I. General Aspects of Neonatal Infections

A. Susceptibility and Virulence

1. Human fetus and neonate are unduly susceptible to a wide variety of microbes, many of which are not pathogenic in more mature individuals
   a) Limitations of innate immunity (first line defense); e.g. skin, epithelial surfaces, complement, macrophages, smaller number of neutrophils
   b) Limitations of adaptive (antigen specific: second line defense) immunity: T cells, B cells: immature and naive
   c) Infection in first trimester often results in miscarriage or stillbirth
   d) Lymphocytes present in fetus by nine weeks, blood by 12 weeks
   e) Newborns have adult levels of IgG from mother
   f) Small amounts of IgM present
   g) T cells and B cells slower to respond
   h) Monocyte handling of antigens normal
   i) Greater the prematurity, greater the immune deficiency
   j) Maternal nutritional imbalance, deficiency or excess, affects neonatal immunity

2. Most common mode of infection is transplacental spread of a blood born infection which the mother experiences for the first time
   a) Placenta may be infected without fetal infection, and fetal infection may occur without placental infection
   b) Infection may occur during parturition
      • E.g. Herpes simplex, bacteria
   c) Extension of infection from adjacent maternal tissues can occur
      • Herpes simplex occasionally spreads from birth canal to fetus, through ruptured or intact amniotic membranes
      • Extension from peritoneum
   d) As a result of invasive methods for diagnosis of fetal disorders
      • Sampling of fetal blood
      • Chorionic villus biopsy
      • Amniocentesis: hepatitis C, toxoplasmosis or HIV/AIDS can be transferred to fetus

3. Virulence is variable
   a) Acquired infection with Toxoplasma in immunocompetent persons is generally an asymptomatic infection.
      • Toxoplasmosis infection of mother in pregnancy: often no symptoms (80-90% of cases) or nonspecific symptoms: fatigue, lymphadenopathy, low grade fever, pharyngitis, myalgia, mimic infectious mononucleosis
      • 70-80% of infected infants asymptomatic at birth (i.e. no clinical features beyond positive titers or cultures)
b) Virulence of toxoplasmosis in Brazil much greater than North America
   • European children: 3% of infected infants have chorioretinitis at birth
   • Brazil: 50%, different subtype of organism

c) Syphilis: positive PCR or serology (e.g. VDRL + FTA in syphilis) will usually result in treatment

d) CMV: no treatment with positive urine culture if no clinical signs present

e) Zika virus: Whether the frequency or severity of congenital infection differs between mothers with asymptomatic Zika infection from those with clinically overt infection is not known.
   • Only 20% of infected mothers have symptoms
   • Only 50% of infected mothers have symptoms or known risk factors

g) Herpes simplex: treat if findings suspicious, do not wait for confirmation; re-evaluate later

B. Timing
1. First trimester: fetal death/ spontaneous abortion/stillbirth common
2. Mild to severe damage at birth may occur, or infection may be asymptomatic at birth
3. Asymptomatic at birth: may not develop clinical signs or effects may be seen much later
   a) Toxoplasmosis: 41% of the new ocular lesions in congenital toxoplasmosis are observed in individuals older than 10 years
   b) CMV hearing loss, cognitive defects may occur later
      • New chorioretinal lesions uncommon but can occur
      • 90% of infants infected but asymptomatic at birth never develop clinical disease
   c) Syphilis
      • Spontaneous abortion or stillbirth may occur
      • 1/3 apparent at birth
      • 2/3 asymptomatic at birth, then develop signs and symptoms up to two decades later
   d) Herpes simplex: usually presents 5-21 days after birth
      • Rarely, disseminated disease at birth

