ANMC Clinical Guideline: Antibiotics for Early Onset Sepsis, Late Onset Sepsis, and Necrotizing Enterocolitis

The following is intended as a clinical guideline and may need to be adapted to meet the special needs of a specific patient, as determined by the medical practitioner.

This clinical guideline was originally developed as part of ANMC's involvement in the Vermont Oxford Network's "Choosing Antibiotics Wisely" campaign to improve antimicrobial stewardship for neonates. It is intended to provide a framework for consistent management of neonates with concern for early onset sepsis, late onset sepsis, and necrotizing enterocolitis.

Early Onset Sepsis (presenting before 72 hours of life) – management depends on gestational age:

≥ 35 weeks: All NICU admissions + select newborns in the MBU (see inclusion criteria) are included in the guideline and their information will be entered into the Kaiser Sepsis Score.

- **a.** For newborns in the MBU, the RN will notify the pediatric provider on-call if a baby is born who meets the inclusion criteria. If the baby is well-appearing with normal vital signs and no clinical concerns, the provider will write an abbreviated note outlining the Kaiser Sepsis Score. A physical exam is not required. If, however, there are clinical concerns (such as abnormal vital signs or ill-appearance), the provider will examine the patient and write a full note, including the Kaiser Sepsis Score. If antibiotics are initiated, consider transfer to the NICU. However, neonates who do not require NICU-level care may also be managed with antibiotics in the MBU.
- **b.** Upon admission to the NICU, the provider will determine the Kaiser Sepsis Score of all patients and manage them accordingly.

< 35 weeks: All patients will be admitted to the NICU due to prematurity. Recommended management of these infants is based off of the 2010 CDC/2011-12 AAP guidelines on early onset sepsis.

Late Onset Sepsis (presenting after 72 hours of life)

Babies with concern for late-onset sepsis require a full sepsis evaluation, including blood, urine, and CSF studies followed by prompt initiation of antibiotics according to the guideline.

Necrotizing Enterocolitis (NEC)

While rarely encountered in the ANMC NICU, necrotizing enterocolitis can cause significant morbidity/mortality. Infants with high suspicion for NEC will generally need to be transferred to the Providence Alaska Medical Center NICU, but this guideline provides recommendations for clinical management while awaiting transfer.

ANMC Early Onset Sepsis (< 72 hours) Guideline

Inclusion Criteria

All babies admitted to NICU
AND
Babies in MBU with any of the following:
- gestational age < 37 weeks
- maternal fever +/- chorioamnionitis
- ROM > 18h
- inadequately treated GBS
- history of sibling with invasive GBS disease
- concern for ill appearance or respiratory distress

For infants whose primary manifestation of clinical illness is respiratory distress, can be reasonable to wait to start antibiotics if clinically improving within first 6h of life

If concern for exposure to HSV, refer to current AAP guidelines

Gestational Age

Less than 35 weeks

Greater than or equal to 35 weeks

Use CDC incidence (0.5/1000)
See reference for intrapartum antibiotic questions.

Clinical signs of sepsis?

No

Maternal chorioamnionitis?

Yes

Work up and start empiric antibiotics

No

Was GBS prophylaxis indicated?

Yes

Was mother adequately pretreated?

No

- Draw blood culture
- At ≥6 hours, draw CBC + diff & CRP
- Consider repeat CRP 24h later
- Observe carefully off of antibiotics

No

Continue routine care without antibiotics

Yes

Apply Kaiser Sepsis Calculator

Work up and start empiric antibiotics

Blood culture, no antibiotics

Obtain vitals q4h

- Draw blood culture
- At ≥6 hours, draw CBC + diff & CRP
- Consider repeat CRP 24h later
- Observe carefully off of antibiotics 36-48h

No culture, no antibiotics

Routine vital signs

Remains clinically well, continue routine care. If maternal diagnosis of chorioamnionitis, observe inpatient at least 48h,

Blood culture positive or clinical signs of sepsis?

Yes

Work up and Empiric Antibiotics
- If baby in MBU, consider NICU transfer as clinically indicated
- Draw blood culture
- Start ampicillin and gentamicin

At 24h of age, draw CBC+diff, CRP, BMP, total bilirubin, newborn screen

At 36h, if infant has clinically improved and blood culture is no growth, discontinue antibiotics

At 48h of age, consider second CRP

If blood culture turns positive:
- Obtain LP (if not done)
- Consult ID and follow recs

If concern for culture negative sepsis or congenital pneumonia, limit antibiotic course to 5 days

Ampicillin Dosing
For standard rule-out sepsis:
< 2kg: 50mg/kg/dose IV q12h
≥ 2kg: 50mg/kg/dose IV q8h
If concern for meningitis:
100mg/kg/dose IV q8h

Gentamicin Dosing
Gestational age 30-34 weeks:
4.5mg/kg IV q36h
Gestational age ≥ 35 weeks:
4mg/kg IV q24h

Ceftazidime Dosing
< 2kg: 50mg/kg/dose IV q12h
≥ 2kg: 50mg/kg/dose IV q8h

Possible Meningitis
Consider LP if sepsis presents at 12-24h of life. Add ceftazidime to ampicilln + gentamicin and adjust ampicillin dosing.

