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 (SBI) 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 ≥38º 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 and 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** (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]; Woeiker, 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]).

(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]).

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

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

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]).*

*(Evidence Discussion & Dimensions for Recommendations 3 through 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]).*

*(Evidence Discussion & Dimensions for Recommendations 8 through 12)*

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]).*

*(Evidence Discussion & Dimensions for Recommendations 8 through 12)*

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]).*

*(Evidence Discussion & Dimensions for Recommendations 8 through 12)*

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]).*

*(Evidence Discussion & Dimensions for Recommendations 8 through 12)*
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

(Evidence Discussion & Dimensions for Recommendations 8 through 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]).

(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]).

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*
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

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

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

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

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

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

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

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

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

ACTION
- Option 1: Defer 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 and Definitions

#### 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

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal Fluid (CSF) pleocytosis</td>
<td>Neonates age 0 to 28 days: CSF white blood cell count ≥15/μL</td>
</tr>
<tr>
<td></td>
<td>Infants 29 to 60 days CSF white blood cell count ≥ 9 μL.</td>
</tr>
<tr>
<td>Fever of uncertain source (FUS)</td>
<td>An acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical exam</td>
</tr>
<tr>
<td>Fever</td>
<td>Temperature ≥ 38°C (100.4 °F)</td>
</tr>
<tr>
<td>Invasive bacterial infection (IBI)</td>
<td>Bacteremia and/or bacterial meningitis in infants ≤ 60 days of age</td>
</tr>
<tr>
<td>Ill-appearing</td>
<td>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</td>
</tr>
<tr>
<td>Neonate</td>
<td>Infant birth to 28 days of age</td>
</tr>
<tr>
<td>Previously healthy</td>
<td>Term Birth (≥ 37 weeks’ gestation)</td>
</tr>
<tr>
<td></td>
<td>Not treated for unexplained hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Not hospitalized longer than mother</td>
</tr>
<tr>
<td></td>
<td>No current or previous antimicrobial therapy</td>
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<tr>
<td></td>
<td>No previous hospitalization</td>
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<tr>
<td></td>
<td>No chronic or underlying illness</td>
</tr>
<tr>
<td>Serious bacterial infection (SBI)</td>
<td>A urinary tract infection, bacterial meningitis, bacteremia, bacterial pneumonia, gastroenteritis, cellulitis, osteomyelitis, or septic arthritis</td>
</tr>
<tr>
<td>Well appearing</td>
<td>Defined by a normal Pediatric Assessment Triangle (PAT): 3 components of the PAT are appearance, work of breathing, and circulation to the skin</td>
</tr>
<tr>
<td></td>
<td>(Horeczko, 2013 [4a]; Dieckmann, 2010 [5a]) (See Appendix C)</td>
</tr>
<tr>
<td>Young infant</td>
<td>Children 29 to 60 days of age</td>
</tr>
</tbody>
</table>
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
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
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  - 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]).

Dimensions of Judging the Recommendation Strength for accurate diagnosis

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
<td>☐ Minimal</td>
</tr>
<tr>
<td>2. Health benefit to patient</td>
<td>☒ Moderate / Neutral</td>
</tr>
<tr>
<td>3. Burden on population to adhere to recommendation</td>
<td>☒ High</td>
</tr>
<tr>
<td>4. Cost-effectiveness to healthcare system</td>
<td>☐ Moderate / Neutral</td>
</tr>
<tr>
<td>5. Directness of the evidence for this target population</td>
<td>☐ Low</td>
</tr>
<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
<td>☐ Moderate / Neutral</td>
</tr>
<tr>
<td>7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)</td>
<td>☒ High</td>
</tr>
</tbody>
</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.)

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Minimal</th>
<th>Moderate / Neutral</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>2. Health benefit to patient</td>
<td>☒</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>3. Burden on population to adhere to recommendation</td>
<td>☒</td>
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<td>4. Cost-effectiveness to healthcare system</td>
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</tr>
<tr>
<td>5. Directness of the evidence for this target population</td>
<td>☐</td>
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<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>
<td>☒</td>
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</tbody>
</table>

Box: ☑ Moderate; ☒ Minimal; ☐ Serious

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

**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 (Nosrati, 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. (Luaces-Cabells, 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).