C. Clinical Features: General Aspects
1. Neonatologists consider TORCHES infections whenever a neonate presents with intrauterine growth restriction (IUGR), microcephaly, intracranial calcifications, conjunctivitis, hearing loss, rash, hepatosplenomegaly, or thrombocytopenia.
   (All TORCHES agents can cause meningoencephalitis and chorioretinitis.)
2. Rubella, CMV, HSV, T Gondii, T pallidum. May present similarly: Purpura, jaundice, hepatosplenomegaly, pneumonitis, meningencephalitis
3. Infection may be detected on prenatal screening
   a) USA: syphilis, gonococcus, rubella, HIV, group B strep, hepatitis B and C, TB, chlamydia, gonococcus: some variation in state laws
   b) By history and exam: herpes simplex (exam often not reliable)
4. By selected testing when appropriate – Ultrasound: CNS calcifications, microcephaly, ventriculomegaly, hepatosplenomegaly
5. Amniocentesis: fetal injury or death 1%
6. Fetal blood sampling: fetal injury or death 1.4%
D. TORCHES Infections

1. 1971 Andres Nahmias proposed TORCH to denote four congenital infections that are sometimes difficult to distinguish: TOxoplasmosis, Rubella, Cytomegalovirus and Herpes Simplex virus

2. 1975 Harold Fuerst proposed adding “one disturbing omission”: syphilis
   - He proposed STORCH (German for Stork)

3. 1972 Roger Brumback proposed TORCHES
   - TOxoplasmosis, Rubella, Cytomegalovirus, HErpes, Syphilis

4. With time the O began to stand for Other, mainly other viruses

5. Other viruses that cause congenital infections and affect the eye:
   a) Lymphocytic Choriomeningitis: LCMV
   b) Zika virus
   c) Human Immunodeficiency virus
   d) West Nile virus

6. Many other viruses/microbes can affect the fetus and newborn: Rubeola, Smallpox, Coxsackie B, Poliovirus, Parvovirus, Plasmodium, TB, Trypanosoma cruzi, VZV (varicella zoster virus), Ebstein Barr virus

7. For the pediatric ophthalmologist: TORCHES
   T - Toxoplasmosis
   O - Other: LCMV, Zika, HIV, West Nile: “West HiLZ”
   R - Rubella
   C - CMV
   HE - Herpes Simplex (and VZV: Varicella Zoster virus)
   S - Syphilis

8. Eight viruses, one protozoan, one bacterium

9. Means of spread:
   a) Human to human contact: CMV, Herpes, Syphilis, HIV, Zika
   b) Other animals, food: toxoplasmosis
   c) Mosquito: Zika, West Nile
   d) Rodents (mice, hamsters): LCMV
   e) Sexual transmission: Zika, HIV, CMV, Herpes simplex, syphilis

II. Toxoplasmosis Gondii

A. Name and Classification

1. Name derived from Green toxon meaning “bow” or “curve”, plasma Greek for “shape”; Gondii name of North African rodent (cteneodactylus gondii) where toxoplasmosis originally found in 1908 (also Brazil in rabbits)
   - Unrelated to Toxocara canis, roundworm with a bow shape

2. Protozoan, technically Sporozoan, now classified as Apicomplexa (with Plasmodium);
   a) Apical complex, compressed microtubules that enable organism to enter host cells
   b) Degenerative evolution: toxoplasma lost cilia and flagellum (other than male gametes); now a parasitic organism, obligate intracellular
      - Moves by “gliding”: lacks normal ciliate locomotion
      - Trojan horse: hides in WBC, which spreads organism to other tissues, especially neural and muscle tissue
   c) Adults are tachyzoites (Greek tachos, for speed) multiply rapidly;
      2-6 microns, pointed anterior end, rounded posterior end
d) 64-128 organisms in one host cell, many more in cysts

