Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

May 7, 2019
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INTRODUCTION / BACKGROUND

Infants presenting with fever of uncertain source (FUS) represent a common conundrum for clinicians, given the broad differential diagnosis. While viral infections remain the most common cause of fever in infants 0 to 60 days of age (Ishimine, 2007 [5]; Woll, 2018 [5a]), a systematic approach to evaluation is paramount in identifying infants at high risk for serious and invasive bacterial infections. Serious bacterial infections (SBIs) are more prevalent in this population when compared with older children (Laupland, 2009 [5a]; Caviness, 2008b [5a]). The prevalence of SBI in febrile young infants is reported to be 8% to 12.5% (Huppler, 2010 [5a]), with a prevalence of up to 20% (Schwartz, 2009 [5a]) reported in infants <28 days of age. SBIs include bacteremia, gastroenteritis, cellulitis, osteomyelitis, septic arthritis, meningitis, pneumonia, and urinary tract infection (UTI) (Byington, 2003 [4b]; Poehling, 2006 [5]). Among these, UTI is the most common type of SBI (Byington, 2003 [4b]). Recently published studies have made the distinction between invasive and noninvasive bacterial infections, with invasive bacterial infections (IBI) defined as bacteremia or acute bacterial meningitis (Gomez, 2016 [3a]; Milcent, 2016 [3a]; Woll, 2018 [5a]). At Cincinnati Children’s Hospital Medical Center, between January 2011 - June 2016, 69 infants 0 to 60 days of age were diagnosed with an IBI. Procalcitonin and CRP were more commonly obtained later, and many have affected care decisions. Between Jan 1, 2017-July 31, 2018, 1183 infants 0 to 60 days were evaluated in the ED with blood culture sent; of those, 6% of the infants had an SBI and 2.1% had an IBI.

A multicenter retrospective review evaluated the most common pathogens associated with bacteremia in infants 0-90 days with FUS (with and without concomitant UTI and/or meningitis) (Biondi, 2013 [4b]). Gram-negative bacteria were the most common pathogens with Escherichia coli (E coli) accounting for 44% and Klebsiella species accounting for 4% of all bacteremia cases (Biondi, 2013 [4b]). Ninety-one percent of cases with E coli bacteremia had a concurrent E coli UTI (Biondi, 2013 [4b]). The most common Gram-positive pathogens isolated include group B Streptococcus (23%), Streptococcus pneumoniae (6%), Staphylococcus aureus (5%), and Enterococcus (4%) (Biondi, 2013 [4b]). Group B Streptococcus was the pathogen most commonly associated with concomitant meningitis in patients with bacteremia (Biondi, 2013 [4b]). Of note, there were no cases of Listeria monocytogenes (Biondi, 2013 [4b]). Another study found that 2.2% of infants 7 to 90 day of age who presented to the emergency department with fever grew a pathogenic organism in blood culture. The most common pathogen was E coli (56%), and 98% of infants with E coli bacteremia had a concomitant UTI. Group B Streptococcus and Staphylococcus aureus accounted for 21% and 8% of bacteremia cases respectively (Greenhow, 2012 [4b]). This cohort had no cases of Listeria monocytogenes bacteremia, which is in line with several studies that have noted the sharp decline in Listeria bacteremia and meningitis in this age group (Leazer, 2016 [1b]; Hassoun, 2014 [4b]; Biondi, 2013 [4b]; Greenhow, 2012 [4b]).

The evaluation and management of febrile infants 0 to 60 days of age significantly varies across hospitals in the United States (Aronson, 2014 [4a]; Jain, 2014 [5a]). While practice variation has not resulted in notable differences in outcomes (e.g. emergency department revisits and hospital readmission rates), evidence supports the positive impact of standardization of practice on infants appropriately identified as having an SBI, decreased hospitalization rates for infants identified as low risk for SBI, and more judicious use of antimicrobial therapy (Byington, 2012 [4a]). Additionally, since the revision of our FUS guidelines in 2010, there is more robust literature available on blood biomarkers (e.g. procalcitonin and C-reactive protein), and the distinction between SBI and IBI is clearly documented, which necessitated updated recommendations.

The objective of this guideline is to provide recommendations for the following question:

What is the appropriate diagnostic evaluation and management for infants 0 to 60 days of age presenting with FUS?

Specific emphasis was placed on answering these related questions:

- In infants 0 to 60 days of age who present with FUS, are other diagnostic studies (e.g. C-reactive protein and procalcitonin), useful in differentiating infants who are high risk for an IBI?
- In infants 0 to 60 days of age who present with FUS and are well appearing, if the urinalysis (UA) is indicative of a UTI can a lumbar puncture (LP) be deferred?
- In infants 0 to 28 days who present with FUS, is ampicillin and a 3rd generation cephalosporin or gentamicin the appropriate antimicrobial coverage?
- In infants 0 to 60 days of age who present with FUS and are admitted, is 24 hours of inpatient observation versus 36 hours of observation reasonable if all cultures are no growth at 24 hours?

Definitions for terms marked with * and Abbreviations may be found in an Abbreviations and Definitions section below.
TARGET POPULATION FOR THE RECOMMENDATION

Inclusion Criteria

Infants 60 days of age or less who present to the Emergency Department (ED), Urgent Care (UC), or Primary Care Provider’s (PCP’s) office with fever of unknown source defined as a febrile illness (temperature of ≥38°C) in the absence of an apparent source after a thorough history and physical examination.

Exclusion Criteria

✓ Infants with underlying disorders that affect their immunity or might otherwise increase their risk for serious infections
✓ Infants on current antimicrobial therapy
✓ Infants who have received an immunization within 48 hours
✓ Infants presenting with seizures
✓ Infants requiring intensive care management
✓ Infants with a focal source on history and physical exam (i.e. respiratory symptoms, skin and soft tissue infection)

TARGET USERS FOR THE RECOMMENDATIONS

Include but are not limited to:

• Emergency Medicine and Urgent Care providers
• Inpatient providers (hospitalists, community pediatricians, nurse practitioners, physician assistants)
• Nurses
• Patients and families
• PCPs
• Physician trainees (residents and fellows)

EVIDENCE-BASED CARE RECOMMENDATIONS

Click on the Evidence Discussion & Dimensions for Recommendation # hyperlink for the Discussion/Synthesis of the Evidence and the Table of Dimensions for Judging Recommendation Strength related to individual recommendation statements.

Laboratory Studies

Care Recommendation Statement 1

It is recommended that the following laboratory studies be performed in neonates (0 to 28 days of age) with FUS: (Woelker, 2012 [3a]; Mintegi, 2014 [4a]; Diaz, 2016 [4b])

- Complete blood count (CBC) with differential including Absolute Neutrophil Count (ANC) (Woelker, 2012 [3a]; Mintegi, 2014 [4a]; Gomez, 2012b [4a]; Diaz, 2016 [4b])
- Blood culture (Gomez, 2010 [4b])
- Urinalysis (UA) and urine culture (Schroeder, 2015 [4a])

Note 1: Urethral catheterization and, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens (Roberts, 2012 [5a]).

- Cerebrospinal fluid (CSF) studies:
  - Tube 1: protein and glucose
  - Tube 2: culture and Gram stain
  - Tube 3: cell count and differential
  - Tube 4: hold for additional studies

(Local Consensus, 2018-2019 [5]).

Note 2: If a lumbar puncture (LP) is not obtained (due to unsuccessful attempt or family refusal), consider obtaining procalcitonin (PCT), which may be useful to trend over time (Local Consensus, 2018-2019 [5]).

Note 3: Evaluate and treat for herpes simplex virus based on the HSV algorithm (See Appendix A) (Local Consensus, 2018-2019 [5]).

(Evidence Discussion & Dimensions for Recommendation 1 and 2)
**Care Recommendation Statement 2**

It is recommended that the following laboratory studies be performed in infants **29 to 60 days of age** (Woeker, 2012 [3a]; Mintegi, 2014 [4a]; Diaze, 2016 [4b]; Luaces-Cubells, 2012 [3a]; Nosrati, 2014 [4a]; Olaciregui, 2009 [4a]; Roberts, 2012 [5a]; AAP, 2011 [5a]; Kuppermann, 2019 [3a]; Local Consensus, 2018 [5])

- CBC with differential with particular focus on the ANC (Kuppermann, 2019 [3a]; Woeker, 2012 [3a]; Mintegi, 2014 [4a])
- Blood culture (Gomez, 2010 [4b])
- Procalcitonin (Kuppermann, 2019 [3a]; Luaces-Cubells, 2012 [3a]; Woeker, 2012 [3a]; Nosrati, 2014 [4a]; Olaciregui, 2009 [4a])
- UA and urine culture (Schroeder, 2015 [4a])

**Note 1:** Urethral catheterization, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens (Roberts, 2012 [5a]).

**Note 2:** Obtain laboratory studies simultaneously (and not sequentially) (Local Consensus, 2018-2019 [5]).

*(Evidence Discussion & Dimensions for Recommendation 1 and 2)*

**Care Recommendation Statement 3**

It is **not** routinely recommended that providers obtain an LP for CSF analyses in infants **29 to 60 days of age** with FUS who meet **all applicable low-risk clinical and laboratory criteria** (See **FUS Algorithm**) (Gomez, 2016 [3a]; Milcent, 2016 [3a]; Velasco, 2015 [3a]; Scarfone, 2017 [4a]; Bressan, 2012 [4a]; Gomez, 2012 [4a]; Local Consensus, 2018-2019 [5]).

**Note 1:** See Care Recommendation 4 regarding infants with laboratory findings indicative of UTI.

**Note 2:** If antimicrobial therapy will be initiated in infants who meet low-risk criteria (whose labs are NOT indicative of UTI), collect CSF specimens prior to treatment (Local Consensus, 2018-2019 [5]).

