thus, most infants (>75%) with neonatal HSV are born to asymptomatic mothers who have no past history of genital HSV infection or clinical findings during pregnancy

Neonatal HSV Infections

Type of Infection	%
Skin, Eyes, Mucus Membranes (SEM)	45%
Disseminated Infection	25%
CNS Infection	30%

NEONATAL HSV INFECTION

- **Skin, eyes and/or mouth (SEM)**
 - 7-14 days of life
 - Vesicles-often at sites of trauma (scalp electrode site)
 - Conjunctivitis
 - No mortality with treatment
 - 5% morbidity with treatment
 - 75% progress without treatment



Neonatal Disseminated HSV Infection

- **Disseminated disease**
 - 5-12 days of life
 - 58% have skin lesions
 - Lesions often absent at presentation
 - Mimics bacterial sepsis
 - DIC
 - Pneumonia
 - Hepatitis
 - CNS involvement (60-70%)
 - Seizures in 22%

Neonatal Disseminated HSV Infection

- **Disseminated disease**
 - Rapid deterioration
 - Unremitting shock
 - Progressive liver failure
 - Bleeding
 - Respiratory failure
 - 30% mortality with treatment

Neonatal HSV Encephalitis

- **Encephalitis (CNS)**
 - 16-19 of life
 - 45-63% have skin lesions
 - Seizures (generalized or focal)
 - Lethargy
 - Irritability
 - Poor feeding
 - Temp instability

NEONATAL HERPES SIMPLEX INFECTIONS:DIAGNOSIS

- Diagnosis difficult in absence of vesicular lesions- need high clinical suspicion
- **Viral Culture**
 - cutaneous lesion
 - nasopharynx
 - CSF
 - conjunctiva
 - urine
- **Direct Fluorescent Antibody**
 - rapid diagnosis
 - requires vesicular lesions
- **Polymerase Chain Reaction-CSF**

Treatment of Neonatal HSV Infections

- Intravenous acyclovir treatment of choice
 - 20mg/kg/dose q8h IV standard dose
 - Monitor for neutropenia (20%) and nephrotoxicity (renal tubular crystalization with dehydration)
- 21-day course for disseminated or CNS infections
- 14-day course for SEM disease

Outcome of Neonatal HSV Infections

Table 3. Outcome of Neonatal Herpes.^a

Site of Disease	Death		Normal Outcome [†]	
	No Therapy	IV Antiviral Therapy	No Therapy	IV Antiviral Therapy
	<i>percent</i>			
Disseminated	85	31	Rare	83
Central nervous system	50	6	Rare	31
Skin, eyes, and mucosa	0‡	0	62	100

^a Data on patients who did not receive therapy are from Whitley et al.²¹ and data on patients who received intravenous (IV) antiviral therapy are from Kimberlin et al.²²

[†] A normal outcome is defined as the achievement of developmental milestones within 24 months after infection.

[‡] Skin, eye, and mucosal infection will progress to encephalitis or disseminated disease in the absence of antiviral therapy in a high proportion of infants.

Corey L, Wald A. NEJM 2009;361:1376

NEONATAL ENTEROVIRAL INFECTIONS

- Echoviruses 9,11,30 and Coxsackie B viruses most common today
- Most neonatal infections mild and non-specific, but 20% severe and life-threatening
- Diagnosis very difficult to distinguish from bacterial or HSV infection

NEONATAL ENTEROVIRAL INFECTIONS: CLINICAL FEATURES

- Macular or maculopapular rash-- 40%
- Hepatitis/Hepatic necrosis
- Myocarditis
- Meningoencephalitis
- Maternal history of viral illness
- Lack of obstetrical complications
- Summer and fall
- Isolation of virus from NP, throat, stool, CSF confirms Dx



IN UTERO CONGENITAL INFECTIONS

COMMON MANIFESTATIONS OF IN UTERO INFECTIONS

- **General Characteristics**
 - Manifestations present at birth or shortly thereafter
 - Presence of congenital defects (CHD, ocular abnormalities, calcifications, etc)

COMMON MANIFESTATIONS OF IN UTERO INFECTIONS

- **Specific Features**
 - Small for Gestational age
 - CNS: microcephaly, seizures, cerebral calcification
 - Skin: icterus, petechiae, purpura, vesicles
 - Eye: chorioretinitis, cataracts, microphthalmia
 - Heart: PDA, PS
 - Abdomen: HSM, hepatitis
 - Lung: pneumonitis
 - Musculoskeletal: bone lesions, limb hypoplasia

QUESTION #5

Of the following, the most common agent causing congenital infection is:

- A. *Toxoplasma gondii*
- B. Cytomegalovirus
- C. Rubella
- D. Parvovirus B 19
- E. Varicella-zoster virus

Question #6: Which is a true statement concerning congenital cytomegalovirus infection?