B. Epidemiology and Life Cycle
1. Seroprevalence in USA in adolescents and adults 22%, women of childbearing age 11%; 20-30% worldwide (variable between countries); highest incidence Brazil, sub-Saharan Africa; also high in France/Austria (raw/partially cooked meat popular), lower prevalence USA, Canada, Great Britain
   • USA 400-1000 new cases congenital toxoplasmosis yearly
2. Congenital infection in 0.2 to 1.0 per 1,000 births
3. Found in most warm blood animals and birds: Cats and other felids, lamb, mutton, veal, pork, chicken, goats, horses, rabbits, deer, cows, bears, seal caribou, kangaroo, boars
4. Life cycle: sexual cycle in cat, especially kittens, asexual all other organisms
   a) Indoor cat/kitten low risk, unless eats mice or raw meat
   b) Sexual cycle: cat/kitten ingests oocyst, (“eggs”: can persist for years) or tissues containing tissue cysts containing brachyzoites; brachyzoite initiates sexual reproduction (sporogony and gametogenesis), kitten/cat excretes oocyst containing sporozoites, may excrete millions of cysts, but only for 1-3 weeks of their life, then the cat/kitten becomes immune.
   c) Asexual cycle: warm blooded animal ingests oocysts (raw or uncooked meat), sporozoites released, become adult tachyzoites, spread throughout body, mainly muscle and neural tissues, immune responses causes tissue cysts containing brachyzoites to form, tissue cysts can persist for years or lifetime of host, can reactivate and resume active proliferation of tachyzoites
5. Mother: new infections highest risk, temporary parasitemia, tachyzoite crosses placenta to reach fetus; usually asymptomatic infection, may have flu like illness
   • Lower transmission rates in early pregnancy, but infection more lethal; higher transmission rate later in pregnancy, but often infant asymptomatic, overall 20-50% transmission to infant, 13% clinical infection of infant

C. Pathology and Clinical Features
1. CNS: encephalitis, especially cerebral hemispheres, brainstem cerebellum
   a) Seizures, ventriculomegaly, porencephaly, hydrocephalus requiring shunt, calcifications (1-3 mm) reflect cellular damage, often periventricular, microcephaly (more common in CMV), neurological deficits, developmental delay
   b) See intracranial calcifications best on CT scan, MRI best detail
2. Ocular: retinchoroiditis, iridocyclitis, papillitis (indicates CNS disease), optic neuritis, macular scars, retinal detachment, phthisis, microphthalmia (5%), cataract (3%), strabismus, amblyopia
   • Chorioretinitis: macular scars common, (50-65%), bilateral in 40-50%, vision with macular scars variable (20/20 to 20/400), new lesions often appear for years, either adjacent to old scars or in previously normal retina (41% of new lesions appear after age ten years)
3. Systemic findings: hepatosplenomegaly, jaundice, ascites, maculopapular rash, generalized lymphadenopathy, IUGR (intrauterine growth retardation), thrombocytopenia (petechiae), hearing loss (mastoid and inner ear, brainstem)
4. In one series of 300 cases:
   • 76% ocular findings
   • 51% neurologic findings
   • 32% intracranial calcifications
• 26% microcephaly or hydrocephalus

D. Diagnosis
1. No routine prenatal screening USA, screen mother if high risk, findings on ultrasound; routine screening France, Austria, Brazil (higher incidence)
2. Seroconversion of mother during pregnancy confers high risk
3. Amniocentesis with PCR testing (nucleic acid amplification)
3. Neonate (routine screening Mass./N.H.); IgM or IgA indicates infection (neither positive until 1-2 weeks after infection), or IgG persistent at 12 months
4. PCR testing available, serology used most

E. Treatment
1. **Prenatal:** Spiramycin (macrolide, similar to azithromycin) under 18 weeks gestation (not available USA), if seroconvert; after 18 weeks, pyramethamine (Daraprim) and sulfadiazine, or other sulfa (drugs potentially toxic: bone marrow suppression, renal failure; teratogenic in animals), so used only with documented infection
   a) Folic acid antagonist, so give folinic acid i.e. Leucovorin (not used by parasite), not folic acid (used by parasite)
   b) Trimethoprim/ sulfamethoxazole (bactrim, cotrimazaole), clindamycin not widely studied for prenatal or neonatal use (used in older children, adults)
2. **Neonate:** pyramethamine plus a sulfa (sulfadiazine or trisulfapyrimidine), with folinic acid for one year
   a) Some treat with exposure only, no clinical signs
   b) Both medications can cause bone marrow suppression and renal failure
      • Other agents—azithromycin, trimethoprim/sulfa, clarithromycin may be useful but not well studied