Additional Information

How to use Kaiser Sepsis Calculator
(for further questions, see appendix 1)

- Incidence of Early-Onset Sepsis = 0.5/1000
- Gestational age
- Highest maternal antepartum temperature (including up to 1 h after delivery)
- ROM duration in hours
- Maternal GBS status
- Type of intrapartum antibiotics and time prior to delivery:
  - "GBS specific antibiotics" = penicillin G, ampicillin, or cefazolin only
  - "Broad-spectrum antibiotics" = two antibiotics given for chorioamnionitis, i.e. ampicillin + gentamicin
  - "None or antibiotics given < 2 hours prior to delivery" also includes erythromycin, clindamycin, or vancomycin alone

Kaiser Sepsis Score Table: Clinical Illness

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 O2 ≥ 2 hours to maintain oxygen saturations > 90% (outside of the delivery room)
Equivocal	Persistent physiologic abnormality ≥ 4 hrs OR two or more physiologic abnormalities lasting ≥ 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 O2 Note: abnormality can be intermittent
Well Appearing	No persistent physiologic abnormalities

Indications for Maternal GBS Prophylaxis

- Mother is GBS-positive late in gestation and is not undergoing cesarean delivery before labor onset with intact amniotic membranes
- GBS status is unknown and there are 1 or more intrapartum risk factors, including < 37 weeks' gestation, rupture of membranes for ≥ 18 hours, or temperature of ≥ 100.4°F
- GBS bacteriuria during current pregnancy; or
- History of a previous infant with GBS disease

Adequate GBS Treatment?
Received ampicillin, cefazolin, or penicillin > 4h prior to delivery

Lab Considerations
Both CBC + diff and CRP are most useful when obtained at least 6h after birth to allow for inflammatory response to affect values

CBC + diff
The following values are all associated with culture-proven sepsis, but the majority of infants with sepsis have a normal CBC:

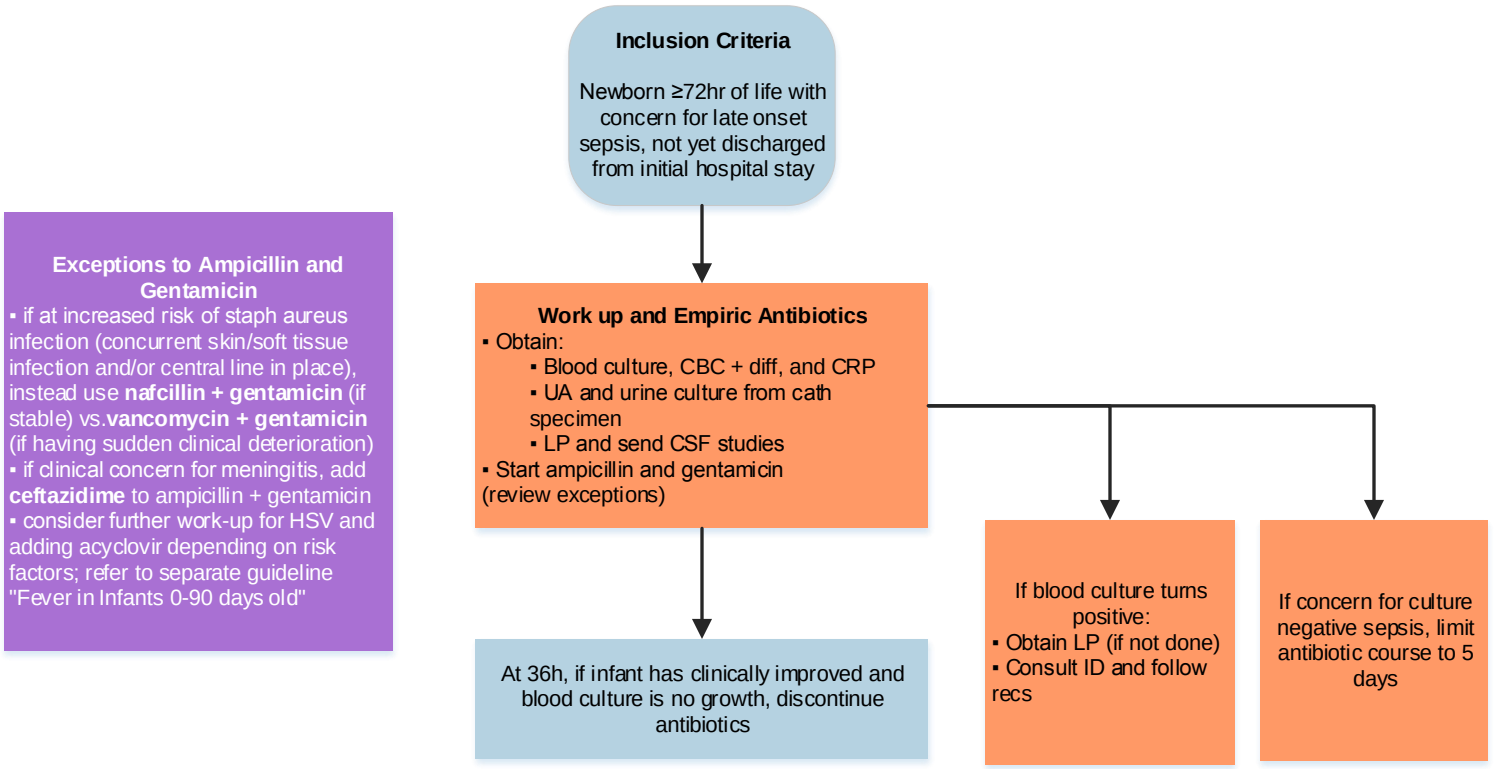
- low total WBC (< 5k)
- low ANC (< 7500 at 6h of age for GA > 36 weeks vs < 3500 at 6h of age for GA 28-36 weeks)
- elevated I:T ratio (> 0.2)

