DR note in RED

Neonatal Infections

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Part II

Viral Infections in the Neonate

Vertically Transmitted Viral Infections in the Neonate

- Herpes Simplex Virus (HSV)
- Varicella Zoster Virus (VZV)
- Hepatitis B
- Cytomegalovirus (CMV)

Herpes simplex virus (HSV)

Any Detail about HSV should be know because the Mortality rate is high even if the baby is improving 80% of them will end with neurological seizure

when suspected hsv should start the treatments . Regardless of Culture and PCR result

- Herpes simplex virus (HSV) has been associated with neonatal disease for more than 6 decades.
- Over the past 20 years, there have been major advances in our knowledge of the epidemiology, pathogenesis and natural history of this disease. In addition, the availability of effective antiviral therapy has resulted in major advances in the management of neonatal HSV infections.
- Despite these advances, HSV remains a major cause of morbidity and mortality among neonates.

When you have to treat ?

Any baby have sepsis with convulsions Immediately use acyclovir and Don't wait until you know the result of culture because The only thing will be beneficial for this patient is the acyclovir, it will improve the prognosis and decrease the mortality rate

Epidemiology

- **Incidence of neonatal infection:**
- Data from the Canadian Paediatric Surveillance Program (CPSP) indicate that, between 2000-2003, there were 43 cases of neonatal HSV (5.9 per 100,000 live births in Canada) and a case fatality rate of 15.5%.
- While the incidence varies across regions in the USA, a rate of 1 in 3200 deliveries was recently documented.
- approximately 70% of neonatal disease is caused by HSV type 2 and 30% by HSV type 1.

Herpes Simplex Virus (HSV)

- Large, enveloped DNA virus
  - HSV type II (usually genital)
  - HSV type I (usually facial and oral)
  - Either type can exist at either location
- Transmission to the neonate occurs via the birth canal or by ascending infection
- Postnatal transmission can occur

Routes of Transmission

- 85% via infected maternal genital tract
  - Ascending infection , or when pass through the birth canal .
- 10% postpartum
- 5% (or less) – intrauterine/congenital infection

- HSV2 = 70-75%, HSV1 = 25-30%

(HSV)
Postnatal Transmission

- Mother or father with non-genital infection
  - hands, mouth, nipple
- Nosocomial spread from infected infant to non infected infant
  - usually via the hands of nursery personnel

(HSV)
Risk of Neonatal Infection

- Primary maternal infection
  - Risk of transmission to infant 33-50%
- Recurrent maternal infection
  - Risk of transmission to infant 3-5%
- Relative risk varies:
  - Vaginal delivery vs. Cesarean section
  - Length of time membranes ruptured >6hr
  - Also At Risk: Premature, Fetal scalp monitoring

(HSV)
Clinical Manifestations of Neonatal Disease

- Symptoms usually occur from birth to two weeks but can occur as late as 4-6 weeks
- **Three clinical syndromes**:
  - Multiple organ, systemic Disseminated infection
  - Localized central nervous system disease
  - Localized infection to skin, eyes (conjunctivitis, keratitis, chorioretinitis), ,mouth (SEM) and the presenting part .

more than 50% will not have skin lesions , because that will be delayed of diagnosis and bad prognosis . So any case have high index of suspension should start the treatment because it not mandatory to complain of skin lesions

