Neonatal sepsis is a major cause of death in the first month of life

- Early onset sepsis is sometimes difficult to diagnose
  - Blood cultures remain negative despite signs of sepsis
  - Intrapartum antibiotics may skew culture results

- Nosocomial sepsis may occur in 250 out of 1000 births
- Increased risk of developing meningitis in late onset sepsis
  - 40% of survivors have neurologic sequelae

Types of Neonatal Infection

- Incidence: 1-8 in 1000 births (term) and 1 in 250 births (preterm)

- Most common organisms:
  - Early onset – E Coli, GBS, L. monocytogenes, H influenza, Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa
  - Late onset – coag neg staph, s aureus, Candida albicans, K pneumoniae, P aeruginosa, Serratia

- Common sites:
  - Blood, CSF, Lungs, Urinary Tract
History of Neonatal Infection

- 1930 to 1940 – group A Streptococcus
- 1940 to 1950 – *E coli*
- 1950 to 1960 – *S aureus*
- 1970 to 1980 – *GBS, E Coli, L monocytogenes, Haemophilus influenzae*
- 1990’s – *Staph epi, MRSA*

Maternal Risk Factors

- **Antepartum**
  - Inadequate prenatal care
  - Low socioeconomic status
  - Substance abuse
  - STD’s
- **Intrapartum**
  - ROM > 12 hours
  - GBS colonization
  - Chorioamnionitis
  - Preterm labor

  - UTI
  - Invasive procedures
  - Maternal tachycardia
  - Fetal tachycardia

Neonatal Risk Factors

- Prematurity (<32 weeks - ↑ risk 4-25 times)
- Low birth weight (<2500 grams)
- Difficult delivery
- Asphyxia
- Meconium staining
- Resuscitation
- Congenital anomalies
- Male infants
- Black infants
- Multiple births
Transmission of Infection

- Vertical
  - Transplacental (placenta to fetus)
    - Treponema pallidum
    - Listeria monocytogenes
  - Ascending (via uterus near delivery)
    - Intrapartum - at delivery

- Horizontal (nosocomial)
  - Employees and equipment to infant

Clinical Signs

- “Not right”
- Temperature instability
- Neuro signs – lethargy, seizures
- Respiratory – grunting, retractions, apnea, tachypnea *most common clinical sign
- Cardiovascular – tachycardia, ↓ or ↑ bp
- GI – poor feeding, vomiting, distention
- Skin – rash, pustules, jaundice
- Metabolic – glucose instability, acidosis
- Hepatomegaly, splenomegaly
Case #1

- 28 day old female with adjusted age of 32 weeks
- On nasal cannula oxygen; has been weaning
- On caffeine; has infrequent spells
- On full feeds
- Begins to have more spells and is not as active

Baby continues to have spells; nasal cannula flow increased

CBC:
- WBC 35 (20 segs, 12 bands)
- Hct 28
- Platelets 125

Blood culture grows gram positive cocci

Gram-positive Cocci

- Staphylococcus
  - Staph epi (coag neg)
    - Part of normal skin flora
    - Colonized by 2-4 days of life
    - Serious pathogen associated with invasive procedures
  - Staph aureus (coag pos)
    - Major source of horizontal transmission
    - Also associated with ET, UAC
    - Colonization in 40-90% by 5 days of life
    - Some strains are methicillin resistant
- Streptococcus (Group A, B, D)
Case #2

- 38 week infant
- Vaginal delivery; meconium stained fluid (none below cords)
- Respiratory distress – retractions, grunting, oxygen requirement

Blood culture grows gram positive rods
Mom reports eating soft cheeses (brie and feta)
She also reports having 2 previous miscarriages
Gram-positive Rods
- Listeria monocytogenes
- Corynebacterium diptheriae
- Bacillus cereus
- Clostridium
  - Difficile
  - Perfringens
  - Botulinum
  - Tetani

Listeria
- Gram-positive rod shaped bacterium
- Acquired transplacentally or from vaginal canal
- Suspect if:
  - Preterm infant passes meconium
  - Maternal history of previous stillbirths
  - Brown amniotic fluid
- May result from fulminant, disseminated early-onset sepsis with multi-organ involvement

Gram-negative? Gram-positive?
- Hans C Gram (microbiologist)
- Gram negative – cells do not retain the stain or are discolored by alcohol during Gram’s method of staining
- Gram-positive – retain the stain
  - Cell walls are tougher; harder to kill bacteria
Case #3

