

**Consensus Clinical Guidelines for Early Onset Sepsis (EOS) Screening & Management in Infants  $\geq$  34 weeks GA**  
**UCSF NCNC (Northern California Neonatology Consortium)**

**PART I: SCREENING**

- **Background:**
  - **Prior sepsis screening guidelines:**
    - CDC 2002 Guidelines
    - CDC/COFN/AAP 2010-2012 Guidelines
  - **Limitations of CDC/AAP/COFN 2010 guidelines:**
    - Definition of chorioamnionitis is subjective
    - CDC risk groups don't adequately segregate risk of sepsis
    - No specification of severity/duration of clinical signs of illness that should lead to EOS evaluation
    - No specification of how to interpret recommended laboratory tests
- Inclusion criteria: Infants born at  $\geq$ 34 weeks GA
- **Kaiser Newborn Sepsis Calculator, 2015 (APPENDIX 1):**

Interactive online tool based on a validated prediction rule to calculate the probability of EOS in infants  $\geq$  34wks GA using specified maternal risk factors and the infant's clinical status. Calculator provides a basic clinical recommendation for management based on calculated risk (RED, YELLOW, GREEN). *NOTE:* clinical status classification and management recommendations are based on expert consensus since strong evidence-based guidelines are lacking.

  - Formatted for computers:  
<https://neonatalesepsiscalculator.kaiserpermanente.org/>
  - Formatted for handheld devices:  
[www.Newbornsepsiscalculator.org](http://www.Newbornsepsiscalculator.org)
- **Clarifying notes for use of Kaiser Sepsis Calculator:**
  - Screening logistics:
    - Criteria for screening:
      - Risk factors for EOS:
        - Gestational age  $<$ 37wks
        - Prolonged ROM ( $\geq$  18 hours)
        - Maternal fever or chorioamnionitis
        - Maternal GBS+
        - Need for resuscitation / signs of clinical illness at birth
        - Consider for vital sign or clinical exam abnormalities in the first 12 hours after birth
    - Timing of screening:
      - First hour for infants with EOS risk factors
      - When abnormal vital signs / clinical symptoms are detected in the first 12 hours after birth

- *NOTE:* At risk infants should have clinical reassessment performed and documented frequently in the first 4-6 hours of life because classification of clinical status and management recommendations may change
  - Personnel:
    - Sepsis calculator screening may be performed by either clinician or nursing staff
- Baseline Incidence of EOS:
  - Use institution-specific data for baseline EOS incidence if available
  - Evidence-based options:
    - Kaiser 0.3/1000 – closed healthcare system, unique population, (appropriate for NCNC hospitals)
    - CDC 0.5/1000 – national incidence
  - If institution-specific data unavailable, use the most conservative evidence-based incidence (CDC national incidence = 0.5/1000 live births) since patient population/demographics, access to prenatal care, and other factors that affect neonatal sepsis vary from site-to-site
- Neonatal Reassessment:
  - Clinical reassessment of infant in first 4-6 hours after birth is crucial / may move risk stratification category and change recommended management in Newborn Sepsis Calculator
  - Clinical reassessment (by MD or RN) of high risk or symptomatic infants should be documented frequently in the first 4-6 hours after birth
- Alternative Diagnoses:
  - Consider relative likelihood of alternative diagnoses that increase/decrease risk for sepsis when risk stratifying symptomatic infants and determining clinical management
  - Suspect transient tachypnea of the newborn (TTN) in infants with few or no risk factors for infection (sepsis risk at birth <0.3/1000), mild to moderate respiratory distress, and risk factors for TTN including delivery after short or no labor. If TTN is the top differential diagnosis, use clinical judgment when interpreting Newborn Sepsis Calculator recommendations and determining management. Frequent reevaluation of clinical status is warranted to confirm diagnosis or change management.
- Additional Factors in Clinical Presentation Classification (APPENDIX 2):
  - To supplement the “clinical presentation classification” table in the Sepsis Calculator, the following additional signs/symptoms of clinical illness may be considered for individualized decision-making but are not validated characteristics in the Sepsis Calculator model:
    - Lethargy – abnormal or change in mental status / activity level
    - Apnea – recurrent/persistent, requiring stimulation, in first hours after birth
    - Metabolic acidosis on newborn blood gas (base excess < -8)
      - Worsening base deficit/pH compared with cord blood gas
      - Persistent abnormality on newborn blood gases over 4-6

hours

- Babies who are 34+0 to 34+6/7 weeks GA who had maternal cervical incompetence, preterm labor, PROM, clinical concern for IAI (intra-amniotic infection), or acute onset of unexplained non-reassuring fetal status are at highest risk for EOS. These infants should have a blood culture regardless of Kaiser calculator score and an appropriately-timed CBC should be considered. Strongly consider empiric antibiotics based on Kaiser calculated risk, the clinical appearance of the infant, and CBC results if obtained.