F. Prevention
1. 50% of cases USA from eating or handling raw meat, or handling foods that contact raw meat, especially wild game, but beef still a risk
2. Indoors cats low risk, change litter in under 24 hours (oocysts not infectious for 24 hours); keep cats indoors, do not feed raw meat, keep cats from birds, rodents/mice, uncooked meats and insects (mechanical vector)
3. Wash vegetables, especially carrots and lettuce
4. Gardening only with gloves
5. Raw or unpasteurized milk, especially goat’s milk
6. Cook meat or freeze three days
7. Hand washing before meals

III. Other Viruses

A. Lymphocytic Choriomeningitis: LCMV
1. Spread from animals, mainly rodents (mice, hamsters) to humans; no person-to-person spread
   a) Transmitted by urine, feces, saliva or bites of infected rodents
2. Arenavirus, natural host Mus musculus, common house mouse
3. Congenital infection occurs with primary maternal infection during pregnancy
4. 5% of adults seropositive
5. Diffuse cerebral calcifications in 80%, chorioretinitis in 90% of cases
6. Usually normal birth weight (not IUGR)
7. Usually damage to eyes and CNS, not other organs
   a) Rash uncommon
   b) No hepatosplenomegaly, jaundice, IUGR, thrombocytopenia
8. CNS: meningitis, encephalitis, severe brain injury, hydrocephalus, periventricular calcifications, porencephalic cysts, neuronal migration disturbances, seizures, cerebral palsy, blindness
9. Chorioretinal lesions
   a) Macular or peripheral, can be similar to toxoplasmosis/CMV
   b) May have scalloped borders
   c) Lesions may resemble Aicardi syndrome
10. No treatment available

CLINICAL POINTS:
Consider LCMV when see chorioretinal lesions, tests for toxoplasmosis, CMV and others negative, and no lesions outside CNS and eyes.

B. Zika Virus
1. Arbovirus named after a forest in Uganda, identified in Rhesus monkey 1947, few human cases until 2007 Micronesia, then Polynesia, then Brazil
2. Transmitted by mosquito: Aedes, esp. Aedes aegypti (yellow fever, dengue), also sexual intercourse (male to female only), and breast milk
3. Introduced to northern Brazil in 2014 from Polynesia, documented in 52 countries by March 2016
4. CNS: microcephaly, intracranial calcification, lissencephaly, hydrocephalus
5. Diagnosis by PCR of amniotic fluid, CSF, blood or urine; serology not reliable due to cross reactivity with dengue, yellow fever and others
6. Ocular findings in 34% of cases, bilateral in 70%
   a) Chorioretinal scars in macula or periphery
      • Severe chorioretinal atrophy (all vessels gone)
      • Circumscribed areas of pigment clumping
   b) Optic nerve abnormalities 47%: hypoplasia, severe cupping
   c) Lens subluxation
   d) Bilateral iris coloboma
   e) No vasculitis or uveitis; no conjunctivitis in one large series

C. HIV: Human Immunodeficiency Virus
1. 2.5 million children age 15 years or less have HIV worldwide
2. Ocular complications in 70% of adults and 50% of children without treatment
3. Neonatal infection can be acquired in utero, at delivery or with breast-feeding
   • Transmission mother to fetus markedly reduced with antiretroviral therapy (25% to 2% in USA)
4. Four categories of HIV infection in children under 18 months:
   1) Definitely HIV infected: grade with CD4+ T cell percentages
   2) Presumptively HIV infected
   3) Presumptively uninfected with HIV
   4) Definitely uninfected with HIV
5. Ocular findings
   a) Distinctive HIV retinitis, 3% HIV children USA, France, 35% Africa
• Periphlebitis more than periarteritis
• Often with systemic lymphadenopathy
b) CMV retinitis in 5% of children (30% or more of adults)
c) Toxoplasma chorioretinitis, non-CMV herpetic retinitis, syphilis, chorioretinitis
   of unknown cause all seen
d) Disc swelling, macular edema, small white punctate lesions
e) Orbital cellulitis
f) Orbital tumors: lymphoma, Kaposi’s sarcoma
g) Fetal AIDS syndrome: downward sloping eyes, prominent palpebral fissures,
   hypertelorism, blue sclera
h) Anterior segment complications: keratoconjunctivitis sicca, infectious keratitis,
   molluscum lesions, conjunctival telangiectasias

