Febrile Neonate Clinical Pathway
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Rationale:

This protocol was developed by a consensus group of JHACH Pediatric Emergency Medicine Physicians, Critical Care Physicians, Hospitalists, and Advanced Practice Providers to create an evidence-based clinical pathway to standardize the management of febrile neonates less than or equal to 28 days of age. The algorithm will begin in the emergency department and continue through the inpatient process until discharge. It addresses the following clinical questions or problems:

1. How to evaluate and manage a febrile neonate.
2. What diagnostic testing is appropriate for a complete evaluation?
3. Which medications are appropriate for empiric management?
4. What is the time-frame for observation?
5. What are the discharge criteria?
Background and Reasoning:

Fever in children is one of the most common chief complaints encountered in the emergency department. Infants, specifically those less than or equal to 28 days old, are at the highest risk of developing a potentially life-threatening illness due to their immature immune system and their atypical clinical presentation. Although the majority of fevers in this age group are caused by viruses, 12-28% are due to bacterial pathogens and can lead to serious bacterial illness (SBI). Common diagnoses associated with SBI include meningitis, bacteremia, pneumonia, skin and soft tissue infections, bone and joint infections, and UTI. The most common bacterial pathogen identified in neonates is Escherichia coli (42%), closely followed by Group B Streptococcus (23%), Staphylococcus aureus (5%), and Listeria monocytogenes being a less common pathogen. Although meningitis due to herpes simplex virus (HSV) is uncommon in this patient population (0.3%), serious viral infection (SVI) caused by HSV increases morbidity and mortality and carries a fatality rate of approximately 15% if not properly recognized and treated. Various criteria identifying risk stratification for febrile infants have been developed and are regularly utilized; however, they fail to accurately depict risk for infants less than or equal to 28 days of age.

The physical exam alone is not predictive of SBI or SVI in this age group thus further diagnostic testing is necessary. The consequences of missing an SBI or SVI can result in adverse patient outcomes thus all infants meeting criteria will undergo a full sepsis workup and subsequent hospitalization. Our clinical pathway was developed with evidence based consensus to aid in prompt recognition, assessment, and disposition of this vulnerable age group.
Johns Hopkins All Children’s Hospital
Febrile Neonate Emergency Center Pathway

Exclusion criteria:
> 28 days of age, known immunodeficiency, central venous access, or VP shunt
Patients presenting with unstable vitals, toxic appearance, or requiring immediate resuscitative efforts. For these patients, please evaluate and treat in accordance with PALS guidelines.

Neonate ≤ 28 days old with rectal temperature ≥ 38°C or ≤ 36°C reported or present upon visit?

Proceed with regular systems based assessment of infant

YES

Assess infant

Respiratory symptoms: rhinorhea, congestion, cough, respiratory distress, increased work of breathing, or diminished breath sounds

YES

Add respiratory viral PCR panel (nasal washing sample preferred), and AP/Lateral CXR

Obtain labs and perform LP

GOAL:
Assessment, IV access, LP and labs sent, empiric antibiotics and antiviral administration within 1 hour.

Triage will implement the Febrile Neonate Order Set and place topical anesthetic for all infants meeting criteria.

If unable to obtain IV access after 2 attempts, DO NOT DELAY, contact charge nurse for vascular access consultation.

Labs:
- CBC, CMP, Blood culture
- UA with culture (cathed)
- HSV 1&2 Serum PCR
- HSV viral PCR from bilateral conjunctiva, bilateral nares, oropharynx, rectum, scalp electrode site if present, or any vesicles if present

CSF Studies:
- Gram Stain and Culture
- Glucose and protein
- Cell count and differential
- Meningitis Encephalitis PCR panel
- HSV 1 & 2 by PCR, Qualitative, CSF

Empiric Medications:
- Amoxicillin IV
  - If ≤7 days old: 100 mg/kg/dose
  - 8 days and older, 75 mg/kg/dose
- Ceftazidime IV 50 mg/kg/dose*
- Acyclovir IV 20 mg/kg/dose

*Cefotaxime is the considered the first choice cephalosporin however is not available due to a national shortage. Ceftazidime has been substituted in its place.

Admit neonate:
- Contact NICU if neonate is ≤ 14 days.
- Contact Hospitalist if neonate is > 14 days, hemodynamically stable, and there is no concern for meningitis based on lab studies.
  - If CSF gram stain positive and/or there are clinical signs of instability, contact either NICU or PICU based on age.
  - If gram stain is negative with no signs of hemodynamic instability, patient suitable for general pediatrics admission.
- All neonates will be admitted under inpatient status.

