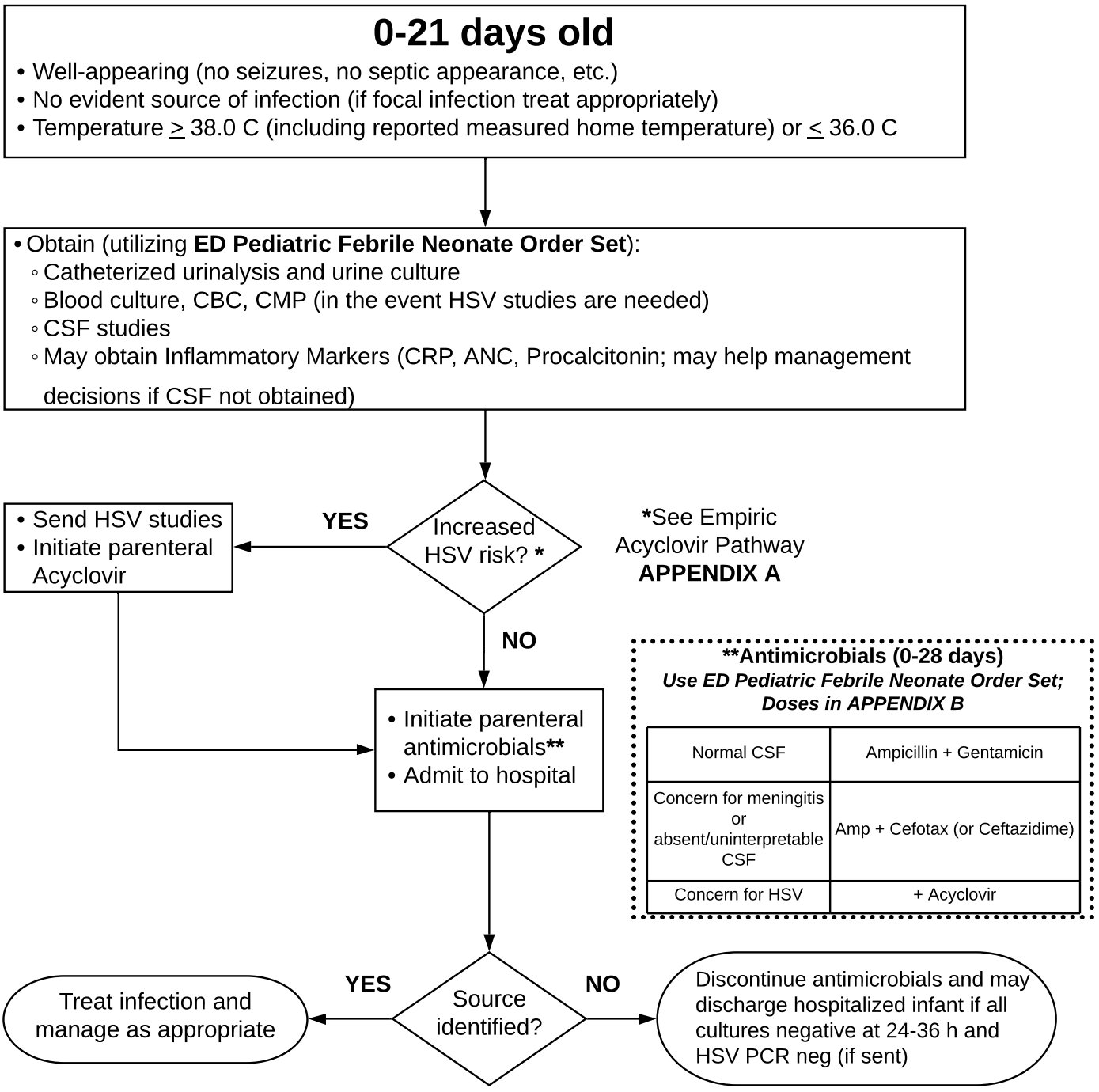
UNC Children's Febrile Neonate/Infant Clinical Pathways
0-21 days old, 22-28 days old, & 29-60 days old

The following information is intended as a guildeline for the management of well-appearing febrile neonates and infants. Preterm infants (< 37 weeks gestation), those with a complicated perinatal course or chronic condition, or recent antibiotic use are considered high-risk and fall out of the scope of this pathway.
Management of your patient may require a more individualized approach.
Background, specific clinical scenario rationale, antimicrobial dosages, and references included in **APPENDIX B**.