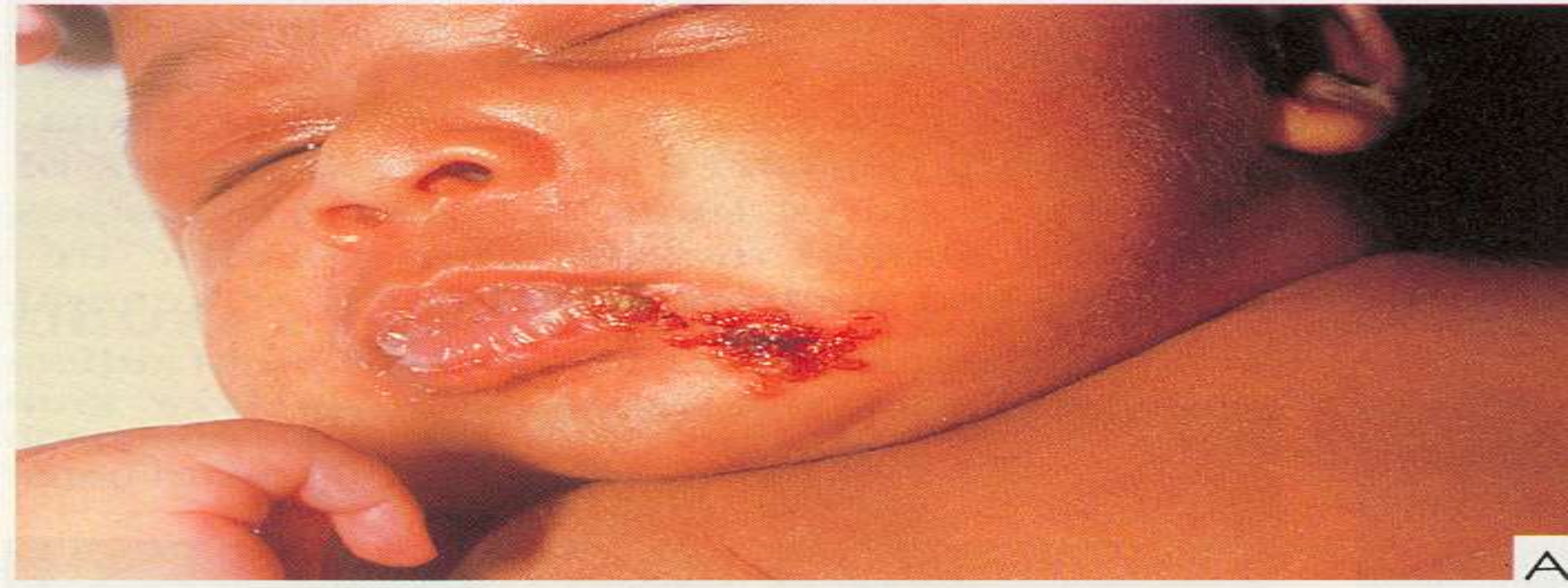
(HSV) Skin Lesions

- Vesicles may have already ruptured and may look more like impetigo or mild cellulitis
- Usually at presenting part of baby or site of instrumentation
- 1/3 of infants with systemic disease will lack skin lesions
- Another 1/3 will manifest skin lesions **AFTER** onset of systemic disease

Skin, Eye, Mouth (SEM)

- Approximately ½ of all HSV infections
- 1st-2nd week presentation
- Limited to skin, eye, mouth/mucous membranes
- 60-70% of untreated patients progress to CNS/disseminated disease
- Long term neurologic sequelae seen in 30% of cases – even if treated

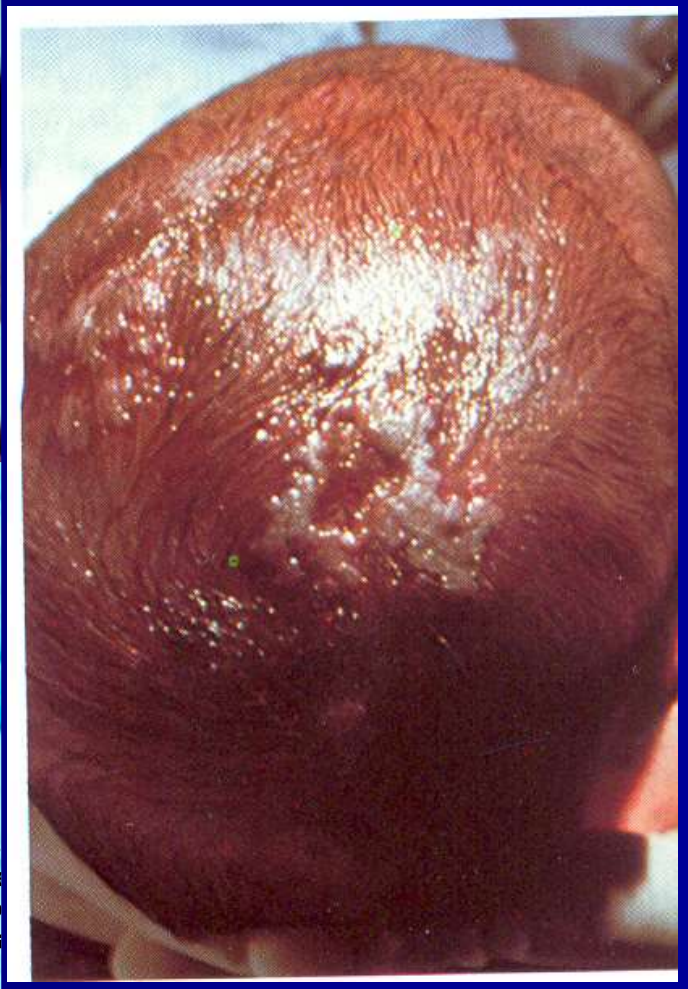

Groin Vesicles
16 Days of Life
HSV-1, This Infant
Had a Cardiac Cath
(Groin Line)
At 3 Days of Life



