Neonatal Sepsis

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Objectives

- Define neonatal sepsis
- Signs and symptoms of neonatal sepsis
- Evaluation
- Interpretation of results
- Treatment
- New guidelines

Neonatal Sepsis

- Clinical syndrome in an infant 28 days of life or younger
- Systemic signs of infection
- Isolation of a bacterial pathogen from the blood stream.
- Important cause of morbidity and mortality among newborns.
- Low threshold for evaluation and treatment of possible sepsis.
**Terminology**

- Term infants
  - Those born at a gestational age of 37 weeks or greater.
  - 37-38 weeks is now considered Early Term
- Late preterm infants
  - Near-term
  - Those born between 34 and 36 completed weeks of gestation
- Preterm infants
  - Those born at less than 34 weeks of gestation

**Classification**

- Early-onset sepsis
  - Onset of symptoms before 7 days of age
  - Vertical transmission.
  - Maternal chorioamnionitis
  - Use of forceps and electrodes
- Late-onset sepsis
  - Onset of symptoms at \( \geq 7 \) days of age
  - Vertical transmission
  - Horizontal transmission

**Incidence**

- Overall incidence
- Incidence of early-onset sepsis has decreased primarily due to reduction in group B streptococcal (GBS) infections
  - Intrapartum antibiotic prophylaxis (IAP)
- Higher incidence in late preterm than term infants
Case Study: Baby J

- 24 year old mother G1P1
  - 39.2 weeks gestation
  - HBsAg Neg/RPR non-reactive/Rubella Immune/HIV negative/GBS negative
  - No medications during pregnancy
  - Uncomplicated pregnancy

- Labor
  - Multiple decelerations
  - MSAF
  - No concern for Triple I
  - Apgars 8/8
  - No resuscitation needed
  - Transitioned with mother and went to couplet care

- Initial did well in couplet care
  - Breast fed x2, voided and stooled
  - NICU asked to assess infant at ~20 hours of life
    - Infant with respiratory distress, lethargy, and hypoperfusion
  - Admitted immediately to NICU with Differential Diagnoses of...

- CBC, blood culture sent on admission to NICU and Ampicillin/Gentamicin initiated
  - Cefepime added with worsening clinical status

- Assessment:
  - Lethargic
  - Respiratory failure (required intubation within 1 hour of admission and placed on HFOV)
    - Initial CBG 6.9/101/50/18/9
    - Initial CXR: bilateral patchy infiltrates, worse on the right side (MAS vs. atelectasis)
  - Oxygenation worsened, infant required iNO (OI >40 despite 100% oxygen and iNO)
  - Metabolic acidosis worsened, requiring NS boluses
  - Electrolyte abnormalities
Case Study: Baby J

- Infant continued to worsen:
  - DIC - requiring blood, platelet, FFP transfusions
  - UAC/UVC placed for fluid resuscitation, continuous blood pressure monitoring, and central line access
- HSV work-up completed due to worsening clinical status
  - Acyclovir added
- PPHN, continued OI >40 - ECMO candidate
- Transferred to ECMO center within 24 hours

Case Study: Baby J

- Sepsis confirmed
  - Blood culture positive at 8.5 hours with gram negative bacilli, later identified as E. coli.
  - CSF not sent prior to transport due to clinical instability
- Outcome…

Etiologic Agents

- Group B Streptococcus (GBS) and Escherichia coli (E. coli) are the most common causes of both early- and late-onset sepsis
  - Approximately 2/3 of early-onset infections
- Other agents
  - Listeria monocytogenes
  - Staphylococcus aureus
  - Enterococcus
  - Other gram-negative bacteria
  - Coagulase-negative staphylococci
Maternal Risk Factors

- GBS status
- Algorithm
- Prolonged rupture of membranes
- Prolonged labor
- Vaginal exams (especially with ruptured membranes)
- Cervical insufficiency
- Nulliparity
- MSAM
- Internal fetal or uterine monitoring
- Presence of genital tract pathogens
- Alcohol and tobacco use
- Previous IAI
- Stripping of membranes

Triple I

- Clinical chorioamnionitis
  - Historically, infection of the chorion, amnion, or both
  - Does not consistently convey the degree and severity of maternal or fetal illness
- IAI (Intra-amniotic infection)
  - Infection often involves the amniotic fluid, fetus, umbilical cord, or placenta as well as the fetal membranes
- Triple I (Intrauterine Infection or Inflammation)
  - Defined by strict diagnostic criteria
  - Not yet universally adopted