CRP
Values < 1 mg/dL x 2 (at 8-24h of life + 24h later) make sepsis very unlikely (negative predictive value of 99.7%), but role of elevated CRP values is less clear with respect to antibiotic duration

Antibiotic Duration
Prolonged antibiotic courses (> 5 days) have been associated with increased rates of late-onset sepsis, NEC, and death among premature (< 32 weeks) and low birthweight (<1000-1500g) infants.

Management of culture-negative sepsis and congenital pneumonia with ≤ 5 days of antibiotic therapy does not have increased adverse events compared to longer durations.

ANMC Late Onset Sepsis (≥ 72 hours) Guideline



Ampicillin Dosing

< 7 days of age:
- For standard rule-out sepsis:
  - < 2kg: 50mg/kg/dose IV q12h
  - ≥ 2kg: 50mg/kg/dose IV q8h
- If concern for meningitis:
  - 100mg/kg/dose IV q8h

≥ 7 days of age:
- For standard rule-out sepsis:
  - 1.2-2kg: 50mg/kg/dose IV q8h
  - ≥ 2kg: 50mg/kg/dose IV q6h
- If concern for meningitis:
  - 75mg/kg/dose IV q6h

Gentamicin Dosing

≤ 7 days of age:
- Gestational age 30-34 weeks: 4.5mg/kg IV q36h
- Gestational age ≥ 35 weeks: 4mg/kg IV q24h