Additional Optional Labs:
If frequent diarrhea is present, consider stool studies: stool pathogen panel and rectal culture.
EC Management, Diagnostics, and Disposition:

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
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<tbody>
<tr>
<td>Rectal temperature $\geq 38^\circ C$ or $\leq 36^\circ C$ in infants less than or equal to 28 days of age presenting to the Emergency Center, present on arrival or reported.</td>
<td>Infants $&gt;28$ days with fever will follow an algorithmic pathway based on their presentation. Patients of any age with known immunodeficiency, central venous access/indwelling lines, VP shunts, or with otherwise septic appearance requiring immediate resuscitative efforts should be managed according to the JHACH Sepsis Pathway or PALS guidelines.</td>
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</table>

Once evaluated in Emergency Center triage and found to meet criteria, RN is to implement an order set as detailed below in this document. The order set is comprised of a complete sepsis workup including blood, urine, mucosal, and CSF studies, weight-based doses for empiric antibiotic and antiviral coverage, as well as medications for topical anesthesia and oral analgesia. The triage RN is to place topical anesthetic on the L3-L5 region of the infant’s back so the lumbar puncture site will be anesthetized prior to the procedure. If this step is not completed, an LP will not be delayed as this is a time sensitive procedure. An oral 24% sucrose solution is included in the order set as a PRN order and is to be used for pain control during procedures.

The patient will be brought to an examination room in a timely manner with the goal of physical examination, diagnostic evaluation, and administration of empiric treatment for suspected serious bacterial and/or viral illness within one hour. If IV access is unable to be obtained after two attempts, vascular access consultation will be obtained. If an LP is unsuccessful while in the EC, do not delay empiric antibiotic and antiviral treatment. The procedure may be repeated once admitted; timing of the procedure will be determined by the managing inpatient team.

- Serum studies include: CBC, CMP, blood culture, and serum HSV 1&2 PCR.
- Urine studies include: a catheterized sample of urine sent for urinalysis with culture.
- CSF studies include: gram stain with culture, glucose, protein, cell count with differential, HSV 1 and 2 CSF PCR, and Meningitis and Encephalitis (M/E) PCR panel.
  - The M/E panel takes 1 hour and is run 0600-2100 daily.
- Respiratory studies include: Respiratory PCR Panel and/or CXR.
  - If the infant has signs or symptoms of respiratory distress, rhinorrhea, increased work of breathing, cough, diminished or adventitious breath sounds on exam, a respiratory PCR panel should be obtained via nasal washing and a chest x-ray as indicated.
- Stool studies include: a stool pathogen panel and rectal culture.
○ If the infant is experiencing significant diarrhea, a stool pathogen panel and rectal culture can help to identify a causative bacterium and/or organism.

● HSV surface mucosal testing includes: a total of 5 surveillance swabs for HSV 1&2 PCR.
  ○ Swabbing of mucosal surfaces will be obtained from the infant’s left eye, right eye, bilateral nares, oropharynx, and rectum.
  ○ The Emergency Center RN will swab each aforementioned surface once with dacron polyester swabs and place all 5 swabs into one tube of Bartel’s viral media. The tube will be labeled “HSV Surface PCR.”

CBC analysis in isolation, specifically the presence or absence of leukocytosis, is not an accurate predictor of SBI; gram stain analysis of CSF is crucial to determine patient disposition. If the patient is well appearing with stable vital signs and there is no evidence of bacteria on CSF gram stain or Meningitis/Encephalitis PCR panel, they may be managed on the pediatric floor. Also consider ICU if there is any evidence of pleocytosis with depressed glucose on CSF studies. Patients that have any of these findings on lab studies and/or symptoms concerning for declining condition (ill appearing, unstable vital signs, severe dehydration, severe respiratory distress) should be admitted to the ICU for close observation and further management.

All infants will be admitted under inpatient status.

