Baystate Children's Hospital

Division of Newborn Medicine

Guidelines for Antibiotic Utilization and Management of Suspected or Proven Sepsis in Neonates

Background:

Early-onset sepsis remains one of the most common causes of neonatal morbidity and mortality, both for preterm as well as term infants.

Diagnostic tests for neonatal sepsis have a poor positive predictive accuracy.

The optimal treatment of infants with suspected early-onset sepsis is broad spectrum antimicrobial agents. Once a pathogen is identified, antimicrobial therapy should be narrowed.

Recent data suggest an association between prolonged empirical treatment of preterm infants (≥ 5 days) with broad-spectrum antibiotics and higher risks of late onset sepsis, necrotizing enterocolitis, and mortality. Additionally, early exposure to antimicrobial agents may alter the gastrointestinal microbiome leading to long term impacts such as childhood and adult obesity in exposed infants when compared to non-exposed infants.

To reduce these risks, carefully consider risk factors, clinical status and lab data in conjunction when initiating a course of antimicrobial agents and consider discontinuation at 48hours in clinical situations where the probability of sepsis is low.

When considering the duration of therapy in infants with negative blood cultures, the decision should include consideration of the clinical course as well as the risks associated with longer course of antimicrobial agents. The course may be truncated to 3-5 days as opposed to complete 7 days in these infants who are clinically well appearing.

Intrapartum antimicrobial agents are indicated for the following situation:

1. Positive antenatal culture or molecular test at admission for group B streptococcus (GBS) [except for women who have a cesarean delivery without labor or membrane rupture]
2. Unknown maternal colonization status with gestation < 37 weeks, prolonged rupture of membranes (PROM) > 18 hours, or temperature > 100.4°F (>38°C)
3. GBS bacteriuria during the current pregnancy
4. Previous infant with invasive GBS disease

Clinical Challenges:

1. Identifying neonates *with clinical signs of sepsis* with a "high likelihood" of early-onset sepsis who require antimicrobial agents soon after birth
   a. Most infants with early-onset sepsis exhibit abnormal signs in the first 24 hours of life
   b. Critically ill infant with no known reason i.e prenatal diagnosis of congenital anomalies (Cardiac, GI, Respiratory), should be evaluated and receive empirical broad-spectrum antimicrobial therapy after culture, even when there are no obvious risk factors for sepsis
   c. In term neonates without risk factors for infection who clinically improve over the first 6 hours of life, it is reasonable to withhold antimicrobial therapy and monitor closely

2. Identifying *healthy-appearing* neonates with a "high likelihood" of early-onset sepsis who require antimicrobial agents soon after birth
   a. Includes infants with a sepsis risk factor
      i) Colonization with GBS (not a risk factor if mother received adequate intrapartum therapy with penicillin, ampicillin, or cefazolin for at least 4 hours before delivery or has a cesarean delivery with intact membranes in the absence of labor)
      ii) PROM > 18 hours
      iii) Maternal chorioamnionitis
   b. The greatest risk of early-onset sepsis occurs in infants born to women with chorioamnionitis who are also colonized with GBS and did not receive intrapartum antimicrobial agents
   c. The decision of whether to treat high-risk infants depends on the risk factors present, the frequency of observations, and gestational age.