Pathogenesis
- Most common pathway to IAI
- Other

Categories of maternal fever
- Isolated Maternal Fever (not Triple I)
- Suspected Triple I
- Confirmed Triple I
Triple I

- Presumptive diagnosis
  - Fever on two occasions, 30 min apart without another clear source
    - AND one or more of the following:
  - Baseline fetal HR >160 bpm for 10+ minutes
  - Maternal WBC count >15,000 in the absence of corticosteroids and ideally showing a left shift (bandemia)
  - Purulent-appearing fluid coming from the cervical os

- Confirmed diagnosis
  - Previous criteria AND one or more of the following:
    - Positive Gram stain of amniotic fluid
    - Low glucose level in amniotic fluid
    - Positive amniotic fluid culture
    - High WBC count in amniotic fluid in the absence of a bloody tap
    - Histopathologic evidence of infection or inflammation or both in the placenta, fetal membranes, or umbilical cord vessels

Triple I: Management of the Newborn

- In late preterm and term infants, it will be rare to have a “confirmed” Triple I at the time of delivery
- All infants <34 weeks regardless of symptomatology, born to mothers with any class of Triple I, will need to be evaluated and treated for 36-48 hours of IV antibiotics.
Triple I: Management of the newborn

Fetal and neonatal outcome of Triple I
- Perinatal death
- Asphyxia
- Early-onset neonatal sepsis
- Septic shock
- Pneumonia
- Meningitis
- Intraventricular hemorrhage (IVH)
- Cerebral white matter damage
- Long-term disability including CP
- Morbidity related to preterm birth

Clinical Manifestations
- What does “symptomatic neonate” mean?
Clinical Manifestations

Case Study: Baby C.

- 25 year old mother G6P5
  - HBsAg Neg/RPR non-reactive/Rubella Immune/HIV negative/GBS unknown
  - Mother received Gentamicin, Magnesium Sulfate, Penicillin, Zithromax, and Ancel prior to delivery
  - Pregnancy complicated by premature onset of labor and premature rupture of membranes at 23 weeks gestation.
- Labor
  - Concern for chorioamnionitis – confirmed Triple I (amniotic fluid WBC count 22k)
  - Labor progressed despite tocolytics and infant was born via c-section at 24.5 weeks
  - Required intubation and surfactant administration in the delivery room
  - Apgars 5/8

Case Study: Baby C.

- Fairly uncomplicated NICU stay for gestational age
- Of note, infant found to have MCAD deficiency on newborn screens, treated with frequent feedings during the newborn period
Case Study: Baby C.

- Around 1 month of life, infant began to require increasing respiratory support and oxygen requirements.
  - CXR concerning for pneumonia
  - CBC, blood culture, urine culture, tracheal aspirate sent
  - Ampicillin and Gentamicin ordered

- Serial CBCs left-shifted
- Blood culture and tracheal aspirate positive for gram negative bacilli, later identified as Haemophilus influenza Type A
  - Sensitive to Ampicillin
- Urine culture negative at final
- LP done, not indicative of meningitis
  - CSF culture negative at final
- Outcome?

Late-Onset Sepsis

- Clinical manifestations
- Evaluation
- Empiric therapy?
  - Community admission
  - Hospitalized since birth
- Supportive care
Differential Diagnoses

Laboratory Tests and Evaluation

- Early onset vs. Late onset
- CBC with platelets and differential
- Blood Culture(s)
  - At least 1 ml for optimal detection of bacteremia
  - Cord blood cultures (UCBC cultures)
    - Benefits
    - Risks
- Urine culture if > 3-7 days of life
Laboratory Tests and Evaluation

- Chest radiograph (if respiratory symptoms present)
- CRP?
- Pro-calcitonin?
- Cytokines?
- LP
- Interpretation

CBC interpretation

- Leukopenia vs. Leukocytosis
- Neutrophils
  - Two types:
    - Bands – immature (also metamyelocytes, myelocytes, promyelocytes, monoblasts)
    - Segmented neutrophils - mature
- Left shift
  - Bandemia
  - Indicates possible bacterial infection
  - I:T ratio >0.2

CBC interpretation

- Lymphocytes
  - Produced in lymphatic system
    - B Cells: humoral immunity
    - T Cells: cell-mediated immunity
  - Indicates acute viral or chronic bacterial infection
Laboratory Tests and Evaluation

- CBC with differential and platelets
  - I:T ratio
    - Immature Neutrophils (Bands)
    - Total Neutrophils (Bands+Segs)
  - ANC
    - \(((\text{Bands} + \text{Segs}) \times \text{WBC}) \div 100\)
    - Bands% + Segs% x WBC (actual)

