Seton
Family of Hospitals

Management of Neonates and Young Infants with Fever without a Source or Suspected Serious Bacterial Infection

Objective To develop guidelines for prescribers within the Seton Healthcare Network for the empiric antimicrobial treatment of infants with fever without a source (FWS) or suspected serious bacterial infections (SBI). This guideline excludes patients admitted to any of the Neonatal Intensive Care Units.

Introduction Approximately 20% of infants and young children with fever have no identifiable source of infection following a thorough history and physical examination.[1] Of these, a small percentage may have a serious bacterial infection such as bacteremia, urinary tract infection, pneumonia, sepsis and rarely meningitis. There is a considerable difference in the management and prescribing of antimicrobial agents in infants with FWS or suspected SBI. The reasons for this are varied; but ultimately depend on the physician's overall clinical assessment, based on the patient's past medical history, physical examination, clinical status, and age. Other factors which may influence treatment include intravenous access, reliability of caregivers to follow up, and current antimicrobial susceptibilities (at the institution when available). In general, the physician will need to determine whether the patient is at low or high risk for SBI based on the history, physical exam, clinical status, and medical evaluation. Patients at high risk for SBI may be treated with empiric antimicrobial agents until the workup is complete. Due to the possibility of life-threatening infections (*e.g. sepsis and meningitis*) in this high-risk patient population, empiric treatment should focus on providing medications which have the ability to reach potential sequestered sites of infection (i.e. central nervous system).

Definition of Serious Bacterial Infection (SBI) For the purposes of this guideline, serious bacterial infection includes possible or suspected meningitis, sepsis, bacteremia, urinary tract infections (UTI), and pneumonia, as well as positive cultures of urine, blood, and/or cerebrospinal fluid.

Definition of Fever For the purposes of this guideline, a fever is defined as a temperature of 38°C (100.4°F) or greater taken rectally.[2] Some patients with serious and/or life-threatening infectious diseases, especially young infants, may not have fever to this degree, but may actually be hypothermic (below 36°C or 96.8°F); however, most of these patients will have other signs of serious illness.[1] Tympanic membrane temperatures should be considered unreliable.[1] In infants and young children, axillary temperatures do not reliably reflect rectal/oral temperatures and should be interpreted with caution as they may underestimate a rectal temperature by 0.4° C to more than 1°C.[3]

Age Stratification Infants and children have traditionally been stratified in the medical literature into the following age groups: neonates (0-28 days), young infants (29-90 days), older infants and young children (3-36 months), and older children (3-18 years).

Prepared by Ronda Machen, PharmD
Reviewed and edited by PCRS (Mark Shen, MD, Lynn Campbell, MD, Lynn Thoreson, DO), DCMC ED (Eric Higginbotham, MD), and Pediatric Infectious Disease (Natascha Ching, MD, Sarmistha Hauger, MD, Marisol Fernandez, MD).
Last Revised 2/6/11

Literature Analysis

The management of neonates and young infants is particularly challenging because of the relatively high prevalence of SBI and the inability to quickly and accurately determine the source of infection (i.e. bacterial vs. viral). Although several studies and protocols have been published to stratify risk criteria, as well as determine which patients should be empirically treated, no single study or protocol has been universally recognized as being a comprehensive resource. This is primarily due to the debate over the differences between the studies, and includes factors such as age, definition of fever, clinical and laboratory criteria, and criteria to distinguish infants at low or high risk for SBI.[4] The four common published approaches to managing febrile neonates and young infants under 3 months of age without a fever source are the Philadelphia protocol for infants 29-60 days old,[5] the Rochester criteria for infants ≤ 60 days old,[6] the Boston criteria for infants 28-89 days of age,[7] and the Pittsburgh criteria for infants ≤ 60 days old.[8] See **Table 1** for a comparison of these approaches. The common goal of these approaches is to identify febrile neonates and young infants at low-risk for infection who can be managed as outpatients with or without antibiotics, and those at high-risk requiring hospitalization for empiric treatment with intravenous antibiotics. Refer to **Table 2** for the types of infections and organisms identified in these studies.

