Neonatal
Infectious Diseases

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I have no conflict of interest in relation to this program or presentation.

Infection and Immunology topics per NCC website:

- Interpret laboratory values: CBC, CSF
- Discuss immature host defenses of the neonate
- Review neonatal sepsis and meningitis
- Discuss viral and fungal infections
- Discuss specific bacterial infections
- Review infection control measures and nosocomial infections

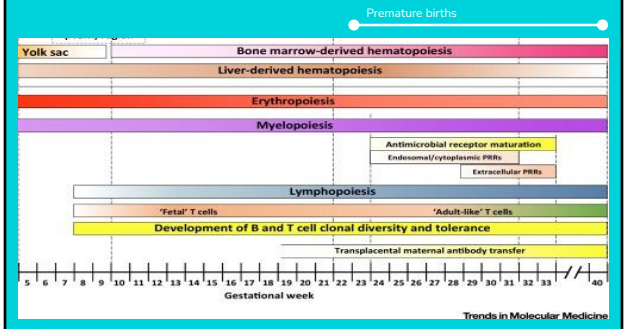
Neonatal Sepsis

- **Life threatening** condition
- **Infection** that leads to a cascade of systemic inflammatory immune responses
- **Isolation** of a bacterial, viral or fungal pathogen from a normally sterile bodily fluid
- Major cause of **morbidity and mortality**

Classify neonatal sepsis:

- Early Onset Sepsis (EOS): **first** 72 hours of life
- Late Onset Sepsis (LOS): **after** 72 hours of life

Development of the Immune System



Neonatal Immune System

- Ineffective physical defense
- Impaired chemical barriers
- Decreased stores & function of phagocytic cells
- Lack of passive immunity
- Medications
- Preterm diagnoses & complications
- Increased invasive devices and procedures

Neonatal Infection

Timing of infection:

- Early-onset (EOS): <72 hours of life
- Late-onset (LOS): >72 hours of life
- Very late-onset sepsis

Age of onset:

- Suspected mode of acquisition
- Microbiology
- Clinical presentation
- Mortality and morbidity

Transmission

VERTICAL

Intrauterine acquisition:
- Maternal bloodstream
- Infected uterus
- Ascend from genital tract

Intrapartum acquisition:
- Ascend genital tract after ROM
- Aspirate infected amniotic fluid
- Colonization during delivery

Postpartum acquisition:
- Maternal breast milk

HORIZONTAL ⟷

Hospital Acquired Infections
- Caregivers
- Equipment
- Environment

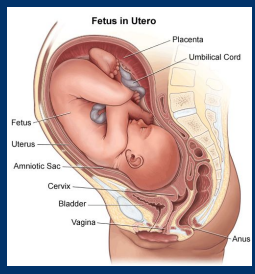
Early Onset Sepsis

EOS vs LOS

	EOS	LOS	Very LOS
Timing/Onset	<72 hours of life	> 72 hours	> 30 days
Clinical Course	Severe, sudden onset, often respiratory	Slow, gradual or sudden onset	
Transmission	Primarily Vertical Frequently acquired before or during delivery Pathogens reflect maternal GU and GI colonization.	Primarily Horizontal Most organisms acquired in nursery	Vertical colonization leading to infection later Horizontal related to hospital acquired infections

Risk Factors for EOS

- **Prematurity**
- **Low birth weight**
- Premature ROM (before onset of labor)
- Prolonged ROM >18 hours
- Maternal Peripartum infection
- Preterm labor
- GBS colonization or prior infant with GBS infection
- Fetal and intrapartum distress
- Multiple gestation



Early Onset Sepsis Calculator

Calculates risk of infection based on these criteria:

- Incidence of infection (CDC, others)
- Gestational Age
- Duration of ROM
- Highest maternal temp
- Maternal GBS status
- Administration of maternal antibiotics
- *Newborn clinical condition*

Recommend: VS frequency, blood culture, antibiotics
NOT valid for < 34 weeks and does NOT apply to LOS

Adverse Effects of Antibiotic Use in Infancy

Increased risk for long-term effects when receive in first 6 months of life:

- Increased BMI, obesity
- Increased wheezing
- Change in intestinal microbiome

Preterm infants exposed to antibiotics early in life:

- NEC
- Antibiotic Resistance
- Late onset infection
- Death

EOS Calculator & Antibiotic Stewardship

2018 - AAP Committee of the Fetus and Newborn guidelines

Goal:

- Identify & treat infants who will develop EOS
- Avoid treating a significant portion of infants that are uninfected
- Reduce antibiotic use, practicing antibiotic stewardship

EOS Calculator Protocol Results:

- Decreased antibiotic use by ~50%, without short-term safety concerns
- Decreased NICU admits and # of painful procedures
- Decreased practitioner practice variability
- Promoted family bonding
- Decreased financial burden to patient, hospital, community

Late Onset Sepsis

Risk Factors for LOS

- Prematurity
- LBW
- Invasive procedures, devices
- Prolonged mechanical ventilation
- Extended hospital stay
- Delayed enteral feeds; microbiome
- Critical illness
- Staff, caregivers, visitors
- Use of antimicrobial agents

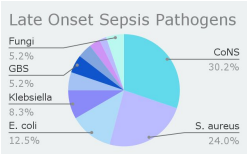
LOS Pathogens

Gram positive bacteria:

- **>50% of bacteremia in premature babies: CoNS (coagulase-negative *Staphylococcus)***
- Staphylococcus aureus; ~10-20% MRSA
- Enterococcus species
- Group B Streptococcus

Gram negative pathogens:

- ***Escherichia coli***
- *Klebsiella*
- *Pseudomonas*
- *Enterobacter*
- *Serratia*



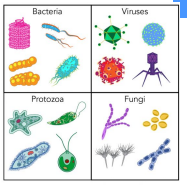
LOS Pathogens

Fungal pathogens:

- Candida species: *Candida albicans, Candida parapsilosis*

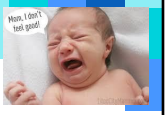
Viral pathogens:

- Parainfluenza
- Echo-, entero-, coxsackie-, adeno-, rhino-, and coronavirus



Evaluation

Signs & Symptoms of Sepsis



****Nonspecific, subtle to severe****

Neurologic: Lethargy, seizures, temperature instability
RESPIRATORY: Tachypnea, A/B, cyanosis
CV: HR changes, poor perfusion, hypotension, pallor
GI: Poor po feeding, feeding intolerance, abdominal distention, vomiting, diarrhea, bloody stools, hepatomegaly, jaundice
Metabolic: Acidosis, hyperglycemia, hypoglycemia
Focal infections: Cellulitis, abscess, omphalitis, conjunctivitis, osteomyelitis

Evaluation for Sepsis

- Blood cultures: 1 for EOS, 2 for LOS
- CBC + differential: WBC, platelets, I:T ratio, ANC
- Urine culture: catheter specimen; only LOS
- Acute phase reactants
- CSF: via lumbar puncture
  - Positive blood culture
  - Clinical concern for meningitis
  - Worsening clinical status despite antibiotics

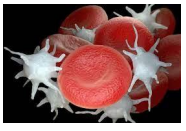
CBC Analysis

****SCREENING TOOL****

- **Best used to rule OUT sepsis**
- Optimal time: 6-12 hrs of life

Platelet count: Normal 150,000-450,000

Thrombocytopenia: <150k
- Late sign of sepsis
- Many other causes



WBC Analysis

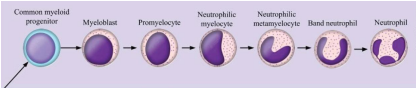
WBC: 5,000-30,000 cells/µL; Leukopenia: <5,000 cells/µL

Neutrophils: first responders to fight infection

Absolute neutrophil count (ANC): ability to fight infection

Neutropenia: <1800 cells/µL
- Decreased cells to fight infection

I/T ratio: immature to total neutrophil count; "left shift"
- Ratio >0.2-0.25 may be indicative of infection
- Best as negative predictor value; <0.2 decreased risk



Acute Phase Reactants

Increase due to an acute inflammatory event
- Infection, trauma, cell injury

CRP: Non-specific acute-phase reactant globulin
- ↑ in acute inflammatory process
- Serial CRP levels most valuable
- Increases at 6-8 hours; peaks at 24-48 hours

Others: Procalcitonin, proinflammatory cytokines, Polymerase chain reaction (PCR), Granulocyte stimulating Factor (G-CSF)
- Limited diagnostic usage; do not rule in or rule out infection

Lab Results

Blood culture: MOST positive 24-36 hours
- EOS: 1 culture
- LOS: 2 cultures
- If positive, perform ID and sensitivity

Urine culture: obtain via sterile catheterization

Urinalysis results suggestive of UTI:
- WBC: >5 WBCs/hpf
- Positive Nitrites
- Leukocyte esterase
- Gram stain: bacterial count >50-100k organisms/ml