(Back to Statement 1 & Statement 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-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

## Guideline 10

### 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 | ☛ Significant | ☐ Moderate / Neutral | ☐ Minimal |
| 3. Burden on population to adhere to recommendation | ☛ Cost-effective | ☛ Inconclusive | ☛ Not cost-effective |
| 4. Cost-effectiveness to healthcare system | ☛ Low | ☛ 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 | ☛ 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.)

### 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 \(\geq 10\) WBC per high power field) if:

1. they meet all other low risk clinical criteria and
2. PCT is \(\leq 0.5\) ng/mL regardless of the ANC value


### 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 | ☚ Significant | ☛ Moderate / Neutral | ☛ Minimal |
| 3. Burden on population to adhere to recommendation | ☛ Cost-effective | ☚ Inconclusive | ☚ Not cost-effective |
| 4. Cost-effectiveness to healthcare system | ☚ Low | ☚ 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 | ☚ 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.)

### 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 \(\leq 0.5\) 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

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.)

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

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.)

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

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 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 (Galletto-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, Kupperman 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.
Evidence-Based Care Guideline for Management of Infants
0 to 60 days with Fever of Unknown Source

Guideline 10

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 | ☐ 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.)

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 | ☐ 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.)
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])

### 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 | □ 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 | ☒ 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.

(Notice 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

| 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 | ☒ 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.

(Notice 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]).

**Note 2:** Document blood, urine and CSF culture review by the laboratory in the electronic health record before considering discharge (Local Consensus, 2018 [5]).
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Guideline 10

- 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 | ☒ 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 (Biondi, 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]). This study factors into our suggestion that the CSF culture should be reviewed prior to discharge and a clear plan for follow up by an outpatient primary care provider (Local Consensus, 2018-2019 [5]).

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

| 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.)

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

| 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.)
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

<table>
<thead>
<tr>
<th>Recommendation Statement</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
<th>Consensus Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
<td>☒ Minimal</td>
<td>☐ Moderate / Neutral</td>
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<td></td>
</tr>
<tr>
<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>4. Cost-effectiveness to healthcare system</td>
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<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>
<td></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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<tr>
<td>7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)</td>
<td>☐ High</td>
<td>☒ Moderate</td>
<td>☒ Low</td>
<td>☐ Very 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.)

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

<table>
<thead>
<tr>
<th>Recommendation Statement</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
<th>Consensus Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
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<td>☐ Moderate / Neutral</td>
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<tr>
<td>2. Health benefit to patient</td>
<td>☒ Significant</td>
<td>☐ Moderate / Neutral</td>
<td>☐ Minimal</td>
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<tr>
<td>3. Burden on population to adhere to recommendation</td>
<td>☒ Low</td>
<td>☐ Unable to determine</td>
<td>☐ High</td>
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<tr>
<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>
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<tr>
<td>6. Impact on quality of life, morbidity, or mortality</td>
<td>☒ Positive</td>
<td>☐ Moderate / Neutral</td>
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<td>7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)</td>
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<td>☒ Moderate</td>
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<td>☐ Very 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 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

<table>
<thead>
<tr>
<th>Recommendation Statement</th>
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<th>Moderate</th>
<th>Weak</th>
<th>Consensus Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety / Harm (Side Effects and Risks)</td>
<td>☒ Minimal</td>
<td>☐ Moderate / Neutral</td>
<td>☐ Serious</td>
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<tr>
<td>2. Health benefit to patient</td>
<td>☒ Significant</td>
<td>☐ Moderate / Neutral</td>
<td>☐ Minimal</td>
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<tr>
<td>3. Burden on population to adhere to recommendation</td>
<td>☒ Low</td>
<td>☐ Unable to determine</td>
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<td>4. Cost-effectiveness to healthcare system</td>
<td>☒ Cost-effective</td>
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<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>
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<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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<tr>
<td>7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)</td>
<td>☐ High</td>
<td>☒ Moderate</td>
<td>☒ Low</td>
<td>☐ Very 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.)
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).

(Back to Statement 13, Statement 14, Statement 15, Statement 16, and Statement 17)

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.

