New AAP Guidelines for Early Onset Sepsis

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Nothing to Disclose

Early Onset Sepsis (EOS)

- Positive Blood OR CSF Culture within 72 hrs of birth
- Before GBS prophylaxis: 3-4 cases/1000 live births
- After GBS prophylaxis:
  - Overall 0.8 cases/1000 live births
  - 0.5 cases/1000 live births at ≥ 37 weeks
  - 1 case/ 1000 live births at 34-36 weeks
  - 6 cases/1000 live births at <34 weeks
  - 20 cases/1000 live births at <29 weeks
  - 32 cases/1000 live births at 22-24 weeks

Morbidity & Mortality of EOS

- Full term/ Late Preterm (LPT)
  - 60% of FT infants require intensive care for Respiratory Distress and/or BP support
  - Mortality:
    - 2-3% at ≥35 weeks
    - 1.6% at ≥37 weeks
    - 3.5% at ≥ 1500 g
- Preterm
  - 95% require intensive care for Respiratory distress and/or BP support
  - Mortality:
    - 30% at 25-28 weeks
    - 50% at 22-24 weeks
    - 35% at <1500 g

Pathophysiology of EOS in FT infants

- Begins in utero
- Most commonly:
  - Ascending colonization and infection of the uterine compartment with maternal GI/GU flora during labor
  - Subsequent colonization and invasive infection of the fetus and/or fetal aspiration of infected amniotic fluid
- Rarely before onset of labor
  - Acquired hematogenously across the placenta OR
  - Ascending route
- Can be a cause of 3rd trimester stillbirth

Pathophysiology of EOS in FT infants

- Typical organisms
  - GBS - 40-45% of all cases
  - E coli – 10-15%
  - Other Gram + (strep viridans, enterococci)
  - Other Gram negatives – 5%
  - S aureus - 3-4%
- Listeria monocytogenes – 1-2%
  - Usually transplacental hematogenous spread of infection BEFORE the onset of labor
  - Infrequent cause

Pathophysiology of EOS in Preterm Infants

- Begins in utero
- May be the same as for FT if after PROM or during PTL that is induced for maternal indications
- Usually is BEFORE onset of labor in PTL and/or PROM
  - Microbial-induced maternal inflammation can initiate parturition and elicit fetal inflammatory responses
- Inflammation from immune-mediated rejection of the fetal or placental compartment from maternal extrauterine infection or incited by the microbiota
- Can be a cause of 2nd and 3rd trimester stillbirths

Pathophysiology of EOS in Preterm Infants

- Organisms
  - Primarily vaginal in origin
  - Including low virulence organisms
    - Ureaplasma
    - Anaerobic species
  - E.Coli – 50%
  - GBS – 20%
  - Other Gram positives – 10% (strep viridans, enterococci)
    - Maternal oral flora (transplacental pathway)
  - Other Gram negatives – 20%
  - S aureus – 1-2%
  - Listeria monocytogenes – 1%
  - Anaerobes – 15% (B fragilis)

Risk Factors for EOS in Term and LPT Infants

- Predictive value
  - Gestational age
  - Maternal intraamniotic infection (IAI)
    - intrapartum fever
    - OB clinical diagnosis of chorioamnionitis
  - Duration of ROM
  - Maternal GBS colonization
  - Administration of appropriate intrapartum antibiotic therapy
  - Newborn clinical condition

Risk Factors for EOS in Term and LPT Infants

- Additional risk factors, but NOT independent predictors
  - African American maternal race
  - Twin gestation
  - Fetal tachycardia
  - Meconium stained amniotic fluid

Relationship between EOS and Chorioamnionitis

- Chorioamnionitis – risk factor for EOS?
  - Most infants with EOS are born to women with chorio – poor specificity
  - Only small proportion of infants born to mom's with chorio develop EOS
  - NNT 450 FT infants who were exposed to chorio would have to be treated per case of confirmed EOS
    - Argument against using clinical diagnosis of chorio as a sole indicator of risk for EOS
  - NNT 6-40 preterm infants

Diagnosis of Chorioamnionitis

- ACOG chorio = intraamniotic infection
- Confirmed diagnosis
  - + amniotic fluid Gram-stain and/or culture
  - By placental histopathology
- Suspected diagnosis
  - Maternal fever
    - Single intrapartum temp ≥39.0 C OR
    - Temp of 38.0 C-38.9 C that persists for > 30 minutes
    - AND 1 or more of the following:
      - Maternal leukocytosis
      - Purulent cervical drainage
      - Fetal tachycardia