0-21 days old

- Well-appearing (no seizures, no septic appearance, etc.)
- No evident source of infection (if focal infection treat appropriately)
- Temperature ≥ 38.0 C (including reported measured home temperature) or ≤ 36.0 C



****Antimicrobials (0-28 days)**
Use ED Pediatric Febrile Neonate Order Set; Doses in APPENDIX B

Normal CSF	Ampicillin + Gentamicin
Concern for meningitis or absent/uninterpretable CSF	Amp + Cefotax (or Ceftazidime)
Concern for HSV	+ Acyclovir

Developed by Pediatric Hospital Medicine, Pediatric Emergency Medicine, Pediatric Infectious Disease, and Pediatric Pharmacy
Adapted from Pantell RH, Roberts KB, Adams WG et al. Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. *Pediatrics.* 2021
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Updated: 1/14/22

22 to 28 days old

- Well-appearing (no seizures, no septic appearance, etc.)
- No evident source of infection (if focal infection treat appropriately)
- Temperature ≥ 38.0 C (including reported measured home temperature) or ≤ 36.0 C

- Obtain (utilizing **ED Pediatric Febrile Neonate Order Set**):
  - Catheterized urinalysis and urine culture
  - Blood culture
  - Inflammatory Markers (Temperature, CRP, ANC, Procalcitonin)
    - Abnormal
      - Temp > 38.5 C
      - CRP >20 mg/L
      - ANC >4000 mm3
      - Procalcitonin > 0.5 ng/mL
  - If increased HSV risk refer to management on Empiric Acyclovir Pathway (**Appendix A**)

Abnormal Inflammatory Markers or UA?

YES → Perform LP

NO → May perform LP but not required

Suggested approach
If IMs and UA are both normal LP is not required (unless patient desires to be discharged to home)

LP Performed?

YES → CSF Interpretable and no pleocytosis

NO → Admit to hospital without antimicrobials

NO (*ABNORMAL CSF or uninterpretable*)

YES (*NORMAL CSF*) → Observation at home?

Consider
If UA and inflammatory markers normal, and unsuccessful LP consider observing in hospital and withholding abx

- Give parenteral antimicrobials**
- Admit to hospital

YES →
- Give parenteral antimicrobials (Ceftriaxone)
- Observe at home
- F/u in 24 hours

NO →
- Give parenteral antimicrobials**
- Admit to hospital

Source identified?

YES → Treat infection and manage as appropriate

NO → Discontinue antimicrobials and may discharge hospitalized infant if all cultures negative at 24-36 h and HSV PCR neg (if sent)

****Antimicrobials (0-28 days)**

Use ED Pediatric Febrile Neonate Order Set; Doses in APPENDIX B

Normal CSF	Ampicillin + Gentamicin
Concern for meningitis or absent/uninterpretable CSF	Amp + Cefotax (or Ceftazidime)
Concern for HSV	+ Acyclovir

Who can be observed at home?

- Normal UA
- Normal Inflammatory Markers
- Normal CSF (or entero positive)
- Availability of 24 hour PCP follow up

29 to 60 days old

- Well-appearing (no seizures, no septic appearance, etc.)
- No evident source of infection (if focal infection treat appropriately)
- Temperature ≥ 38.0 C (including reported measured home temperature)

- Obtain (utilizing **ED Pediatric Febrile Neonate Order Set**):
  - Catheterized urinalysis and urine culture
  - Blood culture
  - Inflammatory Markers (Temperature, CRP, ANC, Procalcitonin)
    - Abnormal
      - Temp > 38.5 C
      - CRP >20 mg/L
      - ANC >4000 mm3
      - Procalcitonin > 0.5 ng/mL
  - If increased HSV risk refer to management on Empiric Acyclovir Pathway (**Appendix A**)

Suggested approach
If only a single IM is mildly abnormal. consider engaging family in shared decision making regarding need for LP vs. observation in the hospital off antibiotic

Abnormal Inflammatory Markers?