<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>
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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: • 01/2000 to Present</td>
<td>9/25/2018</td>
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<td>*CINAHL</td>
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<td>*Cochrane Database for Systematic Reviews</td>
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<td>• UTI.mp. *</td>
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<td>• cerebrospinal fluid</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.
Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Guideline 10

TEAM MEMBERS & CONFLICTS OF INTEREST

**Group / Team Members**

**Multidisciplinary Team**

**Team Leader/Author:**
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Angela Statile, MD, MEd Associate Professor, Division of Hospital Medicine, Cincinnati Children’s Hospital Medical Center

**Team Members/Co-Authors:**
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Karen Jerardi, MD, MEd, Associate Professor, Division of Hospital 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.

☐ 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.

**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?
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):

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a† or 1b†</td>
<td>Systematic review, meta-analysis, or meta-synthesis of multiple studies</td>
</tr>
<tr>
<td>2a or 2b</td>
<td>Best study design for domain</td>
</tr>
<tr>
<td>3a or 3b</td>
<td>Fair study design for domain</td>
</tr>
<tr>
<td>4a or 4b</td>
<td>Weak study design for domain</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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</thead>
<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>
</tr>
<tr>
<td>Low</td>
<td>Good or lesser quality, Lower-level with results that may be inconsistent</td>
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<tr>
<td>Very Low</td>
<td>Few Good or Lesser quality, Low-level studies that may have inconsistent results</td>
</tr>
<tr>
<td>Grade Not Assignable</td>
<td>Local Consensus</td>
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### Table of Language and Definitions for Recommendation Strength (see link above for full table):

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<th>Language for Strength</th>
<th>Definition</th>
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<tbody>
<tr>
<td>It is strongly...</td>
<td>When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly outweigh risks and burdens. (or visa-versa for negative recommendations)</td>
</tr>
<tr>
<td>It is strongly...</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 suggested...</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>There is insufficient evidence to make a recommendation...</td>
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</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 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>
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<td>Oct, 2010</td>
<td>Revision</td>
<td>Revised Guideline</td>
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<tr>
<td>June, 2003</td>
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</tr>
<tr>
<td>May, 1998</td>
<td>Original Publication</td>
<td>New guideline developed and published</td>
</tr>
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Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

Guideline 10

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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.

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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]
4. Leazer, R; Perkins, AM; Shomaker, K; and Fine, B: A Meta-analysis of the Rates of Listeria monocytogenes and Enterococcus in Febrile Infants. Hospital Pediatrics, 6(4): 187-95, 2016. [1b]
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51. 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].
Appendix A

Neonatal Herpes Simplex Virus: Risk Assessment, Testing and Treatment

Start: 51B days of age and undergoing evaluation for serious bacterial infection

Yes

No

High Risk

High Risk Factors?

Yes

No

Non-High Risk

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 q8h

1 In addition to SBI evaluation per CEMAC guidelines

Workup

s21 days CSF PCR

22-28 days Hold CSF

2 In addition to SBI evaluation

3 See CSF Risk Factors

CSF Risk Factors?

Yes

No

No acyclovir

6 Unless CSF HSV PCR is positive or there is a change in clinical condition

High Risk Factors

- Historical and Physical Exam Findings
  - Seizure or abnormal neurologic exam
  - Vascular 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

Note: This list is not inclusive of all risk factors for neonatal HSV disease.

7 Disseminated HSV disease can present with respiratory distress.

8 Preterm infants are at higher risk for hypothermia and apnea related to non-HSV viral infections or environmental factors. Consider discussing workup of these patients with neonatal intensive care.

CSF Risk Factors

- Pleocytosis (CSF WBCs >5) with no organisms on gram stain
  - AND
  - <50% neutrophils

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

Traumatic lumbar puncture: Interpret number of WBCs regardless of CSF HBC count. Do not correct for RBCs.

