**PHASE I (E.D.)**

**Inclusion Criteria**
- Fever ≥38°C (or a reliable history of fever) 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

---

**Begin clinical assessment**

**Focal Infection** (e.g., omphalitis, pneumonia)

- 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)

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

**Go to Inpatient Phase** (0-30d)

---

**Inability to obtain CSF in ED**

**Considerations for Pretreated CSF**
- Administer antibiotics (GOAL: within 60 minutes)
- Refer to IR for lumbar puncture as inpatient
- Rapid CSF Bacterial PCR can be sent on pre-treated CSF that demonstrates pleocytosis

---

**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/mm³ without clear bacterial infection (e.g., + Gram stain)

---

For questions concerning this pathway, contact: **NeonatalFever@seattlechildrens.org**

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Neonatal Fever v4.0: ED Phase (31-60 days old)

**Inclusion Criteria**
- Fever ≥38°C (or a reliable history of fever) 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

**Symptoms of Bronchiolitis:** (increased work of breathing, cough, feeding difficulty, tachypnea, wheezing)

- 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?**
- Yes
  - Ceftriaxone contraindicated with hyperbilirubinemia
  - ConSIDER NEONATAL FEVER 31-60 W BRONCH ED PHASE
- No
  - Obtain CSF studies
  - Begin ceftriaxone
  - Considerations for severely ill patients and other clinical scenarios
  - Admit

**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

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

**Inability to obtain CSF in ED**
- Considerations for Pretreated CSF
  - Administer antibiotics (GOAL: within 60 minutes)
  - Refer to IR for lumbar puncture as inpatient
  - Rapid CSF Bacterial PCR can be sent on pre-treated CSF that demonstrates pleocytosis
Neonatal Fever v4.0: Inpatient Phase (0-30 days old)

PHASE II (INPATIENT)

Inclusion Criteria
- Fever ≥38°C (or a reliable history of fever) 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

CSF Pleocytosis >20WBC/mm³?
- Ampicillin + cefotaxime
- Positive cultures
  - Improve and meets discharge criteria?
    - Yes: Discharge
    - No: Further evaluation per primary team
- Negative cultures: Daily re-evaluation

Inability to obtain CSF in ED

Considerations for Pretreated CSF
- Administer antibiotics (GOAL: within 60 minutes)
- Refer to IR for lumbar puncture as inpatient
- Rapid CSF Bacterial PCR can be sent on pre-treated CSF that demonstrates pleocytosis

When to discontinue acyclovir
- Treat specific condition (e.g., UTI)
- Narrow antibiotic agent if possible
- If HSV+, transfer to ID service

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

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

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In patients PRESENTING with fever and bronchiolitis, the risk of bacteremia and meningitis is low. The risk of UTI is higher and should be considered in patients who are persistently symptomatic with fever or vomiting.

Symptoms of Bronchiolitis: (increased work of breathing, cough, feeding difficulty, tachypnea, wheezing)

Signs of poor perfusion or mental status changes or sepsis score > 3

YES → Continue workup per Neonatal Fever (31-60d) pathway

NO

Consider UA/Culture in patients who are persistently febrile or vomiting

UA +

Blood CX

Ceftriaxone

Admit to inpatient on UTI and Bronchiolitis pathway

UA −

OR

UA NOT INDICATED

Off Pathway

CONSIDER BRONCHIOLITIS PATHWAY
PHASE II (INPATIENT)

Inclusion Criteria
- Fever ≥38°C (or a reliable history of fever) 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

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

Inability to obtain CSF in ED
Considerations for Pretreated CSF
- Administer antibiotics (GOAL: within 60 minutes)
- Refer to IR for lumbar puncture as inpatient
- Rapid CSF Bacterial PCR can be sent on pre-treated CSF that demonstrates pleocytosis

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

Further evaluation per primary team

Yes

Improving and meets discharge criteria?