## PART II: EVALUATION

### ○ Clinical exam:

- “Clinical presentation classification” table categorizes at risk neonates (APPENDIX 2):
  - Clinical Illness – \* additional signs/symptoms to consider
  - Equivocal
  - Well Appearing
- *NOTE:* at risk infants should be reevaluated frequently with documentation of status in the first 4-6 hours after birth as classification of clinical presentation and management recommendations may change

### ○ Vital Signs & Observation Period:

- Follow Sepsis Calculator “clinical recommendation” based on risk stratification:
  - If recommendation is “no additional care” for infant with any risk factors:
    - Routine well newborn vital signs per institution protocol
    - Observation period of 24-48 hours depending on clinical scenario
  - If recommendation is for increased level of monitoring / observation:
    - Vital signs Q4 hours x 24 hours
    - Vital signs per NICU protocol if infant admitted to NICU
    - Observation period of 24-48 hours depending on clinical scenario

### ○ Laboratory studies:

- **Blood Culture:**
  - Indications:
    - Follow Sepsis Calculator “clinical recommendation” except in 34+0/7 to 34+6/7 week infants as above
  - Collection:
    - Site: sterile peripheral draw or newly placed umbilical catheter
    - Blood volume: 1 mL or greater
  - Timing:
    - Prior to initiation of antibiotics
  - Impact on management:
    - Pediatric Infectious Disease consultation recommended

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- If positive and infant is receiving antibiotics → consider time to positivity and identified organism to determine likelihood of true pathogen versus contaminant (see APPENDIX 3 for common neonatal pathogens)
          - If suspected pathogen: Attempt lumbar puncture (LP), continue antibiotics for appropriate treatment course
            - Consider repeat blood culture at 48-72 hours of treatment to confirm clearance
          - If suspected contaminant: repeat blood culture, re-evaluate infant's clinical status, continue antibiotics until organism speciation complete and proven negative follow-up culture x 24 hours
        - If negative and infant is receiving antibiotics → determine duration of antibiotic therapy based on other maternal / perinatal risk factors, clinical status, and laboratory indices (see recommendations below)
        - If negative and infant is not receiving antibiotics →
          - Asymptomatic infants may be discharged from hospital once blood culture is negative for >24 hours
          - Symptomatic infants should have clinical status classification reviewed for revised recommendations or consider alternative diagnoses
- **CBC:**
  - Background:
    - WBC, I/T ratio, and ANC are not sensitive predictors for EOS
  - Indications:
    - While CBC is not a useful tool in determining the presence or absence of EOS, it may be a useful diagnostic instrument for determining the underlying cause of clinical illness
      - Consult neonatology for markedly abnormal CBC results
  - Timing:
    - Obtain CBC at the same time as blood culture
      - Draw CBC with blood culture <4 hours of age if empiric antibiotics will be started based upon clinical status of infant
      - Wait until ≥4 hours if clinically appropriate / stable infant
- **CRP:**
  - Indications:
    - Consider obtaining CRPs in infants receiving empiric antibiotics
    - *NOT* useful as a metric for determining whether or not to initiate empiric antibiotics
  - Timing:
    - Consider obtaining 12 and 36hrs of age for infants on antibiotics
    - 0 and 24hrs relative to initiation of sepsis evaluation if evaluation is initiated later due to change in clinical status / risk factors remote

- from birth
  - Interpretation:
    - Good negative predictive value for two negative / low CRPs, but **poor positive predictive value** for elevated CRPs
  - Impact on management:
    - Two negative / low or decreasing CRPs and asymptomatic infant OR *improving* clinical course → stop empiric antibiotics
    - Elevated or increasing CRPs → DO NOT use as a sole reason to continue antibiotic therapy; use other laboratory and clinical factors to determine whether to continue or stop empiric antibiotics
- **Lumbar puncture (LP):**
  - Indications:
    - Infants in CLINICAL ILLNESS zone with neurologic symptoms (e.g. mental status changes, seizures, apnea in term infant, fever or hypothermia, hypotonia, bulging fontanelle)
    - Infants with blood culture positive for pathogen (see APPENDIX 3)
    - Consider LP in infants with negative blood culture but who are receiving empiric antibiotic course for sepsis
    - *NOTE:* LP should only be performed in infants whose clinical condition can tolerate procedure
  - Timing:
    - Pre-antibiotics: infants in “clinical illness” zone with neurologic symptoms
    - Post-antibiotics (ASAP): infants with blood culture positive for pathogen
  - Impact on management:
    - Abnormal CSF findings may increase recommended duration of antibiotic treatment, and impact monitoring for complications as well as long-term prognosis
    - Consider pediatric infectious disease consult for guidance