Note regarding discharge

- Floor team will be responsible for calling PCR tech for all samples sent after 5pm on Friday until Monday morning
- Recommend awaiting results of PCR prior to discharge to home
- Lab-Contact Information: Monday-Saturday 513-636-9620
- 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>
</tbody>
</table>
| **Risks**        | • Missed meningitis                                                              | • Traumatic lumbar puncture
Note: In one prospective cohort, multicenter study, 0.8% of infants with a negative UA and an ANC > 4090/mm³ had meningitis. |
|                  |                                                                                  | • Unable to obtain CSF
• Hematoma (making future attempts more challenging) |
| **Next Steps**   | The infant should be admitted to the hospital OFF of antibiotics for observation of: |
|                  | • Blood and urine cultures
• Clinical stability                                                               | Consider initiating empiric antibiotics and admit to the hospital. |
|                  | If blood culture becomes positive or infant becomes ill-appearing, obtain CSF studies and initiated antibiotics. |

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.
**Appendix C**

**Pediatric Assessment Triangle**

Dieckmann R et al. *Pediatr Emerg Care* 2010. PMID 20386420
ER CAST: 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><strong>T</strong> one</td>
<td>Move spontaneously, resists examination, sits or stands (age appropriate)</td>
</tr>
<tr>
<td><strong>I</strong>nteractiveness</td>
<td>Appears alert/engaged with clinician or caregiver, interacts well with people/environment, reaches for objects</td>
</tr>
<tr>
<td><strong>C</strong>onsolability</td>
<td>Stops crying with holding/comforting by caregiver, has differential response to caregiver vs. examiner</td>
</tr>
<tr>
<td><strong>L</strong> ook/gaze</td>
<td>Makes eye contact with clinician, tracks visually</td>
</tr>
<tr>
<td><strong>S</strong> peech/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><strong>P</strong>allor</td>
<td>White/pale skin or mucous membranes</td>
</tr>
<tr>
<td><strong>M</strong>ottling</td>
<td>Patchy skin discoloration due to variable vasoconstriction</td>
</tr>
<tr>
<td><strong>C</strong>yanosis</td>
<td>Bluish discoloration of skin/mucous membranes</td>
</tr>
</tbody>
</table>

---

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

Guideline 10

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September 5, 2018

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### Diagnostic Studies for Accurate Serious Bacterial Infection Diagnosis

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Study Type</th>
<th>N Sample Size</th>
<th>Population (Setting, Patients)</th>
<th>Intervention / Comparison Groups</th>
<th>Outcomes</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>England, 2014</td>
<td>Meta-analysis</td>
<td>3217</td>
<td>7 studies involved infants &lt;91 days with fever ≥ 38°C, with use of procalcitonin in initial assessment.</td>
<td>Cutoffs for PCT included 0.3, 0.12, and 0.5 ng/mL depending on the study.</td>
<td>Relative risk of SBI averaged 3.97 (CI 3.41-04.62) for PCT above cutoff used for study.</td>
<td>1a</td>
</tr>
<tr>
<td>Hu, 2017</td>
<td>Systematic review</td>
<td>17 articles included – 1415 pts total</td>
<td>5 studies included our age (&lt;3 months) in varying ranges</td>
<td>Diagnostic value of PCT and CRP (separately) figuring out if SBI in patients with FUO</td>
<td>In meta-analysis:</td>
<td>1b</td>
</tr>
<tr>
<td>Leazer, 2016</td>
<td>Meta-analysis – rates of Enterococcus and Listeria among febrile infants</td>
<td>16 studies</td>
<td>Studies conducted in US published between 1998-2014</td>
<td>Describing rates of Listeria and Enterococcus – no comparisons</td>
<td>20703 bld cx: 0.03% Listeria, 0.09% Entero 13775 CSF cx: 0.02% Listeria, 0.03% Entero 18283 urine cx: 0 Listeria, 0.28% Entero</td>
<td>1b</td>
</tr>
<tr>
<td>Irwin, 2016</td>
<td>Review of multiple prospective studies via medline and Cochrane</td>
<td>33 studies were reviewed. 14 of these involved infants &lt; 3 months</td>
<td>In the 0-3 months group (14 studies) Rochester and Philadelphia criteria were used.</td>
<td>Review evaluated both Rochester and Philadelphia criteria to see when infants under 3 months can be safely discharged from the ER after fever.</td>
<td></td>
<td>1b</td>
</tr>
<tr>
<td>Brown, 2002</td>
<td>Systematic Review</td>
<td>5247 infants with bacteremia and/or meningitis</td>
<td>Studies assessing febrile infants &lt;3 mo in outpatient setting (ED, clinic, etc) for presence of SBI. Studies reported prevalence of L. monocytogenes &amp; enterococci.</td>
<td>Describe prevalence of infections requiring ampicillin in febrile pts &lt;3 mo of age undergoing ruleout for SBI, with cultures.</td>
<td></td>
<td>1b</td>
</tr>
</tbody>
</table>