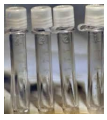
CSF Analysis

WBC: Normal: 0-35 WBCs

Gram-stain: May ID class of agent rapidly

Glucose: Compare to serum; normal ½-⅔ serum

Protein: 50-100 mg/dl



Suggestive of Meningitis:
WBC: >20-30 cells with predominance of leukocytes

Protein: >150 mg/dl preterm, >100 mg/dl term

Glucose: <20 mg/dl preterm, <30 mg/dl term

Culture: **Positive - definitive diagnosis of meningitis**

Neonatal Infections

Bacteremia: positive blood culture
UTI: positive urine culture
Meningitis: positive CSF culture
Pneumonia: infection/inflammation of the lungs; diagnosed based on x-ray findings & clinical exam
NEC: Infection/inflammation of the intestinal tract
Cellulitis: Infection of the skin
Culture negative sepsis: clinical and possibly lab concerns for sepsis but cultures are negative

Meningitis

Inflammation/infection of the meninges and CNS

- Most common: GBS and gram-negative rods (esp E coli)
- Many cases of meningitis have negative blood cultures

Common clinical signs:

- Temperature instability (most common)
- Lethargy/Irritability
- Seizures, bulging fontanelle, poor feeding

Indications for CSF:

- Positive blood culture, clinical/lab concerns for meningitis, worsening clinical status on antibiotics

Diagnosis: Positive CSF culture (Lumbar puncture)
Treatment: Antibiotics 14-21 days
Outcomes: Mild-severe neurodev. sequelae, death

Management of Sepsis

Prompt initiation of antibiotics CRITICAL

Antibiotic Treatment:

- Initiate ASAP upon suspicion of sepsis, ideally after cultures are obtained
- Broad-spectrum: gram - and gram + coverage
- Narrow antibiotic coverage with ID/sensitivity
- Pathogens vary among regions and NICUs - choose antibiotics wisely

Supportive therapy:

- Respiratory, Hemodynamic, GI bowel rest, etc

The Microorganisms that cause Neonatal Sepsis

Group B *Streptococcus* (GBS)

Streptococcus agalactiae: Gram-positive bacteria

- **Most common cause of EOS for term babies**
- 20-40% women colonized genital tract; common GI tract

Transmission: primarily via birth canal after ROM

Treatment: Penicillin G; Ampicillin

CDC Guidelines for Prevention of Perinatal GBS Disease

- Universal screening at 36-38 weeks
- Intrapartum antibiotic prophylaxis (IAP)for GBS colonization
- PCN or Ampicillin recommended; guidance for allergy

Escherichia coli - E. coli

Gram-negative bacteria: rod-shaped bacterium

- Normal in **GI tract**
  - Most common EOS bacteria in preterm infants
  - Predominant organism for VLBW infants
  - 2nd most common EOS in term
  - Most common - UTI

Treatment:

Antibiotics based on sensitivities

- Bacteremia: 10-14 days
- Meningitis: 21 + days

Coagulase negative Staphylococcus species

CoNS

- **Gram positive bacteria**, found in "clusters"
- #1 cause of LOS in NICU
- Most common in NICU: *S. epidermis, S. haemolyticus*
- Normal flora of skin and mucous membranes
- Neonates colonized within first days of life
- Associated with indwelling central venous catheters - can adhere to plastic/foreign bodies
- Contamination vs Pathogen?
- Treatment - antibiotics
- If cultures remain positive despite antimicrobial treatment, need to remove any invasive devices

Staphylococcus aureus: MSSA & MRSA

Gram positive cocci, found in "clusters"

- Normal skin flora and in upper respiratory tract
- MSSA colonizes nose, umbilicus, groin by 1 week of age
- Increased resistance to antibiotics
- High morbidity and mortality

Methicillin-Resistant Staphylococcus aureus

- Resistant to beta-lactam antibiotics (Penicillins & others)
- Vancomycin 1st line therapy for MRSA
- Empiric Vancomycin for colonization, invasive devices

Colonization vs MRSA infections:

- Colonization: presence of bacteria without causing disease
- Infection: pathogen has entered the body, causing disease

Syphilis

Treponema pallidum – thin, motile spirochete
Transmission: vertical untreated 60-90% transmission
Presentation:MOST asymptomatic

- Symptomatic: Nasal discharge, long bone abnormalities, respiratory distress, hepatomegaly, maculopapular rash: copper color, palms and soles

Diagnosis: RPR/VDRL test; same as mother's

- If reactive, serologic testing & titers (confirm)
- CSF, long bone x-rays

Treatment: Penicillin 10-14 days
Prevention: Screen women early pregnancy & L&D

- If treated in pregnancy, follow-up test after treatment to ensure adequately treated.