### PART III: TREATMENT

- **Treatment duration:**
  - **Rule-out sepsis**
    - *NOTE:* Timing is based on incubation time of blood culture, not number of doses of antibiotics
    - Stop antibiotics at 24 hours following blood culture receipt by lab if asymptomatic infant, negative blood culture, and/or normal / low CRP (if sent). Do NOT give antibiotic doses at the 24 hour time point if culture remains negative.
      - *NOTE:* Infant should not be discharged from hospital until at least 36-48 hours after birth
    - Stop antibiotics at 48 hours if negative blood culture, persistent

- respiratory symptoms with no apparent source of infection (e.g. no pneumonia), and/or normal / low CRP x 2 (if sent)
- In the case of an initial abnormal but non-specific CXR, if the infant's respiratory symptoms have completely resolved by 24-48 hours, the likelihood of bacterial infection is low.
    - Little utility of repeat CXR
    - Antibiotics should be discontinued at this point
- **Empiric treatment course (culture negative but significant clinical illness consistent with infection)**
    - Generally seven days but no strong evidence for guidance
    - Longer duration of antibiotics is warranted for infants with concern for / confirmed CNS involvement
      - Consider lumbar puncture; discuss with medical team and family
  - **Culture positive treatment course**
    - Recommend pediatric infectious disease consult
- **Antibiotic choice:**
    - Empiric:
      - Ampicillin & Gentamicin
    - Identified organism:
      - Modify antibiotic coverage based on final culture results; consult pediatric infectious disease
      - Examples:
        - Gram negative organism → switch to Ceftazidime (or appropriate narrow spectrum sensitive antibiotic and discontinue Ampicillin and Gentamicin)

# APPENDIX 1: Kaiser Newborn Sepsis Calculator screen shots, 2015



## Probability of Neonatal Early-Onset Sepsis Based on Maternal Risk Factors and the Infant's Clinical Presentation

Predictor	Scenario
Incidence of Early-Onset Sepsis	<input type="text" value="0.3/1000 live births (KPNC incidence)"/>
Gestational age	<input type="checkbox"/> weeks <input type="checkbox"/> days
Highest maternal antepartum temperature	<input type="text"/> Fahrenheit
ROM (hours)	<input type="text"/>
Maternal GBS status	<input type="radio"/> Negative <input type="radio"/> Positive <input type="radio"/> Unknown
Type of intrapartum antibiotics	<input type="radio"/> Broad spectrum antibiotics $\geq$ 4 hrs prior to birth <input type="radio"/> Broad spectrum antibiotics 2-3.9 hrs prior to birth <input type="radio"/> GBS specific antibiotics $\geq$ 2 hrs prior to birth <input type="radio"/> No antibiotics or any antibiotics $<$ 2 hrs prior to birth

	Risk per 1000/births	Clinical Recommendation
<b>EOS Risk @ Birth</b>		

Clinical Exam	Risk per 1000/births	Clinical Recommendation
Well Appearing		
Equivocal		
Clinical Illness		

**Classification of Infant's Clinical Presentation** (Hide) ✖

Clinical Exam	Description
<b>Clinical Illness</b>	1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room) 2. Hemodynamic instability requiring vasoactive drugs 3. Neonatal encephalopathy /Perinatal depression <ul style="list-style-type: none"> <li>• Seizure</li> <li>• Apgar Score @ 5 minutes <math>&lt;</math> 5</li> </ul> 4. Need for supplemental O <sub>2</sub> $\geq$ 2 hours to maintain oxygen saturations $>$ 90% (outside of the delivery room)
<b>Equivocal</b>	1. Persistent physiologic abnormality $\geq$ 4 hrs <ul style="list-style-type: none"> <li>• Tachycardia (HR <math>\geq</math> 160)</li> <li>• Tachypnea (RR <math>\geq</math> 60)</li> <li>• Temperature instability (<math>\geq</math> 100.4°F or <math>&lt;</math> 97.5°F)</li> <li>• Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O<sub>2</sub></li> </ul> 2. Two or more physiologic abnormalities lasting for $\geq$ 2 hrs <ul style="list-style-type: none"> <li>• Tachycardia (HR <math>\geq</math> 160)</li> <li>• Tachypnea (RR <math>\geq</math> 60)</li> <li>• Temperature instability (<math>\geq</math> 100.4°F or <math>&lt;</math> 97.5°F)</li> <li>• Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O<sub>2</sub></li> </ul> Note: abnormality can be intermittent
<b>Well Appearing</b>	No persistent physiologic abnormalities