#### Significant Results and Conclusions

- **Studies reported prevalence of L. monocytogenes & enterococci.**
- **Studies assessing febrile infants <3 mo in outpatient setting (ED, clinic, etc) for presence of SBI.**
- **Studies conducted in US published between 1998-2014.**
- **Studies involved infants <91 days with fever ≥ 38°C, with use of procalcitonin in initial assessment.**
- **Cutoffs for PCT included 0.3, 0.12, and 0.5 ng/mL depending on the study.**
- **Relative risk of SBI averaged 3.97 (CI 3.41-04.62) for PCT above cutoff used for study.**
- **Of 641 pts with PCT > cutoff, SBI in 42.7%.**
- **Of 1676 pts with PCT < cutoff, SBI in 12.5%**
- **PCR < 0.3 ng/mL had a “low” risk of SBI, those > than cutoff had a RR that averaged 3.97**
- **PCT alone is a poor predictor of SBI and does not stand alone for discriminating SBI patients in this age group.**
- **PCT may be used in combination with a clinical prediction rule.**
- **Not focused on our age group so gives us support for including PCT and CRP but not sure we can go further than that.**
- **Note different cut offs in each study so does not help us with that problem either.**
- **We really don’t see Listeria in US after birth due to changes to USDA food laws – can screen families to ask about high risk travel but empiric abx to cover may not be necessary.**
- **Combos of both criteria could safely be used to predict d/c.**
- **Prevalence of Listeria/Enterococcus per 1000 febrile infants**
- **Patients with bacteremia and/or meningitis:**
  - **Month of Life**
  - **n**
  - **Prevalence**

<table>
<thead>
<tr>
<th>Month</th>
<th>n</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1754</td>
<td>4.0% (95%CI 1.6 - 8.2)</td>
</tr>
<tr>
<td>2</td>
<td>3088</td>
<td>0.6% (95%CI 0.1 - 2.3)</td>
</tr>
<tr>
<td>3</td>
<td>405</td>
<td>2.7% (95%CI 0.6 -17.2)</td>
</tr>
</tbody>
</table>

**Number Needed to Cover**

<table>
<thead>
<tr>
<th>Month</th>
<th>Number Needed to Cover</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>251 (95%CI 122 to 623)</td>
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</table>
### Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