- 16 hour old term infant in newborn nursery
- ROM 12 hours; mom had received 2 doses of ampicillin
- Baby is feeding less well, is cyanotic and is lethargic

Maternal history

Diagnostic workup
- CBC: WBC 32.5 (segs 42, bands 2)
- Platelets 212
- Hct 45
- Blood culture: gram positive cocci in chains
Group B Streptococcus

- Most common organism responsible for early-onset infection in the neonate
- 15-35% of women are colonized
- Universal prenatal screening at 35-37 weeks
- Intrapartum antibiotics – penicillin
- Algorithm for treatment for preterm delivery
- Incidence has decreased with prevention efforts

GBS (cont)

- Early-onset (vertical transmission)
  - Fulminant presentation – usually in the first 24 hours
- Late-onset (horizontal transmission)
  - Insidious presentation
  - Common complication – meningitis
  - Mortality rate has declined to 10%
- Treatment
  - Antibiotics
  - Fluid and volume management
Case #4

- Former 26 week infant who presents on day of life 42 (32 weeks corrected age)
- On nasal cannula, increased spells and very frequent desats - required intubation
- Erythema and swelling noted on left lower cheek

- Facial submandibular cellulitis associated with late-onset group B streptococcal infection.
- Pickett, KC, Gallaher, KJ.
- Department of Neonatology, Cape Fear Valley Medical Center, Fayetteville, NC 28302, USA.

Diagnostic Work-up

- CBC
  - WBC may be normal. ↑ WBC is not normal
    - May be sepsis or PIH
  - Differential count
    - ANC
    - Neutropenia - < 1500
  - I/T ratio
    - > 20 indicates infection
  - Platelet count
    - ↓ associated with bacterial sepsis or viral infection
    - Severe - DIC
Culture
- Peripheral or central
- Falsely negative if mom received antibiotics in labor
- Follow at 24 and 48 hours and at 5 days
- 92% of positive cultures will be positive by 24 hours

CRP
- Protein found in the blood - levels rise in response to inflammation
- Latency period of 6-8 hours - draw 24-48 hours into treatment
- Determines effectiveness of treatment, resolution of therapy, and duration of antibiotic therapy
- CSF
  - LP – controversial
    - Unsuccessful or bloody
  - Normal results for preterm
    - Leukocyte count 0-25/mm³
    - Protein 65-150 mg/dl
    - Glucose 55-105%
    - No microorganisms on gram stain
    - Negative culture
      - Duration of antibiotics is based on first negative culture if initially positive

- Urine
  - Sterile cath or suprapubic to avoid false positives
  - Bagged cultures may indicate colonization
  - > 50,000-100,000 organisms indicates infection
  - If a positive blood, urine or CSF culture is obtained, follow up specimen should be collected
  - Persistent bacteremia is caused by
    - Bacterial resistance
    - Incorrect administration of antibiotics
    - Occult infection site (may require surgery)
    - Central venous catheters

Treatment of Infection - Antibiotics
- Ampicillin with an aminoglycoside for initial broad spectrum coverage
  - Amp and cefotaxime if meningitis is suspected
  - Cefotaxime and Ceftazidime have increased antimicrobial activity against gram negative bacilli and better penetration via blood brain barrier as compared to gent
- Dosages and frequencies vary with gestational age, weight, and post-conceptual age
Length of Treatment
- 10 - 14 days for proven sepsis
- 14 days for meningitis; 21 days if gram negative
- 48 – 72 hours if cultures are negative
- If mom treated before delivery, course may be extended even with negative cultures

Treatment of Infection - Immunotherapy
- IVIG
  - Must contain antibodies specific to infection causing organism
  - May be effective in reducing mortality
- Granulocyte transfusion
  - Provides increased WBCs
- Exchange transfusion
  - To remove bacterial endotoxins, ? effectiveness
- Granulocyte colony-stimulating factor

Case #5
- 27 week infant presents at 11 days of age with a red umbilicus and a pustule on his scalp.
- Baby with residuals - KUB with ileus.
- Blood culture and pustule drainage culture were both positive with E. coli sensitive to zosyn and gentamicin. Follow up blood culture negative.
E Coli

- Most common gram-negative organism causing sepsis and meningitis in neonatal period
- Found in female genital tract; high incidence of neonatal colonization
- May cause severe, fulminant infection (respiratory distress, cardiovascular collapse, multiorgan failure)
- May cause localized infection (septic arthritis, cellulitis, pneumonia, UTI, otitis media)
- Sensitive to aminoglycosides (gent); include amp initially

