Neonatal Sepsis

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Session Summary

Despite improvements in neonatal care, the morbidity and mortality associated with neonatal sepsis remains high. Neonatal sepsis presents in an early or late onset pattern. The best outcomes for newborns with infection depend upon recognition of illness, early identification of the causative microorganism, and the administration of the appropriate antimicrobial agent. This presentation covers the basics of newborn infection and the role that inflammatory response is thought to play. The presentation will also review the clinical presentation, diagnosis tests, and treatment of neonatal sepsis.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- identify the clinical settings of sepsis;
- discuss the pathophysiologic consequences of the systemic inflammatory response syndrome (SIRS) and its role in the development of sepsis;
- identify precipitating factors for development of sepsis;
- identify the most common microorganisms responsible for newborn infection;
- recognize signs of infection in the newborn;
- discuss a multi-disciplinary approach to screening and treating client with sepsis;
- determine the most-likely appropriate antimicrobial agent based upon history, physical examination finding, and laboratory test results.

Test Questions

1. A newborn with sepsis may exhibit worsening after they receive an initial dose of antibiotics due to:
   a. drug interaction leading to toxicity
   b. decrease in white blood cell count
   c. production of B cell antibody
   d. release of endotoxin
2. Diapedesis is a process in which:
   a. neutrophils migrate from the bloodstream to an injured tissue site
   b. neutrophils stick to capillary walls
   c. there is oxygen-dependent killing of cells
   d. bacteria are “coated” with opsonin

3. Your patient has a WBC count of 6.1 with an absolute neutrophil count (ANC) of 300. This result indicates:
   a. normal WBC with neutropenia
   b. leukopenia and neutropenia
   c. leukocytosis and neutrophilia
   d. normal WBC and neutrophilia

4. To determine whether a newborn acquired an infection in utero, antigen specific antibody to which of the following classes should be measured?
   a. IgA
   b. IgG
   c. IgM
   d. IgD
   e. Ig E

5. When used in reference to the WBC differential a “shift to the left” means
   a. an increase in segmented neutrophils
   b. an increase in immature lymphocyte cells
   c. an increase in total WBC count
   d. an increase in neutrophil bands

References


Session Outline

See presentation handout on the following pages.
Neonatal Sepsis
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Is This Scenario Familiar?
Two infants...same gestational age, same maternal history and care, both GBS positive
One alert and active...the other...the sickest baby in the ICU

Is This Scenario Familiar?
- What happened?
- Was anything missed?
- Could these changes have been recognized earlier?
- Need to look at how the host responds to the bacteria
- Systemic reaction by the host to bacteria that gives us the signs & symptoms

“Classic” Definition
- Clinical syndrome of systemic illness accompanied by bacteremia in the first month of life
Clinical Settings

- Early-onset disease
  - multisystem fulminate illness
  - colonized with pathogen in perinatal period
  - can have rapid progression to septic shock

Clinical Settings

- Late-onset disease
  - pathogens similar to early onset
  - increased predilection for CNS
  - less severe systemic & cardiovascular symptoms

Clinical Settings

- Nosocomial disease
  - pathogenesis multifactorial
  - related to:
    - underlying illness
    - altered flora in NICU environment
    - antibiotic & steroid use
    - use of H₂ blockers
    - invasive monitoring

Pathogens

- Primary sepsis
  - GBS
  - E.coli
  - Listeria
  - enterococci
  - bacteroides
Pathogens
- Nosocomial (late onset)
  - Staphylococci
  - Staph epi, staph aureus & MRSA
- Gram negative rods
  - Pseudomonas, Klebsiella, Proteus, Serratia
- Fungal
  - Candida albicans, candida parapsolosis

Maternal Risk Factors
- Chorioamnionitis
- PROM
- Maternal fever
- Premature labor/prolonged labor
- Bacteremia
- UTI
- Amniotic fluid problems
- Maternal substance abuse

Immature Host Defense Mechanisms
- Fragile skin & mucus membranes
- ↓ response to chemotaxis
- ↓ ability to perform migration
- ↓ antibody production
- ↓ phagocytosis
- ↓ killing ability

Complement
- Consists of 20 serum proteins
- No transplacental passage
- Synthesized in liver & alveolar cells
- Classic pathway - antibody/antigen mediated
- Alternative pathway - endotoxin release
Complement

- Initiates intrinsic clotting cascade
- results in bradykinin formation
- Increases hypotension
- Decreased activity in term infants
  - ½ adult level
  - normal values by 3-6 months (classical)
  - normal values by 12 months (alternative)

Phagocytosis

- Most important function of neutrophil
- Can phagocytize 5-20 bacteria
- Killing occurs via “respiratory burst”
Systemic Inflammatory Response (SIRS)

- Widespread inflammatory response
- Initiated by variety of insults
- Encompasses several stages of infection
  - sepsis
  - septic cascade

Normal IR Response

- Septic cascade
- Mediator release
- Vasodilation
- Microvascular Permeability
- Cellular Activation
- Coagulation

Septic cascade

- Discrete reaction
  - ↑ nutrient delivery to tissues
  - ↑ WBCs to area
  - ↑ phagocytosis
  - Wall off injury
  - Promote host defense healing

Uncontrolled vasodilation
- ↑ microvascular permeability
- Overwhelming cellular activation
- Overstimulation of coagulation

Diffuse reaction
- Hypotension
- Third spacing
- Microthrombi
- Further mediator release
- DIC

Inflammatory Mediators

- Mediator
  - Bioactive substance that exerts a physiologic or pathophysiologic change in body cells or tissues
- Septic Triad
  - Endotoxin
  - Tumor necrosis factor (TNF)
  - Interleukin-1 (IL-1)
Inflammatory Mediators

