Consensus Clinical Guidelines for Early Onset Sepsis (EOS) Screening & Management in Infants ≥ 34 weeks GA
UCSF NC^2 (Northern CA 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

- **Kaiser Newborn Sepsis Calculator, 2015 (APPENDIX 1):**
  Interactive online tool based on a validated prediction rule to calculate the probability of EOS in infants ≥ 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:
    www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx
  - Formatted for handheld devices:
    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 (≥ 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
        - 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

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"
        - 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
            - 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: repeat blood culture, consider CNS evaluation, continue antibiotics for appropriate treatment course
                    - If central line in place OR culture is positive for Staph aureus or Candida → repeat blood culture Q24 hours until clear
                    - If no central line and other suspected pathogen → repeat blood culture x 1 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:
        - Reliability and predictive value of CBC indices improve with increased time from birth (for at least 4 hours)
        - CBC is helpful for clinical decision-making primarily in equivocal cases when infant is close to the treatment threshold
            - *Not* useful in first hour of life
            - *Least* helpful in asymptomatic infants <4hrs of age
            - *Most* helpful in at risk, symptomatic infants >4hrs of age
    - Indications:
        - Obtain CBC if antibiotics will be initiated
        - CBC is not necessary if antibiotics will not be initiated
    - 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
    - Interpretation of CBC indices:
        - Low WBC and low ANC increase concern for sepsis
        - High WBC is not associated with increased risk of EOS
        - Platelet count is not a useful metric for clinical decision-making in the first 3 days of life unless extremely abnormal (high or low) with associated clinical findings
    - Impact on management:
        - CBC may be used to evaluate severity of sepsis (e.g. marked leukopenia or neutropenia may indicate high risk of severe sepsis and rapid deterioration) or may identify hematologic abnormalities that require intervention (e.g. anemia, thrombocytopenia)
            - Consult neonatology for markedly abnormal CBC results
- **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:
        - 12 and 36hrs of age if sepsis evaluation is initiated at birth
        - 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 → 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)
        - 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 if asymptomatic infant, negative blood culture, and/or normal / low CRP (if sent)
            - *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)

    - **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; consult pediatric infectious disease
        - Examples:
            - Gram negative organism → switch to Cefotaxime (discontinue Ampicillin and Gentamicin)
            - Gram positive organism (Staph) → switch to Vancomycin + Gentamicin (discontinue Ampicillin)

PART IV: CLINICAL PATHWAY

- See APPENDIX 4 for EOS Pathway

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	0.3/1000 live births (KPNC incidence)
Gestational age	weeks days
Highest maternal antepartum temperature	Fahrenheit
ROM (hours)	
Maternal GBS status	Negative Positive Unknown
Type of intrapartum antibiotics	Broad spectrum antibiotics ≥ 4 hrs prior to birth Broad spectrum antibiotics 2-3.9 hrs prior to birth GBS specific antibiotics ≥ 2 hrs prior to birth No antibiotics or any antibiotics < 2 hrs prior to birth

	Risk per 1000/births	Clinical Recommendation
EOS Risk @ Birth		

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

Classification of Infant's Clinical Presentation (Hide)

Clinical Exam	Description
Clinical Illness	1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room) 2. Hemodynamic instability requiring vasoactive drugs 3. Neonatal encephalopathy /Perinatal depression • Seizure • Apgar Score @ 5 minutes < 5 4. Need for supplemental O_2 ≥ 2 hours to maintain oxygen saturations > 90% (outside of the delivery room)
Equivocal	1. Persistent physiologic abnormality ≥ 4 hrs • Tachycardia (HR ≥ 160) • Tachypnea (RR ≥ 60) • Temperature instability (≥ 100.4°F or < 97.5°F) • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 2. Two or more physiologic abnormalities lasting for ≥ 2 hrs • Tachycardia (HR ≥ 160) • Tachypnea (RR ≥ 60) • Temperature instability (≥ 100.4°F or < 97.5°F) • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 Note: abnormality can be intermittent
Well Appearing	No persistent physiologic abnormalities

APPENDIX 2: Classification of Infant's Clinical Presentation, 2015.
(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
Clinical Illness *	1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room) 2. Hemodynamic instability requiring vasoactive drugs 3. Neonatal encephalopathy / Perinatal depression a. Seizure b. Apgar score <5 @ 5 minutes 4. Need for supplemental O2 ≥ 2 hours to maintain oxygen saturations >90% (outside of the delivery room)
Equivocal	1. Persistent physiologic abnormality ≥ 4 hours: a. Tachycardia (HR ≥ 160) b. Tachypnea (RR ≥ 60) c. Temperature instability (≥ 100.4F or ≤97.5F) d. Respiratory distress (grunting, flaring, retracting), not requiring supplemental O2 2. Two or more physiologic abnormalities lasting ≥ 2 hours: a. Tachycardia (HR ≥ 160) b. Tachypnea (RR ≥ 60) c. Temperature instability (≥ 100.4F or ≤97.5F) d. Respiratory distress (grunting, flaring, retracting), not requiring supplemental O2 *NOTE:* abnormality can be intermittent
Well Appearing	No persistent physiologic abnormalities

