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 developed as part of ANMC’s involvement in the Vermont Oxford Network’s “Choosing Antibiotics Wisely” campaign to improve antimicrobial stewardship for neonates. Management of infants with early onset sepsis, late onset sepsis, and necrotizing enterocolitis can vary widely between practitioners, so this guideline is an effort to provide a framework for more consistency in antibiotic usage.

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

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

a. For babies in the MBU, the RN is to 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 can write a brief note outlining their Kaiser Sepsis Score but does not need to examine the patient at that time. If there are clinical concerns (such as abnormal vital signs or ill-appearance), the provider is to examine the patient and write a full note, including the Kaiser Sepsis Score. If antibiotics are indicated, the baby may need to be transferred to the NICU if clinically indicated, although some babies can be managed with antibiotics in the MBU if otherwise not requiring NICU-level care.

b. For babies admitted to the NICU, the provider is to enter the baby’s information into the Kaiser Sepsis Score at the time of NICU admission and manage them accordingly.

< 35 weeks: Babies will be admitted to the NICU anyway 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 before 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.
Preterm infants at highest risk for EOS: Infants born preterm because of cervical insufficiency, preterm labor, PROM, intra-amniotic infection, and/or acute and otherwise unexplained onset of non-reassuring fetal status are at the highest risk of early-onset sepsis. Consider blood cultures and empiric antibiotics in this situation, depending on clinical condition.

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.

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

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
• PROM > 18h
• inadequately treated GBS
• history of sibling with invasive GBS disease
• concern for ill appearance or respiratory distress

Less than 35 weeks
Clinical signs of sepsis?
Yes → Work up and start empiric antibiotics
No
Maternal chorioamnionitis?
Yes → Was GBS prophylaxis indicated?
No → Was mother adequately pretreated?
Yes → Continue routine care without antibiotics
No

Gestation Age
Greater than or equal to 35 weeks

Apply Kaiser Sepsis Calculator

Work up and start empiric antibiotics

Blood culture, no antibiotics

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

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

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

Cefepime Dosing
• ≤ 2kg: 30mg/kg/dose IV q12h
• > 2kg: 50mg/kg/dose IV q12h

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

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

Possible Meningitis
Consider LP if sepsis presents at 12-24h of life. Switch to meningitic dosing ampicillin + cefepime; consider adding gentamicin if CSF gram stain shows GNR in consultation with peds ID.

At 48h of age, consider second CRP

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

At 24h of age, consider second CRP

If no culture, no antibiotics

Obtain vitals q4h

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

Blood 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

Work up and Empiric Antibiotics
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**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

**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
- History of a previous infant with GBS disease

**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 l: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

Inclusion Criteria
Newborn ≥72hr of life with concern for late onset sepsis, not yet discharged from initial hospital stay

Exceptions to Ampicillin and Gentamicin
▪ if at increased risk of staph aureus infection (concurrent skin/soft tissue infection and/or central line in place), instead use nafcillin + gentamicin (if stable) vs. vancomycin + gentamicin (if having sudden clinical deterioration)
▪ if clinical concern for meningitis, switch to meningitic dosing ampicillin + cefepime; consider adding gentamicin if CSF gram stain shows GNR in consultation with peds ID.
▪ consider further work-up for HSV and adding acyclovir depending on risk factors; refer to separate guideline "Fever in Infants 0-90 days old"

Work up and Empiric Antibiotics
▪ Obtain:
  ▪ Blood culture, CBC + diff, and CRP
  ▪ UA and urine culture from cath specimen
  ▪ LP and send CSF studies
▪ Start ampicillin and gentamicin (review exceptions)

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

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

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

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

Cefepime Dosing
≤ 2kg: 30mg/kg/dose IV q12h
> 2kg: 50mg/kg/dose IV q12h

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
Inclusion Criteria
Infant with concern for necrotizing enterocolitis

- Make NPO and start on IV fluids if not already running
- Obtain:
  - blood culture
  - CBC + diff
  - CRP
  - BMP
  - lactate
  - abdominal films (AP and left lateral decubitus)
- Start empiric piperacillin/tazobactam as soon as blood culture obtained
  - add vancomycin if central line in place

Discuss potential transfer to Providence with neonatologist on-call

**Piperacillin/Tazobactam Dosing**

(112.5mg/kg provides 100mg/kg piperacillin component)

- ≤ 7 days of age: 112.5mg/kg/dose IV q12h
- 8-28 days of age: 112.5mg/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


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


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.


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

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<table>
<thead>
<tr>
<th>Calculator Input</th>
<th>Value to be entered</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of Early-Onset Sepsis</strong></td>
<td>Local incidence if known If not, use 0.5/1000 live births (CDC national incidence)</td>
<td></td>
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<tr>
<td><strong>Gestational Age</strong></td>
<td>Gestational age at birth, in weeks and days</td>
<td>&quot;Weeks&quot; value range 34-43 “Days” value range 0-6</td>
</tr>
</tbody>
</table>
| **Highest Maternal Intrapartum Temperature**      | Enter the value and remember to choose “Fahrenheit” or “Celsius” for the temperature unit.  | Value may be whole number or number with single decimal place  
**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.  
**Examples:** 101, 101.0 and 101.5 are all acceptable entry values |
| **ROM (hours)**                                   | Duration of time between rupture of membranes 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    | 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 two more antibiotics given in combination 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.**