Infants 0-28 days of age Neonates are most commonly infected via perinatal vertical transmission or postnatal exposure to organisms. Perinatal vertical transmission usually manifests within 48 to 72 hours after birth. Early-onset sepsis is defined as occurring within the first week of life and late-onset sepsis occurs beyond 7 days of age. Although the risk of SBI in low-risk infants under 28 days is very small (0.2%),[2,6] all high-risk patients in this age group should be hospitalized and empirically treated while awaiting culture results. The initiation of empiric therapy is especially critical in the high risk population because the signs and symptoms of sepsis may be subtle and the patient may rapidly deteriorate.[2] Alternatively, low-risk patients may be admitted and observed closely without antibiotics, while hospitalized, pending culture results.[2,9]

The most common organisms identified in term infants of this age with SBI are Group B *streptococcus, Escherichia coli, Listeria monocytogenes,* and *Klebsiella pneumoniae* (refer to **Table 2** and **Table 3**). The recommended first-line empiric treatment for patients of this age is ampicillin and gentamicin.[10] *Group B streptococcus* and *Listeria monocytogenes* are widely susceptible to ampicillin,[10] and the other targeted gram-negative organisms are covered with gentamicin. When the cerebrospinal fluid (CSF) is indicative of bacterial meningitis, or there is concern for infection of the central nervous system (CNS) with gram-negative bacilli, treatment with cefotaxime and ampicillin is preferred as aminoglycosides exhibit poor penetration into the CSF. Of note, at Dell Children's Medical Center, recent antibiograms show poor susceptibility of *E. coli* to ampicillin at approximately 44%.[11,12] When there is concern for infection with methicillin resistant *S. aureus* (MRSA), treatment with vancomycin and cefotaxime is preferred.[10] Vancomycin and gentamicin can be also used as an alternative in this situation; however, due to the poor penetration of vancomycin (in the absence of meningeal irritation) and gentamicin into the CSF,[10] this regimen is not preferred. When

CSF pleocytosis is suggestive of viral meningoencephalitis, acyclovir should be added to the regimen.[2] Refer to **Table 3** for antimicrobial dosing.

The targeted organisms for preterm infants are *Escherichia coli,* Group B *streptococcus, Haemophilus influenzae* type b, Coagulase-negative *staphylococcus*, and *Staphylococcus aureus*.[13,14] The recommended treatment for patients of this age is the same as for term infants mentioned above.[15,16,17] However, it is important to note that antimicrobial dosing in preterm infants differs from term infants due to a larger volume of distribution and slower clearance in these patients. Please see **Table 4** for drug dosing in preterm infants.

Maternal risk factors also play a significant role in the selection of empiric antimicrobials in both term and preterm infants. Early-onset sepsis should be considered in those infants with a maternal history of traumatic or difficult deliveries, and gram negative organisms should be considered. Early, late or very late-onset infection with Group B *streptococcus* (GBS) should also be considered.

The risk criteria for early-onset neonatal sepsis with GBS are maternal colonization with the organism, gestational age less than 37 weeks, rupture of membranes greater than 12 hours prior to delivery, intra-amniotic infection, intra-partum fever greater than 37.5°C, young maternal age, black race, low maternal levels of GBS-specific anti-capsular antibody, and previous delivery of an infant with invasive GBS disease.[18] The most significant risk factor is maternal colonization with GBS; mothers who are colonized are at a much higher risk for having infants with infection than those with one risk factor but no colonization.[18] Risk factors for late-onset neonatal sepsis with GBS are not well understood. Late-onset sepsis due to GBS is most common in babies who are born prematurely (< 37 weeks), and those whose mothers tested group B strep positive. [18] The current CDC guidelines recommend the screening of all pregnant women between 35 and 37 weeks gestation for GBS; and colonized women should all be offered intrapartum antibiotic prophylaxis (IAP) during labor.[18]

A thorough patient history should be obtained regarding maternal GBS status and risk factors, adequate IAP, and risks for early onset sepsis, in infants presenting with FWS. Late or very late onset sepsis should still be considered as a possible source of infection, regardless of maternal GBS or IAP.

While IAP has dramatically reduced the incidence of perinatal GBS infections, there has been an increase in the number of gram-negative, ampicillin-resistant organisms causing early-onset neonatal sepsis born to mothers who received IAP.[18] Most of the initial studies were small and these infections were found to be limited to preterm or low-birth-weight infants.[18] The recent literature now shows a significant increase in late onset sepsis with *E.coli* in both preterm and term infants, with intrapartum ampicillin exposure determined to be an independent risk factor.[19] Another study found that 53% of the mothers received intrapartum antibiotics, and of those, 70% received ampicillin or penicillin. Risk factors for early onset *E.coli* infection were low gestational age (≤33 weeks), intrapartum fever, and membrane rupture ≥18 hours).[20] Based on expert consensus, it is currently recommended to begin empiric antimicrobial therapy with ampicillin and cefotaxime for infants born to mothers known to be GBS positive with unknown sensitivities or resistant to ampicillin. Ampicillin remains in the treatment

plan because it covers *L. monocytogenes* and GBS. Cefotaxime covers all other targeted organisms with the exception of MRSA.