3. Understanding the role of CBC: Total white blood cell counts have little value in the diagnosis of early-onset sepsis and have a poor positive predictive accuracy. Neutropenia may be a better marker for neonatal sepsis and has better specificity than an elevated neutrophil count, because few conditions besides sepsis (maternal pregnancy-induced hypertension, asphyxia, and hemolytic disease) depress the neutrophil count of neonates. **Neutropenia** defined by Schmutz et al in their study, peak values occurred at 6 to 8 hours after birth; the lower limits of normal at that time were 7500/mm3, 3500/mm3, and 1500/mm3 for infants born at >36 weeks' gestation, 28 to 36 weeks' gestation, and <28 weeks' gestation, respectively**. I/T ratio** has the best sensitivity of any of the neutrophil indices. The I/T ratio is <0.22 in 96% of healthy preterm infants born at <32 weeks' gestational age. Maximum normal values for the I/T ratio occur at birth (0.16) and decline with increasing postnatal age to a minimum value of 0.12. In healthy term infants, the 90th percentile for the I/T ratio is 0.27. A single determination of the I/T ratio has a poor positive predictive accuracy (approximately 25%) but a very high negative predictive accuracy (99%).The I/T ratio may be elevated in 25% to 50% of uninfected infants.
   Counts obtained 6 to 12 hours after birth are more likely to be abnormal than are counts obtained at birth, because alterations in the numbers (and ratios) of mature and immature neutrophils require an established inflammatory response. Therefore, once the decision is made to start antimicrobial therapy soon after birth, it is worth waiting 6 to 12 hours before ordering a white blood cell count and differential count.

4. Understanding the role of CRP in early onset sepsis and inflammation: CRP concentration increases within 6 to 8 hours of an infectious episode in neonates and peaks at 24 hours. The sensitivity of a CRP determination is low at birth, because it requires an inflammatory response (with release of interleukin-6) to increase CRP concentrations. The sensitivity improves dramatically if the first determination is made 6 to 12 hours after birth. Recent studies have demonstrated that **excluding** the value at birth, 2 normal CRP determinations (8–24 hours after birth and 24 hours later) have a negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis. If CRP determinations remain persistently normal, it is strong evidence that bacterial sepsis is unlikely, and antimicrobial agents can be safely discontinued. Data are insufficient to recommend following sequential CRP concentrations to determine the duration of antimicrobial therapy in an infant with an elevated value (≥1.0 mg/dL).

Based on these clinical challenges, algorithms have been suggested by both the Center for Disease Control (CDC) and the American Academy of Pediatrics Committee on Fetus and Newborn (COFN)

Scope:
To provide evidence based algorithm for initiation and discontinuation of antibiotics for neonates with suspected or proven early onset sepsis, late onset sepsis, GI pathologies [Necrotizing Enterocolitis (NEC) and spontaneous intestinal perforation (SIP)], surgical peri-op coverage, urinary tract infections and/or fungal sepsis. The current guidelines are being proposed with the understanding that occasionally clinical situations may warrant deviation from the suggestions.

Scenarios:

Scenario	Point of Emphasis
1. Suspected or Proven Early Onset Sepsis • For well appearing infants > 35 weeks follow Algorithm in Appendix A • For secondary prevention of GBS disease in neonate follow Algorithm in Appendix B • Clinically ill-appearing infant err on the side of initiating empiric therapy with Ampicillin and Gentamicin • Consider obtaining 1st CBC/CRP at 6-12 hrs of life for most accurate reflection of lab values	• Clinically well appearing infant can be cared for in the newborn nursery • Clinically ill-appearing infant needs transfer to the NICU for care provision • Note the most important issues is careful ongoing clinical monitoring • For culture positive sepsis discuss tailoring the ongoing therapy and duration with ID team based on identity + sensitivity pattern of the isolate • For culture negative well appearing or rapid clinical improvement strongly consider discontinuation of antibiotics at 48hours or a short course of 5 days • If treating beyond 48 hours get the Gentamicin levels around the 3rd dose (Trough 30 minutes before and Peak 30 minutes after administration of dose)
2. Suspected or Proven Late Onset Sepsis • Send CBC with differential and CRP and Blood culture • If central line present send 2 blood cultures with optimally 1 cc in each bottle but a minimum of 0.5ml from two different sites • If intubated with respiratory changes/decompensation or CXR changes concerning for pneumonia present then send ETT aspirates at the time of drawing cultures • Consider sending a Urine Culture and urinalysis • Start on Vancomycin and Gentamicin for appropriate initial coverage • In azotemic, anuric infant consider checking Gentamicin troughs to titrate the dosing or replacing with Cefotaxime	• Obtain Pedi ID consultation for all patients with S. aureus Bacteremia. • Consider presence of foreign bodies (central lines, tracheal tubes) and need for Staph coverage • DO NOT draw a culture from an indwelling central line • For culture positive sepsis discuss tailoring the ongoing therapy and duration with ID team based on identity + sensitivity pattern of the isolate • For culture negative well appearing or rapid clinical improvement strongly consider discontinuation of antibiotics at 48hours or a short course of 5 days • DO NOT prolong course beyond 7 days in