- A. Chorioretinitis is the most common clinical manifestation
- B. 1% of all infants born have CMV infection
- C. Fetal infection occurs only after primary maternal infection
- D. Infants with asymptomatic infection have no risk of long-term sequelae
- E. Serology represents the most reliable diagnostic test

CMV:EPIDEMIOLOGY

- Most common congenital infection
- 1% of all newborn infants have congenital CMV infection
- Virus transmitted from both immune mothers as well as non-immune mothers
 - Severe fetal damage occurs almost exclusively w/1^o infection
- Infection can occur prenatally, natally, or postnatally

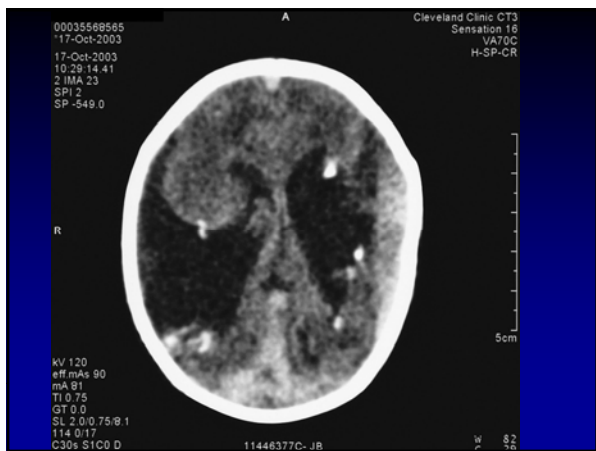
SIGNS OF PRENATAL CMV INFECTION IN THE NEWBORN

<u>Finding</u>	<u>Frequency</u>
Asymptomatic	90%
Symptomatic	10%
Petechiae	76%
Thrombocytopenia	77%
Jaundice	67%
HSM	60%
SGA	50%
CT Calcifications	50%
Microcephaly	53%
Retinitis	10%
Seizures	7%

FEATURES OF CONGENITAL CMV IN SYMPTOMATIC INFANTS

- Elevated transaminases-83%
- Thrombocytopenia (<100K)-77%
- Conjugated hyperbilirubinemia-81%
- Hemolysis-51%
- Increased CSF protein (>120mg/dL)-46%





LONG-TERM OUTCOME OF CONGENITAL CMV INFECTION

- Symptomatic infants
 - Death (30%)
 - Sensorineural hearing loss(58%)
 - IQ<70 (55%)
 - Microcephaly, seizures, paresis (52%)
 - Chorioretinitis (20%)
- Asymptomatic infants
 - Sensorineural hearing loss (7%)
 - IQ < 70 (4%)
 - Microcephaly (3%)
 - Chorioretinitis (2.5%)

LABORATORY DIAGNOSIS OF CONGENITAL CMV INFECTION

- Definitive
 - Isolation of virus from urine or saliva by three weeks of age
- Not Useful
 - CMV IgG and IgM antibody
 - False positives and negatives common

QUESTION #7

A newborn infant has microcephaly, is SGA, has a “blueberry muffin” rash, and bilateral cataracts. The most likely congenital heart lesion associated with this infection is:

- A. PDA
- B. ASD
- C. TGA
- D. Tricuspid atresia
- E. Coarctation of the aorta

CONGENITAL RUBELLA INFECTION

- Almost all cases due to maternal **primary** infection
- Overall risk to fetus 20% (70% in first trimester)
- Imported cases from Asia and Europe
- No congenital infection seen with inadvertent maternal vaccination during pregnancy
- Diagnosis
 - Viral culture from NP, urine, cataract

CONGENITAL RUBELLA:CLINICAL MANIFESTATIONS

- Most infants asymptomatic at birth
- Cataracts
- Blueberry muffin spots (dermal erythropoiesis)
- CHD (PDA, PS)
- “Salt and pepper” retinopathy
- IUGR and postnatal growth restriction
- Reticuloendothelial (HSM, jaundice)



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CDC Public Health Image Library



QUESTION #8

Which of the following is True regarding congenital *Toxoplasma* infection?