**Guideline 10**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Population</th>
<th>Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuppermann, 2019</td>
<td>Prospective observational multicenter study</td>
<td>Infants 0-60 days of age who presented to the ED with FUS (documented at home in the past 24 hours, another healthcare setting or in the ED on presentation)</td>
<td>Prospectively examined rates of bacteremia, meningitis or UTI (SBI). Conducted recursive partitioning analysis to identify low risk cohort of infants: Cutoffs chosen for each predictor using decision trees in derivation set. Random assignment of 908 to derivation set, and 913 to validation set</td>
<td>For prediction rule: 1. UA + - ANC &gt;4090 - PCT &gt; 1.71 ng/ml - For IBI: sensitivity 96.7%, 95%CI 83.3-99.4) and specificity was 61.5% (95% CI, 59.2-63.9). Only missed 1 pt with bacteremia: Enterobacter, PCT 0.14. This pt was admitted for poor feeding, afebrile initially, then 38.1C. Blood cx positive, then started abx for transient bacteremia. Repeat cx prior to abx was negative. Uneventful course</td>
<td>- A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections - 1821 infants enrolled; 1806 (99.2%) had CBCs, 1775 (97.5%) had urinalyses, 1399 (76.8%) had lumbar punctures performed (including 871 of 1266 infants aged 29-60 days (68.8%)) - Of the 1821 infants,908 were randomly allocated to the derivation set and 913 to the validation set - No patient who did not have CSF cultured obtained were later found to have bacterial meningitis - SBIs diagnosed in 170 infants (9.3%; 95% CI, 8.1-10.8), including 151 (8.3%; 95%CI,7.1-9.6) with UTIs ,26 (1.4% ;95%CI,1.0-2.1) with bacteremia, and 10 (0.5%; 95%CI,0.3-1.0) with bacterial meningitis;16 (0.9%,95%CI,0.5-1.4) had concurrent bacterial infections - Of the 16 with multiple infections,1 had UTI, bacteremia, and meningitis; 5 had bacteremia and meningitis; and 10 had UTI and bacteremia - 4 patients had HSV infections (all were hospitalized). 3 were &lt;28 days (aged 10, 12, 20 days) &amp; had +CSF for HSV; the other was 33 days &amp; had HV detected in nasal swab only.</td>
<td></td>
</tr>
<tr>
<td>Cruz, 2017</td>
<td>Prospective Observational Multicenter</td>
<td>Febrile (&gt;38°C), previously healthy, full-term infants &lt;60 days old who visited a pediatric ER &amp; had blood cultures drawn.</td>
<td>97 (2.2%) had bacteremia or bacterial meningitis (IBI). Specifically, 1.7% had isolated bacteremia. 0.6% had bacterial meningitis.</td>
<td>- Markers = CBC parameters WBC, ANC, platelet count. All markers with low sensitivity for IBI dx. - All patients either had CSF culture (77%) or 7-day telephone follow-up to ascertain missed bacterial meningitis</td>
<td>- ANC did best, all AUCs were classified as poor discriminatory value (&lt;0.7) or minimally accurate (0.7-0.8). - AUC of 0.70 for all ages (4.1K threshold), 0.73 for 0 – 28 day infants (5.4K threshold), 0.60 for 29 – 60-day old infants (4.1 K threshold), - For WBC, AUC of 0.57 for all ages (threshold 11.6), 0.57 for 0-28 day of age (threshold 11.6), 0.52 for 29-60 day of age (threshold 9.0). - Neither thrombocytosis nor thrombocytopenia had adequate accuracy. - CBC parameters alone are not suitable.</td>
<td></td>
</tr>
<tr>
<td>Gomez, 2016</td>
<td>Retrospective cohort</td>
<td>Infants &lt; 3 months, well appearing, fever without a source (SBI)</td>
<td>For prediction rule: IBI = pathogen from blood or CSF - PCT: OR for IBI 21.7 (7.9-59.23)</td>
<td></td>
<td>- Patients with bacteriuria (all Enterococcus): Month of Life prevalence and cutoffs: 1.7% had isolated bacteremia. 0.52 f 29-60 day of age (threshold 9.0). - Neither thrombocytosis nor thrombocytopenia had adequate accuracy. - CBC parameters alone are not suitable.</td>
<td></td>
</tr>
</tbody>
</table>
Evidence-Based Care Guideline for Management of Infants
0 to 60 days with Fever of Unknown Source

Guideline 10

### Milcent, 2016

| Prospective cohort | 2047 infants | 7-91 days, 15 French EDs, 2008-11 | 139 SBI (6.8%), 21 IBI (1%) 13 bacteremia & 8 meningitis Procal vs CRP Cutoff 0.3 for procal Neg LR: 0.3 for SBI, 0.1 IBI Cutoff 20 mg/L CRP LR 0.3 for SBI & IBI. | • Sensitivity and negative predictive value for ruling out an IBI
• Step by Step 92.0% and 99.3% (7 misclassified but 6 were only febrile for 2 hours at time of testing)
• Rochester: 81.6% and 98.3% (16 misclassified) Lab score: 59.8% and 98.1% (35 misclassified)
• HI risk – full eval <21 days, leukocytoria, procal;
• Procal vs CRP: step by step compared to Rodchester
• Step by step approach-high risk is ill appearing, < 21 days, PCT ≥.5 intermediate risk CRP>20, ANC>10000
• Findings:
  • support adding PCT/CRP to lab evaluation of febrile infants to identify IB;
  • supports use of StepbyStep method (ie procalcitonin +CRP).
• Age cutoff of 21 days is controversial- need to discuss further