No

! If CSF pleocytosis consider CSF Rapid Viral Qual PCR

! Ceftriaxone contraindicated with Calcium containing fluids or hyperbili

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

For questions concerning this pathway, contact: NeonatalFever@seattlechildrens.org
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Last Updated: September 2017
Next Expected Revision: February 2018
This training module is the result of many hours of work by your colleagues at Seattle Children’s Hospital. Our goal was to create an evidence-based guideline that standardizes the diagnosis and management of fever in neonates age 0-60 days. To that end, we have included summary statements of that key evidence which are highlighted in blue.

The foundation for this work began with a comprehensive review of the literature. From this, specific treatment recommendations were created using the best available evidence. We believe that this pathway represents “state of the art” care.

We sincerely hope that this module will enhance your learning and better the lives of your patients and their families.
Learning Objectives

Upon completion of this module, participants will be better able to:

1. Determine which subset of infants should be evaluated for Herpes Simplex Virus (HSV).
2. Select appropriate antibiotics choice for febrile neonates in the Emergency Department and the inpatient medical unit.
3. Identify which infants in the 31-60 day age group are considered low risk for serious bacterial infection.
4. Determine when a febrile neonate is eligible for discharge.
Background

Fever is a common presenting symptom in neonates and young infants:

- 12-28% will have a serious bacterial infection (which include bacteremia/sepsis, bacterial gastroenteritis, cellulitis, osteomyelitis, septic arthritis, meningitis, pneumonia and urinary tract infection)
  (Source: Cincinnati Children's Hospital; Fever of Uncertain Source Guideline)
  - UTI is the most common.
  - 0-1.2% of all febrile neonates will have bacterial meningitis
- 0.3% will have HSV (Caviness)

Because the clinical exam alone is unreliable to predict serious illness in this age group, clinicians must rely on a combination of history, physical exam and diagnostics tests to determine a patient’s risk of Serious Bacteria infection (SBI) and balance this risk with the cost and morbidity of empiric treatment.
Practice Highlights in this Pathway

- Define a subgroup of 0-30 day olds who should have HSV Workup
- Recommend narrowed antibiotic coverage for those patients 0-30 days with low risk of meningitis
- Standardize antibiotics given in the Emergency Department
- Implement a low risk criteria for determining who needs an LP in 31-60 day population
- Implement inpatient discharge at 36 hours of negative cultures
Introduction – Neonatal Fever

This clinical standard work pathway is meant to guide the management of febrile neonates age 0-60 days in the Emergency Department and Inpatient Medical Unit.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38 C</td>
<td>Patients currently admitted to ICU or admitted &gt;3 days</td>
</tr>
<tr>
<td>Hypothermia &lt;36 C in children &lt;60 days of age</td>
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</tr>
<tr>
<td></td>
<td>Patients with central venous catheters or VP shunts</td>
</tr>
</tbody>
</table>

Febrile neonates 0-60 days will enter on this Neonatal Fever pathway and may move to another CSW pathway, such as UTI, pneumonia or bronchiolitis when diagnosis is established.
Pathway Inclusion/Exclusion Criteria

**Inclusion Criteria**
- Fever ≥38°C (or a history of fever) or hypothermia <36°C in children 31-60 days of age with signs of bronchiolitis

**Exclusion Criteria**
- Patients currently admitted to ICU or admitted >3 days
- Known immunodeficiency or cancer
- Patients with central venous catheter or VP shunts

The Neonatal Fever (31-60 days old) with bronchiolitis ED Phase is to be used for:
- Patients age 31-60 days
- Presenting with fever AND clinical symptoms of bronchiolitis:
  - Increased nasal secretions
  - Increased work of breathing
  - Cough
  - Feeding difficulties
  - Tachypnea
  - Wheezing

Risk of Serious Bacterial infections in patients with bronchiolitis and/or RSV

Bacteremia and meningitis are uncommon in patients with bronchiolitis and/or RSV

Ralston 2011: Systematic review of studies reporting SBI data for febrile infants <90 days with bronchiolitis and/or RSV.
- Studies selected reported on culture results for admitted patients with bronchiolitis (11 studies selected).
- Outcome measures are rates of UTI, bacteremia, meningitis.
  - UTI rate was cumulatively 3.3%.
  - Rates of UTI higher with RSV positivity than clinical bronchiolitis alone (5.1% v 2.0%).
  - Bacteremia too rare to perform statistical analysis across studies (5 cases out of 1749 patients).
  - Zero cases of meningitis.