**Note 3:** If all applicable low risk clinical and laboratory criteria are NOT met, CSF analyses includes:
- Tube 1: protein and glucose
- Tube 2: culture and Gram stain
- Tube 3: cell count and differential
- Tube 4: hold for additional studies

*(Local Consensus, 2018-2019 [5]).*

*(Evidence Discussion & Dimensions for Recommendations 3 through 7)*

**Care Recommendation Statement 4**

It is **not** routinely recommended that providers obtain an LP in infants **29 to 60 days of age** with FUS, when the UA is indicative of a UTI (UA with ≥10 WBC per high power field) if:

1) they meet all other low risk clinical criteria **and**

*(Evidence Discussion & Dimensions for Recommendations 3 through 7)*

**Care Recommendation Statement 5**

It is suggested that the risks and benefits of obtaining, delaying, or omitting an LP for CSF analyses be considered in infants **29 to 60 days of age** with FUS who meet **intermediate risk criteria** (Negative UA, PCT ≤ 0.5 ng/mL, but ANC >4,000) (See **FUS Algorithm**) (Kuppermann, 2019 [3a]; Velasco, 2017 [4a]; Mintegi, 2010 [4b]; Local Consensus, 2018-2019 [5]).

**Note 1:** Discuss the risks and benefits of the LP with families. Parents may express concern about risks such as damage to the spinal cord, bleeding, or introduction of infection. Counsel parents that these events are rare and are minimized through the use of appropriate technique (See **Appendix B**) (Local Consensus, 2018-2019 [5]).

**Note 2:** If an LP is deferred, admit the patient for observation; do not empirically start antimicrobials (Local Consensus, 2018-2019 [5]).

**Note 3:** If antimicrobial therapy will be initiated in infants who meet intermediate risk criteria, collect CSF specimens prior to treatment (Local Consensus, 2018-2019 [5]).
Note 4: If discharge is considered, have a collaborative discussion with:
- The patient’s PCP prior to discharge to ensure the family has a reliable follow-up plan within the next 24 hours (appointment or phone call if no office hours available the next day) (Local Consensus, 2018-2019 [5]).
- The family to ensure they have documented working phone and understand the importance of close follow up with PCP and reasons to call/return (Local Consensus, 2018-2019 [5]).

Note 5: Consider repeating a PCT in 8 hours (time based on previous PCT lab draw). Evidence supports that PCT may be most useful for infants who present with FUS 6 or more hours after fever onset (Milcent, 2016 [3a]).

Consensus Statement 6
Consider obtaining an LP for CSF analyses in infants 29 to 60 days of age with FUS who have a positive urinalysis AND applicable laboratory criteria considered high risk (PCT >0.5 ng/mL, regardless of the ANC) (See FUS Algorithm) (Kuppermann, 2019 [3a]; Local Consensus, 2018-2019 [5]).

Consensus Statement 7
Consider testing for enteroviruses, influenza A and B viruses, rotavirus, and respiratory syncytial virus selectively for infants with fever, based upon history, physical exam, sick contacts, season, community infection patterns, or other clinical factors noted by the clinician, recognizing that a confirmed viral illness does not exclude a concomitant bacterial infection (Local Consensus, 2018-2019 [5]).

Management Recommendations

Emergency Department Discharge Criteria

Consensus Statement 8
Consider outpatient management of young infants 29 to 60 days of age with FUS if all the following conditions are present:
- Low-risk clinical and laboratory criteria (See FUS Algorithm) have been met (Irwin, 2016 [1b])
- There is a collaborative discussion with:
  o The patient’s PCP prior to discharge to ensure the family has an established follow up plan within the next 24 hours (e.g. appointment or phone call if no office hours available the next day)
  o The family to ensure they have a documented working telephone number and understand the importance of close follow up with the PCP and reasons to call/return to the ED
(Local Consensus, 2018-2019 [5]).

Admission Criteria

Care Recommendation Statement 9
It is recommended that all neonates 0 to 28 days of age with FUS be admitted to the hospital (Gomez, 2010 [4b]; Local Consensus, 2018-2019 [5]).
Consensus Statement 10

Consider admitting young infants 29-60 days of age with FUS to the hospital if they have a UA indicative of a UTI but meet all other low risk clinical and laboratory criteria (Local Consensus, 2018-2019 [5]).

Note: For infants being discharged from the ED ensure there is a collaborative discussion with:
- The patient’s PCP prior to discharge to inform the PCP of pending blood and urine culture results, discuss the antibiotic plan, and ensure the family has an established follow up plan within the next 24 hours (e.g. an appointment or phone call if no office hours available the next day)
- The family to ensure they understand the importance of close follow up with the PCP and reasons to return to the ED. Providers should also verify that the family has a reliable phone number clearly documented in the electronic health record.

(Local Consensus, 2018-2019 [5])

Consensus Statement 11

It is recommended that young infants 29 to 60 days of age with FUS be admitted to the hospital if they meet intermediate or high risk by clinical or laboratory criteria and/or when social or family concerns (e.g. transportation problems, lack of resources for prompt medical follow-up) are present (Local Consensus, 2018-2019 [5]).

(Local Consensus, 2018-2019 [5])

Inpatient Discharge Criteria

Care Recommendation Statement 12

It is suggested that providers consider discharge of infants 0 to 60 days of age with FUS at 24 hours, if all cultures are “no growth” at that time and the patient meets all other discharge criteria (McGowan, 2000 [3a]; Leazer, 2017 [4a]; Lefebvre, 2017 [4a]; Biondi, 2014 [4a]; Local Consensus, 2018-2019 [5]).

Note 1: The countdown to 24 hours starts from the time of final culture collection (Local Consensus, 2018 [5]).

Note 2: Document blood, urine and CSF culture review by the laboratory in the electronic health record before considering discharge (Local Consensus, 2018 [5]).
- CSF cultures are only reviewed by the microbiology lab once per day in the morning. A CSF culture preliminary read is only documented in the electronic medical record once (on the first day that the culture is reviewed). A final negative read is documented on day 5. Documentation is ONLY updated if the CSF culture is positive.
- Use clinical discretion in determining how this process impacts discharge time for hospitalized infants with FUS.

Note 3: Be cautious regarding discharge at 24 hours if reliable follow up with the PCP, including plan for appointment or telephone call within the next 24 hours, cannot be arranged (Local Consensus, 2018-2019 [5]).

Note 4: Discharge criteria include:
- Well-appearing
- Eating well
- Culture results no growth at 24 hours
- Family:
  - Confident in caring for the infant at home
  - Has an established follow up and transportation plan
  - Has documented working phone number for follow up calls (i.e. if culture results return abnormal)
  - Understands the importance of close follow up with PCP and reasons to call/return
- PCP contacted by inpatient team and in agreement with the discharge and follow up plan.

(Local Consensus, 2018-2019 [5]).
Neonates 0 to 28 Days of Age

Care Recommendation Statement 13

It is strongly recommended that infants 0 to 28 days of age with FUS are empirically treated with ampicillin and a third generation cephalosporin (Brown, 2002 [1b]; Hassoun, 2014 [4b]; Byington, 2003 [4b]).

**Note:** It is reasonable to consider gentamicin in place of a third-generation cephalosporin for specific circumstances (e.g. third generation cephalosporin shortage) (Local Consensus, 2018-2019 [5]).

(Evidence Discussion & Dimensions for Recommendations 13 through 17)

Consensus Statement 14

Consider using vancomycin in place of ampicillin for infants at risk for infection with S. aureus, and in severely ill infants (Local Consensus, 2018-2019 [5]).

(Evidence Discussion & Dimensions for Recommendations 13 through 17)

Young Infants 29 to 60 Days of Age

Care Recommendation Statement 15

It is strongly recommended that infants 29 to 60 days of age with FUS in whom antibiotic therapy is indicated are empirically treated with a third generation cephalosporin (Leazer, 2016 [1b]; Brown, 2002 [1b]; Biondi, 2013 [4b]).

(Evidence Discussion & Dimensions for Recommendations 13 through 17)

Care Recommendation Statement 16

It is recommended that for infants admitted with a UA suggestive of a UTI, IV ampicillin be considered as an addition to the antibiotic regimen to ensure coverage of Enterococcus (Brown, 2002 [1b]; Biondi, 2013 [4b]; Greenhow, 2012 [4b]).

(Evidence Discussion & Dimensions for Recommendations 13 through 17)

Consensus Statement 17

Consider adding vancomycin to the antibiotic regimen in infants who are at risk for infection with S. aureus (Local Consensus, 2018-2019 [5]).

**Note:** If these infants have findings suggestive of a UTI, utilize vancomycin in place of ampicillin (Local Consensus, 2018-2019 [5]).