	culture negative ill appearing infant, remember that it may take longer to resolve inflammation after the infection has resolved • If culture positive send repeat blood culture at least daily till 2 consecutive cultures negative • If unable to clear blood stream and central line in place remove and await replacement till culture negative. *For Candida sepsis central lines have to be immediately discontinued per ID recommendations.* • If culture positive consider LP based on the isolate and discussion with ID, may impact duration of treatment
3. Necrotizing Enterocolitis/Spontaneous Intestinal Perforation • Send CBC, manual differential, CRP and blood culture (2 if central line in place) • Start on Vancomycin and Zosyn	• Discuss coverage with Pediatric ID stewardship team. • Vancomycin and Zosyn provide broad spectrum aerobic as well as anaerobic coverage • Confirmed Medical NEC (Modified Bell's Stage II) treat for 7-10 days with antimicrobials from negative culture date. • Surgical NEC (Modified Bell's Stage III) with either penrose drain or laparotomy treat for a minimum of 10-14 days with antimicrobials from negative culture date • Consider discontinuing Vancomycin at 48 hours if culture negative and complete course with Zosyn alone for both medical and surgical NEC • **For culture positive NEC**, daily cultures needed until 2 subsequent cultures negative as well as tailor antibiotics for the isolate • May need to perform LP based on isolate which may impact duration of treatment • May need to remove central line, if present, for persistent positive cultures • Suspected NEC treat for 7 days **ONLY** with antimicrobials from negative culture date
4. Surgical Peri-operative prophylaxis • G-tube placement – Cefazolin • Tracheostomy – Cefazolin • Hernia repair – Clean Surgery hence no need for	• Most of these elective procedures are either clean = surgical wound class 1, or clean contaminated = surgical wound class 2 • Coverage rarely recommended beyond

prophylaxis, may use Cefazolin at the discretion of the surgical attending physician • TEF repair- Cefazolin • Ostomy creation or reversal – Ancef and Metronidazole	24hours. First dose to be within 60 minutes of incision[1]
5. UTI Rx and prophylaxis: • If suspected send urine specimen obtained by catheterization or suprapubic tap for both urinalysis and urine culture, blood culture and CBC, differential and CRP • UTI treatment initiated as Ampicillin and Gentamicin, then guided by the isolate and its sensitivity • For infants with culture positive UTI, evaluate for structural renal pathology [3] • Amoxicillin po 20 mg/kg/dose, if heplock present and infant npo may use Ampicillin IV	• For infants most common bacteria is E. coli followed by other gram negative, rarely Staph species[2] • Culture proven UTI needs workup including Renal Ultrasound (RUS), Fluoroscopic Voiding Cystourethrogram (VCUG). Additional imaging studies maybe warranted based on renal pathology • For a scheduled VCUG surgical team preference of antibiotic prophylaxis is daily dosing 2 days prior to, then twice a day dosing for the day of and day following the procedure. So total of 4 days of coverage.
6. Fungal sepsis • Amphotericin B as first line of treatment[4] • Fluconazole could be an alternate but does not cover all Candidal species	• Obtain Pediatric ID consultation • Treat based on isolates, duration and dose to be decided in conjunction with Pedi ID • No need to order fungal blood cultures, routine blood culture order will also test for yeast growth • Renal and liver function need to be monitored • Culture proven fungal bloodstream infection should prompt LP, Echocardiography, full abdominal ultrasound and a formal ophthalmology consultation