### Velasco, 2015

| Multicenter observational prospective study | 3401 Infants < 90 days presenting with FWS with CRP, WBC, urine dipstick, urine & blood @ ED of 19 hospital members of Spanish Pedi Emergency Research Group of Spanish Society of Pediatric Emergencies | Compared IBI patients (50) versus non-IBI patients (716) for well-appearing, age, CRP, WBC, and, in 597 patients, procalcitonin. IBI defined as positive blood culture and/or CSF culture (excluding contaminants) 766/3401 infants (22.5%) had altered UA | • Risk factors for IBI =: non-well-appearing, age <21 days, CRP >2.0 mg/dL, procalcitonin >0.5 ng/mL None of these associated with 0% incidence of IBI
• Infants ≤ 21 days old OR 2.42 CI 1.18–4.96,
• Appearance Non-well OR1.82 CI 0.79–4.96, CRP > 20 mg/L OR 3.22 CI 1.27–11.42, PCT > 0.5 mg/mL OR 3.32 CI 1.46–7.56

### Luaces-Cubells, 2012

| Prospective, observational study | 868 Infants (2-36 months) with fever 8 or 24 hours; 325 (37.4%) children were younger than 3 months at a pediatric ED of 7 acute-care teaching hospitals in Spain, March 2008 & Sept. 2009 | Effectiveness of PCT versus CRP to detect invasive bacterial infection (IBI) Battery of diagnostic tests given to infants < 2 months of age included white blood cell count (WBC) with differential, a determination of CRP and PCT and blood and urine culture (urine collection by transurethral bladder catheterization) | • CRP & PTC values significantly higher in IBI group than other 2 groups.
• Pts with fever of 8 hrs duration, only statistically significant differences in PCT values.
• AUC for PCT was 0.87 (optimum cutoff 0.9 mg/mL, sensitivity 86.7%, specificity 90.5%),
• AUC for C-reactive protein was 0.79 (optimum cutoff 91 mg/mL, sensitivity 33.3%, specificity 95.9%).
• In infants with fever < 8 hrs duration, area under the receiver operating characteristic curve was 0.97 for PCT & 0.76 for C-reactive protein
• AUC for all children 0.87 (95% CI: 0.85–0.89) for PCT & 0.79 (95% CI: 0.76–0.81) for CRP, confirming superiority of PCT over CRP

---

• Study supports using procalcitonin, although cutoffs can be discussed further.
• Need to discuss: only 1258 had blood cx drawn? 1326 had LP
• 11 IBI pts not included in model because they did not have procalcitonin determined. This study should be helpful in subset of pts with abnormal dip
• Limitations – pediatric assessment triangle used to evaluate appearance of pts (used in the model),
• PCT values were not determined in all patients

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

#### Guideline 10

**Aronson, 2018**
- Either PCT or CRP had a higher diagnostic reliability than WBC & ANC, in children with duration of fever 8 hrs.
- PCT was the biomarker with highest predictive value. Use Procalcitonin to detect invasive bacterial infection in non–toxic-appearing infants with fever without apparent source in ED
- Optimum threshold of PCT was 0.9 ng/mL; Optimum cutoff for CRP 91 mg/L
- Consistent with previous reports