(Evidence Discussion & Dimensions for Recommendations 13 through 17)
Evidence-Based Care Guideline for Management of Infants
0 to 60 days with Fever of Unknown Source

FUS Algorithm: Fever of Unknown Source in Infants 0 to 60 days of age

**Infant presentation:**
- ill appearing or
- has a chronic illness or
- has an abnormal Pediatric Assessment Triangle

**High risk patient,**
do full work-up including LP.

**Infant ≤ 28 days old**

**Yes**

**High risk patient,**
do full work-up including LP.

**No**

**Infant > 28 days old**

**Yes**

In infants 29-60 days of age
obtain the following labs:
PCT, CBC with diff, blood culture, UA, urine culture

**Low Risk**
- Negative UA (UA with <10 WBC per hpf)
  AND
- Biomarkers below threshold:
  - PCT ≤ 0.5 ng/mL,
  - ANC ≤ 4,000/mm³

**Intermediate Risk**
- Negative UA
- PCT ≤ 0.5 ng/mL
  BUT ANC > 4,000/mm³

**High Risk**
- Negative UA with
  PCT > 0.5 ng/ml
  regardless of ANC value

**Abnormal UA**
- Positive UA: (WBC ≥ 10 per hpf)

**ACTION**
- No antimicrobials, discharge home with close follow up with PCP in next 24 hours
- Family knowledgeable of when to call/return

**ACTION**
- Option 1: Proceed with LP, send CSF studies and consider empiric antimicrobials
- Option 2: Deferral LP and admit for observation OFF antimicrobials

**ACTION**
- Proceed with LP and CSF studies
- Start empiric antimicrobials and admit to hospital

**ACTION**
- Option 1: Deferral LP and treat empirically for presumed UTI if: PCT ≤ 0.5 ng/mL regardless of ANC value; consider admission
- Option 2: Consider LP and sending CSF studies if: PCT > 0.5 ng/mL regardless of ANC value; admit to hospital

(Horeczko, 2013 [4a]; Local Consensus, 2018-2019 [5]; Dieckmann, 2010 [5a])
### Abbreviations

ANC – Absolute neutrophil count  
CSF - Cerebrospinal fluid  
ED - Emergency department  
EV - Enteroviruses  
FUS - Fever of uncertain source/origin  
IBI – Invasive bacterial infection  
LP – Lumbar puncture  
PCT - Procalcitonin  
SBI – Serious bacterial infection  
UTI – Urinary tract infection

### Definitions

**Cerebrospinal Fluid (CSF) pleocytosis**  
- Neonates age 0 to 28 days: CSF white blood cell count ≥15/μL  
- Infants 29 to 60 days CSF white blood cell count ≥ 9 uL.

**Fever of uncertain source (FUS)**  
An acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical exam.

**Fever**  
Temperature ≥ 38ºC (100.4 ºF)

**Invasive bacterial infection (IBI)**  
Bacteremia and/or bacterial meningitis in infants ≤ 60 days of age

**Ill-appearing**  
Infant described as: “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” “irritable” or any findings of the physical examination that indicates any clinical suspicion of sepsis

**Neonate**  
Infant birth to 28 days of age

**Previously healthy**  
Term Birth (≥ 37 weeks’ gestation)  
Not treated for unexplained hyperbilirubinemia  
Not hospitalized longer than mother  
No current or previous antimicrobial therapy  
No previous hospitalization  
No chronic or underlying illness

**Serious bacterial infection (SBI)**  
A urinary tract infection, bacterial meningitis, bacteremia, bacterial pneumonia, gastroenteritis, cellulitis, osteomyelitis, or septic arthritis

**Well appearing**  
Defined by a normal Pediatric Assessment Triangle (PAT): 3 components of the PAT are appearance, work of breathing, and circulation to the skin  
*(Horeczko, 2013 [4a]; Dieckmann, 2010 [5a]) (See Appendix C)*

**Young infant**  
Children 29 to 60 days of age
IMPLEMENTATION

Applicability & Feasibility Issues

Factors that will impact successful implementation of this guideline include:

**Facilitators**
- Leadership support from the Divisions of Emergency Medicine, Hospital Medicine, Infectious Disease, General and Community Pediatrics, or care areas of impact
- Education and dissemination of guideline to key stakeholders, including physician trainees, inpatient providers and PCPs
- Enhancing adherence to guidelines via appropriate order sets in the electronic health record
- Formalized methods of implementation via a robust quality improvement initiative

**Potential Barriers**
- Lack of processes that support use of guideline (i.e. no order sets, leadership support)
- Lack of availability of data to track adherence to guidelines and other key process and outcomes data

**Resource Implications**
- Cost of additional testing (e.g. PCT)

**Relevant CCHMC Tools**
- Order sets
- Patient and family-centered decision-making aids/ materials LP Risks and Benefits (See Appendix B)

**Outcome Measures**
- Rate of IBI identified in infants 0 to 28 days of age with FUS
- Rate of IBI identified in infants 29 to 60 days of age with FUS
- Rate of infants 29 to 60 days of age with FUS appropriately designated as low, intermediate and high risk based on laboratory findings
- Rate of infants 0 to 60 days of age with FUS discharged from the Emergency Department
- Rate of infants 0 to 60 days of age with FUS admitted to the hospital
- Length of stay of infants 0 to 60 days of age admitted with FUS
- Rate of 7-day readmissions
- Rate of missed IBI and SBI
- Rate of 48-hour ED revisits
- Average cost/charge of evaluation and management of infants with FUS
- Rationale for measurements

The guidelines now recommend the use of an additional biomarker (PCT) to aid in distinguishing infants with FUS who are at low risk of having an IBI. It is important to follow the impact of the recommendations on reliable identification of infants with SBI and IBI, rates of admissions, readmissions, ED reutilization rates, and costs. Additionally, the guidelines designate all infants 0 to 28 days of age as high risk, which is a more conservative approach than the Step by Step method (Gomez, 2016 [3a]). The guidelines provide guidance for providers to consider discharge at 24 hours in specific patients who have negative cultures, which may impact inpatient length of stay and overall cost.

**Process Measures**
- Rate of FUS guideline adherence
- Rate of FUS order set use (in the ED and inpatient settings)
- Rate of discharges within 2 hours of meeting medically ready goals
- Emergency department length of stay for infants 0 to 60 days of age evaluated for FUS
- PCT result time
It is recommended that the following laboratory studies be performed in neonates (0 to 28 days of age) with FUS: (Woelker, 2012 [3a]; Mintegi, 2014 [4a]; Diaz, 2016 [4b])

- Complete blood count (CBC) with differential including Absolute Neutrophil Count (ANC) (Woelker, 2012 [3a]; Mintegi, 2014 [4a]; Gomez, 2012b [4a]; Diaz, 2016 [4b])
- Blood culture (Gomez, 2010 [4b])
- Urinalysis (UA) and urine culture (Schroeder, 2015 [4a])

**Note 1:** Urethral catheterization and, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens (Roberts, 2012 [5a])

- Cerebrospinal fluid (CSF) studies:
  - Tube 1: protein and glucose
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  - Tube 4: hold for additional studies

(Local Consensus, 2018-2019 [5]).

**Note 2:** If a lumbar puncture (LP) is not obtained (due to unsuccessful attempt or family refusal), consider obtaining procalcitonin (PCT), which may be useful to trend over time (Local Consensus, 2018-2019 [5]).

**Note 3:** Evaluate and treat for herpes simplex virus based on the HSV algorithm (See Appendix A) (Local Consensus, 2018-2019 [5]).

**Dimensions of Judging the Recommendation Strength for accurate diagnosis**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Minimal</th>
<th>Moderate / Neutral</th>
<th>Serious</th>
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<tbody>
<tr>
<td>1. Safety / Harm <em>(Side Effects and Risks)</em></td>
<td></td>
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<tr>
<td>2. Health benefit to patient</td>
<td>☑️</td>
<td>☑️ Moderate / Neutral</td>
<td>☒️</td>
</tr>
<tr>
<td>3. Burden on population to adhere to recommendation</td>
<td>☑️ Low</td>
<td>☒️ Unable to determine</td>
<td>☑️ High</td>
</tr>
<tr>
<td>4. Cost-effectiveness to healthcare system</td>
<td>☑️ Cost-effective</td>
<td>☒️ Inconclusive</td>
<td>☒️ Not cost-effective</td>
</tr>
<tr>
<td>5. Directness of the evidence for this target population</td>
<td>☐️ Directly relates</td>
<td>☒️ Some concern of directness</td>
<td>☐️ Indirectly relates</td>
</tr>
<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
<td>☑️ Positive</td>
<td>☑️ Moderate / Neutral</td>
<td>☒️ Negative</td>
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<td>7. Grade of the Body of Evidence <em>(See Evidence Table below, “GNA – Grade Not Assignable”)</em></td>
<td>☐️ High</td>
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**Overall Strength of the Recommendation:** ☑️ Strong ☑️ Moderate ☒️ Weak ☒️ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

**Care Recommendation Statement 2**

It is recommended that the following laboratory studies be performed in infants 29 to 60 days of age (Woelker, 2012 [3a]; Mintegi, 2014 [4a]; Diaz, 2016 [4b]; Luaces-Cubells, 2012 [3a]; Nosrati, 2014 [4a]; Olaciregui, 2009 [4a]; (Roberts, 2012 [5a]; AAP, 2011 [5a]; Kuppermann, 2019 [3a]) Local Consensus, 2018 [5])

- CBC with differential with particular focus on the ANC (Kuppermann, 2019 [3a]; Woelker, 2012 [3a]; Mintegi, 2014 [4a])
- Blood culture (Gomez, 2010 [4b])
- Procalcitonin (Kuppermann, 2019 [3a]; Luaces-Cubells, 2012 [3a]; Woelker, 2012 [3a]; Nosrati, 2014 [4a]; Olaciregui, 2009 [4a])
- UA and urine culture (Schroeder, 2015 [4a])

**Note 1:** Urethral catheterization, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens (Roberts, 2012 [5a]).

**Note 2:** Obtain laboratory studies simultaneously (and not sequentially) (Local Consensus, 2018-2019 [5]).

**Dimensions of Judging the Recommendation Strength for accurate diagnosis**

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September 5, 2018
Discussion/Synthesis of Evidence and Dimensions for Recommendations 1 and 2

WBC count alone is not an adequate screen for IBI based on a prospective multicenter observational study (Cruz, 2017 [3a]). PCT may be a better marker of SBI/IBI in infants with FUS (Niosrani, 2014 [4a]; Olaciregui, 2009 [4a]). PCT has a higher sensitivity than CRP; specificity is comparable (Hu, 2017 [1b]). Additionally, PCT has shown to be comparable to Rochester criteria for screening infants who present with FUS (Woelker, 2012 [3a]). Either PCT or CRP has a higher diagnostic reliability than WBC & ANC in children with duration of fever 8 hrs. (Lauces-Cubells, 2012 [3a]). Additionally, a combination of labs/blood biomarkers may be more reliable in identifying infants with FUS who are at risk of IBI (Woelker, 2012 [3a]; Diaz, 2016 [4b]).