Antibiotic Stewardship in EOS Management

- Infants exposed to antibiotics before birth
  - GBS IAP
  - Maternal surgical prophylaxis for C/S
  - Intrapartum antibiotic therapy
- 32%-45% of all newborns exposed to antibiotics
- Consequences
  - Increased risk of later childhood health problems (wheezing, asthma, food allergy, IBD, childhood obesity)
  - Alters the developing gut microbiome
    - Changes in stool bacterial composition
  - Impact breastfeeding – delay due to separation from mom

Risk Stratification for Term and LPT Infants (≥35 weeks)

- 3 approaches based on risk factors to identify who are at increased risk of EOS
- All have limitations and merits
- None can immediately identify all infants who will have EOS or avoid treatment of infants who are not infected
- Need measures to monitor infants who are not initially identified
- Need to minimize duration of antibiotics in infants who are not infected

1. Categorical Risk Factor Assessment

-based on algorithms for management of GBS-specific EOS

Risk Factor Based

1. Ill appearing
2. Maternal chorio
3. Maternal GBS+ and inadequate IAP with ROM>18 hrs, or <37 weeks
4. Maternal GBS+ and inadequate IAP, no additional risk factors

Recommendations

- Laboratory testing and empirical antibiotics for Categories 1 and 2
- Laboratory testing for Category 3
- Observation in the hospital for ≥48 hrs for Category 4

1. Categorical Risk Factor Assessment

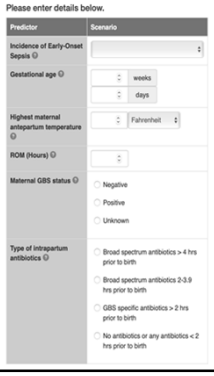
- Advantages
  - Since 1996, multiple versions published
  - Substantial data address the effects on GBS-specific disease and on frequency of neonatal EOS evaluation
- Limitations
  - Lack of clear definitions for newborn clinical illness
  - Difficulty establishing diagnosis of maternal chorio
  - Inconsistent consideration of antepartum antibiotics
  - Absent guidance to define abnormal laboratory test results in the newborn infant

2. Multivariate Risk Assessment

- Individualized synthesis of established risk factors and newborn clinical condition to estimate each infant's risk of EOS
- Predictive models based on a cohort of 608,000 newborn infants based on objective data known at the moment of birth and evolving newborn condition in the the first 6-12 hrs of life

2. Multivariate Risk Assessment

- Objective Data
  - Gestational age
  - Highest maternal intrapartum temperature
  - Maternal GBS colonization status
  - Duration of ROM
  - Type and duration of intrapartum antibiotics

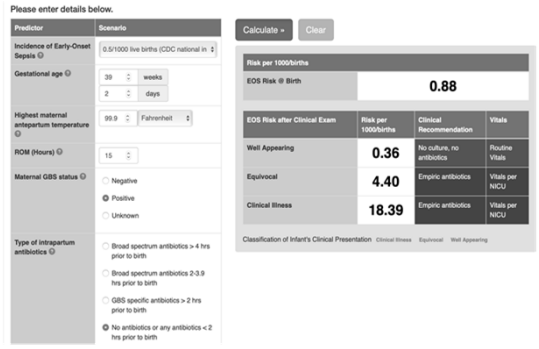


2. Multivariate Risk Assessment

Clinical algorithms are based on the final risk estimate

- EOS risk estimated at >1 per 1000 live births, blood culture and enhanced clinical observation
- EOS risk estimated >3 per 1000 live births, blood culture and empiric antibiotics

https://neonatalsepsiscalculator.kaiserpermanente.org



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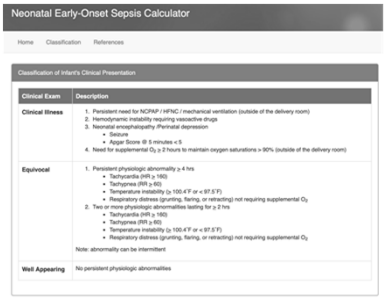

2. Multivariate Risk Assessment

- Prospective validation in 204,685 infants compared to categorical risk algorithm from CDC
- Blood culture testing declined by 66%
- Empirical antibiotic declined by 48%
- No adverse effects during birth hospitalization
- Readmissions for culture-confirmed infection during the weeks after discharge were rare (~5 in 100,000 births); no difference between method (CDC risk algorithm vs sepsis risk calculator)

