Congenital Infections

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Introduction
• Infections that are acquired in utero or during the birth process
• Original TORCH complex was described in 1971
  – Toxoplasmosis
  – Rubella
  – CMV
  – HSV
• List expanded to include other infections
  – Varicella, syphilis, HIV, hepatitis B

Objectives
• Review incidence and pathogenesis of congenital infections including:
  – CMV
  – HIV
  – HSV
• Review treatment and management options for these infections
CMV

• DNA virus of the herpesvirus group
• Most common congenital viral infection
• 40,000 infants born each year with congenital CMV
• More than 8,000 develop mental retardation, CP, or hearing impairment
• Isolated from all body tissues and fluids
• Can also live on plastic surfaces and toys

Prevalence

• 40 to 60% of adults in middle and upper socioeconomic groups have evidence of CMV
• 80% of adults in lower socioeconomic groups
• In developing countries almost all adults are universally infected
Incidence

- Viral excretion in the cervix or urine rises from 3% in 1st trim to 25-50% at term
- Seroconversion during pregnancy 0.7 to 4.1%
- Transmitted in 40% of primary infections and 1-2% of reactivated infections
- Incidence of perinatal and postnatal transmission is higher than intrauterine

Transmission

- Maternal primary infection
- Recurrent or reactivated infection
- Reinfection
- Prenatal- transplacental/ hematogenous
- Natal- infected cervical or vaginal secretions
- Postnatal- breast milk, saliva, blood transfusions

Prenatal Infection

- More likely to occur and is more severe after primary maternal infection
- Incidence of primary infection is 1-4% and is associated with a 40% risk of congenital infection
- 0.2 – 2% of infants born to mothers who are seropositive before pregnancy are infected in utero
- Maternal coinfection with HIV promotes perinatal transmission of CMV
Prenatal Infection

- Most infants infected with CMV will have no clinical signs of disease at birth
- 10-15% of infected infants are symptomatic at birth
- Among those that are symptomatic:
  - IUGR, hepatosplenomegaly, jaundice, “blueberry muffin” spots, microcephaly, chorioretinitis, sensorineural hearing loss, cerebral calcifications

Natal Infection

- 2-28% of seropositive women shed CMV in cervical and vaginal secretions during delivery
- 50% of infants exposed will become infected and develop signs of CMV infection at 4-6 weeks of age
- Develop an afebrile pneumonia, tends to be mild in term infants
- More severe in preterm infants. CMV pneumonitis may exacerbate or cause BPD
- Postnatal steroids for BPD have been associated with progression of the disease
Postnatal Infection

• Breastfeeding
  - 9-98% of seropositive women shed CMV in their breastmilk
  - 50-60% of infants fed infected milk become infected
  - most infants will not develop clinical signs of infection

• Transfusions
  - incidence is 15% in infants less than 1300g
  - occurs when blood has not been treated to remove CMV

Diagnosis

• Pregnant women
  – Less than 25% with primary infection will be symptomatic
    • Flu like syndrome with persistent fever, pharyngitis, fatigue, myalgias
  – Gold standard of diagnosis is maternal seroconversion
    • Detecting CMV specific IgG with low and slowly increasing avidity and increasing levels of CMV specific IgM

Fetal Evaluation

• Ultrasound abnormalities
  – Oligo/Polyhydramnios
  – IUGR
  – Echodensities of bowel, liver
  – Hydrocephalus
  – Microcephaly
  – Ascites or hydrops
  – Necrotic or cystic or calcified lesions in the brain
Fetal Diagnosis

- Virus from amnion confirms in utero infection
- Virus should be obtained from saliva and urine before 3 wks of age
- ID virus by shell-vial culture assay
- PCR can be used on blood, urine, CSF and amnion
- IgG or IgM not recommended

Positive CMV Shell-vial Assay

![CMV Shell-vial Assay](image)

Treatment

- Consists primarily of supportive care
- Evaluation
  - Head ultrasound
  - Hearing screen
  - Ophthalmologic screening
- Ganciclovir
**Ganciclovir**

- Inhibits DNA polymerase, acting as a chain terminator during elongation of newly synthesized viral DNA
- Should be considered in patients who are severely affected (life threatening), hearing loss, chorioretinitis, and preterms who are CMV+ and need steroids
- Severe neutropenia most common adverse effect

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**Ganciclovir**

- Only one phase III randomized trial
  - 100 newborns recruited with symptomatic CMV
    - Randomized to 6 weeks of IV ganciclovir or no treatment, treatment started in first month of life
    - Shown to prevent hearing deterioration at 6 months and 1 year
    - Short term improvement in weight gain, head circumference,
    - Reduced developmental delays at 6 months and 12 months
    - No change in mortality