Several studies cite various lab cutoffs for PCT and CRP. PCT cutoff values cited in the literature ranged from 0.12-0.9ng/mL; a cutoff of 0.5 ng/mL was the most common (Gomez, 2016 [3a]; Bressan, 2012 [4a]; Gomez, 2012 [4a]). Likewise, a CRP value of 2.0 mg/dL was the most commonly cited value in the literature (Gomez, 2016 [3a]; Milcent, 2016 [3a]; Velasco, 2015 [3a]; Gomez, 2012 [4a]). PCT alone lacks sufficient negative predictive power in determining SBI. This is based on a meta-analysis that noted a cutoff of 0.3 for PCT had a low risk of SBI but even with this cutoff, 12.5% of patients included in the meta-analysis with PCT below the cutoff had an SBI (England, 2014 [1a]). Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below).

Care Recommendation Statement 3

It is not routinely recommended that providers obtain an LP for CSF analyses in infants 29 to 60 days of age with FUS who meet all applicable low-risk clinical and laboratory criteria (See FUS Algorithm) (Gomez, 2016 [3a]; Milcent, 2016 [3a]; Velasco, 2015 [3a]; Scarfone, 2017 [4a]; Bressan, 2012 [4a]; Gomez, 2012 [4a]; Local Consensus, 2018-2019 [5]).

Note 1: See Care Recommendation 4 regarding infants with laboratory findings indicative of UTI.
Note 2: If antimicrobial therapy will be initiated in infants who meet low-risk criteria (whose labs are NOT indicative of UTI), collect CSF specimens prior to treatment (Local Consensus, 2018-2019 [5]).
Note 3: If all applicable low risk clinical and laboratory criteria are NOT met, CSF analyses includes:
- Tube 1: protein and glucose
- Tube 2: culture and Gram stain
- Tube 3: cell count and differential
- Tube 4: hold for additional studies

Dimensions of Judging the Recommendation Strength for accurate diagnosis

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

Copyright © 2019 Cincinnati Children’s Hospital Medical Center; all rights reserved. September 5, 2018  Page 11 of 31
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Care Recommendation Statement 4

It is not routinely recommended that providers obtain an LP in infants 29 to 60 days of age with FUS, when the UA is indicative of a UTI (UA with >10 WBC per high power field) if:

1) they meet all other low risk clinical criteria and

Dimensions of Judging the Recommendation Strength for accurate diagnosis

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<tr>
<th>Dimensions of Judging the Recommendation Strength</th>
<th>Minimal</th>
<th>Moderate / Neutral</th>
<th>Serious</th>
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Overall Strength of the Recommendation: ☐ Strong ☒ Moderate ☐ Weak ☐ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Care Recommendation Statement 5

It is suggested that the risks and benefits of obtaining, delaying, or omitting an LP for CSF analyses be considered in infants 29 to 60 days of age with FUS who meet intermediate risk criteria (Negative UA, PCT ≤ 0.5 ng/mL, but ANC >4,000) (See FUS Algorithm) (Kuppermann, 2019 [3a]; Velasco, 2017 [4a]; Mintegi, 2010 [4b]; Local Consensus, 2018-2019 [5]).

Note 1: Discuss the risks and benefits of the LP with families. Parents may express concern about risks such as damage to the spinal cord, bleeding, or introduction of infection. Counsel parents that these events are rare and are minimized through the use of appropriate technique (See Appendix B) (Local Consensus, 2018-2019 [5]).

Note 2: If an LP is deferred, admit the patient for observation; do not empirically start antimicrobials (Local Consensus, 2018-2019 [5]).

Note 3: If antimicrobial therapy will be initiated in infants who meet intermediate risk criteria, collect CSF specimens prior to treatment (Local Consensus, 2018-2019 [5]).

Note 4: If discharge is considered, have a collaborative discussion with:

- The patient’s PCP prior to discharge to ensure the family has a reliable follow-up plan within the next 24 hours (appointment or phone call if no office hours available the next day) (Local Consensus, 2018-2019 [5])
- The family to ensure they have documented working phone and understand the importance of close follow up with PCP and reasons to call/return (Local Consensus, 2018-2019 [5]).

Note 5: Consider repeating a PCT in 8 hours (time based on previous PCT lab draw). Evidence supports that PCT may be most useful for infants who present with FUS 6 or more hours after fever onset (Milcent, 2016 [3a]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

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Overall Strength of the Recommendation: ☐ Strong ☒ Moderate ☐ Weak ☐ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)
Consensus Statement 6
Consider obtaining an LP for CSF analyses in infants **29 to 60 days of age** with FUS who have a positive urinalysis **AND** applicable laboratory criteria considered high risk (PCT >0.5 ng/mL, regardless of the ANC) (See FUS Algorithm) (Kuppermann, 2019 [3a]; Local Consensus, 2018-2019 [5]).

### Dimensions of Judging the Recommendation Strength for accurate diagnosis

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**Overall Strength of the Recommendation:**

- **Strong**
- **Moderate**
- **Weak**
- **Consensus Only**

*Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)*

Consensus Statement 7
Consider testing for enteroviruses, influenza A and B viruses, rotavirus, and respiratory syncytial virus selectively for infants with fever, based upon history, physical exam, sick contacts, season, community infection patterns, or other clinical factors noted by the clinician, recognizing that a confirmed viral illness does not exclude a concomitant bacterial infection (Local Consensus, 2018-2019 [5]).

### Dimensions of Judging the Recommendation Strength for accurate diagnosis

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**Overall Strength of the Recommendation:**

- **Strong**
- **Moderate**
- **Weak**
- **Consensus Only**

*Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)*

Discussion/Synthesis of Evidence and Dimensions for Recommendation Statements 3 through 7
A retrospective cohort study published on the application of the Rochester criteria in identifying infants 60 days of age or younger with IBI found that among 82 febrile infants aged ≤ 60 days of age with IBI, sensitivity of the Rochester criteria were: 92.7% (95% CI, 84.9%-96.6%) overall; 91.7% (95% CI, 80.5%-96.7%) for neonates ≤ 28 days and 94.1% (95% CI, 80.9%-98.4%) for infants aged 29 to 60 days (Aronson, 2018 [4a]). Most importantly, six infants with bacteremia, including 1 neonate with bacterial meningitis, met low-risk criteria (Aronson, 2018 [4a]). Another challenge of the Rochester criteria is that it does not take into consideration new evidence related to the utility of other blood biomarkers (PCT, CRP).

The Lab score was derived from a population of 135 children and validated on a population of 67 children aged 7 days to 36 months recruited from a referral hospital in Geneva, Switzerland (Galetto-Lacour, 2010 [3b]; Lacour, 2008 [4a]). The utility of the Lab-score to identify SBI and IBI was assessed in a cohort of 1012 and 1098 respectively (Bressan, 2012 [4a]). Patients recruited from several EDs in Italy and Spain: SBI found in 28% of patients. At a cut-off value of 3, a sensitivity of 52% (95% CI: 46-58) and specificity of 95% (95% CI: 93-96) were reported. Notably, 30% (7 patients) with IBI were missed by
Lab-score with cutoff of 3. Hence, the Lab-score was more useful for ruling in, than ruling out SBI, and accuracy for IBI prediction was unsatisfactory (Bressan, 2012 [4a]).

The primary objective of the Step by Step method is to identify a low risk group of infants who could be safely managed as outpatients without LP or empirical antibiotic treatment. The evaluation includes the following in sequential order: general appearance of the infant (Pediatric Assessment Triangle), age, UA results, and blood biomarkers: PCT, CRP, ANC. Mintegi et al (2014, 4a) conducted a comparison of Step by Step, Lab-score and Rochester criteria in 1123 febrile infants <3 months of age (Mintegi, 2014 [4a]). Five infants with IBI were misclassified as “low risk” when the Rochester criteria and the Lab-score were each used compared to only 1 patient being misclassified as “low risk” using Step by Step. Additionally, the Step by Step method had a higher sensitivity and specificity than Rochester or lab-only criteria (Gomez, 2016 [3a]). However, 4 out of 7 patients 21-28 days of age with an IBI were missed using the Step by Step method (Gomez, 2016 [3a]). Finally, while the Step by Step model involves a sequential analysis of clinical and laboratory data; obtaining labs simultaneously was a preferred and more practical approach based on local consensus (Local Consensus, 2018-2019 [5]).

Most recently, Kuppermann et al (2019, 3a) conducted a prospective cohort multicenter study in the United States, to derive and validate a clinical prediction rule to identify infants 0-60 days of age with FUS at low risk for SBIs. The prediction rule identified infants at low risk of IBI by using a negative UA, an ANC ≤ 4090/μL and a PCT of ≤ 1.71 ng/mL. In the validation cohort, the prediction rule had a sensitivity and specificity of 96.7% and 61.5% respectively. One infant with bacteremia and two infants with UTIs were missed using the prediction rule. However, no patients with bacterial meningitis were missed. The authors also noted negligible differences in sensitivity and specificity in using more memorable cutoffs for PCT and ANC of 0.5 ng/mL and 4000 uL respectively. Given that the findings could be applied to our patient population with a similar prevalence of SBIs, and the establishment of a reliable prediction rule that does not include CRP, providers agreed that the evaluation suggested in this guideline to be a more practical approach based on local consensus.