D. West Nile Virus
1. Mosquito born flavivirus, noted 1999
2. Mother must contract West Nile during pregnancy from mosquito bite
3. One case child with bilateral chorioretinitis after mother had West Nile encephalitis
   and lower extremity weakness 27th week of pregnancy
4. No treatment available

IV. Rubella
1. RNA virus, humans only host
2. First virus known to act as a teratogen: congenital rubella syndrome (CRS) in 1941:
   congenital cataracts, congenital heart disease and deafness
   • Mother gets rubella, mainly first trimester, transplacental infection to fetus
3. Affects most organs: IUGR, microcephaly, intellectual impairment, hepatosplenomegaly,
   endocrine defects (diabetes), bone defects
4. World wide epidemic 1962-64; in USA: 11,000 fetal deaths, 20,000 infants with CRS,
   cost to US $2 billion
   • Vaccine 1969, few cases in US now, 100,000 worldwide in developing countries
5. Ocular: nuclear cataract, sometimes floats in liquefied cortex, microphthalmos,
   keratoconus, salt and pepper retinopathy in 60% (pseudo RP), chronic iridocyclitis, optic
   atrophy, strabismus
   a) Primary glaucoma in eyes with microphthalmos, usually not with cataracts
   b) Marked inflammatory reaction after cataract surgery, live virus in lens
   c) Retinopathy: good vision, normal ERG, but subretinal neovascularization can occur
      after childhood, cause poor vision
   d) Fuchs heterochromic iritis in adults
6. Diagnosis: IgM 100% first three months, RT-PCR of fetal blood, amniotic fluid, placenta,
   saliva or lens
V. Cytomegalovirus: CMV

A. Name and Classification
1. Largest, most complex member of herpes viruses: 175-200 microns
2. Human CMV replicates only in humans and great ape, other types are found in many mammals (no spread between different types)
3. Lytic phase disrupts cytoskeleton of cell, resulting in greatly enlarged cell (cytomegalic) with owl’s eye appearance on pathology

B. Epidemiology
1. Overall seroprevalence in US 59%, increases with age
2. Affects 1% of all live births: 30,000 yearly USA, 6000 clinically affected at birth or later, preterm at higher risk
   a) Infants with immunocompromise (chemo, HIV) at higher risk
   b) Infection from placental transmission of maternal infection, usually primary infection: 30-40% transmission rate; mother may have recurrent disease or infection with new subtype
3. 90% of infected babies have no signs of disease at birth, other than serology, culture: called asymptomatic
   a) Of these, 10% will develop clinical signs of disease with time, mostly hearing loss/cognitive problems
   b) No treatment unless has clinical signs of disease at birth
   c) Followed closely for hearing loss, cognitive problems
4. 10% have clinical disease at birth (called symptomatic) and are treated
5. All body fluids-saliva, urine, tears, semen, breast milk can harbor CMV, especially young children at day care centers, household members
6. Transmitted sexually, organ donation and blood transfusion
   • Primarily, for women of childbearing age: sexual contacts and children with CMV
7. Most immunocompetent who acquire CMV after birth have no symptoms, may cause mono-like illness, hepatitis

C. Pathology and Clinical Features
1. CNS: periventricular calcifications (less spread in cortex than toxoplasmosis), ventriculomegaly, loss of white/gray matter demarcation, seizures, developmental delay, and cognitive problems
2. Other: hepatitis, hepatosplenomegaly, pneumonitis, sensorineural deafness, IUGR, spastic lower extremities (spastic diplegia), thrombocytopenia, purpura or petechiae
3. Ocular: chorioretinal scars (21%) similar to toxoplasmosis (may have less pigment), macular scars usually unilateral, hemorrhagic lesions only in immunocompromised, may have good vision with macular scar
   a) Cortical vision defect 50%: most common cause of visual disability
   b) Optic atrophy 37%, strabismus 29%
   c) 78% have normal (20/40+) vision, 22% moderate to severe visual loss
   d) Chorioretinitis can activate later (age 10 reported) but usually does not if no clinical features present at birth (2.4% Coats, Paysse)