Risk of Serious Bacterial infections in patients with bronchiolitis and/or RSV

Bacteremia and meningitis are uncommon in patients with bronchiolitis and/or RSV

Levine 2004: 1248 patients < 60 days, 269 (22% with RSV)
- Overall rate of SBIs = 11.4%
- Rate of SBI in RSV+ patients = 7% (all were UTIs, no bacteremia or meningitis)
- Rate of SBI in RSV– patients = 12.5%
- CONCLUSION: Febrile infants <60d who have RSV infections are at significantly lower risk of SBIs than infants without RSV infection

Purcell 2002: 2396 patients, 285 (11.9%) < 6 weeks
- 12 + blood cultures, all deemed contaminants
- 27 + urine cultures

Oray-Schrom 2003: 191 infants with RSV age 0-90 days; complete sepsis work-up performed on 52.5% of febrile cohort
- 5 with UTI (7.2%)
- 1 with bacteremia (1.2%)
- None with meningitis (0%)
Hypothermia

- Septic work-up should not be delayed in neonate with a rectal temperature of less than 36°C
- Neonates should be able to maintain temperature stability when dressed in one layer of clothes more than adults and a hat.
- If there is concern that low temperature is caused by environmental factors: swaddle, place a hat on the baby and have caregivers hold for 30 minutes. Re-check temperature. Low temperatures due to environmental factors should be resolved by these measures.
- Hypothermic babies are at higher risk for hypoglycemia. Consider checking a glucose
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
Infants 0-30 Days: HSV – Complete HSV Work-up

Comprehensive testing for neonatal HSV infection should include:

- Surface swabs from nasopharynx and bi-lateral conjunctivae sent for HSV Rapid PCR and viral culture Herpes group (1 swab)
  - These specimens will be collected by RN
- CSF for CSF Rapid Viral Qual. PCR
- Blood for HSV PCR Quant. blood
- Skin vesicle fluid for HSV Rapid PCR and viral culture Herpes group
  - 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.
HSV

If positive for HSV, continue acyclovir and transfer to ID service.
If CSF Rapid HSV PCR positive, add on quantitative CSF HSV PCR

Discontinue Acyclovir when:

- If patient is **well-appearing and no evidence of HSV SEM disease**: negative surface and CSF Rapid PCRs (may consider discharge before blood HSV PCR result)
- If patient **has a definitive alternate diagnosis** (even if not well-appearing): negative surface and CSF Rapid PCRs
- If **high ongoing HSV suspicion**: wait for all HSV studies (including surface cultures and surface/blood PCRs) to return negative

Discharge Criteria:

- Well-appearing
- Tolerating PO/enteral feeds
- At 36 hours all cultures negative
- Meets HSV discharge criteria, if applicable
- Follow-up available with 48-72 hours
- PMD and family agree with plan
Risk of Serious Bacterial infections in patients with bronchiolitis and/or RSV

Bacteremia and meningitis are uncommon in patients with bronchiolitis and/or RSV

Purcell 2004: 912 patients with bronchiolitis
  • 2 of 470 patients tested had positive blood culture (0.43%)
  • 0 of 101 patients tested had positive CSF (0%)
  • 28 of 234 patients tested had positive urine (12%)

CONCLUSION: Routine sepsis and meningitis work-ups are not necessary in non-toxic appearing infants and young children with RSV lower respiratory tract infections.

Tsolia 2002: 636 infants < 12 months; blood and urine obtained on patients with fever >38 or ill appearing (174 patients)
  • 0 positive blood cultures
  • 8 positive urine cultures (4.6%)
Febrile Infants with bronchiolitis and/or RSV remain at risk for co-infection with UTI