The evidence of multiple studies suggests that the risk of meningitis in well-appearing infants age 28 days of age and greater is very low, including patients with concomitant UTI. In a study of 1975 infants with FUS over 21 days of age who were well-appearing, none were found to have had meningitis (Martinez, 2015 [4a]). Additional studies support the notion that well appearing infants over 28 days of age have a very low likelihood of meningitis (Thomson, 2017 [4a]; Mintegi, 2014 [4a]; Bressan, 2012 [4a]). Thomson, et al (2017,4a) did report that 2 (0.2%) patients over 28 days of age with UTI also had meningitis although both also had positive blood cultures and clinical appearance was not known (Thomson, 2017 [4a]). Paquette et al (2011, 4a) found that only one of 52 patients in their study had both UTI and meningitis; this infant was ill appearing at presentation and was also bacteremic (Paquette, 2011 [4a]). The negative predictive value of abnormal UA for meningitis was 98.2% in this study (Paquette, 2011 [4a]). Tebruegge et al (2011, 4b) reported concomitant bacterial meningitis in infants 0 to 28 days of age 0.9% of the time (95% CI 0.4%-1.8%) compared to 0 in infants 29 to 60 days of age (Tebruegge, 2011 [4b]). Additionally, evidence suggests that UTI alone may result in CSF pleocytosis and thus, evaluation of CSF in well-appearing infant with likely UTI may lead to concern for meningitis due to CSF cell counts alone. The concern over possible meningitis due to CSF pleocytosis has been shown to result in longer duration of IV antibiotic use compared to similar patients with UTI and no CSF pleocytosis (Schnadower, 2011 [4a]). Local consensus deemed that routine evaluation with LP is not warranted in this group of patients 29-60 days of age with UTI as likely source of SBI, due to the risk of additional unnecessary treatment, including longer hospitalization and IV antibiotic use.

Lastly, studies have recently evaluated outcomes related to clinical practice guidelines for management of FUS. The first study limited tested in those patients with likely UTI as source of fever and found lower admission rates, shorter lengths of stay and less antibiotic exposure without any increase in missed SBI (Byington, 2003 [4b]). A second study examined the impact of increased testing to include LP for evaluation of FUS for all patients up to 56 days. The outcomes included no decrease in adverse events including delay in diagnosis of meningitis (Chua, 2015 [4a]). Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below).

(Back to Statement 3, Statement 4, Statement 5, Statement 6, and Statement 7)
Management Recommendations
Emergency Department Discharge Criteria

Consensus Statement 8
Consider outpatient management of young infants 29 to 60 days of age with FUS if all the following conditions are present:

- Low-risk clinical and laboratory criteria (See FUS Algorithm) have been met (Irwin, 2016 [1b])
- There is a collaborative discussion with:
  - The patient’s PCP prior to discharge to ensure the family has an established follow up plan within the next 24 hours (e.g. appointment or phone call if no office hours available the next day)
  - The family to ensure they have a documented working telephone number and understand the importance of close follow up with the PCP and reasons to call/return to the ED

(Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm (Side Effects and Risks)
   - ☐ Minimal
   - ☑ Moderate / Neutral
   - ☐ Serious

2. Health benefit to patient
   - ☐ Minimal
   - ☐ Moderate / Neutral
   - ☑ Significant

3. Burden on population to adhere to recommendation
   - ☑ Low
   - ☐ Unable to determine
   - ☐ High

4. Cost-effectiveness to healthcare system
   - ☑ Cost-effective
   - ☐ Inconclusive
   - ☐ Not cost-effective

5. Directness of the evidence for this target population
   - ☑ Directly relates
   - ☐ Some concern of directness
   - ☐ Indirectly relates

6. Impact on quality of life, morbidity, or mortality
   - ☑ Positive
   - ☐ Moderate / Neutral
   - ☐ Negative

7. Grade of the Body of Evidence
   (See Evidence Table below; *GNA – Grade Not Assignable)
   - ☑ High
   - ☑ Moderate
   - ☑ Low
   - ☑ Very Low

Overall Strength of the Recommendation: ☑ Strong

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.
(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Admission Criteria

Care Recommendation Statement 9
It is recommended that all neonates 0 to 28 days of age with FUS be admitted to the hospital (Gomez, 2010 [4b]; Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm (Side Effects and Risks)
   - ☐ Minimal
   - ☑ Moderate / Neutral
   - ☐ Serious

2. Health benefit to patient
   - ☐ Minimal
   - ☐ Moderate / Neutral
   - ☑ Significant

3. Burden on population to adhere to recommendation
   - ☑ Low
   - ☐ Unable to determine
   - ☐ High

4. Cost-effectiveness to healthcare system
   - ☑ Cost-effective
   - ☐ Inconclusive
   - ☐ Not cost-effective

5. Directness of the evidence for this target population
   - ☑ Directly relates
   - ☐ Some concern of directness
   - ☐ Indirectly relates

6. Impact on quality of life, morbidity, or mortality
   - ☑ Positive
   - ☐ Moderate / Neutral
   - ☐ Negative

7. Grade of the Body of Evidence
   (See Evidence Table below; *GNA – Grade Not Assignable)
   - ☑ High
   - ☑ Moderate
   - ☑ Low
   - ☑ Very Low

Overall Strength of the Recommendation: ☑ Strong

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.
(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)
Consensus Statement 10

Consider admitting young infants 29-60 days of age with FUS to the hospital if they have a UA indicative of a UTI but meet all other low risk clinical and laboratory criteria (Local Consensus, 2018-2019 [5]).

Note: For infants being discharged from the ED ensure there is a collaborative discussion with:

- The patient’s PCP prior to discharge to inform the PCP of pending blood and urine culture results, discuss the antibiotic plan, and ensure the family has an established follow up plan within the next 24 hours (e.g. an appointment or phone call if no office hours available the next day)
- The family to ensure they understand the importance of close follow up with the PCP and reasons to return to the ED. Providers should also verify that the family has a reliable phone number clearly documented in the electronic health record.

(Local Consensus, 2018-2019 [5])

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Overall Strength of the Recommendation: ☐ Strong ☐ Moderate ☐ Weak ☒ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Consensus Statement 11

It is recommended that young infants 29 to 60 days of age with FUS be admitted to the hospital if they meet intermediate or high risk by clinical or laboratory criteria and/or when social or family concerns (e.g. transportation problems, lack of resources for prompt medical follow-up) are present (Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

<table>
<thead>
<tr>
<th>Dimensions of Judging the Recommendation Strength for accurate diagnosis</th>
<th>Minimal</th>
<th>Moderate / Neutral</th>
<th>Serious</th>
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<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
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<tr>
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<td>3. Burden on population to adhere to recommendation</td>
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<td>4. Cost-effectiveness to healthcare system</td>
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<td>☐</td>
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<tr>
<td>5. Directness of the evidence for this target population</td>
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<td>☐</td>
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<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
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<tr>
<td>7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)</td>
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Overall Strength of the Recommendation: ☐ Strong ☐ Moderate ☐ Weak ☒ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Inpatient Discharge Criteria

Care Recommendation Statement 12

It is suggested that providers consider discharge of infants 0 to 60 days of age with FUS at 24 hours, if all cultures are “no growth” at that time and the patient meets all other discharge criteria (McGowan, 2000 [3a]; Leazer, 2017 [4a]; Lefebvre, 2017 [4a]; Biondi, 2014 [4a]; Local Consensus, 2018-2019 [5]).

Note 1: The countdown to 24 hours starts from the time of final culture collection (Local Consensus, 2018 [5]).
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Note 2: Document blood, urine and CSF culture review by the laboratory in the electronic health record before considering discharge (Local Consensus, 2018 [5]).
- CSF cultures are only reviewed by the microbiology lab once per day in the morning. A CSF culture preliminary read is only documented in the electronic medical record once (on the first day that the culture is reviewed). A final negative read is documented on day 5. Documentation is ONLY updated if the CSF culture is positive.
- Use clinical discretion in determining how this process impacts discharge time for hospitalized infants with FUS.

Note 3: Be cautious regarding discharge at 24 hours if reliable follow up with the PCP, including plan for appointment or telephone call within the next 24 hours, cannot be arranged (Local Consensus, 2018-2019 [5]).

Note 4: Discharge criteria include:
- Well-appearing
- Eating well
- Culture results no growth at 24 hours
- Family:
  - Confident in caring for the infant at home
  - Has an established follow up and transportation plan
  - Has documented working phone number for follow up calls (i.e. if culture results return abnormal)
  - Understands the importance of close follow up with PCP and reasons to call/return
- PCP contacted by inpatient team and in agreement with the discharge and follow up plan (Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for admission discharge

| 1. Safety / Harm (Side Effects and Risks) | Minimal | Moderate / Neutral | Serious |
| 2. Health benefit to patient | Significant | Moderate / Neutral | Minimal |
| 3. Burden on population to adhere to recommendation | Low | Unable to determine | High |
| 4. Cost-effectiveness to healthcare system | Cost-effective | Inconclusive | Not cost-effective |
| 5. Directness of the evidence for this target population | Directly relates | Some concern of directness | Indirectly relates |
| 6. Impact on quality of life, morbidity, or mortality | Positive | Moderate / Neutral | Negative |
| 7. Grade of the Body of Evidence (See Evidence Table below, “GNA – Grade Not Assignable) | High | Moderate | Low | Very Low | GNA* |

Overall Strength of the Recommendation: ☐ Strong ☐ Moderate ☒ Weak ☐ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.
(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Discussion/Synthesis of Evidence and Dimensions for Recommendation Statements 8 through 12

Several studies considering the time to positivity of blood cultures contributed to this suggestion. Mean time to positivity for pathogens were noted to be 17.54 hours (McGowan, 2000 [3a]), 14.40 hours (Lefebvre, 2017 [4a]) and 15.41 hours (Blondi, 2014 [4a]); taken together, these three studies found 91-96.1% of known pediatric pathogens were detected within 24 hours. Less data are available regarding CSF culture positivity time, with one retrospective study noting true pathogens grew at a mean time of 28 hours +/- 17 hours (Leazer, 2017 [4a]) and another with 88.7% identified at 24 hours (Aronson, 2018 [4a]). One study reported that 85% of well appearing infants with IBI had a pathogen detected within 24 hours. However with an estimated rate of IBI of 2% in non–ill-appearing febrile infants, only 0.3%, or 1 in 333, will have a pathogen detected after 24 hours (Aronson, 2018 [4a]).

