Early Recognition and Treatment of Infant Sepsis

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Leadership, Education, Accountability, Development

Sepsis

Infection is a major cause of fatality during the first month of life, contributing to 13-15% of all neonatal deaths.

Neonatal Sepsis

- Early Onset Sepsis
  - Onset by 72 hours for NICU patient population
  - Onset by 7 days in a healthy term patient population
- Late Onset Sepsis
  - Sepsis after 72 hours in the NICU patient population
  - Sepsis after 7 days in the healthy term patient population
- Nosocomial Sepsis
  - Sepsis developing during a hospitalization not acquired in the perinatal period

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Early Onset Sepsis

- Early-onset sepsis is associated with acquisition of microorganisms from the mother
- Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize the mother’s genitourinary (GU) tract
  - Chorioamnionitis
- The neonate may also acquire the microorganisms as it passes through the colonized birth canal at delivery.

Common Organisms

- Group B Streptococcus (GBS)
- Escherichia coli
- Coagulase-negative Staphylococcus
- Haemophilus influenzae
- Listeria monocytogenes

Risk Factors

- Low Apgar score (< 6 at 1 or 5 minutes)
- Maternal fever greater than 38°C
- Maternal urinary tract infection (UTI)
- Poor prenatal care
- Poor maternal nutrition
- Low socioeconomic status
- History of recurrent abortion
- Maternal substance abuse
- Low birth weight
- Difficult delivery
- Birth asphyxia
- Meconium staining
- Congenital anomalies
35% of neonatal infections / 50% of deaths due to infection in U.S.

**GBS Burden of Disease**

- Meningitis
- Fatal Sepsis
- Sepsis

**Prevention-GBS**

- CDC 2010 Screening Based GBS prevention Protocol
- Improved specificity as compared to risk based treatment recommendations from 1996
- Decreased infant mortality rate
- 0.36 of 1000 infants develop early-onset GBS disease
Maternal Treatment

Intrapartum prophylaxis indicated
- Previous infant with invasive GBS disease
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or amniotic membrane rupture)
- Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks' gestation*
  - Amniotic membrane rupture ≥10 hours
  - Intrapartum temperature ≥100°F (37.8°C)

Intrapartum prophylaxis not indicated
- Previous pregnancy with a positive GBS screening culture (unless a culture also was positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membranes rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

Preterm Labor

Maternal Treatment

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Recent Trends

Risk Categories

Problems

- Resistance
  - Reports of increasing resistance to Ampicillin and Penicillin in recent years as compared to pre 2002 and 1996 time periods
  - Increased resistance in E coli strains to ampicillin
- Changing status from screening to delivery
### Solutions

- Rapid testing
- Vaccine for GBS
  - Should decrease Early Onset Disease
  - Should also decrease Late Onset Disease
  - Can have devastating effects up to 3 months of age
  - Concerns for Acceptability
- Two different groups are working on possible vaccines at the present time

### Empiric Treatment

- First Line therapy for the infant with suspected infection is
  - Ampicillin and Gentamycin
- The use of a third generation cephalosporin is associated with increased mortality

### Treatment/observation recommendations

- Changes from 2002 to 2010
- Improved sensitivity and specificity in antibiotic treatment recommendations
- Decreased antibiotic use in asymptomatic infants
- This is important in the preterm infant as greater than 5 antibiotic days are associated with several long term negative outcomes including
  - Mortality
  - Late Onset Sepsis
  - Necrotizing Enterocolitis
**Current Treatment Algorithm**

- Signs of sepsis
- History of sepsis
- 37+ weeks gestation?
- 36+ weeks gestation and Pulmonary maturity?
- Bacterial culture taken?
- Methicillin-resistant staphylococcus present?
- VLBW present?
- Do antibiotics cover VLBW?
- Do antibiotics cover maternal source?
- Do antibiotics cover E. coli?
- Do antibiotics cover Gram-negative?
- Do antibiotics cover other gestational ages?
- Do antibiotics cover other sources?