“Presenting Part” (SEM)

HSV 2 Arm Lesions
9 Days of Life
Presenting Limb in a 34 Week
Premature Infant

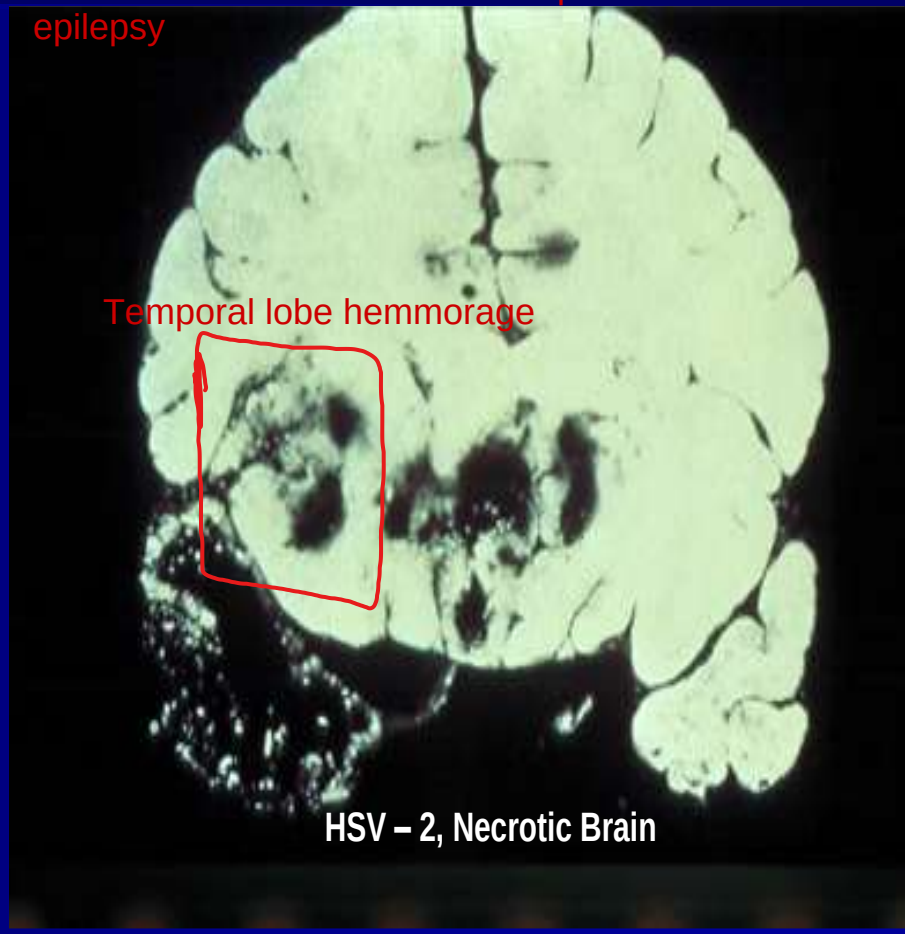
Scalp Lesions
11 Days of Life
HSV-2, Monito
With Scalp Lea



HSV - CNS Disease

- Encephalitis, mainly involving the temporal lobes
- Early to 3rd week of life presentation
- Skin lesions may appear late
- 35% of all cases, only 2-5% untreated survive normally

Brain CT , there is temporal lobe hemmorage , because that patient who have HSV infection will have temporal lobe epilepsy



(HSV)
Symptoms of Systemic Disease

- Appearance of sepsis:
  - Fever, lethargy, poor feeding
  - Must rule out bacterial infection as well
- Respiratory distress
- Seizures:
  - Tend to be recurrent and difficult to control
  - Spinal fluid shows elevated white blood cells (mostly lymphocytes), erythrocytes, and protein , low glucose (mimic bacterial infection) + PCR

the Epstein-Barr virus, CMV , mumps all of them mimic the bacterial infection.
How to differentiate?
If there is no traumatic lumper puncture and the RBC around the 500 and more so you are dealing with HSV