Assessment of risk based upon history and physical findings, used in one study to determine 24 vs 36 hours of observation (Byington, 2012 [4a]), was not included in the recommendation regarding discharge timing in this guideline as no evidence of relation between risk factors and time to positivity of cultures was found. Stipulations regarding all cultures being no growth and the patient being well-appearing and meeting all discharge criteria as outlined are encouraged to ensure appropriate discharge timing based upon all clinical considerations (Local Consensus, 2018-2019 [5]). Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below).

Evidence for admission of infants 29–60 days of age who meet high risk clinical and laboratory criteria is clear; the rationale for a complete evaluation, including an LP given the higher probability of an IBI has been outlined in the discussion of evidence for care recommendations 3-7. Our recommendation for admission of infants 29-60 days of age...
who 1) are considered intermediate risk based on clinical and laboratory criteria and/or 2) have social circumstances that create challenges for reliable and timely follow up is based on local consensus and not a significant body of evidence in the literature. Nevertheless, weighing the risks and benefits of timely identification of IBI in this vulnerable population, our committee chose to use the term “recommend” rather than “consider” (Local Consensus, 2018-2019 [5]).

(Back to Statement 8, Statement 9, Statement 10, Statement 11, and Statement 12)

Medications
Neonates 0 to 28 Days of Age

Care Recommendation Statement 13

It is strongly recommended that infants **0 to 28 days of age** with FUS are empirically treated with ampicillin and a third generation cephalosporin (Brown, 2002 [1b]; Hassoun, 2014 [4b]; Byington, 2003 [4b]).

**Note:** It is reasonable to consider gentamicin in place of a third-generation cephalosporin for specific circumstances (e.g. third generation cephalosporin shortage) (Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

<table>
<thead>
<tr>
<th>1. Safety / Harm (Side Effects and Risks)</th>
<th>☒ Minimal</th>
<th>☐ Moderate / Neutral</th>
<th>☐ Serious</th>
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<td>2. Health benefit to patient</td>
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<td>☐ Moderate / Neutral</td>
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<tr>
<td>3. Burden on population to adhere to recommendation</td>
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<td>☐ Unable to determine</td>
<td>☐ High</td>
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<td>4. Cost-effectiveness to healthcare system</td>
<td>☒ Cost-effective</td>
<td>☒ Inconclusive</td>
<td>☒ Not cost-effective</td>
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<tr>
<td>5. Directness of the evidence for this target population</td>
<td>☒ Directly relates</td>
<td>☒ Some concern of directness</td>
<td>☒ Indirectly relates</td>
</tr>
<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
<td>☒ Positive</td>
<td>☒ Moderate / Neutral</td>
<td>☒ Negative</td>
</tr>
<tr>
<td>7. Grade of the Body of Evidence (See Evidence Table below; <em>GNA – Grade Not Assignable</em>)</td>
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<td>☒ Moderate</td>
<td>☒ Low</td>
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</table>

Overall Strength of the Recommendation: ☒ Strong ☐ Moderate ☐ Weak ☐ Consensus Only

*Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)*

Consensus Statement 14

Consider using vancomycin in place of ampicillin for infants at risk for infection with *S. aureus*, and in severely ill infants (Local Consensus, 2018-2019 [5]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

<table>
<thead>
<tr>
<th>1. Safety / Harm (Side Effects and Risks)</th>
<th>☐ Minimal</th>
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<tbody>
<tr>
<td>2. Health benefit to patient</td>
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<td>☐ Moderate / Neutral</td>
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<td>3. Burden on population to adhere to recommendation</td>
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<td>4. Cost-effectiveness to healthcare system</td>
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<td>☒ Not cost-effective</td>
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<td>5. Directness of the evidence for this target population</td>
<td>☒ Directly relates</td>
<td>☒ Some concern of directness</td>
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<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
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<td>☒ Moderate</td>
<td>☒ Low</td>
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</table>

Overall Strength of the Recommendation: ☒ Strong ☐ Moderate ☐ Weak ☒ Consensus Only

*Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)*
Young Infants 29 to 60 Days of Age

**Care Recommendation Statement 15**

It is strongly recommended that infants **29 to 60 days of age** with FUS in whom antibiotic therapy is indicated are empirically treated with a third generation cephalosporin (Leazer, 2016 [1b]; Brown, 2002 [1b]; Biondi, 2013 [4b]).

**Dimensions of Judging the Recommendation Strength for accurate diagnosis**

1. Safety / Harm (**Side Effects and Risks**) ☒ Minimal ☐ Moderate / Neutral ☐ Serious
2. Health benefit to patient ☒ Minimal ☐ Moderate / Neutral ☐ Serious
3. Burden on population to adhere to recommendation ☒ Low ☐ Moderate / Neutral ☐ High
4. Cost-effectiveness to healthcare system ☒ Cost-effective ☐ Unable to determine ☐ High
5. Directness of the evidence for this target population ☒ Directly relates ☐ Some concern of directness ☐ Indirectly relates
6. Impact on quality of life, morbidity, or mortality ☒ Positive ☐ Moderate / Neutral ☐ Serious
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable) ☒ High ☒ Moderate ☐ Low ☐ Very Low ☐ GNA*

**Overall Strength of the Recommendation:** ☒ Strong ☐ Moderate ☐ Weak ☐ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

**Care Recommendation Statement 16**

It is recommended that for infants admitted with a UA suggestive of a UTI, IV ampicillin be considered as an addition to the antibiotic regimen to ensure coverage of *Enterococcus* (Brown, 2002 [1b]; Biondi, 2013 [4b]; Greenhow, 2012 [4b]).

**Dimensions of Judging the Recommendation Strength for accurate diagnosis**

1. Safety / Harm (**Side Effects and Risks**) ☒ Minimal ☐ Moderate / Neutral ☐ Serious
2. Health benefit to patient ☒ Minimal ☐ Moderate / Neutral ☐ Serious
3. Burden on population to adhere to recommendation ☐ Low ☒ Unable to determine ☐ High
4. Cost-effectiveness to healthcare system ☒ Cost-effective ☐ Inconclusive ☐ Not cost-effective
5. Directness of the evidence for this target population ☒ Directly relates ☐ Some concern of directness ☐ Indirectly relates
6. Impact on quality of life, morbidity, or mortality ☒ Positive ☐ Moderate / Neutral ☐ Serious
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable) ☒ High ☒ Moderate ☐ Low ☐ Very Low ☐ GNA*

**Overall Strength of the Recommendation:** ☒ Strong ☐ Moderate ☐ Weak ☐ Consensus Only

Given the dimensions above for each recommendation and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statements reflect the strength of each recommendation as judged by the development group.

(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

**Consensus Statement 17**

Consider adding vancomycin to the antibiotic regimen in infants who are at risk for infection with *S. aureus* (Local Consensus, 2018-2019 [5]).

**Note:** If these infants have findings suggestive of a UTI, utilize vancomycin in place of ampicillin (Local Consensus, 2018-2019 [5]).

**Dimensions of Judging the Recommendation Strength for accurate diagnosis**

1. Safety / Harm (**Side Effects and Risks**) ☒ Minimal ☐ Moderate / Neutral ☐ Serious
2. Health benefit to patient ☒ Minimal ☐ Moderate / Neutral ☐ Serious
3. Burden on population to adhere to recommendation ☐ Low ☒ Unable to determine ☐ High
4. Cost-effectiveness to healthcare system ☒ Cost-effective ☐ Inconclusive ☐ Not cost-effective
5. Directness of the evidence for this target population ☒ Directly relates ☐ Some concern of directness ☐ Indirectly relates
6. Impact on quality of life, morbidity, or mortality ☒ Positive ☐ Moderate / Neutral ☐ Serious
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable) ☒ High ☒ Moderate ☐ Low ☐ Very Low ☒ GNA*

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Discussion/Synthesis of the Evidence and Dimensions for the Recommendation 13 through 17

While several studies demonstrate declining rates of Listeria in this population (Leazer, 2016 [1b]; Brown, 2002 [1b]; Biondi, 2013 [4b]; Greenhow, 2012 [4b]), a small but persistent proportion of SBIs are attributable to Listeria (Hassoun, 2014 [4b]). Moreover, Enterococcus remains an important pathogen in infants less than 60 days of age, especially in UTIs but also occasionally in bacteremia, thus providing stronger evidence to empirically treat this population with ampicillin (Hassoun, 2014 [4b]). Local culture patterns also reflect the small but persistent incidence of these pathogens (local data). In addition, nearly half of pathogens are not susceptible to ampicillin (Byington, 2003 [4b]; Local Consensus, 2018-2019 [5]), necessitating empiric treatment with either a third generation cephalosporin or gentamicin.

Four of the six studies utilized to generate our recommendations were retrospective and graded 4b; two studies, one systematic review and one meta-analysis, were graded 1b. Taken together, we assigned our evidence a grade of “Moderate” for both the 0 to 28 day old and 29 to 60 day old infants. Given that dimensions one through six were assigned the highest rating, the consensus of our group felt it was reasonable to grade the strength of the recommendations for the 0 to 28 day population as “Strong”. For the 29 to 60 day old population, dimensions one through six were also assigned the highest rating; however, there was more debate amongst the consensus group in formulating these recommendations. Therefore, a moderate strength was assigned to these recommendations. Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below). Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below).

(Clinical Questions, Criteria for Inclusion, and Search Strategies & Results)

Clinical Question

What is the appropriate diagnostic work up/evaluation and management for infants 0 to 60 days (0 to 28 days or 29 to 60 days) of age with fever of uncertain source (FUS)?