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**APPENDIX 2: Classification of Infant's Clinical Presentation.**  
**(Adapted from Kaiser Sepsis Calculator)**

**NOTE: at risk infants should have clinical reassessment performed and documented frequently in the first 4-6 hours of life as classification may change**

CLINICAL EXAM	DESCRIPTION
<b>Clinical Illness *</b>	<ol style="list-style-type: none"> <li>1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room)</li> <li>2. Hemodynamic instability requiring vasoactive drugs</li> <li>3. Neonatal encephalopathy / Perinatal depression               <ol style="list-style-type: none"> <li>a. Seizure</li> <li>b. Apgar score &lt;5 @ 5 minutes</li> </ol> </li> <li>4. Need for supplemental O2 ≥ 2 hours to maintain oxygen saturations &gt;90% (outside of the delivery room)</li> </ol>
<b>Equivocal</b>	<ol style="list-style-type: none"> <li>1. Persistent physiologic abnormality ≥ 4 hours:               <ol style="list-style-type: none"> <li>a. Tachycardia (HR ≥ 160)</li> <li>b. Tachypnea (RR ≥ 60)</li> <li>c. Temperature instability (≥ 100.4F or ≤97.5F)</li> <li>d. Respiratory distress (grunting, flaring, retracting), not requiring supplemental O2</li> </ol> </li> <li>2. Two or more physiologic abnormalities lasting ≥ 2 hours:               <ol style="list-style-type: none"> <li>a. Tachycardia (HR ≥ 160)</li> <li>b. Tachypnea (RR ≥ 60)</li> <li>c. Temperature instability (≥ 100.4F or ≤97.5F)</li> <li>d. Respiratory distress (grunting, flaring, retracting), not requiring supplemental O2</li> </ol> </li> </ol> <p><i>NOTE: abnormality can be intermittent</i></p>
<b>Well Appearing</b>	No persistent physiologic abnormalities

<b>* ADDITIONAL SIGNS/SYMPTOMS OF CLINICAL ILLNESS IN NEONATES:</b>	
These factors may be considered for individualized clinical decision-making but are not validated characteristics in the Sepsis Calculator model	
	<ol style="list-style-type: none"> <li>1. Lethargy (abnormal or change in mental status or activity level)</li> <li>2. Persistent or recurrent apnea requiring stimulation (outside of the delivery room)</li> <li>3. Metabolic acidosis on neonatal blood gas (base excess &lt; -8)               <ol style="list-style-type: none"> <li>a. Worsening pH/base deficit compared to cord blood gas</li> <li>b. Persistent abnormalities on newborn blood gases over 4-6 hours</li> </ol> </li> </ol>



### **APPENDIX 3: Common Pathogens in Neonatal EOS, 2019.**

*NOTE:* Determination of suspected contaminant versus pathogen should take into account the organism isolated and also the circumstances of isolation (site, technique, etc)

*NOTE:* The most common contaminants in peripheral blood culture are skin flora (Coagulase negative Staphylococcus) and Viridans group streptococci

#### **COMMON NEONATAL PATHOGENIC ORGANISMS:**

##### Gram Positive Bacillus:

- *Listeria monocytogenes*

##### Gram Positive Cocci:

- *Staphylococcus aureus*
  - MRSA (methicillin resistant)
  - MSSA
- Beta Hemolytic streptococci
  - Group A Streptococcus
    - *Streptococcus pyogenes*
  - Group B Streptococcus (GBS)
    - *Streptococcus agalactiae*
  - *Streptococcus bovis*
  - *Streptococcus mitis*
- Enterococcus
  - *Enterococcus faecalis*
  - *Enterococcus faecium*

##### Gram Negative Bacilli:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Citrobacter*
- *Enterobacter cloacae*

##### Gram Negative Coccobacillus:

- *Haemophilus influenzae*

##### Fungal:

- *Candida*
  - *Candida albicans*
  - *Candida parapsilosis*

#### **COMMON NEONATAL CONTAMINANT ORGANISMS:**

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*NOTE:* All common contaminant organisms may be pathogenic under the right circumstances (i.e. prematurity, central line, >1 positive blood culture); Pediatric Infectious Disease consultation recommended

Gram Positive Bacillus:

- Lactobacillus

Gram Positive Cocci:

- Coagulase-negative staphylococcus (CoNS)
  - Examples:
    - *S. epidermidis*
    - *S. hominis*
- Viridans group, Alpha-hemolytic streptococci
  - Examples:
    - *S. mutans*
    - *S. mitis*
    - *S. salivarius*
- Peptostreptococci
- Aerococcus

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