D. Diagnosis
1. No prenatal screening or screening of healthy infants USA
2. Infants not universally screened, high risk or signs then evaluated
3. Urine culture in first three weeks of life
4. Can use PCR testing of saliva, urine or blood
5. Serology not helpful: IgM does not cross placenta, and present in only 25-40% of infants infected with CMV; IgG not helpful

E. Treatment
1. Infection (positive culture or PCR), but no clinical features: no treatment
   • 10% of infected with no clinical features at birth will develop later problems, mostly hearing loss (7.5%) and/or cognitive problems
2. Clinical disease at birth: Rx ganciclovir (IV or oral) or valganciclovir (tablets) for six months. Foscarnet or cidofovir may also be used.
   a) Improved outcomes in hearing and cognition at age two years
   b) Effect on chorioretinitis uncertain
3. Side effects of treatment: neutropenia, and in animals, infertility and tumor potentiation, hence all infected not treated

F. Prevention and Screening
1. Main risk for women of childbearing age is exposure to children (wash hands/avoid daycare centers) and sexual contact
2. Clinical features at birth: close follow up, q 3-6 months for 18 months, then q 6-12 months.
3. No clinical features at birth: second exam 3-6 months, then prn or yearly
4. Vaccine under investigation

CLINICAL POINTS:
1. Chorioretinitis from toxoplasmosis often progresses and recurs later in life. Chorioretinitis from CMV usually does not progress after the neonatal period.

2. One cannot tell the difference between toxoplasmosis and CMV retinal lesions by their appearance (possibly more pigment in toxoplasmosis).

3. Acquired toxoplasma chorioretinitis has the same appearance as congenital lesions, or congenital lesions that reactivate.

4. Cerebral calcifications greater tendency to be scattered throughout the cerebral cortex in toxoplasmosis than in CMV. Both have periventricular calcifications.

5. Chorioretinitis more likely to be associated with other major clinical manifestations, such as microcephaly, in CMV than toxoplasmosis.
   • Often chorioretinitis in toxoplasmosis is an isolated finding.

VI. Amblyopia Treatment of Unilateral Macular Scars

A. Unilateral macular scars may lead to amblyopia in infants/children

B. Visual outcomes can be unexpectedly good
C. Case: unilateral scar from toxoplasmosis
1. Found on exam age six months
2. Part time patching until age six, good compliance
3. Followed with Teller cards initially (can use Patti Paddles, Sweep VEP)
4. Final VA 20/40 in affected eye

D. Chisholm, Lueder, poster AAPOS Meeting “Visual Outcomes in Congenital Foveal Toxoplasmosis”
1. Ten infants, ages 8 months to 5 years with unilateral scars from toxoplasmosis
2. 6/10 showed improved vision from part time patching or atropine
3. Their recommendation: “A trial of occlusion should be attempted in children with macular scars secondary to congenital toxoplasmosis.”

VII. Herpes Simplex

A. Name and Classification
1. From Greek “herpes” meaning creeping or to creep, refers to skin condition
2. HSV-1 and HSV-2 (70% of cases) can be transmitted to fetus or newborn infant

B. Epidemiology
1. 50-80% of adults in USA have herpes virus in saliva
2. 23% women of childbearing age in USA infected with HSV-2
3. 1500 cases neonatal herpes yearly in USA
4. Only 20-40% of mothers whose infants develop neonatal herpes have symptomatic genital herpes during or before pregnancy
5. 50-80% of neonatal herpes from mothers who acquire HSV at or near term: greatest risk is seronegative woman who acquires HSV near the time of delivery