L/P done secondary to positive blood and pustule culture.
- RBC 5000
- WBC 136 - monos 32, polys 68
- glucose 17
- protein 30
- Dr. Adholla consulted – treat for 21 days due to…

Meningitis

- More frequent in neonatal period than at other times
- GBS and E Coli major pathogens
- CSF culture may be positive with negative blood culture
- Treatment is 14 - 21 days depending on pathogens and response
Case #6

- 58 day old infant at corrected age of 32+6 weeks on ventilator
- Large amount of secretions following reintubation after self-extubation - hx of nasal injury so placed back on the vent.
- Tracheal aspirate sent - growing heavy staph aureus and GNR
- Worsening CXR (dense upper lobes, chronic changes)

ID of TA: heavy growth of MRSA and heavy growth Klebsiella pneumonia sensitive to vancomycin and zosyn and gentamicin respectively.
- Hx of previous tracheal aspirate that was positive for MRSA (one month prior).
- Blood culture is negative.
- Treated for 7 days.

Pneumonia

- Birth to 7 days: GBS is the most common pathogen – but any organism in the maternal genital tract can cause pneumonia
- Onset after 1 week of life – human contact or equipment
- CXR may show asymmetric densities, pleural effusion and granularity
Case #7
- 40 day old - 31 week adjusted age baby
- Feeding less well
- Temp instability
- Occasional spells

Urinary Tract Infections
- Symptoms are nonspecific – poor growth, poor feeding, temp instability, abd distention, hematuria and proteinuria
- E Coli is most common cause
- VCUG to detect abnormalities of urinary tract
Neonatal conjunctivitis
- Eye drainage and conjunctivitis
- S aureus, P. aeroginosa, Neisseria gonorrhoeae, Chlamydia trachomatis

Gonorrhea
- Gram negative diplococcal bacteria (N. gonorrhoeae)
- Most frequently reported sexually transmitted disease in the US
- Ophthalmia neonatorum – 1st week of life
- Sequelae – rare
- Treatment - third generation cephalosporin
- Prophylaxis – silver nitrate or erythromycin ophthalmic ointment
Chlamydia

- Parasite found in adult female genital tract
  - Incidence – 6-12%, 37% of adolescents
  - Most common sexually transmitted disease in the US
- Delivery through infected vaginal canal results in infected infant
- Conjunctivitis at 4-5 days
- Chlamydial pneumonia at 4-11 weeks

Gastrointestinal Disease

- Breast feeding (IgA) helps prevent illness
- Specific gastrointestinal pathogens
  - Rotavirus
    - Vaccine is now available
  - Clostridium difficile
    - Nec

H. influenza

- Gram-negative coccobacillus
- Low rate of maternal genital colonization; passage to fetus is ascending transcervical route
- 50% chance of symptomatic infection in colonized infant
- Mortality as high as 50% (esp VLBW)
- Hib vaccine at 2, 4 and 6 months
Fungal Infections

- Candida
  - Oral (buccal membrane, tongue)
  - Cutaneous – frequent perianal rash with oral candidiasis
  - Systemic – lungs, kidneys, liver, brain
    - Risk factors – prolonged TPN and lipids, antibiotics
    - Treatment – amphotericin, flucytosine
Viral Infections

- Rubella
- CMV
- RSV
- HSV
- Hepatitis B
- HIV

Rubella

- Postnatal rubella cases are usually subclinical.
- Congenital rubella
  - Wide range of fetal and neonatal outcomes if acquired in pregnancy
  - Severity of disease is increased if acquired in first trimester
- Early manifestations
  - IUGR, hepatomegaly, jaundice, heart disease, blueberry muffin appearance
Diagnosis – rubella-specific IgM, rising serial IgG titers
No antiviral therapy

CMV
- Causes the most congenital viral infections
  - Spread by direct person to person contact
  - From mother to infant before, during or after birth
  - Via transfusions of blood or platelets
- Congenital infection
  - Symptomatic at birth – growth restricted, microcephaly, petechiae, chorioretinitis, periventricular intracranial calcifications
  - Asymptomatic at birth – 5-10% have long term sequelae (hearing loss, decreased IQ)
- Diagnosis – isolation from urine or saliva or a high anti-CMV titer

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RSV

- Most common respiratory pathogen in infants; season runs Nov. through Apr.
  - Major cause of bronchiolitis and pneumonia in the first 3 years
  - Initial infection most commonly occurs during the first year – esp in:
    • premature
    • chronic lung disease
    • Congenital heart disease
- Presentation – nonspecific → respiratory symptoms → increased resp distress