Infants 29-90 day of age Patients in this age group are also stratified by high and low risk. Low risk patients are most often managed in the outpatient setting because SBI in low-risk patients is minimal (0.67-2.23%).[1,9] While empiric drug therapy is not always necessary, when given, intramuscular ceftriaxone is the most common agent used in the outpatient setting. At a minimum, urine and blood cultures should be taken prior to initiating empiric drug therapy. Some physicians may also choose to perform a lumbar puncture to culture the CSF prior to initiating antibiotic treatment and pending culture results. High-risk patients must be admitted to the hospital for empiric intravenous antibiotics.[1]

The most common organisms identified in patients of this age with SBI are *Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae* type b and non-typeable, *Group B streptococcus,* and *Escherichia coli* (refer to **Table 2** and **Table 3**). The recommended first-line empiric treatment for patients of this age is ceftriaxone. Ceftriaxone has been used safely in this age group in several studies, covers the targeted organisms, and penetrates well into the CSF. [2,7,9,10,12] See **Table 5** for the CSF penetration values of the antibiotics listed in this guideline. Due to the extremely rare occurrence of meningitis due to *Listeria monocytogenes* in the United States, and even lower possibility of infection in infants of this age (i.e. older than 1 month), the use of ampicillin is not necessary unless this particular organism is suspected.[21] Alternatively, cefotaxime, another third generation cephalosporin, can be used.[10] However, ceftriaxone is considered to be equivalent to cefotaxime in terms of activity, and can be dosed once or twice daily vs. four times daily with cefotaxime. When there is concern for infection with MRSA or penicillin-resistant *S.pneumoniae*, the addition of vancomycin to ceftriaxone is preferred.[10] Risk factors for infection with MRSA include close skin-to-skin contact with a person who is colonized with or who has recently been infected with MRSA (including maternal history of mastitis due to known or suspected MRSA), openings in the skin such as cuts or abrasions, exposure to contaminated items and surfaces, crowded living conditions, poor hygiene and those who attend athletic facilities, dormitories, and daycare centers.[22]

It is important to note that at the Dell Children's Medical Center of Central Texas, where most neonatal and pediatric cultures are taken within the Seton Healthcare Network, there have been some recent changes in the resistance patterns to antimicrobials – specifically, MRSA, *S. pneumoniae*, and *H. influenzae* non-typable isolates. Please refer to **Table 6** for specific meningitis and non-meningitis antibiogram data. Due to the dynamic nature of the antibiograms, the antimicrobial resistance patterns may change annually. Consequently, it is strongly recommended that each prescriber take care to reference the most current antibiogram for accurate antimicrobial sensitivity prior to initiating empiric drug therapy.

Table 1. The Four Most Common Strategies for Managing Febrile Infants[2]

	Philadelphia Criteria[5]	Rochester Criteria[6]	Boston Criteria[7]	Pittsburgh Criteria[8]
Age	29-60 days	≤60 days old	28-89 days	≤60 days old
Temperature	≥38.2°C (Rectal)	≥38°C (Rectal)	≥38°C (Rectal)	≥38°C (Site unknown)
History	Not specified	• Term infant • No perinatal antibiotics • No underlying disease • Not hospitalized longer than the mother	• No immunizations within preceding 48 hours • No antimicrobial within 48 hours • Not dehydrated	• Term infant • No underlying disease • No previous hospitalizations • No perinatal antibiotics • No antibiotics in 7 days • No siblings with Group B Strep
Physical Examination	• Well-appearing • Unremarkable examination	• Well-appearing • No ear, soft tissue, or bone infection	• Well-appearing • No ear, soft tissue, or bone infection	• Well-appearing • No focal infection (excluding otitis media)
Lab Parameters (Defines lower risk patients)	• WBC < 15,000/mm^3 • Band-neutrophil ratio <0.2 • UA WBC <10/hpf • Urine Gram stain negative • CSF WBC <8/mm^3 • CSF Gram stain negative • Chest radiograph: no infiltrate • Stool: no blood, few or no WBCs on smear	• WBC >5,000 and <15,000/mm^3 • Absolute band count <1,500/ mm^3 • UA WBC ≤10/hpf • Stool smear ≤5 WBC/hpf	• CSF <10/mm^3 • UA WBC <10/hpf • Chest radiograph: no infiltrate • WBC < 20,000/mm^3	• WBC 5,000 to 15,000/mm^3 • Absolute band count <1,500/ mm^3 • Enhanced urinalysis WBC ≤9/mm^3 and negative gram stain • CSF WBC <5/mm^3 and negative gram stain • Stool WBC <5 per field in infants with diarrhea • Chest radiograph: no infiltrate
Higher Risk Patients	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics
Lower Risk Patients	• Home • No antibiotics • Follow-up required	• Home • No antibiotics • Follow-up required	• Home • Empiric antibiotics • Follow-up required	• Home • No antibiotics • Follow-up required
Reported Statistics	Sensitivity 98% (92-100%) Specificity 42% (38-46%) PPV[a] 14% (11-17%) NPV[a] 99.7% (98-100%)	Sensitivity 92% (83-97%) Specificity 50% (47-53%) PPV[a] 12.3% (10-16%) NPV[a] 98.9% (97-100%)	Sensitivity – Not available Specificity 94.6% PPV[a] – Not available NPV[a] – Not available	Sensitivity – 100% (89.7-100%) Specificity – Not available PPV[a] – Not available NPV[a] – 100% (96.7-100%)