2. Multivariate Risk Assessment

- Advantages:
  - Provides info on an individuals infant's risk
  - Includes only objective data, not a clinical diagnosis of maternal chorio
  - Few well-appearing infants are treated with empiric antibiotics
- Concerns:
  - Increased clinical surveillance for some infants in the well nursery/postpartum care unit
  - Classification as ill, equivocal, or well appearing requires ongoing clinical assessment over the first 12 hrs after birth
    - Workflow changes, increased frequency of vitals and other assessments

3. Risk Assessment Primarily Based on Newborn Clinical Condition

- Based on clinical signs of illness
- Ill at birth or develop signs of illness over the first 48 hrs
- Treated with empiric antibiotics or further evaluated by laboratory screening
- Good clinical condition at birth is associated with reduction in risk for EOS of 60-70%

3. Risk Assessment Primarily Based on Newborn Clinical Condition

- Italian study of 7,628 term infants managed by categorical approach vs 7,611 infants managed by serial physical exams q 4-6 hrs x 48 hrs
- Decrease in use of lab tests, blood cultures, and empiric antibiotics
- 2 infants developed EOS and were identified as they showed signs of illness

3. Risk Assessment Primarily Based on Newborn Clinical Condition

- Advantages:
  - Reduction in rate of antibiotic use
- Disadvantages:
  - Significant changes to newborn care to accommodate universal serial, structured, documented exams
  - Clear criteria for additional evaluation and empiric antibiotic use
  - Frequent exams
    - Variably acceptance by families
    - May add to cost
  - Need to accept that some initially well-appearing infants will develop clinical illness – not a failure of care but expected outcome in this approach

Risk Factors for Preterm EOS

- ***Gestational age (GA)
- Birth weight (BW)
- PROM & Prolonged ROM
- Preterm onset of labor
- Maternal age and race
- Maternal intrapartum fever
- Mode of delivery
- Intrapartum antibiotics

Risk Factors for Preterm EOS

- FT infants – linear relationship between duration of ROM and EOS
- Pretermers –
  - presence of ROM
  - duration of ROM
  - GA
  - +/- chorio
  - administration of latency and intrapartum antibiotics

Risk Factors for Preterm EOS

- Chorioamnionitis = Intraamniotic infection (IAI)
  - Strongly associated EOS in pretermers
    - NNT 6-40 infants per case of confirmed EOS
- Study of 15,318 infants 22-38 weeks
  - C/S, ROM at delivery, No clinical chorio
    - NNT 200 infants
  - Above + no histologic chorio
    - NNT 380 infants
- Study of 5313 VLBW infants, with 109 cases of EOS over 25 years
  - 97% of cases with some combo of PROM, preterm labor or concern for IAI

Risk Categorization for Preterm Infants

- Nearly universal practice of empirical antibiotic use because of uncertainty in EOS risk assessment
- Can't use same strategies as for FT
  - 2/3 of preterm births are associated with PTL, PROM, or IUI
  - Sepsis calculator does not apply <34.0 weeks
- Who is at lowest risk?

Preterm Infants at Lower Risk for EOS

- Obstetrical indication for preterm birth
  - Maternal preeclampsia
  - Noninfectious medical illness
  - Placental insufficiency
- C-section
- Absence of labor, attempts to induce labor, or ROM before delivery
- Acceptable clinical approaches:
  - No labs, no antibiotics OR
  - Blood culture and clinical monitoring
- If no clinical improvement after initial stabilization and/or if have severe systemic instability, consider empirical antibiotics

Preterm Infants at Lower Risk for EOS

- Vaginal delivery or C-section delivery after efforts to induce labor and/or ROM before delivery are associated with EOS.
- If any concern for infection during the delivery process, should be managed like higher risk for EOS
- Recommendations:
  - Blood culture
  - Antibiotics for infants with respiratory and/or cardiovascular instability

Preterm Infants at Higher Risk for EOS

- Cervical incompetence
- Preterm labor
- PROM
- Chorioamnionitis/IAI
- Acute and otherwise unexplained onset of nonreassuring fetal status

- Recommendations:
  - Blood Culture
  - Empiric antibiotics
  - Consider CSF culture, ideally prior to antibiotics

NOW WHAT??