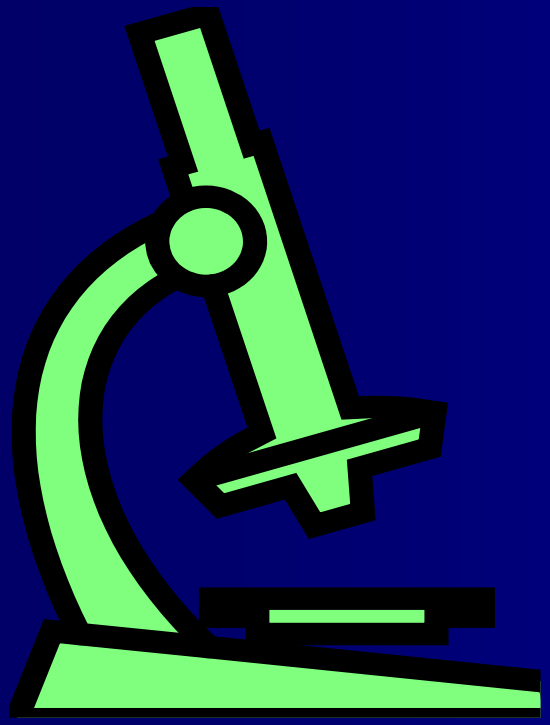
(HSV) Mortality and Morbidity

- Isolated skin, eye, or oral disease (20%)
  - 25% of infants will develop neurologic abnormalities despite lack of symptoms at presentation
- Central nervous system CNS disease (33%)
  - 17-50% mortality
  - 40% of survivors will have neurologic sequelae
    - microcephaly, spasticity, paralysis, seizures, deafness, blindness

(HSV) Disseminated Disease

- Without antiviral therapy:
  - 80% mortality
  - Most, if not all, survivors will have permanent neurologic sequelae
- With antiviral therapy:
  - 15-20% mortality
  - 40-55% of survivors will have permanent neurologic sequelae