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**Hearing Loss**

- Sensorineural hearing loss occurs in 30 to 65% of symptomatic infants, and 5 to 15% of asymptomatic infants
- Is the most common abnormality seen in congenital CMV infection
- Hearing loss develops after the newborn period and tends to be progressive
- 50% of infected infants have further hearing deterioration throughout childhood and into adolescence
- Cochlear implantation has been used successfully in CMV associated hearing loss
**Prognosis**

- More than 90% of infants with symptomatic CMV have abnormalities at f/u exams.
- 90% of asymptomatic infants have no apparent sequelae, but 7% of them may develop some hearing loss.
- Should be enrolled in early intervention programs, and have close optho and audiological follow up.

**Prevention**

Ways a pregnant woman may help reduce her exposure to CMV:
- Washing hands frequently with soap and water, especially after changing diapers, feeding a child, or handling children’s toys.
- Not sharing cups, plates, utensils, food, or toothbrushes.
- Not sharing towels or washcloths.
- Not putting a child’s pacifier in her mouth.
- Cleaning toys, countertops, and anything else that comes in contact with children’s urine or saliva.

**HIV**


HIV

- First recognized in the early 1980s
  - First cases of AIDS in young infants was reported in 1983
- RNA retrovirus
- Lentivirus family
- Single stranded RNA virus
- Two subtypes
  - HIV-1
  - HIV-2

Epidemiology

- 33.8 million people worldwide living with HIV
  - 2.7 million new infections
  - 430,000 children less than 15
- USA
  - In 2010, 48,292 new cases of HIV
    - 162 infants infected via mother to child transmission
Mother-Infant Transmission

- AIDS Clinical Trial Group -076 Protocol (1994)
- Phase III randomized placebo-controlled trial of Zidovudine (AZT) for the prevention of maternal HIV transmission
- Antepartum 100mg AZT PO 5x/day at 14-35 wks gestation
- Intrapartum During labor – 1 hour initial dose 2 mg/kg followed by 1mg/kg/hour continuous infusion until delivery
- Postpartum Infant 2 mg/kg PO Q6 hours for 6 wks
Zidovudine (AZT)

- Decreases maternal viral load in blood and genital secretions
- Crosses placenta → systemic drug levels in fetus which can be protective during delivery
- Postexposure prophylaxis in infant
- For maximal reduction in transmission all prophylaxis is recommended

HIV Transmission

- Mother to infant transmission
  - Prenatally (20-25%)
  - During labor and delivery (35-50%)
  - Postpartum (primarily through breastfeeding, 25-35%)
- Without intervention to reduce transmission, transmission rates range from 13-42%
- Factors that can affect transmission rates:
  - High maternal viral load, low maternal CD4 cell count, advanced disease, prematurity, PROM, mode of delivery, receipt of antiretrovirals in mother and child
Prenatal Testing

- All pregnant women should be screened for HIV as early as possible (opt-out screening)
  - Recommended by ACOG, AAP, CDC
  - Illinois: Illinois Perinatal HIV Prevention Act
  - Missouri: Opt-out screening

Perinatal HIV Testing

- Conventional HIV algorithm
  - Screening test with ELISA to detect antibodies to HIV
    - If positive → confirmatory test with Western blot or immunofluorescence assay (IFA)
    - Sensitivity and specificity of ELISA with confirmatory Western blot > 99%
    - May take up to 2 weeks to complete
Perinatal HIV Testing

- Rapid HIV testing
  - Could also use as standard outpatient test as well as in labor and delivery
    - Negative test is definitive
    - Positive test requires confirmation with supplemental test
  - Sensitivity and specificity equal to or greater than 99%
    - Likelihood of a false positive result is higher in populations with low HIV prevalence

Undocumented Status

- What about woman with undocumented status who arrives at labor and delivery?
  - ACOG recommendation is to screen with rapid HIV test (opt-out screening)
  - 40-85% of infants infected with HIV are born to women whose HIV status is unknown prior to delivery
  - If positive, initiate anti-retroviral prophylaxis without waiting for confirmatory test results
Infant HIV Testing

- Antibody testing cannot be used to determine infection status
  - Maternal HIV antibodies may be present until 18 months of age
  - Positive HIV antibody test identifies exposure to HIV i.e. maternal infection
- Require the use of virological assays
  - HIV-1 DNA PCR
  - HIV-1 RNA PCR