C. Pathology and Clinical Features
1. Infants usually infected at delivery, but may be infected prenatally or postnatally: virus can invade intact amniotic membranes (unusual)
   a) Intrauterine infection 5%
   b) Perinatal infection 85%
   c) Postnatal infection 10%
2. Systemic findings
   a) Skin involved at some point in 70%, often later in course, only 40% initially have skin lesions
      • Macules that become vesicles with erythematos base
   b) Pneumonitis, hepatosplenomegaly, hemolytic anemia, hemorrhagic and necrotizing meningoencephalitis, myocarditis, intracranial calcifications, cranial nerve palsies
3. Ocular: blepharoconjunctivitis, corneal dendrites, chorioretinitis (usually peripheral), vitritis, cataracts, optic neuritis/atrophy, strabismus, nystagmus
4. Presentation: usually 5-21 days after birth
   • Can have severe disease at birth (rare)
   • Can present up to age six weeks
Three clinical forms:
1) Skin, eyes, mouth: 45%; 10-14 days after birth
2) Disseminated infection: 25%, (49% mortality); 9-11 days after birth
3) Encephalitis, with or without skin, eyes, mouth: 30%
   • CNS disease presents 16-19 days

D. Diagnosis
1. PCR testing of skin lesions, throat, conjunctiva, rectum, urine
   a) PCR testing used more than culture
   b) Daily exam for skin lesions
2. PCR of CSF highly specific and sensitive, but can be negative with infection
3. Systemic symptoms may mimic bacterial sepsis or other viral infection
4. MRI can be normal with encephalitis

E. Treatment
1. IV acyclovir 60 mg/kg/day (or vidarabine), 14 days for skin, eye, mouth disease,
   21 days for CNS disease
   • Well tolerated usually, adverse effects low incidence: neutropenia, crystals can
     obstruct renal tubules, occasionally CNS side effects (<1%)
2. High index of suspicion, begin treatment with suspicion for disease even before
   positive lab results
   • Suspicious skin or eye lesions, progressive febrile illness with negative bacterial
     cultures
3. Early acyclovir treatment can reduce mortality and long-term neurological deficits
   a) Encephalitis mortality: 70% untreated, 19% treated
   b) Many survivors have some neurologic impairment (esp. cognitive defects)
4. Ocular: can use topical ganciclovir (Zirgan) but IV treatment usually adequate;
   avoid trifluridine drops (toxicity), vidarabine ointment not available USA

Case: 15 day old with seizures, lethargy, jaundice, cells in CSF (prior to PCR
   testing). Ophthalmology consult delayed, showed mid peripheral salt and pepper
   retinopathy; dx: herpetic encephalitis and chorioretinitis, acyclovir instituted, child
   survived with severe disability

Case: 12 day old with red eye: right third nerve palsy, corneal dendrites: prompt
   admission, IV acyclovir, survived with only mild cognitive defects, corneal scar
   right eye, VA OD CF OS 20/20, had recurrent corneal epithelial disease

CLINICAL POINTS:
Urge pediatric colleagues to begin IV acyclovir if any lesions highly suspicious for
herpes simplex-lids, cornea, fundus- are present in the neonatal period, especially
with any systemic signs (but with only dendrites in neonatal period: treat with IV
acyclovir).
VIII. Varicella Zoster Virus

A. Infection first and second trimester can cause congenital varicella syndrome:
   1. CNS defects, seizures, skin lesions
   2. Ocular: chorioretinitis, cataracts, microphthalmos, optic nerve hypoplasia
   3. Diagnosis: PCR testing on infant, IGM antibodies or IgG beyond age seven months
   4. Pregnant women exposed to varicella and are seronegative should receive varicella zoster immunoglobulin

IX. Congenital Syphilis

A. Name and Classification, Epidemiology
   1. Treponema means turning thread, twisting motion of T. pallidum
      a) Gram-negative bacterium
      b) Humans only host, usually sexually transmitted
   2. Two million pregnant women suffer from syphilis
      a) 2/3 will have adverse pregnancy outcome
      b) Less risk longer mother has syphilis
   3. Syphilis causes over 2% of all deaths among live born infants
      a) 270,000 infants born with congenital syphilis yearly worldwide
      b) 460,000 pregnancies end in abortion or perinatal death
   4. Infection in first trimester causes death to embryo/fetus
   5. Most women who acquire syphilis during pregnancy transmit infection to fetus
   6. Nearly half of infants infected with syphilis at birth die shortly before or after birth
   7. Two-thirds of affected infants asymptomatic at birth, signs and symptoms later

