Neonatal Fever (0-30 days old): ED Phase

Executive Summary | Test Your Knowledge | Explanation of Evidence Ratings | Summary of Version Changes

PHASE I (E.D.)

Inclusion Criteria
- Fever ≥38 C or hypothermia <36 C in children <30 days of age

Exclusion Criteria
- Patients currently admitted to ICU or admitted >3 days
- known immunodeficiency or cancer
- patients with central venous catheters or VP shunts

! Other differential diagnosis for severely ill neonates

! Considerations for Pretreated CSF

Begin clinical assessment

Focal Infection (e.g., omphalitis, pneumonia) — Yes → **Off Pathway**

No

- UA, urine culture
- CBC with diff, Blood culture
- CSF studies
- HSV work up if indicated (see box)
- CXR and respiratory viral panel (if respiratory symptoms)
- Stool culture (if diarrhea)

CSF Normative values
0-30 days: CSf WBC <20/mm3
31-60 days CSF WBC <10/mm3

HSV work up indications
Perform complete work up and begin acyclovir for any of the following:

Historical and clinical features
- Severe illness
- hypothermia
- lethargy
- seizures
- hepatosplenomegaly
- Postnatal HSV contact
- Vesicular rash
- Conjunctivitis
- Interstitial pneumonitis

Laboratory features
- Thrombocytopenia
- CSF pleocytosis >20 WBC/mm^3 without clear bacterial infection (e.g., + Gram stain)

! If CSF pleocytosis add entero / parechovirus PCR; defer LP if unstable.

Begin empiric treatment
- Ampicillin and cefotaxime
- Acyclovir if HSV work up performed
- Admit all patients

! In well-appearing infants with multiple maternal HSV risk factors, consider HSV work up

Go to Inpatient Phase 0-30d

Last Updated: xx/xx/xxxx
Valid until:xx/xx/xxxx

Neonatal Fever (31-60 days old): ED Phase

Executive Summary | Explanation of Evidence Ratings | Test Your Knowledge | Summary of Version Changes

PHASE I (E.D.)

Inclusion Criteria
- Fever ≥38 C or hypothermia <36 C in children 31-60 days of age

Exclusion Criteria
- Patients currently admitted to ICU or admitted >3 days
- known immunodeficiency or cancer
- patients with central venous catheters or VP shunts

! If CSF pleocytosis add entero / parechovirus PCR; defer LP if unstable.

! Considerations for Pretreated CSF

Begin clinical assessment

Focal Infection (e.g., omphalitis, pneumonia)
- Yes → **Off Pathway**
- No ↓

Low Risk Criteria
- Well-appearing
- Previously healthy
- Full term (≥37 weeks)
- No focal bacterial infection
- Negative urinalysis
- WBC >5,000 and <15,000 mm^3
- Absolute bands <1,500 mm^3
- No discrete infiltrates on CXR if done
- Stool smear negative if done

- CBC with diff
- Blood culture
- UA, urine culture
- CXR and respiratory viral panel (if respiratory symptoms)
- Stool culture (if diarrhea)

Meets all low risk criteria?

! Ceftriaxone contraindicated with hyperbilirubinemia

Yes

Discharge Criteria (meets all)
- Eating well and well appearing
- No social/family concerns
- Reliable follow-up in 12-24 hours
- Outpatient plan accepted by PMD and family

Yes → **Discharge Instructions**
- Follow-up in 12-24 hours
- No antibiotics
- If antibiotics given, perform LP prior

No → Admit for observation
CSF studies and antibiotics if worsens → **Go to Inpatient Phase 31-60d**

No

- Obtain CSF studies
- Begin ceftriaxone
- Considerations for severely ill patients and other clinical scenarios
- Admit → **Go to Inpatient Phase 31-60d**

Last Updated: xx/xx/xxxx
Valid until:xx/xx/xxxx

Neonatal Fever (0-30d): Inpatient Phase

Executive Summary | Test Your Knowledge | Explanation of Evidence Ratings | Summary of Version Changes

PHASE II (INPATIENT)

Inclusion Criteria
- Fever ≥38 C or hypothermia <36 C in children <30 days of age

Exclusion Criteria
- Patients currently admitted to ICU or admitted >3 days
- known immunodeficiency or cancer
- patients with central venous catheters or VP shunts

! If CSF pleocytosis add entero / parechovirus PCR; defer LP if unstable.