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Rate of UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine</td>
<td>2004</td>
<td>5.4% (14/261)</td>
</tr>
<tr>
<td>Purcell</td>
<td>2004</td>
<td>14.9% (14/94)</td>
</tr>
<tr>
<td>Purcell</td>
<td>2002</td>
<td>27+ (unknown number collected—2396 in study)</td>
</tr>
<tr>
<td>Oray-Schram</td>
<td>2003</td>
<td>7.2% (5/69)</td>
</tr>
<tr>
<td>Tsolia</td>
<td>2002</td>
<td>4.65 (8/174)</td>
</tr>
<tr>
<td>Randolph</td>
<td>2004</td>
<td>0.6% (1/121)</td>
</tr>
<tr>
<td>Titus</td>
<td>2003</td>
<td>1.3% (2/147)</td>
</tr>
</tbody>
</table>

Risk of UTI in patients with bronchiolitis and/or RSV ranges from 0.6% to 15%
RECOMMENDATIONS:

Febrile Infants **age 0-30 days** of age remain at risk for serious bacterial infections and should have a full sepsis work-up despite the presence or absence of bronchiolitis.

Febrile infants **age 31-60 days** who are non-toxic appearing (no symptoms of poor perfusion, acute mental status changes or significant tachycardia) and have clinical symptoms of bronchiolitis do not require a full sepsis workup. **Blood and CSF cultures are not routinely recommended in this population.**

Urinalysis and culture should be considered in patients age 31-60 days with persistent fever (2 or more occurrences), vomiting or excessive irritability.

---

Initial ED phase 0-30d
Initial ED phase 31-60d
Inpatient Phase 0-30d
Inpatient Phase 31-60d
Neonatal Fever (31-60d) w/Bronchiolitis ED
Late Occurrence of Fever in Patients with Bronchiolitis

Patients with bronchiolitis and/or RSV who develop fever during hospitalization are at higher risk for serious bacterial infection and additional work-up should be considered.

Tsolia: 5 of 636 infants admitted with bronchiolitis subsequently acquired bacteremia during their hospitalization for bronchiolitis

Bloomfield demonstrated increased risk of bacteremia in patients with:
• Nosocomial RSV (OR = 23.4)
• PICU admission (OR = 9.4)
• Ventilatory support (OR = 7.4)
• Cyanotic heart disease (OR = 10.8)

Neonatal Fever (31-60d) w/Bronchiolitis ED
Now that this module has been completed, participants should be better able to:

1. Determine which patients age 31-60 day should be managed using the neonatal fever (31-60 days old) with bronchiolitis ED Phase
2. Determine when additional testing is needed in patients age 31-60 days with fever and bronchiolitis.
3. Understand the risks of bacteremia, UTI and meningitis in patients age 31-60 days with fever and bronchiolitis
Introduction – Neonatal Fever

This clinical standard work pathway is meant to guide the management of febrile neonates age 0-60 days in the Emergency Department and Inpatient Medical Unit.

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Febrile neonates 0-60 days will enter on this Neonatal Fever pathway and may move to another CSW pathway, such as UTI, pneumonia or bronchiolitis when diagnosis is established.
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
Infants 0-30 Days of Age

- Initial ED phase 0-30d
- Initial ED phase 31-60d
- Inpatient Phase 0-30d
- Inpatient Phase 31-60d
Testing for all patients should include:

- CBC with differential
- Blood culture
- UA, urine culture
- CSF studies (obtain 4 tubes)
  - If patient is clinically unstable, LP can be delayed and antibiotics should be administered
- Respiratory viral panel for respiratory symptoms
- CXR for respiratory symptoms not consistent with bronchiolitis
- Stool culture for diarrhea
Patients 0-30 days who present with fever ≥ 38 and symptoms of bronchiolitis should still have a full work-up that includes:

- CBC with differential
- Blood culture
- UA, urine culture
- CSF studies (obtain 4 tubes)
- Chest X-ray can be deferred if patient has clear clinical bronchiolitis (Local Consensus)
Infants 0-30 Days: Herpes Simplex Virus (HSV)

In addition to initial work-up, initiate HSV work-up on patients with ANY of the following:

### Historical and Clinical Features

<table>
<thead>
<tr>
<th>Severe Illness</th>
<th>Seizures</th>
<th>Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>Hepatosplenomegaly</td>
<td>Postnatal HSV contact</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Interstitial pneumonitis</td>
<td>Vesicular rash</td>
</tr>
</tbody>
</table>

### Laboratory Features

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF pleocytosis &gt;20 WBC/mm³ without clear bacterial infection (negative Gram stain)</td>
</tr>
</tbody>
</table>

For well appearing infants with no other HSV risk factors, who have a traumatic tap (>1000 RBC/mm³), consider deferring HSV workup.