Adapted from:

1. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001; 108: 311-6.
2. Herr SM, Wald ER, Pitetti RD, et al. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics*. 2001; 108: 866-71.

[a] PPV = Positive Predictive Value, NPV = Negative Predictive Value

Prepared by Ronda Machen, PharmD
Reviewed and edited by PCRS (Mark Shen, MD, Lynn Campbell, MD, Lynn Thoreson, DO), DCMC ED (Eric Higginbotham, MD), and Pediatric Infectious Disease (Natascha Ching, MD, Sarmistha Hauger, MD, Marisol Fernandez, MD).
Last Revised 2/6/11

Table 2. Organisms Identified in Patients with Bacterial Illness in Studies of the Four Most Common Strategies for Managing Febrile Infants[2]

	Philadelphia Criteria[5]	**Rochester Criteria[6]**	**Boston Criteria[7]**	**Pittsburgh Criteria[8]**
Age	29-60 days	≤60 days old	28-89 days	≤60 days old
UTI	*Escherichia coli* (N=17) *Enterococcus* sp. (N=2) *Group B streptococcus* (N=2) *Klebsiella* sp. (N=1) *Staphylococcus epidermidis* (N=1) *Lactobacillus* sp. (N=1)	*Escherichia coli* (N=19) With bacteremia (N=2) *Group B streptococcus* (N=1) *Enterobacter cloacae* (N=2) UTI dx by UA, no cx (N=12)	*Escherichia coli* (N=3) *Streptococcus faecalis* (N=1) *Group B streptococcus* (N=1) *Klebsiella pneumoniae* (N=1) *Pseudomonas fluorescens* (N=1) *Staphylococcus aureus* (N=1)	*Escherichia coli* (N=27) With bacteremia (N=4) *Klebsiella pneumoniae* (N=1) *Pseudomonas aeruginosa* (N=1)
Respiratory	CXR only	CXR with infiltrate and *Streptococcus pneumoniae* antigen positive (N=1)	*Bordetella pertussis* (N=2)	CXR only, culture negative (N=8) *Chlamydia trachomatis* (N=1) *Bordetella pertussis* (N=1)
Bacteremia	*Group B streptococcus* (N=10) *Haemophilus influenzae* type b (N=4) *Streptococcus pneumoniae* (N=2) *Salmonella* sp. (N=2) *Listeria monocytogenes* (N=1)	*Neisseria meningitidis* (N=1) *Yersinia enterocolitica* (N=1) *Staphylococcus aureus* (N=1) Unknown organism (N=8)	*Group B streptococcus* (N=2) *Escherichia coli* (N=2) *Staphylococcus aureus* (N=1) *Streptococcus pneumoniae* (N=1) *Salmonella* sp. (N=1) *Haemophilus influenzae* type b (N=1) *Neisseria meningitidis* (N=1)	*Streptococcus pneumoniae* (N=1) *Streptococcus agalactiae* (N=1) *Staphylococcus aureus* (N=1)
Meningitis	*Haemophilus influenzae* type b (N=3) Group B streptococcus (N=2) *Streptococcus pneumoniae* (N=2) *Escherichia coli* (N=1) *Listeria monocytogenes* (N=1)	None	None	*Streptococcus pneumoniae* (N=1) *Enterobacter cloacae* (N=1)
Gastroenteritis	*Salmonella* sp. (N=12) *Yersinia enterocolitica* (N=1)	*Salmonella* sp. (N=4) *Yersinia enterocolitica* (N=1)	*Salmonella* sp. (N=8) *Campylobacter jejuni* (N=1) *Yersinia enterocolitica* (N=1)	*Campylobacter jejuni* (N=1)
Skin or soft tissue infection	*Staphylococcus aureus* (N=5) Unknown organism (N=1)	*Staphylococcus aureus* (N=6) *Escherichia coli* (N=3) *Group B streptococcus* (N=1) *Neisseria sp.* (N=1) Unknown organism (N=7)	None	None
SBI/N for each study	N = 64/747 (8.6%)	N = 66/1005 (6.6%)	N = 29/503 (5.8%)	N = 41/404 (10.1%)