! Considerations for Pretreated CSF

CSF Pleocytosis >20WBC/mm^3?

Yes → **Ampicillin + cefotaxime**

No → **Ampicillin + gentamicin**

When to discontinue acyclovir

Daily re-evaluation

Pos. cultures →
- Treat specific condition (e.g., UTI)
- Narrow antibiotic agent if possible
- If HSV+, transfer to ID service

Neg. cultures → **Improving and meets discharge criteria?**

No →
- Further evaluation per primary team

Yes → **Discharge Instructions**
- PMD f/u within 48-72 hours

Discharge Criteria (Meets all)
- Tolerating PO
- Well-appearing
- At 36 hours if cultures negative (and HSV PCR neg. if done)
- Adequate follow-up
- PMD and family agree with plan

! Consider discharge at 24 hours if non-HSV viral studies positive & patient well-appearing

Last Updated: xx/xx/xxxx
Valid until:xx/xx/xxxx

Neonatal Fever (31-60d): Inpatient Phase

Executive Summary | Test Your Knowledge | Explanation of Evidence Ratings | Summary of Version Changes

PHASE II (INPATIENT)

Inclusion Criteria
- Fever ≥38 C or hypothermia <36 C in children 31-60 days of age

Exclusion Criteria
- Patients currently admitted to ICU or admitted >3 days
- known immunodeficiency or cancer
- patients with central venous catheters or VP shunts

! If CSF pleocytosis add entero / parechovirus PCR; defer LP if unstable.

! Considerations for Pretreated CSF

! Ceftriaxone contraindicated with Calcium containing fluids or hyperbili

Daily re-evaluation

Positive cultures →
- Treat specific condition
- Perform LP if not done prior
- Begin antibiotics if not begun prior; narrow antibiotic agent if possible

Negative cultures ↓

Improving and meets discharge criteria?

No →
- Further evaluation per primary team

Yes ↓

Discharge Criteria (Meets all)
- Tolerating PO
- Well-appearing
- At 36 hours if cultures negative and antibiotics begun
- At 24 hours if cultures negative and no antibiotics begun
- Adequate follow-up
- PMD and family agree with plan

Discharge Instructions
- PMD f/u within 48-72 hours

! Consider discharge at 24 hours if non-HSV viral studies positive & patient well-appearing

Last Updated: xx/xx/xxxx
Valid until:xx/xx/xxxx

Executive Summary

Objective

Our goal is to standardize the care of children under 60 days of age who have fever, including workups for meningitis and HSV. In addition to the five core CSW metrics, we will work towards the following goals:

- 85% of patients with negative cultures will be discharged 40 hours from the time cultures were taken by six months after go-live.
- 95% of infants with negative CSF gram stain and with CSF pleocytosis will receive HSV workup by six months after go-live.
- In infants 31-60 days with WBC 5,000-15,000/mm^3 and a negative UA, ≤15% will receive an LP within 6 months after go-live.

Notable Recommendations

AGE GROUP 0-30 DAYS:

1. Do **NOT** routinely perform HSV CSF PCR testing in neonates with fever and without other evidence of HSV infection.
2. Perform HSV testing in patients with any one of the following historical details or clinical symptoms associated with neonatal HSV infection: CSF pleocytosis (≥20 WBC/mm^3), maternal primary HSV, maternal fever, postnatal HSV contact, vesicular rash, hypothermia, lethargy, seizures, severe respiratory distress, hepatosplenomegaly, thrombocytopenia, elevated hepatic enzymes. Vaginal delivery and prematurity are additional risk factors for HSV.
3. Empiric acyclovir should be given to all febrile neonates tested for HSV, and all patients begun on acyclovir should have comprehensive HSV testing.
4. Complete the work-up for HSV in the Emergency Department.