Diagnostic codes should be entered prior to admission as follows: P81.9 Febrile illness of the newborn, P39.8 Need for evaluation of the newborn for rule out sepsis. Additional coding can be entered if the infant meets criteria such as positive laboratory findings, obvious clinical findings, or abnormal vital signs.
Antibiotic and Antiviral Selection:

A combination of ampicillin and a cephalosporin is the ideal treatment modality for neonates being evaluated for SBI. The combination of medications provides adequate initial coverage for potential causative pathogens including *E. coli*, *Streptococcus* species, *Enterococcus* species, and *Listeria monocytogenes*. The use of ceftriaxone in infants equal to or less than or equal to 28 days may theoretically increase the risk of kernicterus by displacing protein-bound bilirubin in neonates with hyperbilirubinemia and can be fatal if combined with calcium or calcium-containing fluids. Use is discouraged in this age group but will be considered when older than 28 days without history of prematurity (PMA >42 weeks) without history of hyperbilirubinemia or use of parenteral nutrition or calcium-containing intravenous fluids. Alternative empiric treatment options have been developed to accommodate drug shortages or patient intolerance. Inpatient physicians may change antibiotic selection based on culture and sensitivity results once available. Empiric antiviral coverage for herpes simplex virus includes the use of acyclovir; it may be discontinued once PCR and viral cultures have been determined negative.

In the EC, the goal is to obtain all necessary cultures and laboratory studies and administer appropriate antimicrobial agents within 60 minutes of triage. As such, all febrile neonates will initially receive ampicillin, cefotaxime (or ceftazidime when cefotaxime unavailable), and acyclovir while in the emergency center. Once admitted, the primary medical team (NICU, PICU, or hospitalist) will need to order the most appropriate empiric antibiotic therapy based on the patient’s risk for meningitis. All febrile neonates will continue on ampicillin and acyclovir until they can be safely discontinued as outlined in the inpatient management algorithm. Cefotaxime is the antibiotic of choice for empiric therapy in combination with ampicillin and acyclovir. When cefotaxime is unavailable due to antibiotic shortages, gentamicin or ceftazidime/ceftriaxone provide adequate empiric treatment for SBI in febrile infants depending on the infant’s risk for meningitis and gestational age. If a provider has a low clinical suspicion for meningitis at the time of admission, gentamicin is to be administered in addition to ampicillin and acyclovir. Providers may use the following clinical criteria to consider febrile neonates as low-risk for meningitis: well-appearing neonate, normal physical examination, no CSF pleocytosis/organisms visible on CSF Gram stain, normal laboratory evaluation, negative M/E panel (if available), and positive respiratory viral panel. Febrile neonates in which one or more of the above criteria are not met, or for whom the admitting provider maintains a high clinical suspicion for meningitis, should receive ceftazidime/ceftriaxone in addition to ampicillin and acyclovir. Guidance on when to use ceftazidime or ceftriaxone can be found below.
EC Antibiotic and Antiviral Selection

Ampicillin
- Dose dependent on postnatal age.

<table>
<thead>
<tr>
<th>Age (PNA)</th>
<th>Dose</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7 days</td>
<td>300 mg/kg/day</td>
<td>8</td>
</tr>
<tr>
<td>8 days or older</td>
<td>300 mg/kg/day</td>
<td>6</td>
</tr>
</tbody>
</table>

AND

Ceftazidime
- 50 mg/kg/dose IV, adjust dosing interval based on PMA and postnatal age.

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 29</td>
<td>0 to 28</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt;28</td>
<td>8</td>
</tr>
<tr>
<td>30 to 36</td>
<td>0 to 14</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt; 14</td>
<td>8</td>
</tr>
<tr>
<td>37 to 44</td>
<td>0 to 7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
<td>8</td>
</tr>
<tr>
<td>≥ 45</td>
<td>ALL</td>
<td>8</td>
</tr>
</tbody>
</table>

AND

Acyclovir
- 20 mg/kg/dose IV every 8 hours.
Inpatient Antibiotic and Antiviral Selection

Ampicillin (as above)

AND

Acyclovir (as above)

AND one of the following:

Cefotaxime (if available)

<table>
<thead>
<tr>
<th>Age (PNA)</th>
<th>Dose</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7 days</td>
<td>50 mg/kg/dose</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 7 days</td>
<td>50 mg/kg/dose</td>
<td>6</td>
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</table>

If no physical exam findings AND no CSF study results suggesting bacterial meningitis:

Gentamicin

- Dosing dependent on postnatal age. Continued use will require drug level surveillance.