**Timing of presentation**
- 85% present within 24 hours
- 5% present at 24-48 hours
- 10% present within 48-72 hours

**Presenting Symptoms**
- Preterm Infant
  - Apnea and bradycardia
  - Respiratory distress
    - Tachynea, grunting, nasal flaring
- Pneumonia is more common in early-onset sepsis
- Meningitis and bacteremia are more common in late-onset sepsis
### Conditions that Mimic Sepsis

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### Evaluation

- Physical examination
  - Critical
  - Must be frequently
  - Account for stage of transition, activity
  - Cyanotic, splinting, skin, neurologic, genetric, endocrinologic, vital signs, pulse ox

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Presenting Symptoms

- Focal
  - Seizures, posturing, bulging fontanel
  - Blood in stool
  - Abdominal tenderness, erythema
  - Conjunctivitis
  - Skin lesions
    - Bullae
    - Vesicles
    - Purpura
    - Jaundice

Mortality

- The majority of mortality from GBS sepsis occurs in the first 24 hours
- Mortality in the preterm infant from EOS also occurs in the first days of hospitalization
- Mortality is very low in term infants with non-GBS sepsis but typically occurs in the first week for EOS
- For LOS mortality is spread throughout the first months of life.

Morbidities

- In the preterm very low birth weight (VLBW) infant
  - Retinopathy of Prematurity (ROP)
    - Can require surgery or lead to blindness
  - Bronchopulmonary Dysplasia (BPD)
    - Oxygen requirement at 36 weeks corrected gestational age (CGA)
    - This is associated with long term poor prognosis, including poor neurodevelopmental status, increased hospitalizations throughout the first year of life, increased wheezing, asthma, increase cost of care
  - Extra Uterine Growth Restriction (EUGR)
    - Also associated with poor neurodevelopmental status
Term Infant Morbidities

- Deafness
- Cognitive delays
- Failure to Thrive

Work-up

- Cultures
  - Can be negative in up to 20% of real sepsis
  - False positives not uncommon
  - 48-72 hours captures 98%+
  - Blood and any suspected source
- WBC with differential
- Acute phase reactants
  - CRP
  - Procalcitonin
- CSF, effusion, urine, abscess
  - Cell count, gram-stain, protein, glucose

Treatment

- “Absence of risk factors ≠ absence of infection”
- Clinician must prove the newborn is well, don’t wait for the newborn to prove he/she is septic
- Do not delay antibiotics for other work-up
- Treatment of choice Ampicillin and Gentamycin
- Rule out sepsis – treat for 48 hours
- Full treatment for sepsis 7 days
- Meningitis uncomplicated 10-14 days
**The Ten Most Common Causes of Infection**

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**Perspectives on Nosocomial Infection**

Perspectives on Nosocomial Infection

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**Late Onset Sepsis (LOS)**

- Also called Nosocomial Infection
- Central line associated
  - PICC lines
  - Broviac
  - Umbilical Venous Lines
- Duration of line use
- Line care bundles
- Nasal cannula or continuous positive airway pressure (CPAP) use
- H$_2$-receptor blocker or proton pump inhibitor (PPI) use
- GI tract pathology

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Populations At Risk for LOS

- Infants less than 1500 grams (VLBW)
  - Host defense impaired
  - Cellular immunity
    - PMNs are vital for effective killing of bacteria. However, neonatal PMNs are deficient in chemotaxis and killing capacity
  - Humoral immunity
    - The neonate’s ability to generate immunoglobulin in response to antigenic stimulation is intact; however, the magnitude of the response is initially decreased, rapidly rising with increasing postnatal age.
  - Barrier function
    - Physical and chemical barriers to infection in the human body are present in the newborn but are functionally deficient

High Risk Term Infants

- High risk infants
  - Short gut
  - Congenital Anomalies
    - Congenital Heart Disease
    - Gastrochisis
    - Congenital Diaphragmatic Hernia
    - Myleomenigephe
  - Immune deficits
    - SCIDS

Organisms

- Coagulase-negative Staphylococcus
- Staphylococcus aureus
- E coli
- Klebsiella
- Pseudomonas
- Coagulase-negative streptococcal sepsis (CONS)
- Enterobacter
- Candida
- GBS
- Serratia
- Acinetobacter
- Anaerobes
Historical Perspective

- Oliver Wendell Holmes (1843)
  Reviewed medical literature on the contagious nature of puerperal fever
- Semmelweis (1860)
  Investigated puerperal fever in Vienna Lying-in Hospital. Reduced mortality rates with institution of chlorine hand washing.