Normal Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Birth 12 hours</th>
<th>24 hours</th>
<th>48 hours</th>
<th>72 hours</th>
<th>&gt;120 hours</th>
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</thead>
<tbody>
<tr>
<td>Absolute Neutrophil Count</td>
<td>1800-5400</td>
<td>7800-14,400</td>
<td>12,600-22,000</td>
<td>9000-18,000</td>
<td>7000-18,000</td>
</tr>
<tr>
<td>I:T Ratio</td>
<td>&lt;0.16</td>
<td>&lt;0.16</td>
<td>&lt;0.13</td>
<td>&lt;0.13</td>
<td>&lt;0.13</td>
</tr>
</tbody>
</table>

CBC Interpretation

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Follow-up at 84 hours</th>
<th>Follow-up at 110 hours</th>
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</thead>
<tbody>
<tr>
<td>WBC</td>
<td>30.0k</td>
<td>51.6k</td>
<td>28.4k</td>
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<tr>
<td>Hemoglobin</td>
<td>14.6%</td>
<td>15.2%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>44.7%</td>
<td>46.8%</td>
<td>42.7%</td>
</tr>
<tr>
<td>Platelets</td>
<td>207k</td>
<td>239k</td>
<td>254k</td>
</tr>
<tr>
<td>nRBC/100 WBC</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>12%</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2%</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>52%</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>Segs</td>
<td>15</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Bands</td>
<td>24%</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>1%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Initial Management in Symptomatic Neonates

- Supportive care
- Respiratory support
  - Maintain adequate oxygenation and perfusion
- Nutrition support
  - NPO?
  - Prevention of hypoglycemia and metabolic acidosis
- Fluid resuscitation
  - Maintain normal fluid and electrolyte status
- Blood products as indicated
- Empiric antibiotic therapy

Initial Management in Symptomatic Neonates

- Initial empiric therapy
  - Early-onset sepsis
  - Late-onset sepsis
    - Admitted from the community
    - Hospitalized since birth
    - Special circumstances

Case Study: Baby R

- Born in a community hospital
- 31 year old mother G1P1
  - 40.5 weeks gestation
  - HBsAg Neg/RPR non-reactive/Rubella Immune/HIV negative/GBS negative
  - No medications during pregnancy
  - Uncomplicated pregnancy
- Labor
  - Prolonged rupture of membranes (18 hours)
  - MSAF, foul-smelling amniotic fluid at delivery
  - Maternal fever
  - Suspected Triple I
  - Apgars 9/9
  - No resuscitation needed
  - Admitted to community hospital’s nursery for sepsis work-up and antibiotic administration per chorio guidelines
Case Study: Baby R

- Community hospital chorio guidelines:
  - CBC and UCBC drawn
  - Ampicillin and Gentamicin initiated
  - Monitored in NICU
- Infant clinically well-appearing
  - Assessment WNL
  - Breast feeding ad lib
  - Voiding/stooling

- Sepsis??
  - UCBC positive at ~48 hours for strep anginosus
  - Peripheral blood culture drawn after UCBC found to be positive
  - LP done at community hospital
  - ID phone consult
    - Communication…

- Upon admission to Scottsdale Shea
  - Infant active/vigorous, well-appearing
  - Breast feeding ad lib
  - Voiding/stooling
  - Peripheral IV in place, receiving Vancomycin and Cefotaxime per previous ID recommendations
  - Re-consulted the same ID physician…
Case Study: Baby R
- Change of plans…
- Peripheral blood culture negative at final
- CSF culture negative at final
- UCBC sensitive to penicillin and ceftriaxone
- Outcome…

Initial Management in Well-Appearing Neonates
- Observation
- Laboratory evaluation
- Preterm vs. term infants

Empiric Antibiotic Therapy
- Whom to treat…
  - Ill-appearing infants
  - Concerning symptoms
  - CSF pleocytosis (WBC count >20-30 cells/microL)
  - Confirmed or suspected maternal chorioamnionitis
  - Positive blood, urine, or CSF culture
Outcomes

- Culture-proven sepsis
  - Gold standard
  - Determine infection vs. contamination
- Probable sepsis
- Infection unlikely

Summary and Recommendations

- Low threshold for evaluation and treatment
- Most common bacteria causing neonatal sepsis
- Maternal risk factors
- Clinical manifestations are nonspecific
- Evaluation and initial management

Summary and Recommendations

- Symptomatic newborns
- Well-appearing newborns
- Late-onset sepsis
- Confirmation of neonatal sepsis
- Differential diagnosis of neonatal sepsis
- New Triple I guidelines
References