Table 3. Guidelines for Initial Empiric Treatment of Term Infants with Fever without a Source or Suspected Serious Bacterial Infection

Age	Targeted Organisms[2,5-8,12,21]	Risk[b]	Treatment[c 2,10,23,24,25,26,27,28,29,30,31,32]	Alternatives[e 2,10,24,25,26,27,33]
0-28 days	*Escherichia coli* *Group B streptococcus* *Klebsiella sp.* *Listeria monocytogenes*	All patients	Term infants ≤ 7 days of age: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[d] Term infants over 7 days of age: Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[d] ▪ If CSF pleocytosis suggestive of viral meningoencephalitis, add Acyclovir 20 mg/kg/dose IV q8h and send CSF HSV PCR	**If CSF pleocytosis, CSF gram stain shows GNR, or mother known to be GBS positive (with unknown sensitivities or resistance to ampicillin): Ampicillin + Cefotaxime** Term infants ≤ 7 days of age: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Term infants over 7 days of age: Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Cefotaxime 50 mg/kg/dose IV q6h x 6 doses **If CSF pleocytosis, gram stain shows GPC, or concern for MRSA[e]: Vancomycin + Ampcillin + Cefotaxime** Term infants ≤ 7 days of age: Vancomycin 15 mg/kg/dose IV q8h x 5 doses[f] + Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Term infants over 7 days of age: Vancomycin 15 mg/kg/dose IV q6h x 6 doses[f] + Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Cefotaxime 50 mg/kg/dose IV q6h x 6 doses
29-90 days	*Escherichia coli* *Group B streptococcus* *Haemophilus influenzae* type b and non-typeable *Neisseria meningitidis* *Streptococcus pneumoniae*	Low Risk	No antibiotics Close observation in house	These patients may be managed as outpatients with careful observation and with or without antimicrobial therapy.
		High Risk	Ceftriaxone 50 mg/kg/dose IV q12h x 3 doses	If CSF pleocytosis, gram stain shows GPC, concern for MRSA[e] or resistant *S.pneumoniae*, add Vancomycin 15 mg/kg/dose IV q6h[f]

[b] See Table 7 for risk criteria
[c] If cultures positive/unknown, or patient ill appearing, antibiotics should be continued and streamlined to appropriate treatment based on ID and sensitivity of microorganism(s). Prior to discontinuing antibiotics, the lab must have checked urine and CSF cultures twice with negative results (the first read no earlier than 8-12 hrs after plating).
[d] Clinical judgment should be exercised regarding antimicrobial levels. No gentamicin levels unless continued for more than 2 doses, SCr above 0.9 mg/dL or UOP below 2 mL/kg/hr. When more than 2 doses planned, check trough and peak around the 2nd dose or around the next dose if the 2nd dose has already been given.
[e] Obtain history of MRSA, risk factors include: close skin-to-skin contact with a person who is colonized with or recently infected with MRSA (including maternal history of mastitis due to known or suspected MRSA), openings in the skin such as cuts or abrasions, exposure to contaminated items and surfaces, crowded living conditions, poor hygiene and those who attend athletic facilities, dormitories, and daycare centers.
[f] Clinical judgment should be exercised regarding antimicrobial levels. No vancomycin levels unless continued for more than 6 doses. When more than 6 doses planned, check trough and peak around the 3rd dose or around the next dose if the 3rd dose has already been given.