YES → May perform LP

NO → **Urinalysis abnormal?**

Urinalysis abnormal?

YES
- Administer antimicrobials***
- May observe closely at home
- F/u in 12-24 hours

NO
- Withhold antimicrobials
- Observe at home
- F/u PCP within 24-36 hours

May perform LP → CSF Interpretable and no pleocytosis

YES (*NORMAL CSF*) → Observation at home?

NO (*ABNORMAL CSF or uninterpretable*)
- Give parenteral antimicrobials**
- Admit to hospital

Consider
For a single, mildly elevated IM and unsuccessful LP consider observing in hospital and withholding antibiotic

Observation at home?

YES
- Give parenteral antimicrobials** (Ceftriaxone)
- Observe at home
- F/u in 24 hours

NO
- Give parenteral antimicrobials**
- Admit to hospital

***First dose **Ceftriaxone** if IV access; **Cephalexin** appropriate for remainder of treatment course. Consult PED UTI Clinical Algorithm for details:* https://tinyurl.com/vpz7s

Source identified?

YES → Treat infection and manage as appropriate

NO → Discontinue antimicrobials and may discharge hospitalized infant if all cultures negative at 24-36 h and HSV PCR neg (if sent)

****Antimicrobials (≥ 29 days)**

Use ED Pediatric Febrile Neonate Order Set; Doses in APPENDIX B

Normal CSF	Ceftriaxone
Concern for meningitis or absent/uninterpretable CSF	Ceftriaxone +/- Vancomycin
Concern for HSV	+ Acyclovir

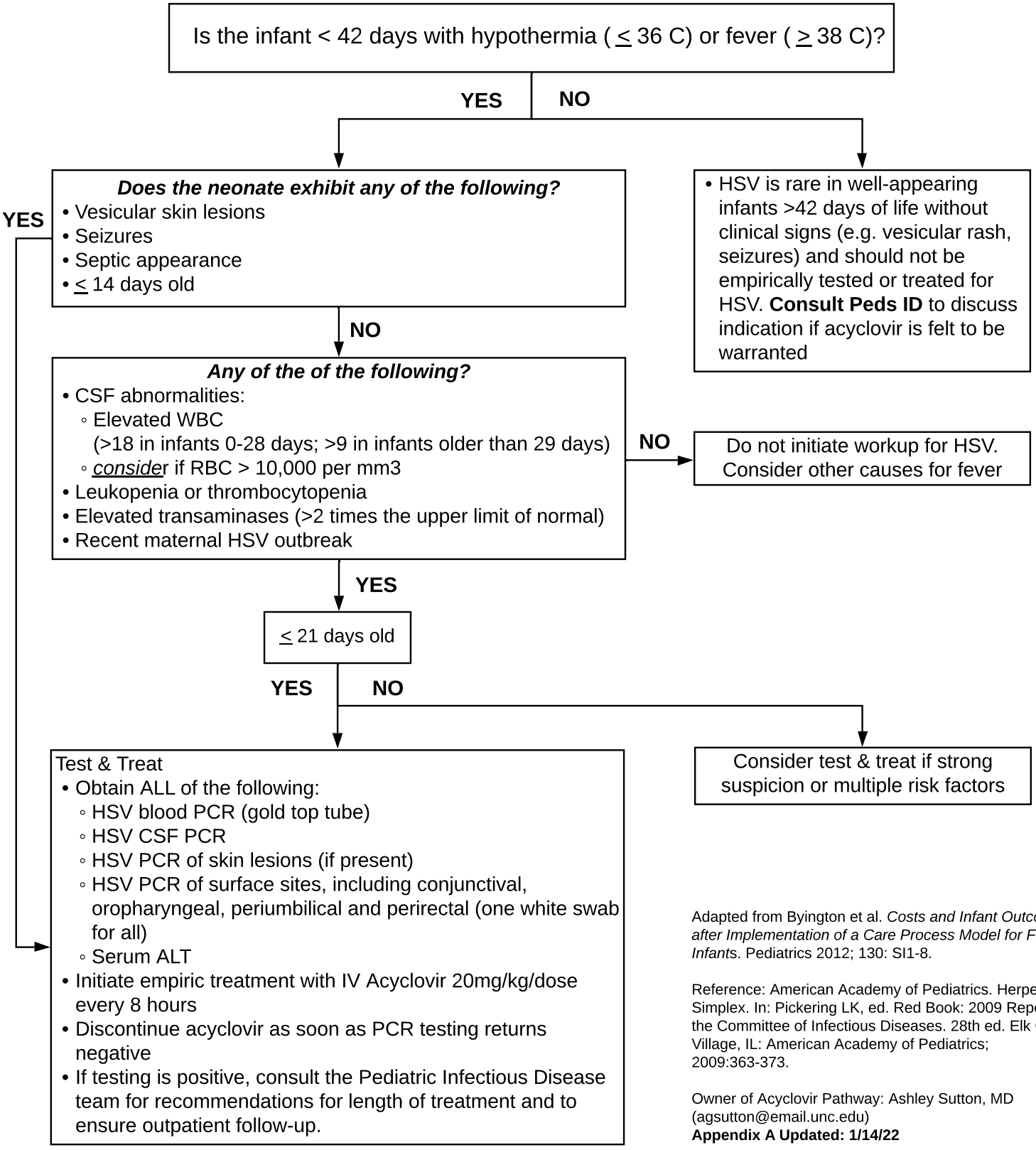
Who can be observed at home?