Virological Assays

- HIV status can be presumptively excluded with 2 negative tests, with one at 2 or more weeks of age and the second at 1 or more months of age.
- Can be definitively excluded with 2 negative tests, with one at 1 or more months of age and the second at 4 or more months of age

Care of HIV Exposed Infants In the Delivery Room

- Avoid invasive procedures
- If possible delay until 1st bath.
  - IM injections
  - glucose sticks
  - Ilotycin
Care of HIV Exposed Infants

- AZT prophylaxis
  - Term 2 mg/Kg/dose PO Q6 hours x 6 wks or 1.5 mg/kg/dose IV Q 6 hours
  - Preterm 2 mg/Kg/dose PO Q 12 hours x 6wks or 1.5 mg/kg/dose IV Q 12 hours
  - Start within 12 hours for maximal benefit
  - Discontinue immediately if any of the PCR studies are positive
- Consult ID team

Care of HIV Exposed Infants

Labs:
- RPR
- HIV DNA PCR by 48 hours, 1 to 2 months, and 4 months
- Urine CMV culture
- Check CBC while on AZT

Pneumocystis carinii Pneumonia

- Indicates a primary infection, unlike adults
- Occurs after 1st month of age
- Life threatening
- Prophylaxis 4 to 6 weeks to 1st year or until HIV infection excluded
- Trimethoprim-sulfamethoxazole 75 mg/m2 BID three times a week
To Breastfeed or Not?

- Not recommended in US
  - HIV-1 is present in varying frequencies
  - Use of formula feedings in this setting has reduced postnatal maternal to child transmission of HIV significantly
- Resource limited settings
  - WHO recommends breastfeeding if formula feeding not possible

Cesarean Delivery

- ACOG recommendations
  - HIV infected women with plasma viral loads > 1000 copies/mL be counseled on benefits of elective cesarean delivery (ECD) to prevent transmission
  - ECD should be performed at 38 completed weeks of gestation
  - Should receive antiretrovirals during pregnancy and not be interrupted before delivery
  - IV AZT be given 3 hours prior to ECD

Cesarean Delivery

- Maternal morbidity
  - Increased risk when compared to HIV uninfected controls
    - Risk of complications correlated with degree of immunosuppression
    - Risks primarily infectious (UTI, pneumonia, wound infection, septicemia)
      - Highest in non-ECD, intermediate with ECD, and lowest with vaginal delivery
  - Does not outweigh benefit of decreased transmission of HIV to the infant
Cesarean Delivery

- Neonatal morbidity
  - Two prospective cohort studies have found that the number of infants with respiratory morbidity was higher among those delivered via ECD when compared to vaginal delivery
- Again, benefits of reduced transmission outweigh the small risk of respiratory morbidity

Anticipatory Guidance

- Routine age appropriate anticipatory guidance
- Educating caregivers on HIV testing schedule
- Importance of antiretroviral therapy as well as PCP prophylaxis
- Same routine vaccines and same schedule

HIV Resources

- ACOG Perinatal HIV – [www.acog.org/goto/HIV](http://www.acog.org/goto/HIV)
HSV

Background

• Herpesvirus family = large dsDNA viruses, characterized by latency and reactivation
• Virus inoculates at site of entry (oral/genital mucosa breakdown) → infection of sensory nerves → DRG
• Reactivation spontaneous or induced (stress, tissues damage, immunosuppression): virus travels back down axons to mucosal sites

Background

• Neonatal HSV: 1500 cases annually, 1/3200 deliveries in US. Much less in other countries.
• 11-33/100,000 livebirths
• Acquired at 3 distinct times
  – 5% in utero
  – 10% postnatal (external shedding from skin)
  – 85% perinatal/intrapartum
Clinical Presentation

1. SEM Disease
   • Accounts for 20% of all neonatal HSV.
   • Discrete vesicles w/ erythematous base, usually 1-2mm diameter.
   • Cluster around sites of trauma (e.g. FSE)
   • Presentation DOL#10-12
   • Good prognosis if treated

Clinical Presentation

2. CNS Disease
   • Encephalitis - 33% of neonatal HSV
   • Manifestations include seizures, lethargy, irritability, poor feeding.
   • Can involve multiple parts of brain; usual have neurologic impairment w/ poor prognosis.
   • Presentation usually btw DOL#16-19, occ 4-6 weeks.