> 7 days of age:
- All gestational ages: 4mg/kg IV q24h

Ceftazidime Dosing

≤ 7 days of age:
- < 2kg: 50mg/kg/dose IV q12h
- ≥ 2kg: 50mg/kg/dose IV q8h

> 7 days of age:
- 50mg/kg/dose IV q8h

Nafcillin Dosing

≤ 7 days of age:
- < 2kg: 25mg/kg/dose IV q12h
- ≥ 2kg: 25mg/kg/dose IV q8h

8-28 days of age:
- < 2kg: 25mg/kg/dose IV q8h
- ≥ 2kg: 25mg/kg/dose IV q6h

Vancomycin Dosing

≤ 7 days of age:
- 15mg/kg/dose IV q12h

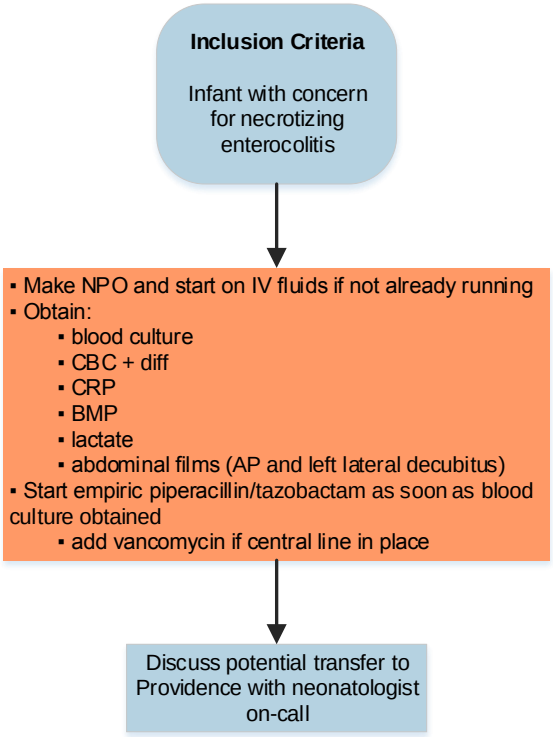
8 – 14 days of age:
- Corrected gestational age 30-36 weeks: 15mg/kg/dose IV q12h
- Corrected gestational age 37-44 weeks: 15mg/kg/dose IV q8h

>14 days of age:
- 15mg/kg/dose IV q8h

Acyclovir Dosing

20mg/kg/dose IV q8h

ANMC Necrotizing Enterocolitis Guideline



Piperacillin/Tazobactam Dosing
(based on piperacillin component)
≤ 7 days of age: 100mg/kg/dose IV q12h
8-28 days of age: 100mg/kg/dose IV q8h

Vancomycin Dosing
≤ 7 days of age:
15mg/kg/dose IV q12h
8 – 14 days of age:
Corrected gestational age 30-36 weeks: 15mg/kg/dose IV q12h
Corrected gestational age 37-44 weeks: 15mg/kg/dose IV q8h
>14 days of age:
15mg/kg/dose IV q8h

References

AAP Committee on Infectious diseases and Committee on Fetus and Newborn. Policy Statement – Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease. Pediatrics 2011; 128: 611–616

Baystate Children's Hospital. Guidelines for antibiotic utilization and management of suspected or proven sepsis in neonates. Updated 2/7/18.

Benitz WE, et al. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 1998; 102; e41.

Benitz WE, et al. Reappraisal of Guidelines for Management of Neonates with Suspected Early-Onset Sepsis. J Pediatr 2015 April; 166(4): 1070–1074.

Brady MT, Polin RA. Prevention and Management of Infants With Suspected or Proven Neonatal Sepsis. Pediatrics 2013; 132: 166-168.

Cantey JB, et al. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis 2016; 16: 1178–84.

Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59(RR-10): 1–36.

Cotten CM, et al. Prolonged Duration of Initial Empirical Antibiotic Treatment Is Associated With Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants. Pediatrics. 2009 January; 123 (1): 58–66.

Doernbecher Children's Hospital - Doernbecher NICU Clinical Consensus Guidelines - Management of Infants with Suspected Sepsis. Accessed 3/29/18 via Vermont Oxford Network LMS - http://von.mycrowdwisdom.com/diweb/share.

Edwards MS. Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 2, 2018.)

Escobar GJ, et al. Stratification of risk of early-onset sepsis in newborns $\geq$ 34 weeks' gestation. Pediatrics 2014; 133: 30-6.

Harriet Lane Service (Johns Hopkins Hospital). Dosing for ampicillin, ceftazidime, gentamicin, nafcillin, piperacillin/tazobactam, and vancomycin. The Harriet Lane Handbook – 21st Edition. Philadelphia, PA: Elsevier, 2008.

Hornik CP, et al. Use of the Complete Blood Cell Count in Early-Onset Neonatal Sepsis. Pediatr Infect Dis J. 2012 August; 31(8): 799–802.

Kuppala VS, et al. Prolonged Initial Empirical Antibiotic Treatment is Associated with Adverse Outcomes in Premature Infants. J Pediatr 2011 November; 159 (5): 720–725.

Kuzniewicz MW, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. JAMA Pediatrics 2017 Apr 1; 171(4): 365-371.

Newman TB, et al. Interpreting Complete Blood Counts Soon After Birth in Newborns at Risk for Sepsis. Pediatrics. 2010 November; 126(5): 903–909.

Polin RA and the Committee on Fetus and Newborn. Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis Pediatrics 2012; 129: 1006–1015.

Puopolo KM, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics 2011; 128: e1155-63.

Puopolo KM. Sepsis Risk Calculator: Guidance to Determine the Risk Estimate at Birth. Updated 3/26/18; distributed via Vermont Oxford Network iNICQ 2018 listserve.