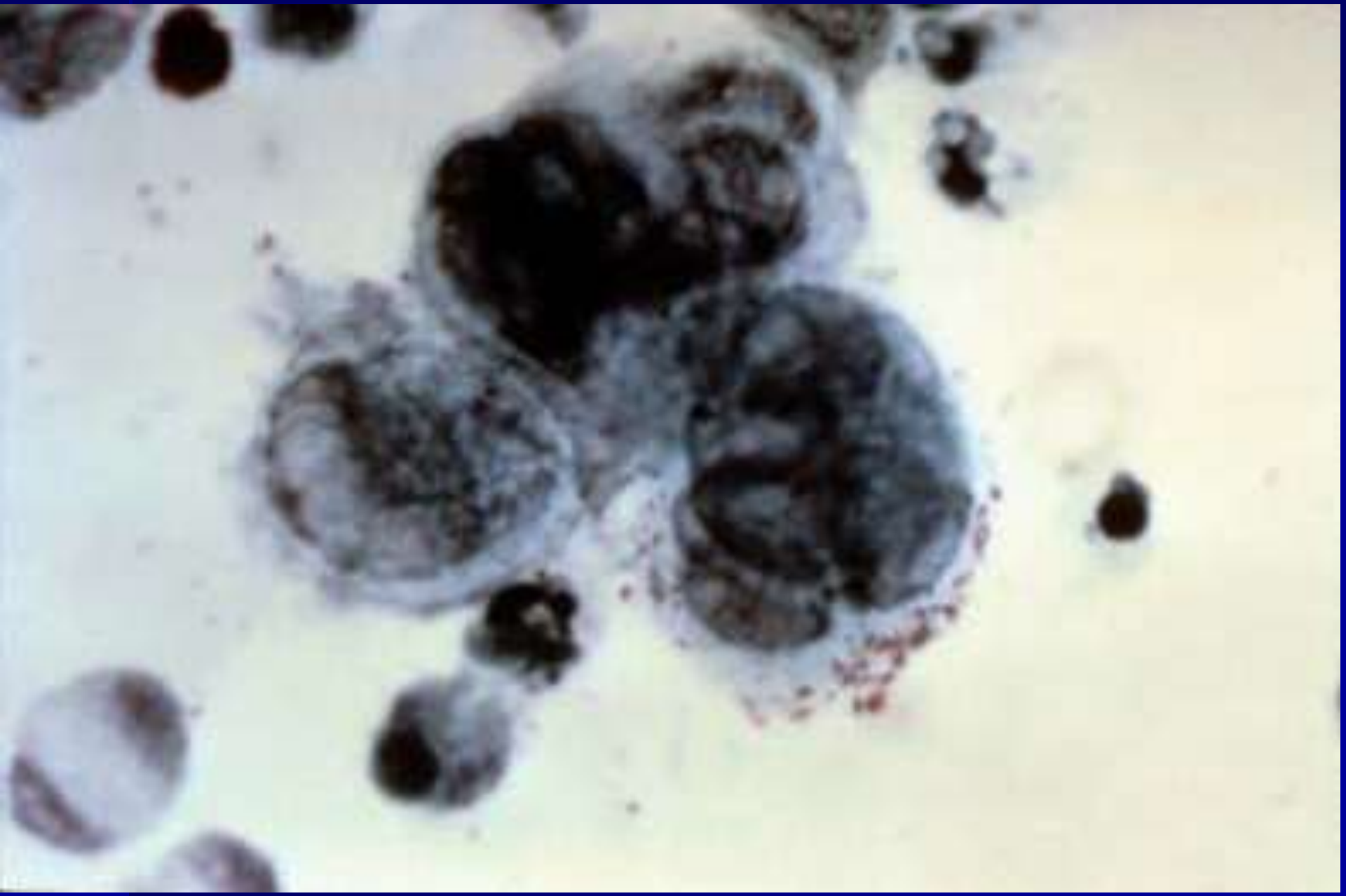
Laboratory Diagnosis



- Tzanck smear
- Serology
- Viral cultures
- Polymerase chain reaction

Tzanck Smear

- Scraping from base of vesicle
- Positive slides will show multinucleated giant cells
- Quick screen but only 75% sensitive



Serology

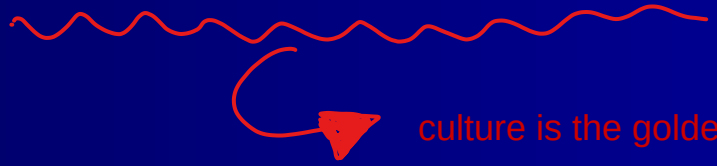
- will demonstrate rising HSV antibody titers
- These rises occur late in the course of disease and are not particularly useful in making treatment decisions
- Recurrent infections in mother often do not produce a rise in titers

Viral Culture

- Still the gold standard
- Viral detection usually positive within 1-3 days of inoculation

Cont...

- Viral cultures from the conjunctiva, naso-pharynx, mouth, stool, and urine at 24-48 hours of life
- Cultures sooner if ***symptomatic***
  - All of the above plus cultures of any *skin lesions* and the spinal fluid
- Always obtain cultures prior to starting empiric acyclovir
- in patients with localized CNS disease, CSF cultures are usually negative. so , polymerase chain reaction (PCR) is an important diagnostic test as it is more sensitive than culture.



Polymerase Chain Reaction

- available
- Relies on amplification of native HSV DNA…..
- Primary limitations include cost and possibility of false positives
- PCR sensitivity rates vary from 75% to 100%

Acyclovir

- Minimum effective dose in neonates is 30 mg/kg/day in three divided doses
  - Most experts recommend higher doses: 45 to 60 mg/kg/day
- Neonatal HSV should be treated with parenteral acyclovir rather than oral therapy
- Minimum length of therapy is 14 days
  - 21 day course may prove more effective

Special Considerations

- Intravenous acyclovir:
  - Ensure adequate hydration to prevent precipitation of drug in kidneys
  - Infuse drug over one hour
  - The use of higher doses of acyclovir is associated with an increased frequency of neutropenia
- Ocular disease:
  - Topical therapy with 1-2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine
  - Requires acyclovir as well

Recurrent Skin Lesions

- Common in surviving infants
- Greater than three recurrences in the first 6 months of life correlates with adverse neurologic and/or ocular sequelae
- Role of prophylactic oral acyclovir not yet clear
- Prolonged oral acyclovir associated with neutropenia

(HSV) Recommended Obstetric Management

- All women in labor should be questioned regarding a history of HSV in themselves or sexual partners
- During the physical exam care should be taken to look for genital and non-genital lesions
- If Cesarean section is to be performed, it is best done within 4-6 hours of membrane rupture
- Scalp monitors and scalp sampling should be avoided
- **Primary and Recurrent genital HSV during pregnancy : give** suppressive acyclovir therapy starting at 36 weeks' gestation at a dose of 400 mg tid

(HSV)
Preterm Infants

- When a woman presents in
  - preterm labor
  - active HSV lesions,
  - AND ruptured membranes
    - ***the course is not clear:***
- Options include:
  - Allow labor to progress (*consider acyclovir for mother*)
  - Delay delivery and give *steroids for lung maturation,* some experts recommend that intravenous acyclovir (15 mg/kg per day in 3 divided doses, maximum 1200 mg/day) be given to the mother if labor and delivery are delayed
  - *Immediate Cesarean section*