Prepared by Ronda Machen, PharmD
Reviewed and edited by PCRS (Mark Shen, MD, Lynn Campbell, MD, Lynn Thoreson, DO), DCMC ED (Eric Higginbotham, MD), and Pediatric Infectious Disease (Natascha Ching, MD, Sarmistha Hauger, MD, Marisol Fernandez, MD).
Last Revised 2/6/11

Table 4. Guidelines for Treatment of Preterm Infants (less than 37 wks) with Fever without a Source or Suspected Serious Bacterial Infection

Age	Targeted Organisms[13]	Risk[g]	Treatment[h 23-32,34]	Alternatives[i 19,27,34]
0-28 days	*Escherichia coli* *Group B streptococcus* *Haemophilus influenzae* type b and non-typeable Coagulase-negative staphylococcus	All patients	Preterm infants ≤ 7 days of age and ≤ 2000 g: Ampicillin 50 mg/kg/dose IV q12h x 3 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[i] Preterm infants ≤ 7 days of age and > 2000 g: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[i] Preterm infants > 7 days of age and ≤ 2000 g: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[i] Preterm infants > 7 days of age and > 2000 g: Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Gentamicin 4 mg/kg/dose q24h x 2 doses[i] ▪ If CSF pleocytosis suggestive of viral meningoencephalitis, **add** Acyclovir 20 mg/kg/dose IV q8h and send CSF HSV PCR	**If CSF pleocytosis, CSF gram stain shows GNR, or mother known to be GBS positive (with unknown sensitivities or resistance to ampicillin):** **Ampicillin + Cefotaxime** Preterm infants ≤ 7 days of age and ≤ 2000 g: Ampicillin 50 mg/kg/dose IV q12h x 3 doses + Cefotaxime 50 mg/kg/dose IV q12h x 3 doses Preterm infants ≤ 7 days of age and > 2000 g: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Preterm infants > 7 days of age and ≤ 2000 g: Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Preterm infants > 7 days of age and > 2000 g: Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Cefotaxime 50 mg/kg/dose IV q6h x 6 doses **If CSF pleocytosis, gram stain shows GPC, or concern for MRSA[j]:** **Vancomycin + Cefotaxime** Preterm infants ≤ 7 days of age and ≤ 2000 g: Vancomycin 15 mg/kg/dose IV q12h x 3 doses[k] + Ampicillin 50 mg/kg/dose IV q12h x 3 doses + Cefotaxime 50 mg/kg/dose IV q12h x 3 doses Preterm infants ≤ 7 days of age and > 2000 g: Vancomycin 15 mg/kg/dose IV q8h x 5 doses[k] + Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Preterm infants > 7 days of age and ≤ 2000 g: Vancomycin 15 mg/kg/dose IV q8h x 5 doses[k]+ Ampicillin 50 mg/kg/dose IV q8h x 5 doses + Cefotaxime 50 mg/kg/dose IV q8h x 5 doses Preterm infants > 7 days of age and > 2000 g: Vancomycin 15 mg/kg/dose IV q8h x 5 doses[k] + Ampicillin 50 mg/kg/dose IV q6h x 6 doses + Cefotaxime 50 mg/kg/dose IV q6h x 6 doses

[g] See Table 7 for risk criteria
[h] If cultures positive/unknown, or patient ill appearing, antibiotics should be continued and streamlined to appropriate treatment based on ID and sensitivity of microorganism(s). Prior to discontinuing antibiotics, the lab must have checked urine and CSF cultures twice with negative results (the first read no earlier than 8-12 hrs after plating).
[i] Clinical judgment should be exercised regarding antimicrobial levels. No gentamicin levels unless continued for more than 2 doses, SCr above 0.9 mg/dL or UOP below 2 ml/kg/hr. When more than 2 doses planned, check trough and peak around the 2nd dose or around the next dose if the 2nd dose has already been given.
[j] Obtain history of MRSA, risk factors include: close skin-to-skin contact with a person who is colonized with or recently infected with MRSA (including maternal history of mastitis due to known or suspected MRSA), openings in the skin such as cuts or abrasions, exposure to contaminated items and surfaces, crowded living conditions, poor hygiene and those who attend athletic facilities, dormitories, and daycare centers.
[k] Clinical judgment should be exercised regarding antimicrobial levels. No vancomycin levels unless continued for more than 6 doses. When more than 6 doses planned, check trough and peak around the 3rd dose or around the next dose if the 3rd dose has already been given.