- **Endotoxin**
  - Component of bacterial cell wall
  - Liberated when bacteria die or multiply
  - Can be present in absence of positive blood culture
  - Gut translocation

- **TNF (tumor necrosis factor)**
  - Levels rise immediately after endotoxin release
  - Cytotoxic to endothelium
  - Activates the clotting cascade
  - Stimulates production of PAF
  - Promotes release of IL-1

Inflammatory Mediators

- **Endotoxin**
  - Produces breakdown of microvascular endothelium
  - Induces release of PAF
  - Initiates complement cascade & coagulation
  - Clinical consequences
    - Worsening hypotension
    - Systemic edema
    - DIC

- **TNF (tumor necrosis factor)**
  - Stimulates arachidonic acid metabolism
    - Leukotrienes
    - Prostaglandins
    - Free oxygen radicals
  - Clinical consequences
    - Hypotension, GI ischemia
    - Alveolar thickening, acute tubular necrosis
Inflammatory Mediators
- Interleukin-1 (IL-1)
  - Released in response to TNF
  - Synergistic effect with TNF
  - Potentiates hypotension
  - Induces hyperdynamic cardiovascular function
  - Stimulates leukocytosis, fever, metabolic changes

Septic Shock
- Gram negative
  - E.coli
  - Klebsiella
  - Enterobacter
  - Pseudomonas
  - Proteus
- Gram positive
  - GBS
  - Staph species
  - Enterococcus
  - Group A strep
  - Listeria

Clinical Signs
- Respiratory
  - Early-onset predominantly pneumonia
  - Presents similar to RDS
  - CXR show infiltrates, bilateral consolidation or pleural effusions
  - Apnea (in first 24 hrs) usually associated with sepsis

Clinical Signs
- Cardiac
  - Pulmonary hypertension
  - Decreased cardiac output
  - Bradycardia
  - Systemic hypotension
- Metabolic
  - Glucose instability
  - Metabolic acidosis
Clinical Signs

- Temperature instability
- Response to pyrogens
- Sympathetic nervous system instability
- Hematologic
  - Thrombocytopenia
  - DIC
  - Neutropenia/neutrophilia

Clinical Signs

- GI
  - Feeding intolerance
  - Jaundice
  - Ileus
  - NEC
- Skin Lesions
  - Pustules, abscesses
  - Cellulitis
  - Necrotic skin lesions

Laboratory

- Blood cultures
  - Positive cultures confirm diagnosis
  - Factors affecting results
    - Maternal antibiotics
    - Organisms difficult to grow & isolate
    - Sampling errors with small volumes
- CSF
  - When to obtain?
    - Those with clinical signs
    - Low yield in asymptomatic infants being treated for maternal/OB risk factor
  - Findings: pleocytosis, elevated protein, low glucose
    - WBC: 0-32 in first month; no higher than 10 after 1 month
    - Protein: term 20 to 170; preterm 65 to 150
    - Traumatic taps: one leukocyte for every 700 RBCs
Laboratory

- CBC with differential
  - May need to follow serial CBCs
  - Immature to total neutrophil count (I/T)
    - Marrow releasing more immature cells
    - Left shift - elevated I/T ratio > 0.2
- Absolute neutrophil count (ANC)
  - ANC of 500-1000 intermediate risk
  - ANC <500 increased risk

Laboratory

- C-reactive protein (CRP)
  - Acute phase protein
  - Elevated in 50-90% of infants with systemic bacterial infections
  - Rises within 24 hours & peaks within 2-3 days
  - Serial values used to determine response to antibiotics, duration of therapy, and/or relapse of infection

Management

- Fluid resuscitation
  - Increased requirements
  - Peripheral vasodilation & capillary leakage
  - Early & effective therapy may prevent progression to shock
  - ? use of colloids vs. crystalloids

Management

- Inotropic support
  - Dopamine & dobutamine
- Oxygenation
- Correct metabolic abnormalities
  - Acidosis, hypoglycemia, hypocalcemia
- Antimicrobials
  - Initial administration
  - ? amplifies IR
Management

- **Antimicrobials**
  - **Initial therapy**
  - Combination of a penicillin & aminoglycoside
  - **Ampicillin**
    - Effective coverage for gram +
    - H. flu., E. coli., Proteus & Listeria
  - **Gentamicin**
    - Coverage against gram - (plus Pseudomonas)
    - Synergistic effect with ampicillin against GBS, E. coli, Listeria & enterococcus
  - **Claforan**
    - Coverage against gram -
    - Better tissue penetration (CSF)

- **Late/nosocomial therapy**
  - Need to consider organisms acquired from NICU environment
  - Addition of a penicillinase-resistant drug
    - Nafcillin, oxacillin or vancomycin
  - Consider anti-fungal therapy

Management

- **Continuation of treatment**
  - Initial cultures negative & infant asymptomatic
    - 2-3 days
  - Clinical or lab evidence of infection but negative cultures
    - 7 days
  - Cultures positive → 7-10 days
  - UTI → 10 days
  - Pneumonia → 10 days
  - CSF → gm + (14 days); gm - (21 days)

- **Strategies to strengthen the immunocompetence of the infant**
  - Granulocyte transfusions
  - Immunoglobulin transfusions
  - Monoclonal antibodies
  - Cytokine therapy
Cytokine Therapy

- Promote differentiation of stem cells into different types of myeloid cells
- rhG-CSF
  - induces dose-dependent neutrophilia
  - increases bone marrow storage & proliferative pools
  - improves NB host defense
    - chemotaxis, adhesion, & killing