- Normal UA
- Normal IMs
- Normal CSF (or entero positive)
- Availability of 24 hour PCP follow up

APPENDIX A

Recommendations for the Use of Empiric Acyclovir in Febrile/Hypothermic Infants Younger than 90 Days

Disclaimer: The following information is intended as a guideline for the use of empiric acyclovir in infants. Management of your patient may require a more individualized approach



Adapted from Byington et al. *Costs and Infant Outcomes after Implementation of a Care Process Model for Febrile Infants*. Pediatrics 2012; 130: SI1-8.

Reference: American Academy of Pediatrics. Herpes Simplex. In: Pickering LK, ed. Red Book: 2009 Report of the Committee of Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:363-373.

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Appendix A Updated: 1/14/22

Appendix B

Background and Introduction

This clinical pathway for the evaluation and management of well-appearing febrile infants at UNC Hospitals was adapted from the 2021 AAP Guidelines by a multidisciplinary group of Pediatric Emergency, Hospital Medicine, and Infectious Disease physicians. A standardized approach is important as the clinical exam alone cannot reliably distinguish between low- and high-risk infants. Around 10-12% of febrile infants ≤60 days of age will have a urinary tract infection (10%), bacteremia (2%), or meningitis (0.5%), with the latter two often referred to together as invasive bacterial infections (IBI).[1,2] The risk of IBI in particular is age-dependent and is 2-4x greater among those in the first 3 weeks of life, therefore, a complete evaluation with empiric treatment is recommended for those ≤21 days, while separate tiered approaches are recommended for infants 22-28 days and ≥29 days of age. This document represents the recommended approach for children treated at UNC hospitals; however, treatment decisions may be individualized based on unique patient circumstances including clinician and family level of risk tolerance, and should involve families in shared decision-making when appropriate.