- A. The incidence is constant despite geographic location
- B. Prenatal diagnosis is not possible
- C. Treatment of infected pregnant women is not recommended
- D. Neurological and visual problems become apparent in the majority of infected asymptomatic infants

CONGENITAL TOXOPLASMOSIS

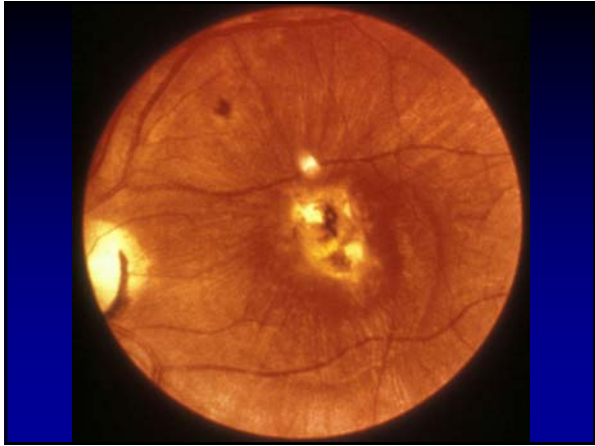
- Exposure to oocytes: cat feces and ingestion of raw beef major sources
- Fetal infection occurs only with maternal primary infection
- Incidence 1/1000-10000 live births

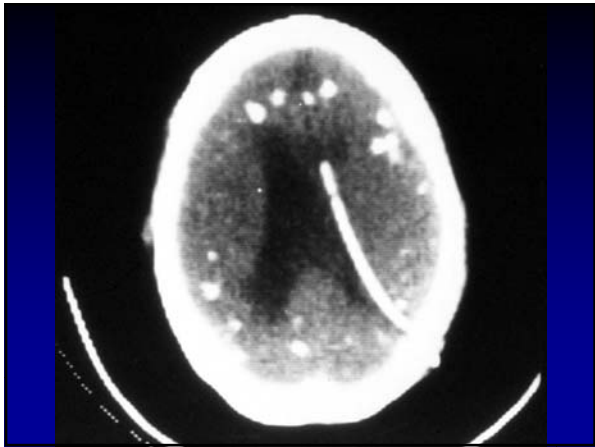
CONGENITAL TOXOPLASMOSIS: FETAL INFECTION RATES

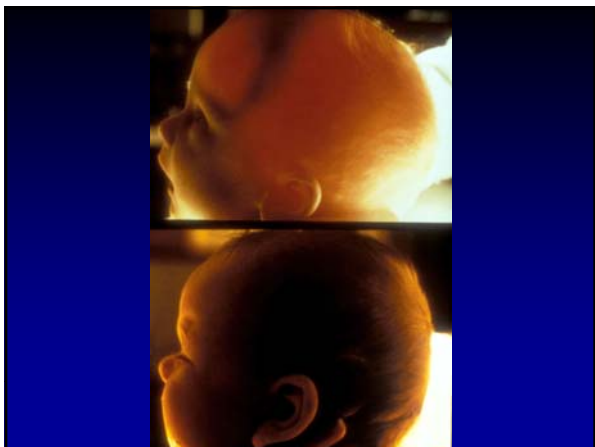
Trimester	1 st	2 nd	3 rd
Overall rate of infection	15%	30%	60%
Subclinical disease	18%	67%	90%
Mild	6%	18%	10%
Severe	41%	8%	0
Stillborn/perinatal death	35%	7%	0

CONGENITAL TOXOPLASMOSIS: CLINICAL FEATURES

- Majority of infected neonates are asymptomatic
 - 80% Develop eye/neuro disease by adulthood
- Classic Triad
 - Chorioretinitis-86%
 - Hydrocephalus-20%
 - Cerebral Calcifications-37%
- Cerebral Calcifications
 - Distributed throughout the brain-unlike CMV
- Chorioretinitis
 - Focal necrotizing retinitis
 - Can be recurrent and progressive
 - May develop later in life without any other features of congenital infection







CONGENITAL TOXOPLASMOSIS:DIAGNOSIS

- Prenatal
 - Toxo DNA in amniotic fluid or fetal blood
 - Isolating parasite by mouse inoculation or tissue culture
 - Serial fetal US—look for increased size of lateral ventricles
- Postnatal
 - *T gondii* DNA by PCR amniotic fluid, fetal blood, blood, CSF
 - Histopathology placenta, infected organ/tissue
 - Mouse inoculation assays of infant's blood, placenta, umbilical cord
 - Serology-IgG, M, A, E on Mom and infant

CONGENITAL TOXOPLASMOSIS:TREATMENT

- Mother
 - Spiramycin to decrease transmission
 - Pyramethamine and sulfadiazine if fetal infection confirmed after 17 weeks gestation
- Infant
 - Decreases severity of disease and frequency of sequelae
 - Pyrimethamine and sulfadiazine
 - Therapy continued for 1 year

QUESTION #9

A 1-week old infant develops a copious bloody nasal discharge, lymphadenopathy, hepatomegaly and hemolytic anemia. Which of the following is the most likely additional feature in this infant?