(HSV)
Vaginal Delivery Over a Primary Genital Infection

- 33-50% risk of infection in the newborn
- Risk is higher if :
  - premature
  - instrumentation during delivery, or if lacerations occur
- Most experts recommend empiric acyclovir treatment at birth
- Obtain viral cultures prior to starting therapy

HSV
Vaginal Delivery Over a ***Recurrent*** Genital Lesion

- Risk of neonatal infection 5% or less
- No emperic therapy required
- Surveillance cultures at 24- 48 hours
- Careful examination for vesicles and systemic signs of infection

HSV
Delivery by Cesarean Section with Active Maternal HSV

- Obtain surveillance cultures at 24-48 hours of life
- Empiric therapy not recommended
  - Consider therapy if primary lesion and membranes ruptured *greater than 6 hours prior to delivery*
  - if culture results from the infants are positive for HSV or if HSV infection is strongly suspected on clinical grounds

HSV
Maternal History of HSV
No Active Lesions

- Not an indication for Cesarean section
- No special isolation required for infant
- Routine viral cultures not necessary

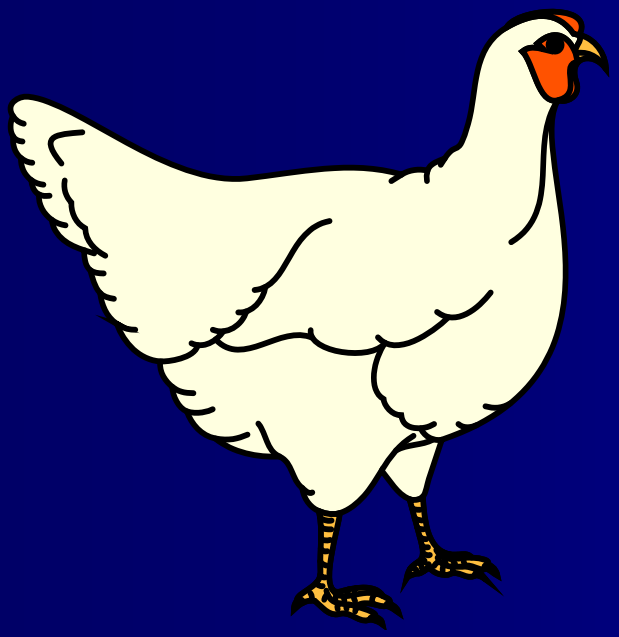
HSV
General Recommendations

- Infants exposed to active lesions should be isolated from other infants in nursery
- Parents should be instructed in *strict hand washing techniques*
- Parents with cold sores should not kiss infants until lesions healed
- Other non-genital herpetic lesions should be covered

HSV
General Considerations

- Breast feeding is NOT contraindicated unless there are lesions on the breast
- Elective circumcisions should be delayed at least one month in high risk infants
- Infection can manifest as late as 6 WEEKS!

(VZV)
Varicella Zoster Virus



- Causes chicken pox and shingles
- Humans are the *only known reservoir*
- *Highly contagious*
- Transmission is by contact or airborne droplets

(VZV) Epidemiology

- Exposure to a household results in infection in virtually all susceptible members
- Incubation period usually 14-16 days
  - Can range 10-21 days
- Patients are contagious from *5 days prior to and 2 days* after the onset of the rash
  - Immunocompromised patients contagious for duration of rash