Schanler RJ. Management of necrotizing enterocolitis in newborns. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 3, 2018.)

Appendix 1 - Sepsis Risk Calculator: Guidance to Determine the Risk Estimate at Birth

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Calculator Input	Value to be entered	Notes
Incidence of Early-Onset Sepsis	Local incidence if known If not, use 0.5/1000 live births (CDC national incidence)	
Gestational Age	Gestational age at birth, in weeks and days	"Weeks" value range 34-43 "Days" value range 0-6
Highest Maternal Intrapartum Temperature	Enter the value and remember to choose "Fahrenheit" or "Celsius" for the temperature unit. ***Note***: Maternal fever that occurs within 1 hour after delivery can be counted as the "highest intrapartum temperature" for the purpose of calculating the risk estimate at birth.	Value may be whole number or number with single decimal place ***Examples***: 101, 101.0 and 101.5 are all acceptable entry values
ROM (hours)	Duration of time between rupture of and birth, in hours	Value may be whole number rounded to the nearest hour OR number with single decimal place ***Example***: ROM time 4 hours and 30 minutes should be entered as 4.5 hours. ***Example***: ROM time 4 hours and 55 minutes can be entered as 4.9 hours or as 5 hours
GBS	Enter maternal GBS screening result	
Type of Intrapartum Antibiotics	Choice must include ***type*** of antibiotic given and ***duration of time*** prior to birth that first dose was given. ***GBS-specific antibiotics*** are currently defined by CDC 2010 GBS guidelines as ONLY penicillin G; ampicillin; or cefazolin given for the purpose of GBS prophylaxis. This should apply only to mothers who are GBS positive or GBS unknown. • If erythromycin, clindamycin or vancomycin ALONE are given for GBS prophylaxis, choose "None or antibiotics given < 2 hours prior to delivery." These medications do not reliably provide neonatal protection from GBS infection, although they may provide some protection to the mother • ***Timing*** of administration of GBS-specific antibiotics is determined by subtracting the time of the first dose of antibiotic from the time of birth	

	Broad-spectrum antibiotics are defined as <u>two more antibiotics given in combination</u> when there is concern for the mother developing chorioamnionitis/intraamniotic infection**. Usually this concern is prompted by maternal intrapartum fever. ***To determine the timing of broad-spectrum intrapartum antibiotic administration***, compare the time of the administration of the second antibiotic in the combination, to the time of birth. • **Example**: ampicillin is given at 2:00 PM; gentamicin is given at 3:30 PM. Birth is at 4:30 PM. Because the second antibiotic of the combination was given 1 hour prior to delivery, choose "None or antibiotics given < 2 hours prior to birth." One could consider choosing "GBS-specific > 2 hours prior to birth" but if that was not the ***intent*** of administering the antibiotics, and the actual intent was to administer ampicillin and gentamicin – the most conservative decision is to choose "None or antibiotics given < 2 hours prior to birth" • **Example**: ampicillin is given at 1:00 PM; gentamicin is given at 2:00 PM. Birth is at 4:30 PM. Because the second antibiotic of the combination was given 2.5 hour prior to delivery, choose "Broad-spectrum antibiotics given 2-3.9 hours prior to birth." • **Example**: ampicillin is given at 10:00 AM; gentamicin is given at 11:00 AM. Birth is at 4:30 PM. Because the second antibiotic of the combination was given >4 hours prior to delivery, choose "Broad-spectrum antibiotics given > 4 hours prior to birth." ***If a mother has been given BOTH GBS-specific antibiotics and broad- spectrum antibiotics due to concern for evolving chorioamnionitis/intraamniotic infection, record the most complete treatment.*** • **Example**: Mother is given ampicillin at 8:00 AM and 12:00 PM for GBS positive status. She develops a fever to 101°F at 2:00 PM, and gentamicin is given at 3:00 PM. Ampicillin is given at 4:00 PM. Birth is at 4:30 PM. In this case, GBS-specific antibiotics were given > 4 hours prior to delivery, but broad-spectrum antibiotics were given only 1 ½ hours prior to delivery. In the calculator, choose "GBS-specific antibiotics given > 2 hours prior to birth."

**ACOG has recently provided guidance for antibiotic choice when there is concern for developing intraamniotic infection. Broad-spectrum antibiotics should be defined per this document.

Heine RP, Puopolo KM, Beigi R, Silverman NS, El-Sayed YY. Committee on Obstetric Practice. American College of Obstetrics and Gynecology. Opinion No. 712: Intrapartum Management of Intraamniotic Infection. *Obstet Gynecol*. 2017;130(2):e95-e101.