AGE GROUP 31-60 DAYS:

1. Do **NOT** routinely perform LP in or prescribe antibiotics to low risk patients.
2. Perform LP on all patients not meeting low risk criteria or to whom antibiotics will be given**.**
3. Admit the following infants aged 31-60 days: Any patient that is ill appearing or clinically unstable, those not meeting low risk criteria, social or family concerns (transportation problems, lack of resources for prompt follow-up),patients unable to follow-up in 12-24 hours

AGE GROUP 0-60 DAYS (ALL PATIENTS ON THIS PATHWAY**):**

1. Define pleocytosis as CSF with ≥20 WBC/mm^3 if 0-30 days, or ≥10WBC/mm^3 if 31-60 days , even in the presence of a traumatic tap.
2. Perform broad range real time PCR and DNA sequencing for bacterial rRNA in pre-treated patients with pleocytosis and a concern for bacterial meningitis.
3. Perform enterovirus CSF PCR on those with CSF pleocytosis, if performing the test might help justify an early discharge.
4. Discharge admitted patients begun on antibiotics at 36 hours if they meet discharge criteria, bacterial cultures after incubation for 36 hours are negative, and applicable viral testing is negative.
5. Discharge admitted patients begun on antibiotics at 24 hours if they meet discharge criteria, bacterial cultures after incubation for 24 hours are negative, and applicable non-HSV viral testing is positive.
6. Discharge admitted patients NOT begun on antibiotics at 24 hours if they meet discharge criteria, and bacterial cultures after incubation for 24 hours are negative.

Executive Summary

Rationale

- Safety - Important safety alerts are imbedded in the algorithm and powerplan to help guide care for children at risk of serious infections.
- Quality of care will improve by:
  - Decreasing unnecessary lumbar punctures
  - Narrowing the range of antibiotics used to treat these babies
  - Standardizing which children will receive a full HSV workup
- Delivery of care will be improved through the use of a detailed learning module for residents, ED providers and nurses, and medical unit providers.
- Engagement is grounded in the fact that the pathway has been developed by RNs and MDs. Residents have been involved in the design of the pathway and training module. The emergency department and inpatient unit had multiple opportunities during its development to provide feedback and suggestions, and the pathway is co-owned by a hospitalist and emergency physician.
- Patient/Family Satisfaction will be addressed by implementing clinical standard work that will assure the highest quality of care. This work makes it clear to families what the discharge criteria are and provides guidelines for safe discharge as early as possible.
- Costs may be reduced by eliminating the use of unnecessary testing and prolonged hospitalization. (Increased HSV testing, with its attendant costs, is also a possible outcome.)

Evidence

Systematic reviews and guidelines from 1996 to date were searched to identify best practices for the treatment of fever in babies 0-30 days old and 31-60 days old. An additional search was performed to identify guidelines around performing lumbar punctures on babies who have been pretreated with antibiotics.

Implementation Items

- Algorithm
- CIS Powerplan
- Evidence & Recommendations document
- Learning module
- Updated discharge instructions

Metrics Plan

- CSW Core Metrics
- Process Metrics

PDCA Plan

The team will meet biweekly until 25% of the expected total yearly patient volume have been treated on the pathway and the team deems the pathway usage to be stable. After that, the team will meet quarterly to review metrics, discuss any new literature, and identify processes on which to focus PDCA cycles.

Revision History

Date Approved: **August 2013**

Next Review Date: **August 2016**

Test Your Knowledge

1.For 0-30 day old infants with fever, which of the following should be used for empiric antibiotics in the Emergency Department?
A)Amoxicillin
B)Ampicillin + Cefotaxime
C)Ceftriaxone
D)Ampicillin + Gentamicin

2.Empiric acyclovir should be started in patients at risk for HSV infection after obtaining which of the following tests?
A)Skin and mucous membrane HSV cultures and HSV FA
B)CSF HSV PCR
C)BUN, creatinine, ALT, AST
D)Blood HSV PCR
E)All of the above

3.Low risk criteria for 31-60 day old infants with fever includes which of the following?
A)WBC >5000 and <15,000
B)Negative urinalysis
C)Well-appearing
D)Full term
E)All of the above

4.A 15 day old infant is admitted to the general medical service after a febrile work-up is completed in the ED. CSF show 3 WBC/ mm^3 and the remaining labs, including urinalysis, are unremarkable. The best antibiotic choice in this scenario is:
A)Ceftriaxone
B)Ampicillin + Cefotaxime
C)Ampicillin + Gentamicin
D)Cefazolin