(VZV)
Congenital Varicella

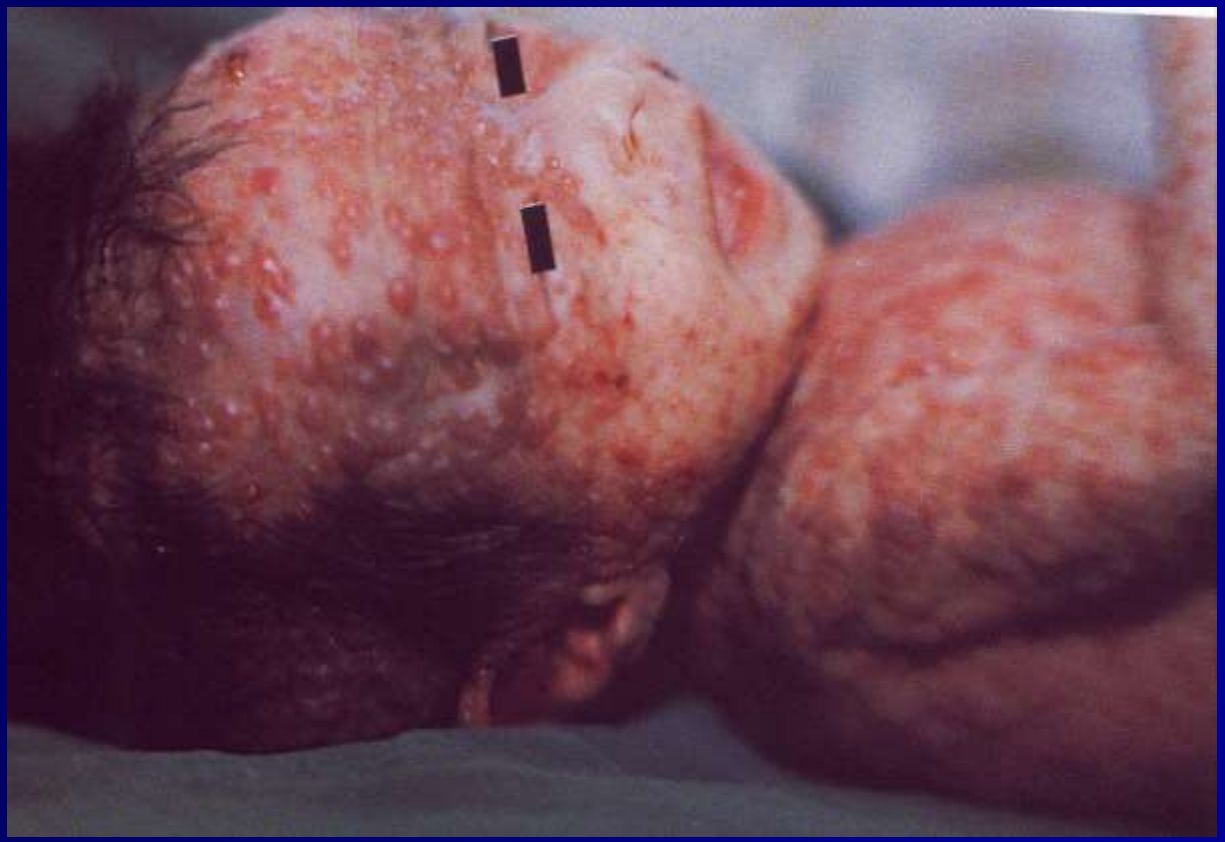
- Caused by maternal infection in the *1st trimester to early 2nd trimester*
  - Greatest risk between 13-20 weeks gestation

- Limb atrophy and scarring
- Chronic encephalopathy and cortical atrophy
- Chorioretinitis, micropthalmia, cataracts

(VZV)
Neonatal Varicella

- Transplacental exposure
- At risk when mother develops varicella *from 5 days prior to 2 days after delivery*
- Can manifest from 1-16 days after delivery
- High risk for disseminated varicella
  - Mortality rates as high as 30%
  - Prognosis much better if lesions develop greater than 5 days after delivery

(VZV)
Neonatal varicella



(VZV) Nosocomial Transmission

- Well documented in pediatric wards

- Rare in newborn nurseries
- High risk infants:
  - Premature infants (> 28 weeks gestation and > 1000 grams) whose mother has no history of varicella
  - Premature infants (≤ 28 weeks gestation or ≤ 1000 grams) *regardless of maternal history*

(VZV)
Varicella Zoster Immune Globulin
(*VZIG*)

- Provides passive immunity
- Not effective once active disease occurs
- Dosage: 125 units/10 kg
  - Minimum dose: 125 units
  - Maximum dose: 625 units
- Never administer intravenously
- Best given within 96 hours of exposure

Indications for VZIG (assuming significant exposure)

- Susceptible pregnant women
- Newborn with onset of maternal varicella within 5 days prior through 2 days following delivery
- Hospitalized premature $\geq$ 28 weeks gestation and no maternal history of varicella
- Hospitalized premature $\leq$ 28 weeks gestation or $\leq$ 1000 grams regardless of maternal history

VZIG

- Term infants exposed after 2 days of life are not at increased risk
  - VZIG not indicated
- All infants who receive VZIG should be in strict isolation
  - 50% of infants still develop varicella though disease tends to be milder
  - VZIG may prolong incubation as long as 28 days

Hepatitis B Virus (HBV)

- HBV is a DNA hepadenavirus
- The virus can be isolated from
  - blood
  - wound exudate
  - semen
  - cervical secretions
  - saliva
- It is not transmitted via the fecal oral route