Prepared by Ronda Machen, PharmD
Reviewed and edited by PCRS (Mark Shen, MD, Lynn Campbell, MD, Lynn Thoreson, DO), DCMC ED (Eric Higginbotham, MD), and Pediatric Infectious Disease (Natascha Ching, MD, Sarmistha Hauger, MD, Marisol Fernandez, MD).
Last Revised 2/6/11

Table 5. Cerebrospinal Fluid Penetration

Drug	CSF % [l]	CSF Level Potentially Therapeutic [m]
Ampicillin	13-14	Yes
Cefotaxime	10	Yes
Ceftriaxone	8-16	Yes
Gentamicin	0-30	No
Vancomycin	7-14	Optimize trough levels (e.g. serum trough level 15-20 mcg/mL) to promote adequate drug penetration into the CSF

Adapted from Gilbert DN, Moellering RC, Eliopoulos GM, Chambers HF, Saag MS. The Sanford Guide to Antimicrobial Therapy. 39th Ed. Sperryville, PA: Antimicrobial Therapy Inc., 2009.

[l] CSF levels with inflammation

[m] Based on drug dose and organ susceptibility; CSF concentration ideally $\geq$ 10 above MIC.

Table 6. Antibiogram Data for Dell Children's Medical Center, July 2007 to June 2009 [n,o,p]

Year	July 2007 to June 2008											July 2008 to June 2009										
Organism	# Isolates	Ampicillin	Cefotaxime (M)	Cefotaxime (N)	Ceftriaxone (M)	Ceftriaxone (N)	Gentamicin	Ciprofloxacin	Levofloxacin	Clindamycin	Vancomycin	# Isolates	Ampicillin	Cefotaxime (M)	Cefotaxime (N)	Ceftriaxone (M)	Ceftriaxone (N)	Gentamicin	Ciprofloxacin	Levofloxacin	Clindamycin	Vancomycin
MSSA	441						97			86	100	474	11					98			88	100
MRSA	712						97			90	100	743						98			90	100
S. pneumoniae	99		95	99	95	99				76	100	109		77	91	77	97				72	100
H. influenzae	1											5										
E. coli	914	41		99		98	96					1150	44		100		98	94				
Salmonella sp.																						
Shigella sp.																						

Adapted from Antibiogram Data (FY 08), July 2007-June 2008 and (FY 09), July 2008-June 2009. Dell Children's Medical Center of Center exas, Austin, Texas.

[n] Data for H. influenzae, Salmonella, and Shigella is pending and will be included when available from the lab.
[o] M = % susceptible using meningitis breakpoint of MIC ≤ 0.5, N = % susceptible using nonmeningitis breakpoint of MIC ≤ 1.
[p] Local and regional differences in sensitivity should be considered regarding antimicrobial susceptibility.

Prepared by Ronda Machen, PharmD
Reviewed and edited by PCRS (Mark Shen, MD, Lynn Campbell, MD, Lynn Thoreson, DO), DCMC ED (Eric Higginbotham, MD), and Pediatric Infectious Disease (Natascha Ching, MD, Sarmistha Hauger, MD, Marisol Fernandez, MD).
Last Revised 2/6/11

Table 7. Risk criteria for Term Infants with Fever without a Source or Suspected Serious Bacterial Infection[35]

0-89 days	**Low-risk clinical criteria**	
	• Well-appearing • Previously healthy[q] • No focal source of infection	
	Low-risk laboratory criteria	
	Urinalysis	• ≤ 10 WBC/hpf • No bacteria on Gram stain (if available)
	CBC	• WBC 5,000 to 15,000/mm^3 • ≤ 1,500 band cells/mm^3
	Chest radiograph (IF obtained)	• No evidence of discrete infiltrate
	Stool smear (when diarrhea is present)	• Negative for blood • ≤ 5 WBC/hpf
	High-risk clinical criteria	
	• Ill-appearing • Known Group B Strep exposure (based on mother's history) or unknown history	
	High-risk laboratory criteria	
	CBC	• WBC > 15,000/mm^3
	CSF	• Pleocytosis • Organisms on Gram stain • Unable to obtain CSF fluid

[q] Born at term (≥ 37 weeks gestation), not treated for unexplained hyperbilirubinemia, not hospitalized longer than the mother, no current or previous antimicrobial therapy, no previous hospitalization, and no chronic or underlying illness

References:

[1] Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann* 2008; 37: 673-9.
[2] Baraff LJ, Bass JW, Fleisher GR, et al. Practice guideline for the management of infants and children 1 to 36 months of age with fever without source. *Ann Emerg Med* 1993: 22: 1198-1210.
[3] Falzon A, Grech V, Caruana B, et al. How reliable is axillary temperature measurement? *Acta Paediatr* 2003;92:309-13.
[4] Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics* 2001; 108: 311-6.
[5] Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med* 1993; 329: 1437-41.
[6] Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection – An appraisal of the Rochester criteria and implications for management. *Pediatrics* 1994; 94: 390-6.
[7] Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr* 1992; 120: 22-7.
[8] Herr SM, Wald ER, Pitetti RD, et al. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics* 2001; 108: 866-71.
[9] Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: Review of the literature. *Pediatrics* 2010;125:228-33.
[10] Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis* 2010; 10:32-42.
[11] Antibiogram Data (FY 09), July 2008-June 2009. Dell Children's Medical Center of Center Texas, Austin, Texas.
[12] Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; 39: 1267-84.
[13] Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med* 2002;347:240-7.
[14] Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;110:285-291.
[15] Muller-Pebody B, Johnson AP, Heath PT, et al. Empirical treatment of neonatal sepsis: Are the current guidelines adequate. *Arch Dis Child Fetal Neonatal Ed* 2010;F2-5.
[16] Clark RH, Bloom BT, Spitzer AR, et al. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk of sepsis is associated with an increased risk of neonatal death. *Pediatrics* 2006;117:67-74.
[17] De Man P, Verhoeven BA, Verbrugh HA, et al. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet* 2000;355:973-8.
[18] Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *MMWR* 2010;59(No. RR-10):1-32.
[19] Bizzarro MJ, Dembry L, Baltimore RS, et al. Changing patters in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics* 2008;121:689-95.
[20] Schrag SJ, Hadler JL, Arnold KE, et al. Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use. *Pediatrics* 2006;118:570-6.
[21] Gilbert DN, Moellering RC, Eliopoulos GM, Chambers HF, Saag MS. The Sanford Guide to Antimicrobial Therapy. 39th Ed. Sperryville, PA: Antimicrobial Therapy Inc., 2009.
[22] Centers for Disease Control and Prevention. People at risk of acquiring MRSA infections. http://www.cdc.gov/mrsa/riskfactors/index.html. Last accessed December 28, 2010.
[23] Taketomo CK, Hodding JH, Kraus DM. Pediatric Dosage Handbook. 15th Ed. Hudson, OH: Lexi-Comp, 2008-2009.
[24] Miron D. Once daily dosing of gentamicin in infants and children. *Pediatr Infect Dis J* 2001;20:1169-73.
[25] Kaplan RL, Harper MB, Baskin MN, et al. Time to detection of positive cultures in 28- to 90-day-old febrile infants. *Pediatrics* 2000;106:1-4.
[26] Garcia-Prats JA, Cooper TR, Schneider VF, et al. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. *Pediatrics* 2000; 105: 523-7.
[27] Rao SC, Ahmed M, Hagan R. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. *Cochrane Database Syst Rev* 2006, Issue 1. Art. No.: CD005091. DOI: 10.1002/14651858.CD005091.pub2.
[28] Nielsen EI, Sandstrom M, Honore PH, et al. Developmental pharmacokinetics of gentamicin in preterm and term neonates. *Clin Pharmacokinet* 2009;48:253-263.
[29] Stolk LM, Degraeuwe PL, Nieman FH et al. Population pharmacokinetics and relationship between demographic and clinical variables and pharmacokinetics of gentamicin in neonates. *Ther Drug Monit* 2002;24:527-531.
[30] Serane TV, Zengeya S, Penford G, et al. Once daily dose gentamicin in neonates – is our dosing correct? *Acta Paediatr* 2009;98:1100-1105.
[31] Agarwal G, Rastogi A, Pyati S, et al. Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants ≥2500g. *J Perinatol* 2002;22:268-274.
[32] Ohler KH, Menke JA, Fuller L. Use of higher dose extended interval dosing aminoglycosides in a neonatal intensive care unit. *Am J Perinatol* 2000;17:285-290.
[33] Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. *Clin Infect Dis* 2011; 52:e18-e55.
[34] Young TE, Mangum B. (2008). Neofax 2008. 21st Ed. Montvale, NJ: Thomson Reuters.
[35] FUS Team, Cincinnati Children's Hospital Medical Center: Evidence-based clinical care guideline for fever of uncertain source in infants 60 days of age or less, http://www.cincinnatichildren.org/svc/alpha/h/health-policy/ev-based/default.htm, Guideline 02, pages 1-14, October 2010.