Criteria for considering studies for this review

| Types of Studies | Systematic reviews, meta-analysis, randomized control studies, prospective cohort studies, retrospective cohort studies were considered for inclusion in the systematic review. |
| Types of Participants | Infants 0 to 60 days of age presenting to the ED with a FUS source were the population of studies included in this systematic review. |
| Types of Interventions | Evidence-based practice compared to current practice in managing FUS were considered for inclusion in the systematic review. |
| Types of Outcomes | Accurate diagnosis and appropriate admission without unnecessary testing were the outcomes which were considered for inclusion in the systematic review. |
| Exclusion Criteria. If any | Infants and children > 60 days |

Search Strategy

Search Methods

To select evidence for critical appraisal by the group for this guideline, the databases below were searched using search terms, limits, filters, and date parameters to generate an unrefined, “combined evidence” database. This search strategy focused on answering the clinical questions addressed in this document and employing a combination of Boolean searching on human-indexed thesaurus terms (e.g., MeSH) as well as “natural language” searching on words in the title, abstract, and indexing terms.
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

<table>
<thead>
<tr>
<th>Search Databases</th>
<th>Search Terms</th>
<th>Limits, Filters, &amp; Search Date Parameters</th>
<th>Date of Most Recent Search</th>
</tr>
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<td>exp &quot;Fever of Unknown Origin&quot;/ or Fever/ or fever of unknown source.mp</td>
<td>Publication Dates or Search Dates:</td>
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<td>UTI.mp. *</td>
<td>• Newborns 0 – 28 days</td>
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<td>cerebrospinal fluid</td>
<td>• Infant 0 to 23 months</td>
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</table>

Search Results

Electronic searches of data bases and manual searches of reference lists were conducted throughout the guideline development process with additional articles identified from subsequent refining searches for evidence. The citations were reduced by eliminating duplicates, review articles, non-English articles, and adult articles (e.g., limits/filters above). The resulting abstracts and full text articles were reviewed by a methodologist to eliminate low quality and irrelevant citations or articles. The dates of the most recent searches are provided above.

Electronic and manual searches for evidence identified 822 articles. This number was reduced by 274 articles because of duplication and 427 articles based on title and abstract review. Six articles were identified for background information only and are not reviewed in the Evidence Table.

One hundred and twenty-one articles met above inclusion criteria and were reviewed in full text appraised using the LEGEND system. Sixty-one studies were discarded because of irrelevance and/or quality. Fifty studies were found to be methodologically acceptable, addressing the clinical questions and are included in the Evidence Table. These along with obtaining local consensus when quality evidence was not available were used to create the guideline care recommendations and statements.

TEAM MEMBERS & CONFLICTS OF INTEREST

Group / Team Members

**Multidisciplinary Team**

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Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

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Paul Steele, MD, Medical Director, Clinical Laboratory, Cincinnati Children’s Hospital Medical Center
Victoria Wurster Ovalle, MD, Clinical Fellow, Division of Emergency Medicine, Cincinnati Children’s Hospital Medical Center

Patient/Family/Parent or Parent Organization:
Christina Harding, Parent

Evidence-Based Care Recommendation Development Support

Methodologist, Consultant:
Karen Vonderhaar, MS, RN, Evidence-based Decision Making Guideline Program Administrator, James M. Anderson Center for Health Systems Excellence, Cincinnati Children’s Hospital Medical Center

Conflicts of Interest were declared for each team member and:
☒ No financial or intellectual conflicts of interest were found.
☒ No external funding was received for development of these recommendation statements.
   Funding for development of this guideline was provided through Cincinnati Children’s salaries.
☐ The following conflicts of interest were disclosed: no conflicts noted.

Conflict of interest declarations information is maintained in Cincinnati Children’s ePAS (electronic Protocol Administration System).

External Funding

☐ No external funding was received for development of this recommendation.
   Recommendations were developed through hospital funding via salaries.
☐ External funding was received for development of this recommendation from Click or tap here to enter text.

Future Research Agenda

1. What role should viral testing play in the evaluation of infants 0 to 60 days of age with FUS?
2. In infants 0 to 60 days with FUS, what combination of or additional biomarkers are predictive of risk of IBI?
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

**LEGEND EVIDENCE EVALUATION SYSTEM** *(LET EVIDENCE GUIDE EVERY NEW DECISION)*

Full tables of the LEGEND evidence evaluation system are available in separate documents:
- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality *(abbreviated table below)*
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation *(Evidence Discussion and Dimensions for Recommendations section)*

**Table of Evidence Levels** *(see link above for full table):*

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<thead>
<tr>
<th>Quality Level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1a† or 1b†</td>
<td>Systematic review, meta-analysis, or meta-synthesis of multiple studies</td>
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<tr>
<td>2a or 2b</td>
<td>Best study design for domain</td>
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<td>3a or 3b</td>
<td>Fair study design for domain</td>
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<td>4a or 4b</td>
<td>Weak study design for domain</td>
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<td>5a or 5b</td>
<td>General review, expert opinion, case report, consensus report, or guideline</td>
</tr>
<tr>
<td>5</td>
<td>Local Consensus</td>
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</table>

†a = good quality study; b = lesser quality study

**Table of Grade for the Body of Evidence** *(see link above for full table):*

<table>
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<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
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<td>High</td>
<td>Good quality, High-level studies with consistent results</td>
</tr>
<tr>
<td>Moderate</td>
<td>Good quality, Lower-level OR Lesser quality, Higher-level studies with consistent* results</td>
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<td>Low</td>
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<td>Very Low</td>
<td>Few Good or Lesser quality, Low-level studies that may have inconsistent results</td>
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**Table of Language and Definitions for Recommendation Strength** *(see link above for full table):*

<table>
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<tr>
<th>Language for Strength</th>
<th>Definition</th>
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<tr>
<td>It is strongly recommended that...</td>
<td>When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly out weigh risks and burdens. (or visa-versa for negative recommendations)</td>
</tr>
<tr>
<td>It is strongly recommended that... not...</td>
<td>When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.</td>
</tr>
<tr>
<td>It is recommended that...</td>
<td>When the dimensions for judging the strength of the evidence are applied, there is weak support that benefits are closely balanced with risks and burdens.</td>
</tr>
<tr>
<td>It is recommended that... not...</td>
<td>When the dimensions for judging the strength of the evidence are applied, there is weak support that benefits are closely balanced with risks and burdens.</td>
</tr>
<tr>
<td>It is suggested that...</td>
<td>There is insufficient evidence to make a recommendation...</td>
</tr>
<tr>
<td>It is suggested that... not...</td>
<td>There is insufficient evidence to make a recommendation...</td>
</tr>
</tbody>
</table>

**EVIDENCE-BASED CLINICAL CARE RECOMMENDATION DEVELOPMENT PROCESS**

The process by which this guideline was developed is documented in the Guideline Development Process Manual; relevant development materials are kept electronically. The recommendations contained in this BEST were formulated by a multidisciplinary working group, which performed a systematic search and critical appraisal of the literature using LEGEND *(see section above)*. The guideline has been reviewed and approved by clinical experts not involved in the development process.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference, and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

**Consensus Process**

All key stakeholders, including community physicians and providers in the Divisions of General and Community Pediatrics, Emergency Medicine, Hospital Medicine, and Infectious Disease were engaged as a means of establishing consensus. Committee members conducted in-person meetings with each of stakeholder group between December 2018 and March 2019 in which proposed recommendations were reviewed. Stakeholder representatives at each in-person meeting was as follows: community physicians: 27, general and community pediatrics: 17 (2 Hopple St, 15 PPC) ED: 23, HM: 30, ID: 15. A survey was sent to all key stakeholders. Respondents were asked to identify their clinical affiliation, clinical role, and for
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

each proposed recommendation, their level of agreement on a 5-point Likert scale. Respondents were able to provide comments for each proposed recommendation. Eighty-nine respondents across all stakeholder groups completed the survey. The initial response rate was 80% with 91% agreement. The Committee reviewed the survey responses and made changes to recommendations based on consensus. Changes were made and shared with all stakeholder groups. Stakeholders were resurveyed. Forty-five respondents completed the resurvey for a 40% response rate generating 100% consensus agreement.

A guideline development team member reviewed the guideline with a parent representative. From the parent perspective, information should be shared in a standardized, simple manner as parents of febrile young infants are likely quite overwhelmed. This is addressed in the risks and benefits decision tool (See Appendix B). In addition, the importance of follow-up and actions taken to assure follow through with the primary care pediatrician were noted to be key components for new parents.

Review Process

This guideline has been reviewed against quality criteria by two independent reviewers from the Cincinnati Children’s Evidence Collaboration.

The guideline was also externally appraised by three independent reviewers using the AGREE instrument (Appraisal of Guidelines for Research and Evaluation) and the results by domain are:

- Scope and Purpose: 94%
- Stakeholder Involvement: 93%
- Rigor of Development: 100%
- Clarity and Presentation: 87%
- Applicability: 94%
- Editorial Independence: 100%

Revision Process

The guideline will be removed from the Cincinnati Children’s website, if content has not been revised within five years from the most recent publication date. A revision of the guideline may be initiated at any point within the five-year period that evidence indicates a critical change is needed. Team members reconvene to explore the continued validity and need of the guideline.

The most recent details for the search strategy, results, and review are documented in this guideline. Details of previous review strategies are not documented. However, all previous citations and content were reviewed for appropriateness to this revision. Experience with the implementation and monitoring of earlier publications of this guideline has provided learnings which have also been incorporated into this revision.

Review History

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>May, 2019</td>
<td>Revision</td>
<td>Revised Guideline</td>
</tr>
<tr>
<td>Oct, 2010</td>
<td>Revision</td>
<td>Revised Guideline</td>
</tr>
<tr>
<td>June, 2003</td>
<td>Revision</td>
<td>Revised Guideline</td>
</tr>
<tr>
<td>May, 1998</td>
<td>Original Publication</td>
<td>New guideline developed and published</td>
</tr>
</tbody>
</table>

Permission to Use the Guideline

This Evidence-Based Care Guideline (EBCG) and any related implementation tools (if applicable, e.g., screening tools, algorithms, etc.) are available online and may be distributed by any organization for the global purpose of improving child health outcomes.