<table>
<thead>
<tr>
<th>Elevated LFTs</th>
</tr>
</thead>
</table>

We are not recommending routine LFT screening for all neonates, as most patients with disseminated HSV tend to be ill appearing and would meet other criteria for HSV work-up.

---

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d
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.
Infants 0-30 Days: Inpatient Management (Cont’d)

Discharge Criteria:

- Well-appearing
- Tolerating PO/enteral feeds
- At 36 hours all cultures negative
- Meets HSV discharge criteria, if applicable
- Follow-up available with 48-72 hours
- PMD and family agree with plan
All patients should receive a single dose of ampicillin and cefotaxime immediately after appropriate cultures are obtained, without waiting for initial CSF counts:

- Rapid administration of appropriate antibiotics is associated with improved outcomes.
- Antibiotics can be narrowed by the admitting team once cell counts are available.

**NOTE: All patients with suspicion of HSV should receive acyclovir**
Infants 0-30 Days: Inpatient Management

Admission Criteria
Recommend admission of all febrile neonates age 0-30 days for empiric antibiotics.
Antibiotic choice is based on concern for meningitis:

<table>
<thead>
<tr>
<th>Concern for Meningitis</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;20 WBC/mm$^3$)</td>
<td>Ampicillin and gentamicin</td>
</tr>
<tr>
<td>High (&gt; 20 WBC/mm$^3$)</td>
<td>Ampicillin and cefotaxime</td>
</tr>
</tbody>
</table>

Continue acyclovir for those with an HSV workup pending:

- Recommend 1.5x maintenance fluids to prevent renal tubular injury for patients on acyclovir
HSV

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

If CSF Rapid HSV PCR positive, add on quantitative CSF HSV PCR

Discontinue Acyclovir when:

- If patient is **well-appearing and no evidence of HSV SEM disease**: negative surface and CSF Rapid PCRs (may consider discharge before blood HSV PCR result)
- If patient **has a definitive alternate diagnosis** (even if not well-appearing): negative surface and CSF Rapid PCRs
- If **high ongoing HSV suspicion**: wait for all HSV studies (including surface cultures and surface/blood PCRs) to return negative
Discharge Criteria:

- Well-appearing
- Tolerating PO/enteral feeds
- At 36 hours all cultures negative (and HSV PCR negative, if done)
- Follow-up available with 48-72 hours
- PMD and family agree with plan
Inpatient discharge at 36 hours:

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Seattle Children's 2012 Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately 90% of bacterial pathogens are identified within the first 24 hours of incubation. (Cincinnati)</td>
<td>Total of 41 patients &lt;61 days of age with a positive blood culture (including NICU).</td>
</tr>
<tr>
<td>In blood cultures of infants age 0-6 months:</td>
<td>Of the 41, 7 patients, or 14%, had their first culture turn positive after 36 hours.</td>
</tr>
<tr>
<td>• Mean time to positivity for true pathogens is approximately 17.5 hours.</td>
<td>Of the 7, only one qualified for the fever pathway and that child was identified with a UTI and treated appropriately.</td>
</tr>
<tr>
<td>• Median time to positivity for urine and CSF cultures are 16 and 18 hours, respectively. (Cincinnati; Byington)</td>
<td></td>
</tr>
</tbody>
</table>
Evidence: All Age Groups (Cont’d)

Inpatient discharge at 36 hours: (Cont’d)

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2190 patients with all 3 cultures (Blood/CSF/Urine):</td>
</tr>
<tr>
<td>• 28 positive blood culture: median time to positivity 16 hours (6-50)</td>
</tr>
<tr>
<td>• 8 positive CSF cultures: median time to positivity 18 hours (3-24)</td>
</tr>
<tr>
<td>• 165 positive urine cultures: median time to positivity 16 hours (1-34)</td>
</tr>
</tbody>
</table>

In low risk patients, 6/6 blood cultures, 14/17 urine cultures were positive within 24 hours (no low risk patients had positive CSF).