* **ADDITIONAL SIGNS/SYMPTOMS OF CLINICAL ILLNESS IN NEONATES:** These factors may be considered for individualized clinical decision-making but are not validated characteristics in the Sepsis Calculator model	
	1. Lethargy (abnormal or change in mental status or activity level) 2. Persistent or recurrent apnea requiring stimulation (outside of the delivery room) 3. Metabolic acidosis on neonatal blood gas (base excess < -8) a. Worsening pH/base deficit compared to cord blood gas b. Persistent abnormalities on newborn blood gases over 4-6 hours

APPENDIX 3: Common Pathogens in Neonatal EOS, 2015.

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:

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

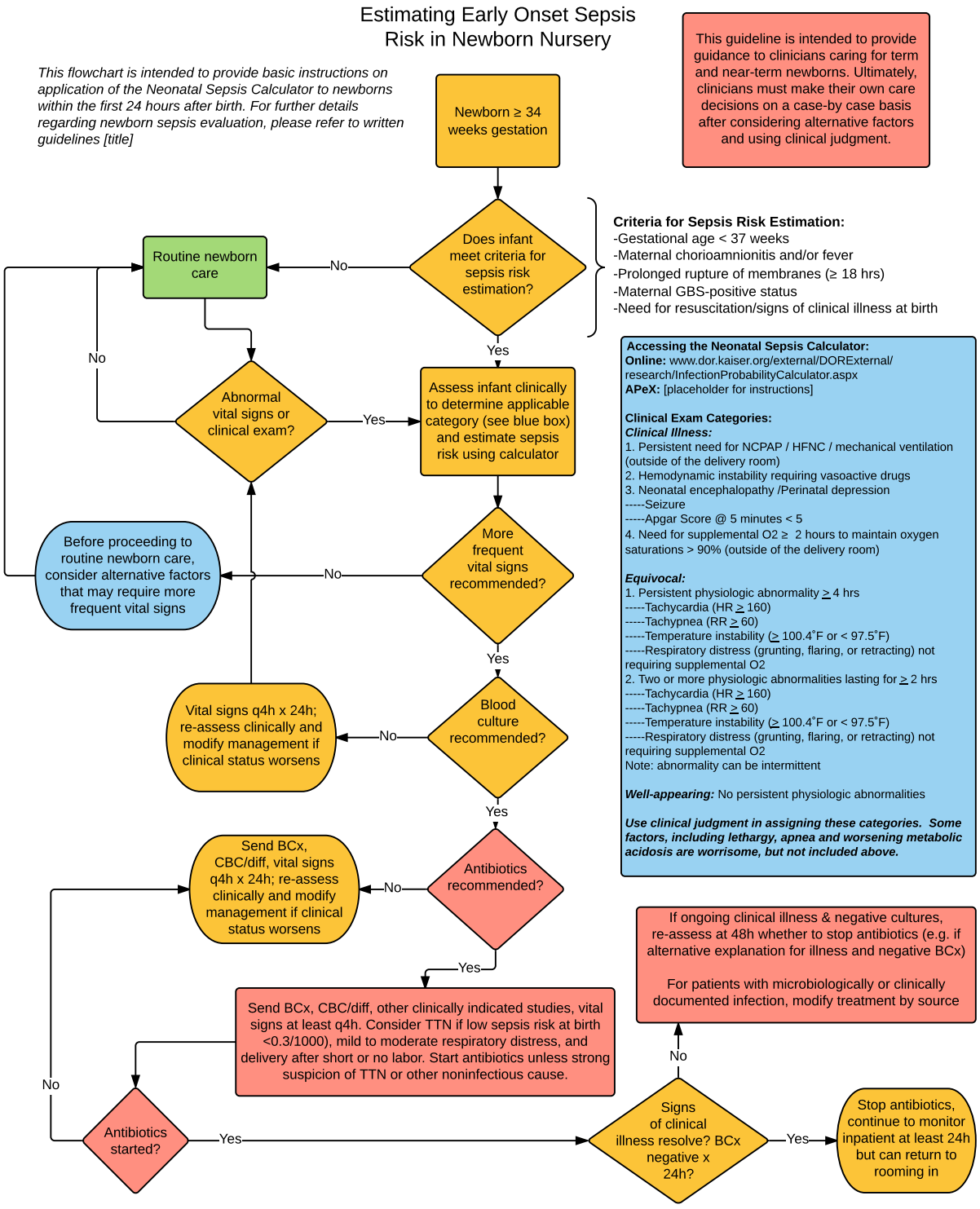
Gram Positive Bacillus:

- 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

APPENDIX 4: EOS Clinical Pathway



These are guidelines only and cannot apply to every situation. Calculator recommendations should be combined with clinical judgment. All patients should be examined carefully to evaluate for focal source of infection, and management should be modified from above if focal infection is suspected.

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