Website address: http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/recommendations/default/

Examples of approved uses of the EBCG include the following:
- copies may be provided to anyone involved in the organization’s (outside of Cincinnati Children’s) process for developing and implementing evidence-based care guidelines;
- hyperlinks to the Cincinnati Children’s website may be placed on the organization’s website;
- the EBCG may be adopted or adapted for use within the organization, provided that Cincinnati Children’s receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification to Cincinnati Children’s (EBDMInfo@cchmc.org) is appreciated for all uses of any EBCG or its companion documents which are adopted, adapted, implemented, or hyperlinked.
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Please cite as
Unaka, N; Statile, A; Bensman, R; Courter, J; Desai, S; Haslam, D; Honerlaw, J; Murtagh Kurowski, E; Rudloff, J; Schaffeld, J; Sosa, T; Steele, P; Wurster Ovalle, V; Vonderhaar, K. (2019). Cincinnati Children's Hospital Medical Center: Evidence-based clinical care guideline for Evidence-Based Care Guideline for Management of Infants 0 to 60 days seen in Emergency Department for Fever of Unknown Source. http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/recommendations/default/, Guideline 02, pages 1- 43, April 2019. Hyperlink the document.

For more information
About this guideline, its companion documents, or the Cincinnati Children’s Evidence-Based Care Recommendation Development process, contact the Cincinnati Children’s Evidence Collaboration at EBDInfo@cchmc.org.

Note/Disclaimer
This guideline addresses only key points of care for the target population; it may not be a comprehensive practice guideline. These care recommendations result from review of literature and practices current at the time of their formulations. This guideline does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this guideline is voluntary. The clinician considering the individual circumstances presented by the patient must make the ultimate judgment regarding any specific care recommendation.

REFERENCES
Evidence Level in [ ]. Table of Evidence Levels in LEGEND section above

3. Irwin, AD; Wickenden, J; Le Doare, K; Ladhani, S; and Sharland, M: Supporting decisions to increase the safe discharge of children with febrile illness from the emergency department: a systematic review and meta-analysis. Archives of Disease in Childhood. 101(3): 259-66, 2016, [1b].
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16. Paquette, K; Cheng, MP; McGillivray, D; Lam, C; and Quach, C: Is a lumbar puncture necessary when evaluating febrile infants (30 to 90 days of age) with an abnormal urinalysis? Pediatr Emerg Care, 27(11): 1057-61, 2011, [4a].

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Local Consensus:

Ishimine, P: conjugate vaccine.
Poehling, KA; Talbot, TR; Griffin, MR et al.: ampicillin Infants.
Diaz, MG; Garcia, RP; Gamero, DB et al.: parenteral ampicillin
Hassoun, A; Stankovic, C; Rogers, A et al.: Blood culture time to positivity in febrile infants with bacteremia. JAMA Pediatr, 168(9): 844-9, 2014. [4a].

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Gomez, B; Mintegi, S; Benito, J; Egireun, A; Garcia, D; and Astobiza, E: Blood culture and bacteremia predictors in infants less than three months of age with fever without source. Pediatr Infect Dis J, 29(1): 43-7, 2010, [4b].
Mintegi, S; Benito, J; Astobiza, E; Capape, S; Gomez, B; and Egireun, A: Well appearing young infants with fever without known source in the emergency department: are lumbar punctures always necessary? European Journal of Emergency Medicine, 17(3): 167-9, 2010, [4b].
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Caviness, AC; Demmier, GJ; Almendarez, Y; and Selwyn, BJ: The Prevalence of Neonatal Herpes Simplex Virus Infection Compared with Serious Bacterial Illness in Hospitalized Neonate. The Journal of Pediatrics, 153(2): 164-169, 2008b, [5a].
Schwartz, S; Raveh, D; Toker, O; Segal, G; Godovitch, N; and Schlesinger, Y: A week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates. Archives of Disease in Childhood, 94(4): 287-92, 2009, [5a].


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Appendix A

Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Neonatal Herpes Simplex Virus: Risk Assessment, Testing and Treatment

High Risk Factors
- Historical and Physical Exam Findings
  - Seizure or abnormal neurologic exam
  - Vesicular or petechial rash
  - Poor perfusion
  - Excessive bleeding
  - Poorly healing scalp electrode site
  - Hypothermia (<36°C) in former term infant
  - Apnea in former term infant
  - Presence of maternal HSV symptoms within 7 days of delivery
  - Known household contact(s) with oral HSV since the infant’s birth

High Risk Factors
- Workup
  - CSF PCR
  - Serum PCR
  - Surface PCR (swab eye, mouth, rectum in order with one swab)
  - Vesicle PCR (if any present)
  - Hepatic Panel
  - Basic Metabolic Panel

AND

Treatment
- Acyclovir 20mg/kg q8hours

High Risk Factors
- Workup
  - s21 days: CSF PCR
  - 22-28 days: Hold CSF

In addition to SBI evaluation
See CSF Risk Factors

CSF Risk Factors
- Pleocytosis (CSF WBCs >15) with no organisms on gram stain
- <50% neutrophils

Non-high risk infants >21 days rarely present with HSV; we do not recommend testing unless CSF risk factors are met.

Note regarding discharge
- Floor team will be responsible for calling PCR tech for all samples sent after 3pm on Friday until Monday morning
- Recommend awaiting results of PCR prior to discharging home
- Lab Contact Information: Monday-Saturday 833-636-9820
- Sunday pager: "PCR Tech" on "Who's on Call"

Note regarding liberty
- Scheduled courier from Liberty to Base: 7am, 11am, 3pm, 7pm, 11pm
- Stat Courier Contact Information: Available at all times
- Contact the main lab at 513-636-7344 or 513-636-7341

Definitions
- HSV = Herpes simplex virus
- CSF = Cerebrospinal fluid
- PCR = Polymerase chain reaction
- SBI = Serious bacterial infection
- WBC = White blood cell
Appendix B

Patient-Centered Decision Making Tool
Intermediate Risk Infants, Age 29-60 Days

Per the "FUS Algorithm: Fever of Unknown Source in Infants 0 to 60 Days of Age" (page 7), intermediate risk infants (age 29-60 days) are defined as:

- Well-appearing
- Absence of chronic illness
- Normal Pediatric Triangle Assessment
- Laboratory results:
  - Negative UA
  - Procalcitonin ≤ 0.5 ng/mL
  - ANC > 4,000/mm³

Management Options:

<table>
<thead>
<tr>
<th></th>
<th>Defer CSF Studies</th>
<th>Obtain CSF Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td>- No pain from lumbar puncture procedure</td>
<td>- Ability to evaluate CSF for signs of infection and obtain CSF culture</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td>- Missed meningitis</td>
<td>- Traumatic lumbar puncture</td>
</tr>
<tr>
<td></td>
<td>Note: In one prospective cohort, multicenter study, 0.8% of infants with a negative UA and an ANC &gt; 4090/mm³ had meningitis.</td>
<td>- Unable to obtain CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hematoma (making future attempts more challenging)</td>
</tr>
<tr>
<td><strong>Next Steps</strong></td>
<td>The infant should be admitted to the hospital OFF of antibiotics for observation of:</td>
<td>Consider initiating empiric antibiotics and admit to the hospital.</td>
</tr>
<tr>
<td></td>
<td>- Blood and urine cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Clinical stability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If blood culture becomes positive or infant becomes ill-appearing, obtain CSF studies and initiated antibiotics.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Discuss the risks and benefits of the lumbar puncture with families. Parents may express concern about risks such as damage to the spinal cord, bleeding, or introduction of infection. Counsel parents that these events are rare and are minimized through the use of appropriate technique.
### Pediatric Assessment Triangle

Dieckmann R et al. *Pediatr Emerg Care* 2010. PMID [20386420](http://blog.ercast.org/2010/05/the-toxic-neonate/)

(Courtesy of Dr. Michelle Reina & Dr. Rob Bryant)

The PAT functions as a rapid, initial assessment to determine "sick" or "not sick," and should be immediately followed by/not delay the ABCDEs. It can be utilized for serial assessment of patients to track response to therapy.

### Appearance: The “Tickles” (TICLS) Mnemonic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal features</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (tone)</td>
<td>Move spontaneously, resists examination, sits or stands (age appropriate)</td>
</tr>
<tr>
<td>I (interactivity)</td>
<td>Appears alert/engaged with clinician or caregiver, interacts well with people/environment, reaches for objects</td>
</tr>
<tr>
<td>C (consolability)</td>
<td>Stops crying with holding/comforting by caregiver, has differential response to caregiver vs. examiner</td>
</tr>
<tr>
<td>L (look/gaze)</td>
<td>Makes eye contact with clinician, tracks visually</td>
</tr>
<tr>
<td>S (speech/cry)</td>
<td>Uses age-appropriate speech</td>
</tr>
</tbody>
</table>

### Work of breathing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abnormal features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal airway sounds</td>
<td>Snoring, muffled/hoarse speech, stridor, grunting, wheezing</td>
</tr>
<tr>
<td>Abnormal positioning</td>
<td>Sniffing position, tripoding, prefers seated posture</td>
</tr>
<tr>
<td>Retractions</td>
<td>Supraclavicular, intercostal, or substernal, head bobbing (infants)</td>
</tr>
<tr>
<td>Flaring</td>
<td>Flaring of the nares on inspiration</td>
</tr>
</tbody>
</table>

### Circulation to skin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abnormal features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>White/pale skin or mucous membranes</td>
</tr>
<tr>
<td>Mottling</td>
<td>Patchy skin discoloration due to variable vasoconstriction</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Bluish discoloration of skin/mucous membranes</td>
</tr>
</tbody>
</table>