HBV Serology

- ***HBsAg*** : (surface antigen)
  - Detection of acutely or chronically infected patients
- ***Anti-HBs*** : (antibody to HbsAg)
  - Patients with immunity following :
    - infection
    - or vaccination
- ***HBeAg*** : ('e' antigen)
  - Patients at increased risk for transmitting HBV

HBV Serology

- ***Anti-HBe*** : (antibody to HBe)
  - Low risk for transmitting HBV
- ***Anti-HBc*** : (Antibody to core antigen, HBcAg)
  - Evidence of acute or past infection
  - *Not present after immunization*
- ***IgM Anti-HBc***: (IgM antibody to HBcAg)
  - Acute or recent HBV infection

HBV
Risk to Newborn

- *Chronic HBV infection* occurs in 70-90% of infants delivered to mothers who are HBeAg positive

- Those who escape perinatal infection remain at high risk for horizontal transmission during the first 5 years

HBV
Chronic HBV Infection

- High risk of acquiring :
  - chronic active hepatitis
  - cirrhosis
  - primary hepatocellular carcinoma
- The risk of chronic infection is inversely proportional to the age at time of infection
- Asymptomatic HBV carriers coinfected with the Hepatitis D virus can develop fulminant liver disease

HBV
Hepatitis B Immune Globulin

- Reserved for *post exposure prophylaxis*
- Prepared from human donors with high anti-HBs titers
- Standard Immune Globulin (IVIG) ineffective

HBV
Hepatitis B *Vaccine*

- Two commercial preparations available in the United States
  - Both products of recombinant DNA technology
- The current vaccines produce an antibody response (after 3 doses) in > 90% of adults and > 95% of infants and children

HBV
Routine HBV Vaccination

- First dose at 0-2 months of age
- Minimal interval between 1st and 2nd dose is one month
- Minimal interval between 2nd and 3rd dose is two months
- Minimal interval between 1st and 3rd dose is four months
- When 1st dose is given between 0-2 months, give 3rd dose after 6 months

HBV
Infants of ***HBsAg + Mothers***

- HBIG 0.5 ml IM
- Hepatitis B Vaccine 0.5 ml IM
  - Both should be given within 12 hours of birth
  - inject at different sites
- No contraindication to breast feeding

HBV
Unknown Maternal Status

- Obtain maternal blood for HBV serology
- Administer HBV vaccine while awaiting results
- If mother determined to be HBsAg +, then give HBIG as previously recommended
  - Dose should be given as soon as possible after results known and within 7 days of birth

HBV
Follow Up

- Vaccinate at 0, 1, and 6 months

- Infants given their first vaccine at < 2 kg, *should be given a 4th dose*

Cytomegalovirus (CMV)

- DNA herpes virus
- 1% of all newborns have CMV infection at birth and are excreting virus
- Virus is transmitted both vertically and horizontally

CMV
Modes of Transmission

- Transplacental
- Via birth canal
- Contact with infected urine or saliva
- Blood transfusions and organ transplants

- Breast milk
  - Most infants infected this way *do not manifest clinical illness*

CMV
High Risk Infants

- Severe disease in *~5% of in utero infections*
- Primary maternal infection at *highest risk* :
  - 10-20% will have mental retardation or hearing loss
  - Fetal risks greatest in first half of pregnancy
- Premature infants
- Immunosuppressed patients

CMV
Clinical Disease

- Most infants are asymptomatic
- Mild to moderate disease:
  - Petechiae
  - Hepatosplenomegaly
  - jaundice
  - intrauterine growth retardation
- Severe (Cytomegalic Inclusion Disease)
  - The above findings plus:
    - Microcephaly
    - brain damage,
    - cerebral calcifications
    - chorioretinitis

CMV Diagnosis

- Virus can be cultured from urine, pharyngeal cultures, leukocytes, human milk, semen, and cervical secretions, tissue and other body fluids
- Fourfold antibody titer rise
- Polymerase chain reaction
  - Proof of congenital infection requires cultures or serology within three weeks of birth

CMV Treatment

- Gancyclovir
  - Beneficial in treating retinitis
  - Limited data on congenital infections though potentially helpful
- CMV Immune Globulin
- Vaccine is currently experimental

CMV Prevention

- STRICT HAND WASHING by hospital personnel
- Use only CMV negative blood in premies and immune suppressed patients
- Human Milk
  - Donor milk should be frozen or pasteurized

Any Questions?