5.The following are all discharge criteria for patients age 0-30 days, EXCEPT:
A)Well-appearing
B)Cultures negative for 36 hours
C)Cultures negative for 48 hours
D)Follow-up arranged

6.Febrile infants age 31-60 days will be admitted to the medical unit if:
A)They do not meet low risk criteria
B)They have a white blood cell count of 25,000
C)Parents do not have reliable transportation to clinic in the next 24 hours
D)Patient is ill appearing
E)All of the above

7.When collecting specimens for an HSV work-up, the RN will collect all of the following EXCEPT:
A)Surface swab from conjunctiva and nasopharynx
B)Swab from lesion
C)Blood for HSV PCR
D)Surface swab from anus

8.The most common serious bacterial infection in neonates and infants is:
A)Sepsis/bacteremia
B)Meningitis
C)UTI
D)Cellulitis
E)Pneumonia

Answer Key

Answer Key

1.b)Ampicillin + Cefotaxime

2.e)All of the above

3.e)All of the above

4.c)Ampicillin + Gentamicin

5.c)Cultures negative for 48 hours

6.e)All of the above

7.b)Swab from lesion

8.c)UTI

Evidence Ratings

We used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial, or observational studies. The rating is then adjusted in the following manner:

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings can be *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Quality of Evidence:
✪✪✪✪ High quality
✪✪✪○ Moderate quality
✪✪○○ Low quality
✪○○○ Very low quality
Expert Opinion (E)

Reference: Guyatt G et al. J Clin Epi 2011: 383-394

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Literature Search

Search Methods, Neonatal Fever, Clinical Standard Work

Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Susan Klawansky. Searches were performed in December 2012 (high level evidence only, 1996 to date), and March 2013 (broader levels of evidence, 2009 to date). The following databases were searched – on the Ovid platform: Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials; elsewhere – Embase, Clinical Evidence, National Guideline Clearinghouse and TRIP. Retrieval was limited to newborn infants and English language. In Medline and Embase, appropriate Medical Subject Headings (MeSH) and Emtree headings were used respectively, along with text words, and the search strategy was adapted for other databases using their controlled vocabularies, where available, along with text words. Concepts searched were fever, fever of unkown origin, and fever without a source.

An additional search was conducted in March 2013 in the databases listed above, from 1996 to date, on the related concepts of cerebrospinal fluid, meningitis, spinal puncture, and pretreatment. This search was also restricted to newborn infants and English.

Retrieval from all searches was limited to certain evidence categories, such as relevant publication types, Clinical Queries, index terms for study types and other similar limits.

Susan Klawansky, MLS, AHIP

July 1, 2013

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Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children's Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.

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Summary of Version Changes

- **Version 1 (8/13/2013):** Go live
- **Version 1.1 (9/5/2013):** Clarified maternal risk factors for HSV and decision to test for neonatal HSV

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Cautions (Cont'd)

Pre-treated CSF:

Consider adding real time PCR and DNA sequencing for bacterial rRNA in pre-treated patients with pleocytosis and a concern for bacterial meningitis.

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d

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Infants 31-60 Days: ED & Inpatient Management

Considerations for Severely Ill Patients:

- Add ampicillin to ceftriaxone if patient is severely ill and has findings suggestive of urinary tract infection to assure coverage for *Listeria (*rare) or *Enterococcus*. (Brown)
- Add vancomycin for patients at risk for *S. aureus* (Cincinnati)

Initial ED phase 31-60d

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Additional Clinical Considerations

Differential Diagnosis for Severely Ill Febrile Neonate:

- Serious bacterial infection
- HSV
- Varicella zoster virus
- *Chlamydia*
- Enterovirus
- Adenovirus

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Initial ED phase 0-30d

Other Exclusions: Focal Infection

Patients with clinical evidence of focal infections (e.g., omphalitis, pneumonia, cellulitis) are excluded from the neonatal fever pathway.