Vienna Lying-in: 1847

* = Chlorine hand washing started

Nosocomial Infection Definitions

- Colonization: microbial flora present on skin or mucous membranes
- Infection: local or systemic invasion by microorganisms
- Sepsis: Infection resulting in clinical manifestations
- Nosocomial: acquired in the hospital; neither present nor incubating at birth
**LOS impact**

- Nosocomial infections are 100 times more common than early-onset bacterial infections
- Recent data from the National Institute of Child Health and Human Development-sponsored "Neonatal Network" indicated that
  - 29% of infants born at 25 to 28 weeks’ gestation
  - 46% of infants born at less than 25 weeks’ gestation
  Experience a serious nosocomial infection during hospitalization in the NICU. (Average length of stay in NICU >2.5 months)

**Epidemiology**

- Studies of nosocomial infection rates in NICU range from 2 - 25%
- Incidence varies because of differences in:
  - definitions of nosocomial infections
  - diagnostic methods
  - NICU setting
  - patent population (severity of illness)

**NICHD Study**

- NICHD Neonatal Network Study
  - 12 Centers; 32 months
  - 7861 LBW infants (401 - 1500 gm)
  - 25% Late-onset (> 3 days) sepsis
  - Center variability 12 - 32 %
  - Mortality Rate 17%

  *NICHD; J Pediatr 1996; 129*
Risk Factors

- Birth weight and gestational age
- Immature host defenses
- Severity of illness
- Alteration of normal flora (antimicrobial agents, H2 blockers, steroids)
- Invasive devices & procedures (ventilators, catheters, PDA ligation)

Risk Factor – Birth Weight

Risk Factor – Gestational Age
Host-Related Risk Factors
Severity of Illness Scores

- Neonatal Therapeutic Intervention Scoring System (NTISS)
- Score for Neonatal Physiology (SNAP)
- Clinical Risk Index for Babies (CRIB)

Risk Factor - Severity of Illness

- Cohort of 302 infants < 1500 g admitted to two NICU’s
- SNAP and NTISS scores at admission
- 17.5% Cumulative incidence of CONS (Coagulase negative staphylococcus) bacteremia

Gray et al; Pediatrics 1995:95:225
Antimicrobial Agents

- Broad-spectrum antibiotics are a risk factor for Candida species colonization and disease
- Gram-negative organisms may develop resistance to beta-lactam agents with prolonged therapy (penicillins and cephalosporins)

Alteration of Normal Flora

- **H₂ Blockers**
  - Use of ranitidine was associated with increase in gastric pH and increased gastric colonization
  
  (Cothran; *J Perinatol* 1997;17:383)
  - Independent risk factor for bloodstream infection
  
  (Beck-Sague; *Pediatr Infec Dis J* 1994;13)

Probiotics

- Probiotic Use has been associated with lower rates of LOS
  - Resistance to colonization
  - Immunomodulation
  - Nutritional contribution
  - Promote intestinal motor function
- **Lactoferrin**
  - Oral lactoferrin prophylaxis reduces the incidence of late-onset sepsis in infants weighing less than 1500 g and is most effective in infants weighing less than 1000 g

  Cochrane Database 2011
**Invasive Devices**

(NICHD, J Pediatr 1996; 129)

**Environmental Risk Factors**

- Staffing
- Crowding
- Nursery design
- Environmental Contamination
  - Sinks & soap dispensers
  - Equipment
  - Medications, parenteral solutions

**Cycle for Nosocomial Infection**
Microbiology

- Mid-late 1800’s: Group A Streptococcus
- 1940-50’s: S. aureus, Streptococci
- 1960’s: Methicillin-resistant S. aureus
- 1970’s: P. aeruginosa, Enterobacteriacea
- 1980’s: Vancomycin-resistant enterococcus (VRE), resistant gram-negatives, S. epi, Candida species

Organisms common to the NICU environment
- S. epidermidis, MRSA, VRE
- Resistant Enterobacteriacea
- Candida sp.

Organisms not typically present in the NICU
- Group A Streptococcus
- Varicella, RSV, Influenza

Late-Onset Sepsis
Distribution of Organisms

(NICHD, J Pediatr 1996; 129)
Procalcitonin

- Increasing literature supporting the use of procalcitonin in the diagnosis of bacterial sepsis in the neonatal population
- Values of < 0.5 ng/ml appear to be associated with low risk of infection
- Values of > 2-2.4 ng/ml are associated with a higher risk of infection
- Studies also evaluating the usefulness of Interleukin-6

Thank you

Questions?