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APPENDIX A[12]

Management of "Well- Appearing" Infants ≥ 35 weeks Gestational age at Risk for Sepsis

Maternal Fever	Additional Risk Factors	Management
Maternal Fever [C] ≥ 101°F	Any of the following additional signs of chorioamnionitis: • Maternal leukocytosis (WBC greater than 15,000 cells/mL) • Maternal tachycardia (greater than 120 beats/minute for 10 minutes or longer) • Fetal tachycardia (greater than 160 beats/minute for 10 minutes or longer)	• Blood Culture at birth and start treatment with Ampicillin and Gentamicin for a potential 48 hour rule out • CBC with differential and CRP at 6hrs of age
Maternal Fever [C] 100.4 – 100.9°F	Any of the following additional signs of chorioamnionitis: • Maternal leukocytosis (WBC greater than 15,000 cells/mL) • Maternal tachycardia (greater than 120 beats/minute for 10 minutes or longer) • Fetal tachycardia(greater than 160 beats/minute for 10 minutes or longer)	• CBC with differential, CRP , Blood Culture at 6hrs • Consider Treatment with Ampicillin and Gentamicin if abnormal values [D]
	Any of the following additional risk factors for neonatal sepsis: • ROM ≥ 18hrs • GA < 37 weeks • GBS Positive[A] with Inadequate Antibiotic Prophylaxis[B] • GBS Unknown with Inadequate Antibiotic Prophylaxis[B]	• CBC with differential, CRP , Blood Culture at 6hrs • Consider Treatment with Ampicillin and Gentamicin if abnormal values [D]
	None	• CBC with differential, CRP , Blood Culture at 6hrs • Consider Treatment with Ampicillin and Gentamicin if abnormal values [D]
No Maternal Fever [C]	Any of the following: • GBS Positive[A] with Inadequate Antibiotic Prophylaxis[B] and ROM ≥ 18hrs • GBS Positive[A] with Inadequate Antibiotic Prophylaxis[B] and GA< 37 wks • GBS Unknown with Inadequate Antibiotic Prophylaxis[B] and ROM ≥ 18hrs • GBS Unknown with Inadequate Antibiotic Prophylaxis[B] and GA < 37 wks	• CBC with differential, CRP , Blood Culture at 6hrs • Consider Treatment with Ampicillin and Gentamicin if abnormal values [D]

[A] Maternal GBS-positive status includes: (1) mothers positive for GBS on screening culture during this pregnancy, (2) mothers with GBS bacteriuria during this pregnancy; and (3) mothers with previous child with GBS disease