Inflammatory Markers

Inflammatory markers (IMs) are crucial for determining whether a febrile infant classifies as low-risk. The WBC count has traditionally been used despite its poor discrimination with an area under the curve (AUC) of 0.48 for IBI, indicating that it performs no better than random chance and so is *not* recommended to rule-in or rule-out infection.[3] Procalcitonin has emerged as the best independent predictor of IBI with an AUC of 0.91, is highly sensitive and specific - 85% each - and is recommended for risk-stratification in infants 22-60 days of age.[2,3] Other IMs recommended for use include CRP and ANC - AUC 0.77 and 0.61, respectively - or a temperature ≥38.5° C. In general, a single abnormal IM places a patient in the high-risk category; however, no IM is 100% sensitive or specific. Therefore, for older infants (≥29 days), clinicians may consider multiple IMs in combination along with the degree of abnormality.

Bronchiolitis and Respiratory Viral Testing

Infants with clinical bronchiolitis are excluded from this pathway and should be managed accordingly. Evidence suggests that concomitant IBI is rare in children with bronchiolitis,[4] however, some clinicians opt to perform a work-up for young febrile infants with bronchiolitis, particularly in the ≤28 day group. Evidence for the utility of respiratory viral testing to aid in the management of young febrile infants is evolving, but should not preclude entry into the pathway or affect management of infants ≤28 days of age. Virus-positive Infants 29-60 days old are at lower risk for IBI, and so targeted, seasonal flu and RSV testing may be considered to help individualize evaluation and management decisions in the second month of life.[1,2]

Urinary Tract Infection After the First Month of Life

UTI is the most common bacterial infection in young febrile infants. Recent data suggests that the presence of UTI does not increase the risk of meningitis among 29-60 day olds,[5] while no cases of missed meningitis occurred among infants treated for a positive UA without CSF testing in a large, multicenter study.[6] Given these findings and accumulating evidence for the efficacy of oral antibiotics, well-appearing febrile infants in the second month of life with a positive UA and negative inflammatory markers are at low risk for IBI, do not require LP, and are recommended for outpatient management.[2]

Home Observation

Observational studies have shown that a substantial minority of young febrile infants are not hospitalized after initial evaluation, and that readmissions related to delays in treating bacterial infections are rare.[7,8] Therefore, children 22-28 days old with negative inflammatory markers and reassuring CSF studies may be managed at home after receiving a dose of ceftriaxone as long as appropriate family education is provided and follow-up plans within 24 hours are ensured.[2] Children ≥29 days old are also eligible for home observation, but unlike those in the 4th week of life do not require an LP if all IMs are normal (and may not require antibiotics depending on the UA results), or may be eligible if only a single IM is mildly elevated and CSF parameters are normal.

Antimicrobials

Empiric antimicrobial recommendations consider patient age and suspected source, and are targeted to the most common bacterial pathogens in this patient population - Group B strep and E. coli. Patients ≤28 days with normal CSF studies should be treated with ampicillin plus gentamicin; however, if meningitis is suspected (or cannot be ruled out), then a third-generation cephalosporin is required for improved CSF penetration. Patients >28 days may be treated with ceftriaxone, with vancomycin added to cover resistant pneumococcus for suspected meningitis. Specific HSV testing and treatment recommendations are shown in Appendix A, although in general occurs most frequently in patients ≤21 days while acyclovir should also be considered for suspected meningitis in patients ≤42 days. Dosing recommendations are shown below:

	Meningitis suspected	**No meningitis**
Ampicillin	<= 7 days: 100 mg/kg q8h 8-60 days: 75 mg/kg q6h	<=28 days: 50 mg/kg q8h 29-60 days: 50 mg/kg q6h
Gentamicin		4 mg/kg PLUS Order Pharmacy Consult to Dose & Monitor
Cefotaxime	<=7 days: 50 mg/kg q8h 8-60 days: 50mg/kg q6h	
Ceftazidime	50 mg/kg q8h	
Ceftriaxone	100 mg/kg q24h	50 mg/kg q24h
Cephalexin		75 mg/kg/day divided TID
Vancomycin	15 mg/kg PLUS Order Pharmacy Consult to Dose & Monitor	
Acyclovir	20 mg/kg q8h	20 mg/kg q8h
Note: these recommendations are for infants ≤60 days of age and >34 weeks GA at birth		

References

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