Viral and Fungal Infections

Toxoplasmosis

Source: Infected cat feces, undercooked meat

Presentation:
If symptomatic, classic **triad** of symptoms

- Hydrocephalus
- Intracranial calcifications
- Chorioretinitis

Diagnosis: Serologic tests; PCR assays (blood, urine, CSF)
Treatment: Antiparasitics min.1 yr; treatable, not curable
Outcomes: Vision, hearing, and/or neurologic impairments - significantly improved outcomes with full year treatment
Prevention: Education, avoid high risk behaviors

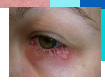
Cytomegalovirus (CMV)

****Most common congenital viral infection**. 50-80% have CMV infection by 40yrs
Transmission: Horizontal or Vertical
Presentation: 90% Asymptomatic

- Symptomatic: Jaundice; Petechiae; IUGR, Microcephaly, Hepatosplenomegaly, Intracerebral calcifications; Retinitis

Antiviral therapy: Oral Valganciclovir for 6 months
Prevention: Education in pregnancy; CMV-negative blood
Prognosis: Intellectual disability, seizures, vision/hearing loss (sensorineural)

Herpes Simplex Virus (HSV)



HSV-1: Face, waist up **HSV-2:** Genital, waist down

- Latent and active periods

Transmission: Horizontal & Vertical; 85% occur intrapartum
3 Classifications of HSV infection:

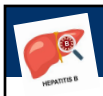
- Localized skin, eye, mouth (SEM) disease
- CNS disease
- Disseminated disease

Diagnosis: Surface swabs, serum PCR, CSF PCR/analysis
Treatment: Acyclovir x 14-21 days; +6 months oral
Prevention: Guidelines for prevention of neonatal HSV

Most neonates that develop HSV infection are born to women without a history of HSV infection or any clinical symptoms at time of delivery.

HSV Comparison

	SEM	CNS	Disseminated
Onset	7-10 days	*2-3 weeks (1-6wks)	1st week of life
Symptoms	Skin: vesicular lesions Eyes: watering, conjunctivitis, erythema, chorioretinitis Mouth: local ulcers mouth, palate tongue	Nonspecific signs: Lethargy Irritability Poor feeding Temperature instability Full fontanelle Seizures/Tremors Abnormal EEG	Non-specific s/s Progressive multi-organ failure, shock, SIRS Primarily affects CNS, liver, lungs, also heart, adrenal glands, kidneys, GI
Outcome	Early treatment: good outcome; Untreated: progress systemic disease	Untreated, 50% die; Treated - many neurologic sequelae	Mortality >80% if NOT treated; 30% with treatment



Hepatitis B Virus (HBV)

DNA double-shelled virus
Transmission: Vertical via infected blood or body fluids
Presentation: Most **asymptomatic**
- Jaundice, macular rash, low platelets, macular rash

Diagnosis: Serologic testing HBsAg & anti-HB seromarkers
Treatment: Mom + or unknown -> Hep B vaccine + **HBIG**
Hepatitis B vaccine: 90-95% efficacy preventing HBV disease
Breastfeeding ok with Hep B vaccine and HBIG given
<2000g at birth: Give Hep B at 30 days/prior to discharge
- Not included in 3 dose vaccine series

Prevention: Screen in pregnancy; vaccinate

Varicella-Zoster Virus (Varicellovirus)

Transmission: vertical or horizontal
Congenital varicella syndrome: Infected 8-20 weeks GA
- Scarring skin lesions, ocular defects, limb abnormalities, CNS (i.e., seizures, cognitive)

Neonatal varicella: Mother exposed/infected <2 wk before birth
- Mild illness to disseminated disease, death

Presentation: Vesicular rash, fever, pneumonia, low platelets
Diagnosis: PCR testing (any source: vesicles, scabs, CSF)
Treatment: Acyclovir, VZIG, supportive therapy
Isolation: Airborne & contact during active disease or exposure 6-21 days prior to delivery

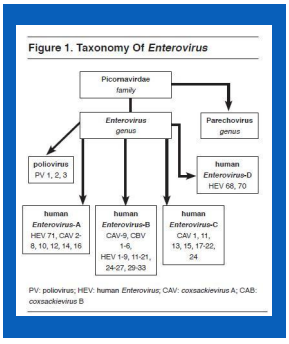
Human Immunodeficiency Virus (HIV)