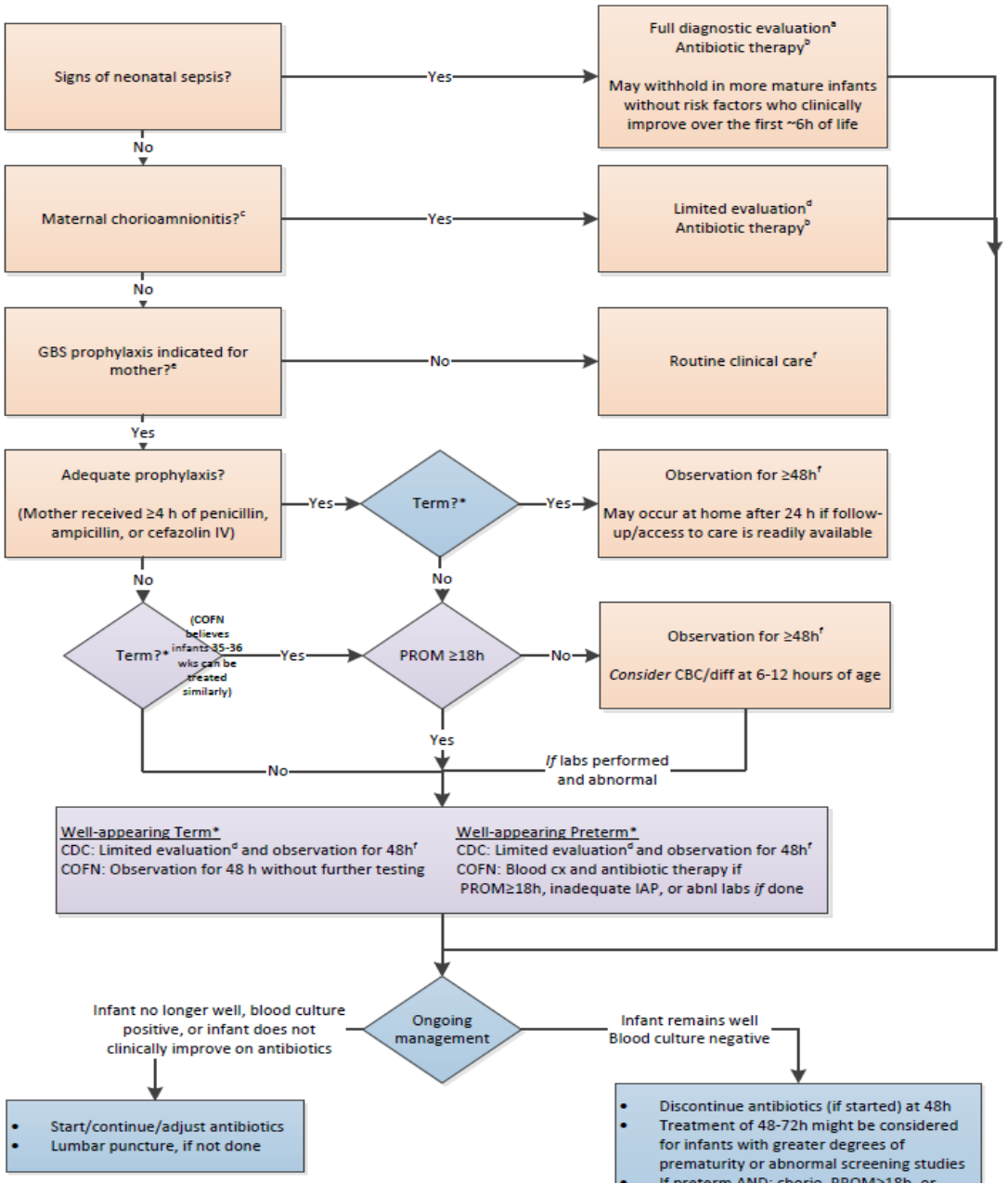
[B] Adequate antibiotic prophylaxis is considered penicillin, ampicillin, or cefazolin 4 hours or greater prior to delivery. Antibiotic prophylaxis is not indicated in setting of C-section with intact membranes before onset of labor, regardless of GBS status

[C] Maternal fever that occurs within one hour after delivery should be considered intrapartum fever. A non-sustained (less than 1 hour), isolated self-resolving maternal fever can be evaluated on the basis of larger clinical context

[D] Remember limitations of CBC and CRP. Abnormal CBC: WBC < 5,000 or I:T ration > 0.2. I:T ratio = [immatures ÷ (immatures+ polys)

APPENDIX B[13]

Secondary prevention of GBS disease – suggested algorithm



[a] Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).
[b] Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.
[c] Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.
[d] Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).
[e] Previous infant with invasive disease, GBS bacteriuria with current pregnancy, positive GBS vaginal-rectal culture in late gestation of current pregnancy, *or* unknown GBS *and* any of the following: <37 weeks, PROM ≥18 h, intrapartum temp ≥ 100.4°F (≥38°C), positive rapid screen (*unless* a caesarian is performed before the onset of labor with intact amniotic membranes, regardless of GBS colonization status or gestational age).
[f] If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.