B. Clinical Features
   1. Early: seen between birth and three months, usually by five weeks
      a) Systemic: Hepatosplenomegaly, pneumonitis, mucocutaneous lesions, osteochondritis, hemolytic anemia, thrombocytopenia, maculopapular rash, cranial nerve palsy, aseptic meningitis, seizures
      b) Ocular: chorioretinitis, interstitial keratitis, glaucoma, uveitis, cataract (due to inflammation), salt and pepper fundus/pigment mottling (peripheral rather than central)
   2. Later:
      a) Systemic: nerve deafness, bone changes, dental changes, saddle nose (concavity in bridge of nose)
      b) Ocular: interstitial keratitis, esp. ages 5-20, corneal edema with neovascularization, ghost vessels, may need steroids and antibiotics

C. Diagnosis
   1. Cannot culture T. pallidum
   2. USA: mothers screened: VDRL preferred test worldwide
      • Need microscope
   3. RPR: simplest test, no microscope needed
4. Prenatal: convert to negative test or 4x decrease in titer
   • Reinfection can occur during pregnancy
5. Treponemal tests: TPHA, TP-PA, EIA, FTA-ABS: stay positive with Rx
6. Darkfield microscopy
7. PCR useful in primary syphilis
8. To diagnose congenital syphilis, need positive VDRL plus one other
criterion (e.g. positive FTA, VDRL spinal fluid, or clinical features or
see organism on darkfield microscopy)

D. Treatment (do not need clinical evidence of disease to treat, positive lab enough)
   1. IV penicillin G aqueous for 10-14 days
   2. Repeat VDRL, see turn negative or 4x decrease in titer

   Case: Infant with cloudy cornea, iridocyclitis, bilateral cataracts, IV penicillin,
cataract surgery OU; lost to follow up 3 ½ years, returned with fairly good vision:
20/60+, 20/80 with correction

X. Neonatal Conjunctivitis: Ophthalmia Neonatorum

A. Incidence under 1% (low as 0.1%) in Developed Countries, 10% East Africa

B. Late 19th century: 30% of blindness in school age children in UK from gonococcal
disease, Crede 1881, OB in Germany

C. Onset
   1. Chemical conjunctivitis: under 24 hours
   2. Neisseria gonorrhoea: 2-5 days; 1% of cases
   3. Chlamydia 5-14 days: 2-40% of cases
   4. Herpes simplex: 2-14 days
   5. Other bacteria: 2-14 days: 30-50% of cases
      • Group A and B strep, pneumococcus
      • Staph aureus
      • Hemophilus
      • Gram negative rod (esp. early): E. Coli, Klebsiella, Pseudomonas

D. Case: One day old with conjunctivitis, eyelid cellulitis, culture E. Coli, improved
with IV antibiotics, topical moxifloxacin

E. Diagnosis: gram stain, culture, PCR testing

F. Treatment:
   1. Gonococcus: 12 % resistant to PCN, 17% to tetracycline
      • Ceftriaxone IV or IM single dose (unless high bilirubin, then ceftazidime),
saline lavage of eye, plus topical fluoroquinolone q 1-2 hours
   2. Chlamydia: topical erythromycin, oral erythromycin 14 days or azithromycin; risk
      of pyloric stenosis may be increased with Rx under six weeks, failure rate of Rx 20%,
may need re-treatment
G. Approach to Treatment
1. No information from stains, no particular organism suspected: erythromycin ointment qid, oral erythromycin 2-3 weeks, mother and sexual partners: oral tetracycline/doxycycline or one gram azithromycin
2. Gram positive cocci: bacitracin ointment qid for two weeks
3. Gram negative bacteria (not gonococcus): gentamicin, tobramycin or flouroquinolone

H. Prevention (not done in United Kingdom, Denmark, Norway and Sweden)
-0.5% erythromycin ointment (best for chlamydia), 1% tetracycline ointment, 1% silver nitrate or 2.5% povidine (5% chemical conjunctivitis and may be ineffective for chlamydia and gonococcus)