Transmission: vertical; 90% if mother infected
Neonatal infection - generally asymptomatic
Diagnosis: HIV DNA PCR or HIV RNA PCR assay
- Testing ASAP after birth if high risk
- Timing of testing dependent infant's risk for transmission; maternal diagnosis, timing and compliance with her treatmentreatment

Prevention: CDC universal screening of pregnant women
- Viral suppression with HAART (highly active antiretroviral therapy) to prevent vertical transmission

Postnatal prophylaxis: Antiretroviral therapy **ASAP**
Updated HIV guidelines 2023

Enteroviruses



Transmission: vertical or horizontal; fecal-oral, respiratory routes
Clinical manifestations: nonspecific; lethargy, poor feeding, fever; hepatitis, coagulopathy, pneumonia, encephalitis, myocarditis
High Risk:
- Maternal symptoms near time of delivery
- Neonate infected in first 2 weeks –> increased severity

Enteroviruses

Diagnosis: RT-PCR
- CSF, blood, urine, nasal swabs, throat swabs, stool
- More rapid and more sensitive than cell culture

Management: Supportive therapy
- Specific therapy limited
- IVIG may be beneficial for life-threatening infections
- Contact isolation; cohort infected infants to avoid outbreak

Prevention: Routine hand washing and hygiene practices
- Vaccines being developed

Prognosis: Most cases mild, recoverable
- Severe infections, CNS involvement - increased risk mortality or CNS sequelae: CP, neurodev impairment
- Degree of illness correlates with neonate acquiring passive immunity from mother and presence/absence of maternal neutralizing antibodies (to fight viral infection)

Candidiasis

Species: *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis*
Transmission: vertical or horizontal
Mucocutaneous Infections:
- **Thrush:** white/creamy/gray patches/plaques present orally on tongue, cheeks, gums; does not wipe off
- **Diaper dermatitis:** erythematous scaly lesions with satellite papules or pustules, frequently in skin folds

Systemic invasive disease: often multiple areas
- **Late Onset** - occurs at several weeks of life
- **S/S:** variable: lethargy, feeding intolerance, respiratory distress, apnea, hypotension, temperature instability
- **Evaluation:** CBC, CRP, blood/urine/CSF cultures and imaging of kidneys, heart; eye exam.
  High risk of spread in body.

Candidiasis

Risk factors: for invasive disease
- Prolonged, frequent use of broad-spectrum antibiotics
- GI tract colonization: delayed feedings, H2 blocker use
- Poor skin integrity
- Catheters and indwelling devices
- Immature immune defenses

Treatment: antifungals - topical, oral, enteral or IV.
- Amphotericin B, fluconazole, 5-fluorocytosine, nystatin.
- Remove invasive devices.

Prevention:
- Central line diligence and caution
- Judicious use of antibiotics

Infection Prevention

Infection Prevention Strategies in the NICU

HAND HYGIENE

Single most important prevention of HAIs

- Diligent hand hygiene ***before*** and ***after*** each patient contact
- Avoid artificial nails and nail polish
- Sinks and hand sanitizer easily available for use

Standard Precautions for each patient contact
- Gloves: to prevent contamination of healthcare workers' hands and avoid transmitting pathogens via contact
- Droplet, Airborne, Combination of precautions based on transmission and virulence of pathogen.
- CDC: guidelines & recommendations
- Health care providers are responsible for following infection control practices, staying informed & up to date on latest guidelines and practices to help prevent HAIs.

Infection Prevention Strategies in the NICU

Prevention of Late Onset Sepsis:

- Antimicrobial stewardship
- Limit use of invasive devices
- Standardization of catheter procedures
- Judicious hand hygiene

Implementation of Care Bundles:

- Evidence-based practice
- Tools and supplies bundled in a unified place, readily available for use to deliver reliable and consistent care
- Specific bundles: PICC insertion, Golden Hour, etc

Educate all healthcare workers & visitors on prevention strategies

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Neutrophil picture on CBC slide: Sousa RBN, Alves LH, Carmo VC, Manso CS, Alves FM, et al. (2022) Applicability of the Neutrophil/Lymphocyte Ratio in Behavioral Studies. Int J Blood Res Disord 9:075. doi.org/10.23937/2469-5696/1410075

Pictures included in this presentation were found on the world wide web.

Questions?