Lab Assessment – Blood Culture

- Diagnostic standard for EOS
- Minimum of 1 ml
- No effect of intrapartum antibiotic therapy on time to positivity
- Median time to positivity is <24 hrs in FT infants and VLBW infants
- 2 separate cultures may be done
- 1 aerobic and 1 anaerobic culture may be done

Lab Assessment - CSF

- Meningitis
  - FT incidence = 0.02 – 0.04 /1000 live births
  - Incidence at 22-28 weeks = 0.7 cases/1000 live births. May be underestimated b/c LP often done after starting antibiotics
  - FT – highest risk are those with critical illness
  - Incidence of culture-confirmed meningitis in the absence of culture-confirmed bacteremia is 1-2 cases/100,000 live births
  - No meningitis in very preterm who were in lower risk category
- CSF Culture
  - Ideally done along with blood culture, before antibiotics
  - Often limited by clinical condition preventing ability to do LP
  - CSF culture and analysis should be done if + blood culture

Lab Assessment – WBC, differential, I/T ratio, ANC

- Affected by:
  - GA
  - sex
  - mode of delivery
  - Fetal bone marrow depression – maternal preeclampsia or placental insufficiency
  - prolonged exposure to inflammatory signals such as in PROM
- As incidence of EOS declines, clinical utility of WBC also declines
- Extreme values have highest likelihood ratios but low sensitivity

Lab Assessment – WBC, differential, I/T ratio, ANC

FT/LPT

- 2 studies – none of the components performed well but extreme values associated with highest LR, but low sensitivity
  - WBC < 5000 or < 1000
  - I/T > 0.3 or >0.5
  - ANC < 2000 or < 100
- I/T Squared (I/T divided by the ANC
  - Modest sensitivity and specificity
  - Independent of age in hours

Preterm

- Likelihood Ratio (LR) >3
  - Likelihood of infection at 3 x higher
  - WBC < 1000
  - ANC < 1000
  - I/T > 0.25
- Modest relationship to EOS
  - WBC >50,000 (LR 2.3)
  - Platelet count <50,000 (LR 2.2)

Lab Assessment – Other Inflammatory Markers

- CRP, procalcitonin, soluble IL-2 receptor, IL-6, IL-8, TNF-alpha, CD64
- CRP and procalcitonin increase in response to inflammatory stimuli
  - Infection
  - Asphyxia
  - Pneumothorax
- Single values of CRP or procalcitonin after birth are neither sensitive or specific
- Consistently normal values of CRP or procalcitonin over the 1st 48 hrs associated with the absence of EOS
- Serial abnormal values alone should not be used to decide whether to administer antibiotics in the absence of culture-confirmed infection

Treatment

FT/LPT

- GBS – 40-45%
- E coli – 10-15%
- Amp and Gent

Preterm

- E coli - ~ 50%
- GBS ~ 20%
- Amp and Gent

Treatment – Amp and Gent

- Effective against GBS, most streptococcal and enterococcal species, Listeria
- 2/3 of E coli are resistant to Amp but majority are sensitive to Gent
- Extended Beta lactamase producing organisms are rare in the U.S., therefore empirical use of broader-spectrum abx may be harmful
- Small percentage of E coli are resistant to both Amp and Gent
  - FT, critically ill – addition of broader spectrum therapy
  - Preterm – severely ill, higher risk for Gram negative sepsis (prolonged PROM, exposed to prolonged antepartum antibiotics) – addition of broader spectrum therapy

Treatment

- Positive blood culture – Need to do LP
- Serial daily blood cultures until sterile
- Duration of therapy
  - Red Book
  - CSF results
  - Achievement of sterile cultures
- Consult ID
  - Complicated by meningitis or other site specific infections
  - Resistant or atypical organisms

Treatment

- Negative blood culture
- Duration of antibiotics – 36-48 hrs, unless evidence of site specific infection
- FT – unexplained critical cardiorespiratory illness may justify full course of antibiotics
  - Continuing empirical antibiotics in response to lab abnormalities is rarely justified among well-appearing term infants
- Preterm – often have persistent cardiorespiratory instability so not an indication alone for prolonged antibiotic therapy
  - Continuing empirical antibiotics in response to lab abnormalities, particularly in the setting of maternal obstetrical conditions know to affect fetal hematopoiesis is rarely justified

Prevention

- Appropriate maternal intrapartum antibiotic prophylaxis (IAP)
  - GBS
  - IAI – suspected or confirmed
- IAP or neonatal EOS practices do not prevent late-onset infections
  - Preterm infants susceptible to late onset GBS infection
    - 40% of late onset GBS is in $\leq$ 34.6 weekers

Summary

- Identification and empirical antibiotic treatment of newborns who are at risk for EOS
- These practices do not prevent EOS
- Risk stratification is different for FT and preterm infants
- Diagnosis is by positive blood or CSF cultures, not other lab tests
- Amp and Gent – empirical antibiotic coverage for EOS
- Discontinue empirical antibiotics at 36-48 hrs if cultures are negative, unless there is clear evidence of site specific infection