Clinical Presentation

3. Disseminated Disease
   • 50-66% of neonatal HSV
   • Common presentations – viral sepsis, respiratory distress, liver failure, hepatitis, pneumonitis.
   • Can affect multiple organs – develop pleural effusion, NEC, DIC
   • Presentation DOL#10-12
Maternal Infection & Transmission

- Infection w/ HSV-2 common in pregnant women – some studies show 20-30%
- Presence of antibodies is good marker for persistent infection
- Most women w/ serologic evidence of HSV-2 are asymptomatic
- Timing of seroconversion, effects on pregnancy/neonate intensely studied topics

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Maternal Infection & Transmission

- Seroconversion: appearance of antibodies to HSV (either type-1 or -2) at time of labor not detected on prior prenatal visit.
- Primary infection: no antibodies present initially but infection w/ HSV-1 or -2 present at labor.
- Non-primary first episode (NPFE): new infection w/ one virus type, no antibodies to other virus type (usually HSV-1 present initially).
- Recurrent infection: pre-existing antibodies to type from genital tract (usually HSV-2).

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Maternal Infection & Transmission

Brown ZA et al – NEJM 1997
Observational study of acquisition of HSV during pregnancy, outcomes on pregnancy
- 8538 women with serum samples obtained at first prenatal visit and at time of labor
- 7046 women susceptible to HSV infection (no Abs or only type-1 or -2 detected)
- 94 (1.3%) women seroconverted
Maternal Infection & Transmission

• Of 94 seroconverts, 60 women (64%) had subclinical infections.
• Of 60 women w/ known trimester of infection, risk of acquisition relatively uniform throughout pregnancy
• 9 women not included in major cohort (did not seroconvert by time of labor): all acquired genital HSV lesion near onset of labor; 4 infants developed neonatal HSV (compare w/ 0 of 94 who did seroconvert)

Conclusions:

• ~2% of susceptible women acquire HSV during pregnancy
• Seroconversion completed before onset of labor does not affect pregnancy outcome
• Infection acquired near time of labor associated w/ neonatal herpes

Brown ZA et al – JAMA 2003
Cohort study examining effects of viral shedding, serologic status, route of delivery on risk of HSV transmission.
• 58,362 pregnant women – HSV cultures obtained at delivery and maternal serologic status determined
• Outcome = neonatal HSV infection
### Maternal Infection & Transmission

**Conclusions:**
- Neonatal infection rates can be reduced by preventing maternal acquisition of HSV-1 or -2 near term.
- Neonatal infection rates can be reduced by C-section and by limiting use of invasive monitors during labor.

### Diagnosis & Treatment

- **Gold standard for diagnosis is PCR in CSF**
- Direct viral examination and viral culture best for skin lesions/other body sites
- Ancillary studies – CBC, AST/ALT, coags, EEG, CT/MRI
- Treatment – high dose acyclovir 60mg/kg/day IV divided tid
- Both diagnosis and treatment must be done promptly

### Recurrence & Relapse

Kimura et al – *Arch Dis Child Fetal Neonatal Ed* 2003

Observational study to determine features of and risk of relapse
- 32 neonates enrolled, 31 known cases of HSV status
- 33-41 wks, BW 1920-4030g, all survived
- All treated w/ SD/HD acyclovir 5-28 days
Conclusions:
• HSV-2 have greater risk of relapse
• Patients w/ relapse had worse outcomes

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariate analysis of factors related to relapse</th>
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<tbody>
<tr>
<td>Factors</td>
<td>Odds ratio</td>
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<tr>
<td>Control type</td>
<td>1.0</td>
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<tr>
<td>Viral type (type 2)</td>
<td>10.4</td>
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<tr>
<td>Initial acyclovir treatment</td>
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<tr>
<td>Dose (mg/kg)</td>
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<tr>
<td>Duration (days)</td>
<td>1.18</td>
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*By logistic regression analysis. Bold letters indicate significant results.

Recurrence & Relapse
Suppressive therapy:
• Debate still ongoing, trials still pending
• Oral acyclovir x 6 months after recommended treatment of IV acyclovir
• Acyclovir resistance has been documented

Prevention & Screening
• Cochrane Database Syst Rev 2008
  – Third trimester antiviral prophylaxis for preventing maternal HSV recurrences and neonatal infection.
  – Meta-analysis of RCTs comparing anti-viral vs placebo or no therapy.
  – 7 studies qualified = 1,249 participants
  – Maternal outcomes – reduced viral shedding, recurrence at delivery, and C-section rate.
  – No cases of symptomatic neonatal herpes in any groups.
Prevention & Screening

- Overall, risk of neonatal infection is low
- Obtaining sequential cultures closer to time of delivery in women w/ hx of genital herpes is futile.
- ACOG Practice Bulletin 1999: appropriate to do vaginal deliveries on women w/ hx of genital herpes but no active disease at time of delivery.

References


References


Questions?