- A. hydrocephalus
- B. periostitis
- C. limb hypoplasia
- D. seizures
- E. hydrops

CONGENITAL SYPHILIS

- 30-40% of infected fetuses are stillborn
- Of infected neonates who are live-born, 70% are asymptomatic at birth and are identified by prenatal maternal screening
- Because fetus acquires infection via hematogenous route, widespread involvement (rather than primary stage) is usual

UNIQUE FEATURES OF CONGENITAL SYPHILIS

- Generalized lymphadenopathy more common than other congenital infections
- Coombs-negative hemolytic anemia
- Snuffles (rhinitis)-in 25% of infants
- Exanthem
 - maculopapular rash with scaling and desquamation most common
 - vesicobullous lesions (pemphigus syphiliticus)

UNIQUE FEATURES OF CONGENITAL SYPHILIS

- Bony lesions-may be most frequently encountered manifestation
 - osteochondritis
 - osteomyelitis
 - periostitis
- CNS manifestations
 - pleocytosis; high protein, reaginic antibody
- Chorioretinitis
 - "salt & pepper"-like Rubella





INDICATIONS FOR EVALUATION OF CONGENITAL SYPHILIS

- Mother with positive non-treponemal tests confirmed by a positive treponemal test and:
 - Untreated or inadequately treated syphilis
 - Treatment in pregnancy with non-penicillin regimen
 - Lack of expected decrease in non-treponemal antibody titer after treatment
 - Treatment < 1 month before delivery
 - Treatment not documented
 - Insufficient follow-up to assess response

Evaluation for Congenital Syphilis

- PE
- Quantitative nontreponemal (RPR) and treponemal (FTA-ABS) test on infant's serum
- Antitreponemal IgM if available
- CSF for VDRL, cell count, protein
- Long-bone radiographs
- CBC, platelets
- Chest radiography, LFT's
 - as clinically indicated

Congenital Syphilis: Who needs Treatment?

- Infants with proven or probable disease
- Infants who warrant evaluation in which infection cannot be ruled out
- Infants whose follow-up cannot be assured
- Infants whose infected mothers can't be treated, treated inadequately, or treated within 1 month of delivery
- Infants of mothers not having 4-fold decrease in titer

Treatment for Congenital Syphilis

- Aqueous Penicillin G for 10-14 days preferred therapy for proven or presumed infection
- Procaine penicillin (IM) may also be used
 - CSF concentrations may not be adequate
- Single dose benzathine Penicillin
 - recommended by some experts for:
 - asymptomatic infants with normal evaluation and whose follow-up can be assured, but whose mothers have not been treated adequately or do not have 4-fold decrease in titer

Question #10

Of the following, the congenital infection most associated with hydrops fetalis is:

- A. Varicella-zoster virus
- B. HIV
- C. Human herpes virus 6 (HHV-6)
- D. Parvovirus B19
- E. *Borrelia burgdorferi*



EPIDEMIOLOGY OF PARVOVIRUS B19 INFECTIONS

- About 50% of women are seropositive for the virus prior to pregnancy
- Likelihood of infection after a close exposure estimated to be 30-50%
- Estimates of fetal loss following infection during pregnancy range from 2-6%
- Thus, overall risk of fetal loss due to this virus is 1-2%

CONGENITAL PARVOVIRUS B19 INFECTION

- Consequences of maternal parvovirus infections
 - Asymptomatic newborn
 - IUGR
 - Hydrops fetalis
 - severe anemia
 - high output cardiac failure
 - extramedullary hematopoiesis
 - Stillbirth
 - Isolated pleural or pericardial effusions

Answers to Questions

- 1. C
- 2. A
- 3. A
- 4. B
- 5. B
- 6. B
- 7. A
- 8. D
- 9. B
- 10. D



Every life deserves world class care.