Diagnosis
- Clinical findings
- Rapid viral antigen screen (NP)

Treatment
- Supportive care – oxygen, hydration

Isolation
- Transmission based

Prophylaxis
- Synagis – monoclonal antibody administered IM q month during RSV season
HSV (Herpes simplex)

- Cause of serious disease in fetus and neonate
- Types:
  - HSV-1: nongenital type
  - HSV-2: genital type; more often associated with neonatal disease

HSV

- Transmission
  - 85-90% acquired at time of delivery
  - >75% are born to moms with no history of active HSV infection
  - Greatest risk is with primary infection at birth
    • 40-50% transmission rate; 4-5% transmission rate with reactivation of disease

HSV

- Diagnosis
  - Positive culture
  - Diagnostic yield with CSF is <50%
    • Do PCR test with CSF

- Treatment
  - Acyclovir

- Prognosis
  - If untreated – half die
  - Morbidity and mortality rates highest with CNS or disseminated disease
Hepatitis B

- Virus is found in body secretions, but only serum, semen and saliva are infectious.
- Presentation
  - Infected in utero – no symptoms
  - Infected at delivery or after birth – do not have HBsAg for at least 2-5 months
- Prevention
  - Routine screening of all pregnant women
  - Routine neonatal immunization

- Treatment
  - 85-95% effective if born to HBsAg (+) mom
    - Bath carefully
    - Give HBIG, Hepatitis B vaccine
- Isolation
  - Standard precautions
  - Gloves when handling baby before bath

HIV

- RNA retrovirus
- Suppresses T-helper cells
  - Defects in cell-mediated immunity
- Transmission
  - Through blood or blood products
- Symptoms – rare in neonatal period, but then failure to thrive, lymphadenopathy, recurrent mucosal infections, systemic bacterial infections
- Diagnosis – HIV PCR
Management
- Treat infections
- Combination antiretroviral therapy

Perinatal prophylaxis
- Zidovudine – initiate at 14-34 weeks, continued through pregnancy
- Intrapartum dosing
- Neonatal administration – begin at 8-12 hours of age

Prevention
- C-section not shown to prevent transmission
- Should not breast feed

Isolation
- Standard precautions

Prevention
- C/S if lesions present
- Active recurrent infection - vag or C/S – cultures at 24-48 hours and treatment if symptomatic
- Primary infection
  - Vaginal delivery – acyclovir until cultures back
  - C/S – consider acyclovir esp if ROM > 6 hours or if baby has symptoms
Toxoplasmosis
- Caused by an intracellular protozoan parasite
  - Congenitally acquired via vertical transmission
- Maternally acquired - uncooked meat, cat feces
- CNS involvement – microcephaly or hydrocephalus
- Sequelae – mental retardation, learning disabilities, visual impairments
- Treatment – pyrimethamine, trisulfapyramides, folic acid

Syphilis
- Caused by T. pallidum (spirochete)
- Transmission – sexual contact or maternal-fetal
- Presentation – sometimes asymptomatic; petechiae, copper-colored maculopapular rash at 1-3 weeks of age
- Diagnosis
  - Maternal RPR early in pregnancy and at delivery
  - Neonatal – high VDRL, reactive RPR, serum IgM > 20 mg/dl
- Prevention
  - Important to determine adequacy of maternal treatment and possibility of re-exposure
- Treatment
  - Penicillin
  - Neonatal therapy – if maternal treatment is uncertain OR if treatment was given within the last 4 weeks of pregnancy
- Isolation – standard precautions
Case #8

- 31+3 week female – 1235 grams – born by vaginal delivery. Mom with incompetent cervix. Etiology for growth restriction was unclear.
- Urine CMV is negative.
- IgM drawn on admission - 234.
  - IgM specific for CMV <0.9.
  - Repeat IgM down to 163 on day 9 and down to 85 on day 18.
- DNA PCR for HSV, CMV and Toxoplasmosis are negative.
- Serum IgA was 15; repeated day 7 and <6.
- HUS with no evidence of intracranial calcifications or CMV.
- Eye exam did not show chorioretinitis.

Humoral Immunity

- Types of immunoglobulin
  - IgG - immunity against bacterial and viral pathogens
  - IgM – increased levels (>20 mg/ml) with intrauterine infection
  - IgA – GI and respiratory tract, in breast milk
  - IgE - ? Role in allergic reactions
  - IgD – least understood

Infection Control

- Types of Precautions
- Handwashing
References

- Up to Date