Source: Kaplan RL
Infants 31-60 Days of Age

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d
Rationale for avoiding Lumbar Puncture:

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of bacterial meningitis in the reviewed studies ranged from 0-1.2%, with the majority (12/15) demonstrating rates less than 0.5%.</td>
</tr>
</tbody>
</table>

Source: Bachur, Baker, Bonsu, Brik, Paquette, Garcia, Rudinsky, Garra, Pantell, Gomez, Levine, Martinez, Mintegi, Morley, Olaciregui

Patients stratified as low risk using a variety of decision rules demonstrate lower rates of bacterial meningitis.

Source: Bachur, Baker, Baraff, Brik, Paquette
Testing for all patients will include:

<table>
<thead>
<tr>
<th>TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
</tr>
<tr>
<td>CBC with diff</td>
</tr>
<tr>
<td>CXR (for respiratory symptoms not consistent with bronchiolitis)</td>
</tr>
<tr>
<td>Stool culture (if diarrhea present)</td>
</tr>
<tr>
<td>UA urine culture</td>
</tr>
</tbody>
</table>

Further management will depend on whether patient is stratified as high or low risk for serious bacterial infection.
Bronchiolitis:

- Can defer CBC and blood culture in patients 31-60d with clinical bronchiolitis and a single fever up to 38.5, if otherwise well appearing.
- Perform CBC, urine culture, and blood culture in patients 31-60d with bronchiolitis with persistent fever (≥2 episodes of documented fever ≥ 38).
- Patients with classic features of bronchiolitis who are otherwise well-appearing can be considered “well-appearing” when determining if patient meets low risk criteria.
- Chest X-ray can be deferred if patient has clinical findings consistent with bronchiolitis.
Low Risk Criteria:

- Well-appearing
- Previously healthy
- Full term (≥37 weeks)
- No focal bacterial infection
- Negative urinalysis
- WBC >5,000 and <15,000 mm³
- Absolute bands <1,500 mm³
- No discrete infiltrates on CXR if done
- Stool smear negative if done
ED Discharge: Low Risk Criteria

Discharge low risk patients if they meet all of the following criteria:

- Feeding well and well appearing
- No social/family concerns
- **Reliable follow-up in 12-24 hours**
- Outpatient plan accepted by PMD and family

A subgroup of low risk patients will not meet discharge criteria. These patients will be admitted without antibiotics for observation.
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.
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)

Initially ED phase 31-60d
Infants 31-60 Days: Inpatient Management

Admission Criteria:

Low risk patients who do not meet ED discharge criteria will be admitted for observation without antibiotic administration.

Patients with the following will be admitted with empiric antibiotics:

• Ill appearing
• Pre-term (< 37 weeks)
• Positive urinalysis
• WBC count < 5,000/mm$^3$ or > 15,000/mm$^3$
• Band count > 1,500/mm$^3$
• Infiltrate on chest x-ray
• Stool positive for PMNs
Empiric Antibiotics:

- Recommend continuing empiric ceftriaxone pending culture results for all patients not meeting low risk criteria (Cincinnati; Gomez B; Morley EJ)
- Ceftriaxone is contraindicated in the following patients:
  - Those with hyperbilirubinemia
  - Those receiving calcium containing IV fluids
Daily Re-evaluation, if positive culture:

- Treat specific condition (if identified) and transfer to appropriate CSW pathway (UTI, Pneumonia) if applicable
- If LP was not performed at admission, obtain LP prior to starting antibiotics
- Narrow antibiotics as appropriate per culture results
Discharge criteria:

Meet all of the following criteria:

- Well appearing
- Tolerating PO
- **At 36 hours:** if cultures negative and high risk patient (i.e. antibiotics begun)
- **At 24 hours:** if cultures negative and low risk patient (i.e. admitted for observation without antibiotics)
- Adequate follow-up
- PMD and family agree with plan
Information for All Age Groups
Interpreting CSF:

<table>
<thead>
<tr>
<th>CSF Normative Values</th>
<th>Seattle Children’s 2012 Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days: CSF WBC &lt;20/mm³</td>
<td>50-60 CSF samples were obtained that met criteria for pleocytosis as defined above</td>
</tr>
<tr>
<td>31-60 days CSF WBC &lt;10/mm³</td>
<td></td>
</tr>
</tbody>
</table>
Interpreting CSF (Cont'd):

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three studies attempted to define normative CSF values in infants, and found that CSF WBC &gt;16, regardless of whether it was a traumatic tap or not, was a statistical outlier and represented pleocytosis. (Dubos, F)</td>
</tr>
<tr>
<td>Other factors associated with bacterial meningitis were:</td>
</tr>
<tr>
<td>• high protein (&gt;120mg/dL)</td>
</tr>
<tr>
<td>• low glucose(&lt;40mg/dL)</td>
</tr>
<tr>
<td>• neutrophil predominance (&gt;75%)</td>
</tr>
<tr>
<td>An absence of neutrophils makes bacterial meningitis unlikely.</td>
</tr>
<tr>
<td>Source: Bonsu, B.K</td>
</tr>
</tbody>
</table>

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d
Inability to obtain CSF

Consider administration of antibiotics and referral to IR for lumbar puncture (LP) for any patient where LP is unsuccessful in the ED.
• Goal is to complete LP and administer antibiotics within 60 minutes of arrival to ED.

**Pre-treated CSF:**
Consider adding Rapid CSF Bacterial PCR Qual Panel – detects E.coli, Listeria Monocytogenes, Neisseria meningitides, streptococcus agalactiae (Strep B), Streptococcus pneumonia and Haemophilus Influenzae in pre-treated patients with pleocytosis and a concern for bacterial meningitis.
Differential Diagnosis for Severely Ill Febrile Neonate:

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

Consider CSF Rapid Viral Qual. PCR on all patients with CSF pleocytosis:

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Source: Dewan,M</td>
</tr>
</tbody>
</table>

**NOTE:** CSF Rapid Viral Qual. PCR Panel will detect HSV 1 & 2, Enterovirus, Human Parechovirus, VZV, CMV, HHV-6. *Turn around time is approximately 2 hours and the test is run 24/7.*
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

<table>
<thead>
<tr>
<th>Situation for Performing Microscopies</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any positive result on the reagent strip, with the exception of positive ketones or urobilinogen</td>
<td></td>
</tr>
<tr>
<td>If the dipstick is positive for bilirubin</td>
<td></td>
</tr>
<tr>
<td>Specific request is ordered - e.g. look for cystine crystals</td>
<td></td>
</tr>
<tr>
<td>Unusual color or the drug Mesna in the urine that could interfere with a reagent strip result</td>
<td></td>
</tr>
<tr>
<td>The reagent strip is negative but the urine has an abnormal odor</td>
<td></td>
</tr>
</tbody>
</table>

Initial ED phase 0-30d

Initial ED phase 31-60d

Inpatient Phase 0-30d

Inpatient Phase 31-60d
Discharge at 24 hours if Viral Testing Positive:

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

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
1. Cincinnati Children’s Hospital Medical Center. “Fever of Uncertain Source”. 2010
7. Bilavsky, E.; Yarden-Bilavsky, H.; Amir, J.; Ashkenazi, S. “Should complete blood count be part of the evaluation of febrile infants aged <=2 months?” Acta Paediatrica. 2010; 99 (9) 1380-1384
Summary of Version Changes

- **Version 1.0 (8/13/2013):** Go live
- **Version 1.1 (9/5/2013):** Clarified maternal risk factors for HSV and decision to test for neonatal HSV
- **Version 2.0 (2/26/2016):** Addition of the Neonatal Fever (31-60 days) with Bronchiolitis ED Phase
- **Version 3.0 (2/21/2017):** Modification of HSV management (0-30 days)
- **Version 4.0 (9/11/2017):** Modification- Guidance on inability to obtain CSF and fever at home
Neonatal Fever Approval & Citation

Approved by the CSW Neonatal Fever for August 13, 2013
Updated by the CSW Neonatal Fever Pathway Team February, 2017

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