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 35</td>
<td>ALL</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

***Note: gentamicin has poor CSF penetration and will not provide adequate coverage for bacterial meningitis.
If physical exam findings **OR** CSF study results suggest bacterial meningitis, the antibiotic choice depends on the following criteria:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates with a PMA (gestational age + postnatal age) ≤ 42 weeks</td>
<td>CefTAZidime</td>
</tr>
<tr>
<td>Neonates ≤ 28 days of age receiving parenteral nutrition or intravenous fluids containing calcium</td>
<td>CefTAZidime</td>
</tr>
<tr>
<td>Neonates ≤ 28 days of age with hyperbilirubinemia</td>
<td>CefTAZidime</td>
</tr>
<tr>
<td>All other neonates (PMA &gt; 42 weeks NOT receiving parenteral nutrition or calcium-containing IV fluids AND WITHOUT hyperbilirubinemia)</td>
<td>CefTRIAXone</td>
</tr>
</tbody>
</table>

**Ceftriaxone**
- 50 mg/kg/dose IV every 12 hours

***ALL MEDICATIONS ABOVE ASSUME NORMAL RENAL FUNCTION. IF EVIDENCE OF OR CONCERN FOR ABNORMAL RENAL FUNCTION PLEASE CONTACT PHARMACY PRIOR TO ADMINISTERING ANTIBIOTICS.***
**CSF, urine, and stool cultures are manually reviewed once daily in the a.m. (0600-1000). Provider will need to contact lab to request review of cultures if discharge occurring after 1000. **Failure to do so could result in neonate being inappropriately discharged with positive culture that was not yet identified and/or reported to the EMR.**
Inpatient Management and Discharge

Admission Decision:
The appropriate admission location for a febrile neonate should be determined based on age and clinical appearance of the patient. In general, infants postnatal age 0-14 days should be considered for admission to NICU under their discretion; however, clinically stable, well-appearing infants may safely be admitted to the pediatric hospital medicine service after discussion with the neonatologist and admitting hospitalist. Well-appearing neonates postnatal age 15-28 days can be admitted to the pediatric hospital medicine service. Infants who have physical exam findings suggestive of sepsis and/or meningitis should be admitted to the NICU or PICU depending on postnatal age. These findings include but are not limited to: bulging fontanelle, lethargy, delayed capillary refill, persistent tachycardia, and hypotension. Additionally, all neonates with organisms visualized on the CSF gram stain should be admitted to the NICU or PICU depending on postnatal age.

Inpatient Management:
Results of CSF gram stain, CSF cell count, and ALT/AST should be obtained and reviewed in the Emergency Center prior to the neonate being admitted. Additionally, the receiving physician should confirm that all necessary laboratory studies outlined in the Emergency Center Algorithmic Pathway have been ordered and collected prior to transfer out of the Emergency Center. All emergency care documentation should be reviewed during the admission history and physical. Admissions should be placed utilizing the Febrile Infant-Non-NICU Order Set.

Pharmacotherapy:
Empiric therapy for all infants will be initiated within the emergency center as outlined in the “EC Antibiotic and Antiviral Selection” section. The admitting service will need to continue antimicrobial therapy at appropriate intervals according to the “Inpatient Antibiotic and Antiviral Selection”. The goals for admitting a febrile neonate are primarily to:

1) provide appropriate empiric antibiotic coverage for neonates at-risk for SBIs and
2) discontinue unnecessary antimicrobial and other medical interventions for infants at no- or low-risk for SBIs in a timely manner

As such, the discontinuation of therapies is stratified based on factors that reduce an infant’s risk for SBIs including bacteremia, UTI, and meningitis:

Febrile neonates presenting with seizure activity, unexplained elevation in liver transaminases (ALT/AST) ≥2x the upper limit of normal, or who have skin vesicles on examination are at increased risk for neonatal HSV infection; any neonate with at least one of these findings are excluded from this pathway and should be referred to the JHACH Neonatal HSV Clinical Pathway. Acyclovir can be discontinued on all other well-appearing, clinically improving infants for whom the surface HSV PCR, serum PCR, and HSV result from the M/E panel are negative. If clinical suspicion for HSV remains high despite negative PCR-based testing, it is recommended that acyclovir be continued and the Infectious Disease service be consulted to discuss the timeline for appropriate discontinuation of acyclovir.
Febrile neonates with positive respiratory viral panel (RVP) testing are at a lower risk for SBI than infants with negative testing. To avoid unnecessary testing, neonates should only receive respiratory viral panel testing in the emergency center if presenting with clinical symptoms of a respiratory infection. Neonates with a positive respiratory viral panel test result could be considered for an expedited discharge at 24 hours assuming the lumbar puncture is interpretable, there was no pleocytosis of the CSF based on age-appropriate normal values, and all remainder discharge criteria are met (see Inpatient Pathway To Discharge). Although rare, positive respiratory viral panel testing does not preclude an infant from having meningitis. As such, the studies obtained from the lumbar puncture must be interpretable to be considered for expedited discharge. Criteria resulting in a non-interpretable lumbar puncture include but are not limited to:

- Failure to obtain sufficient volume for ALL CSF studies listed in Emergency Center Algorithmic Pathway
- CSF color described as bloody
- Documented traumatic or bloody tap
- Infant who received enteral or parenteral antibiotics prior to collection of CSF (i.e. “pre-treated”)
- Any additional scenario in which the clinician questions the reliability of the CSF test results

Antibiotic therapy can be discontinued as summarized in the Inpatient Pathway To Discharge diagram and as below:

<table>
<thead>
<tr>
<th>Discontinuation at 24 hours from time of culture collection</th>
<th>Meets ALL of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>❑ RVP-positive for virus</td>
</tr>
<tr>
<td></td>
<td>❑ LP interpretable</td>
</tr>
<tr>
<td></td>
<td>❑ No CSF pleocytosis based on age-appropriate values</td>
</tr>
<tr>
<td></td>
<td>❑ CSF, blood, and urine cultures negative ≥24 hours</td>
</tr>
<tr>
<td></td>
<td>❑ Blood and surface HSV PCRs negative</td>
</tr>
<tr>
<td></td>
<td>❑ All M/E panel results negative</td>
</tr>
<tr>
<td></td>
<td>❑ Infant well-appearing*</td>
</tr>
<tr>
<td></td>
<td>*Infants who meet all criteria except they are not well-appearing at 24 hours can have antibiotics discontinued at 36 hours once they become well-appearing and show clear signs of clinical improvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation at 36 hours from time of culture collection</th>
<th>Meets ALL of the following:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>❑ RVP-negative OR not obtained</td>
</tr>
<tr>
<td></td>
<td>❑ CSF, blood, and urine cultures negative ≥36 hours</td>
</tr>
<tr>
<td></td>
<td>❑ Blood and surface HSV PCRs negative</td>
</tr>
<tr>
<td></td>
<td>❑ All M/E panel results negative</td>
</tr>
<tr>
<td></td>
<td>❑ Infant well-appearing</td>
</tr>
</tbody>
</table>
Infants with a positive culture (CSF, blood, or urine), positive surface or blood HSV PCRs, or positive result on the M/E panel are not eligible for an expedited discharge as outlined in this pathway. Certain positive testing in the CSF via the M/E panel (such as enterovirus) may significantly lower a neonate's risk for concomitant SBI and may facilitate early discontinuation of antibiotics after 24 hours, however this decision should be made by the primary medical team and not this pathway. Additionally, all neonates with testing or physical exam findings suggestive of or confirmatory for an SBI should be managed per standard of care by the primary medical team and not this pathway. Consultation with the infectious diseases service is recommended where appropriate.

Discharge:
Well-appearing neonates presenting with fever who improved clinically during a hospitalization are eligible for discharge as outlined above. Discharge from the hospital can be considered when the following criteria are met:

1. CSF, blood, and urine culture results have been reviewed with the laboratory and confirmed as no growth**
2. Tolerating oral intake to support adequate hydration and nutrition
3. Well-appearing
4. Follow-up scheduled with primary care provider within 72 hours of discharge
5. Family and primary medical team agree with discharge plan

**CSF and Urine cultures are manually reviewed once daily in the a.m. (0600-1000). Provider will need to contact lab to request review of cultures if discharge occurring after 1000. Failure to do so could result in neonate being inappropriately discharged with positive culture that was not yet identified and/or reported to the EMR.

**The Meningitis-Encephalitis panel, which contains HSV and Enteroviruses, takes 1 hour and is run 0600-2100 daily.

It is important to note that only 96% of blood cultures and 81% of CSF cultures from infants with SBIs are positive at 36 hours. As such, providers must provide appropriate anticipatory guidance during discharge planning and ensure outpatient follow-up for continued monitoring prior to discharge. All families should be informed that pending cultures will continue to be monitored and that the family will be contacted in the event of a positive culture.
References


**Outcome Measures**

EC Length of stay
Time to antibiotics in the EC
Rate of success with obtaining ALL studies in EC
Hospital length of stay
Duration of antibiotics (hours; co-variate with hosp. LOS; this will capture the infants who have ABx stopped but are observed for longer)
IV infiltrates
Number of IVs during hospitalization
Transfer to NICU/PICU
7-day readmission rate
Frequency of ID consultation
Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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