- These patients may still need to undergo a “febrile neonate” work-up
- Based on site of infection, empiric antibiotic choice may be different

Initial ED phase 0-30d

Initial ED phase 31-60d

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Infants 0-30 Days: HSV – Complete HSV Work-up

Comprehensive testing for neonatal HSV infection should include:

- Surface swabs from nasopharynx, conjunctivae, and anus sent for HSV culture and FA
  - These specimens will be collected by RN
- CSF for HSV PCR
- Blood for HSV PCR
- Skin vesicle fluid for HSV culture and FA (if present)
  - Provider will unroof vesicle and swab lesion
- CBC with differential, BUN, creatinine, AST and ALT

Complete the work-up for HSV in the Emergency Department.

Source: AAP 2012 Red Book; Local Consensus

Initial ED phase 0-30d

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Infants 0-30 Days: HSV – Maternal Risk Factors

Infants at greatest risk of neonatal HSV are those born vaginally (especially with use of invasive monitoring or with history of leaking membranes prior to delivery) to mothers with any of the following risk factors for **primary maternal HSV** infection:

- Mother's current or past sex partners have a history of genital or oral HSV
- New sexual partner in pregnancy, especially late in gestation
- Sores in the vagina, or opening of the vagina, during pregnancy, especially bilaterally on the vulva late in gestation
- Urinary retention (sometimes misdiagnosed as an UTI)
- History of frequent yeast infections
- Receipt of oral sex during the last half of pregnancy from partner with history of cold sores

NOTE: These are maternal risk factors for primary HSV infection. Use clinical judgment in determining if HSV work up is indicated in well-appearing infants born to mothers with multiple risk factors.

Source: Adapted from SCH Neonatal HSV Guideline, Lisa Frenkel 2006

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Initial ED phase 0-30d

Additional Clinical Considerations (Cont'd)

Enterovirus Testing of CSF

Consider Enterovirus PCR on all patients with CSF pleocytosis:

Evidence
Examined the CSF of 361 infants age 56 days or younger and determined that when adjusted for other variables, length of stay is DECREASED by 26% in patients with positive CSF PCRs. Source: Dewan,M

NOTE: Turn around time is variable; consult LabMan to determine if timing of results will potentially reduce length of stay

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d

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Additional Clinical Considerations (Cont'd)

Low Risk Criteria – Negative Urinalysis

Definition is consistent with published stratification studies and the CSW UTI pathway:

- <10 WBC/hpf, negative Leukocyte esterase, and negative nitrites
- No bacteria on Gram Stain

Seattle Children's Lab: Situations for Performing Microscopies
Any positive result on the reagent strip, with the exception of positive ketones or urobilinogen
If the dipstick is positive for bilirubin
Specific request is ordered - e.g. look for cystine crystals
Unusual color or the drug Mesna in the urine that could interfere with a reagent strip result
The reagent strip is negative but the urine has an abnormal odor

Initial ED phase 31-60d

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Infants 31-60 Days: ED Management (Cont'd)

High Risk of Serious Bacterial Infection:

Patients who do not meet low risk criteria are at higher risk for serious bacterial infection, including meningitis, therefore:

1. Obtain CSF studies (4 tubes)
2. Administer empiric ceftriaxone
3. Admit for empiric antibiotics

NOTE: All patients started on antibiotics should receive an LP prior to antibiotic administration, unless they are clinically unstable.

Go to Inpatient Phase 31-60d

Infants 0-30 Days: Inpatient Management (Cont'd)

HSV

If positive for HSV, continue acyclovir and transfer to ID service.

Discontinue Acyclovir when:

- If patient is well-appearing: negative blood and CSF PCR
- If patient not-well-appearing: but alternative diagnosis made: negative blood and CSF PCR
- If high ongoing HSV suspicion: wait for all HSV studies (including surface FA/cultures) to return negative

(Brown; Local Consensus)

Inpatient Phase 0-30d

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Additional Clinical Considerations (Cont'd)

Discharge at 24 hours if Viral Testing Positive:

Evidence
Studies have shown that patients with bronchiolitis or other viral infections are at lower risk of serious bacterial infections
Approximately 90% of bacterial pathogens are identified in the first 24 hours of incubation Source: Cincinnati
Consider discharge at 24 hours for all patients who are well-appearing and have a positive (non-HSV) viral study Source: Byington CL