| Woelker, 2012 | Prospective cohort | 159 enrolled. 8.4% with SBI | Akron Children’s Hospital ED. Infants 2d to 60d with fever and generally well appearing. | Children with documented bacterial infection. Blood, CSF, stool pathogen, urine pathogen. Comparison to Rochester Criteria | • Sensitivity, specificity, NPV of PCT like Rochester Criteria (depending on PCT cutoff: specificity improved with higher cutoff). • Addition of urine WBC increased Odds ratio for SBI |
| McGowan, 2000 | Prospective | 711 positive blood cultures, 250 of them had pathogens | All ages <1 to 24 years (mean 2 years) 3 years 1993-1996 at CHOP | Compared isolates with pathogens vs contaminant time to positivity | Looking at our ages: • 0.6 mo mean time to positivity for pathogen was 17.54 (15.93–19.15) vs contaminant was 27.96 (24.54–31.38) • Full group: 14% were positive • @12 urs, 87% @ 24 hrs, 92% @ 36 hrs, 95% @ 48 hrs, 98% @ 60 hrs, @ 72 hrs, 99.7% |
| Galetto-Lacour, 2010 | Prospective | 408 children aged 7 days to 36 months with fever without source (FWS) | Validate Lab-score in a population of children with FWS different from derivation model diagnostic characteristics for detection of SBI calculated for Lab-score & any single variable used in the Italian study | Validation |
| Aronson, 2018 | Retrospective – planned secondary analysis of cross-sectional study | 360 bacteremia 62 meningitis 42 had both bacteremia & meningitis | Limited to 10 sites with TTP for CSF cultures available Babies ≤ 60 days of age presenting to ED over 5 years (2011-16) with positive blood and/or CSF cultures with a pathogen not treated as contaminant | Defined time to positivity • Time to positivity ill-appearing vs non-ill appearing infants in each group • Compared time to pathogen detection between non-ill-appearing and ill-appearing infants | • Bacteremia: o 87.8% within 24 hours o 95.3% within 36 hours • Lower proportion of non-ill appearing infants with positive blood cx within 24 hours vs those who looked sick • Meningitis: o 88.7% within 24 hours o 95.2% within 36 hours |

- • Time to pathogen detection was similar for infants <28 days and infants 29-60 days (median 14 vs 13 hours respectively)
- • Time to pathogen detection was also similar for infants pre-treated with antibiotics vs not (15 vs 14 hours respectively)
- • Overall, 87.8% pathogens detected on blood culture within 24 hours, 95.3% detected within 36 hours
- • Time to detection shorter for ill-appearing infant vs non-ill appearing (median 13 vs 14 hrs) with similar results when limited to febrile infants
- • Fewer non-ill appearing infants had pathogen on bld culture within 24 hrs vs ill appearing (85% vs 93%, meaning 15% of non-ill appearing infants still had neg. bld culture at 24 hrs); however, prevalence of bacteremia and/or meningitis in non-ill appearing febrile infants is low at 2%
- • 63% of infants with meningitis had a positive gram stain; 89% pathogens detected within 24 hours, 95% detected within 36 hours
- • At 24 hours, proportion of CSF pathogens detected did not differ between ill- and non-ill appearing infants (88% vs 89%)
- • 13% of infants had blood and/or CSF pathogens identified >24 hours (and 20% of those had a UTI); 5% detected at >36 hours, 90% of those were bacteremia without meningitis, and 68% were non-ill appearing, 26% were non-ill appearing with normal laboratory parameters
- • 37% of those with pathogens identified at >36 hours were Staph aureus (most common)
<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>Study Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronson, 2018b</td>
<td>Multicenter Retrospective cohort study</td>
<td>82 infants with IBI</td>
<td>Retrospective multicenter cohort study of 82 infants with IBI. Invasive bacterial infection was identified in 28% of infants within 24 hours. For ≤ 60 days, sensitivity of Rochester criteria were: Overall 92.7% (95% CI, 84.9%–96.6%). Neonates ≤ 28 days 91.7% (95% CI, 80.5%–96.7%). Infants aged 29 to 60 days old 94.1% (95% CI, 80.9%–98.4%).</td>
</tr>
<tr>
<td>Leazer, 2017</td>
<td>Retrospective</td>
<td>410 CSF cultures</td>
<td>Review of positive cultures to determine the time to detection for positive cerebrospinal fluid (CSF) cultures and to provide an update on the current epidemiology of bacterial meningitis in term infants.</td>
</tr>
<tr>
<td>Lefebvre, 2017</td>
<td>Retrospective</td>
<td>3559 blood cultures → 96 infants 98 positive</td>
<td>Time to positivity (TTP) calculated from time bld culture registration in lab system to time of Gram stain. Determine if 36-hr period sufficient to detect all bld cultures positive for pathogenic bacteria in infants ≤ 90 days old undergoing a septic workup.</td>
</tr>
<tr>
<td>Scarfone, 2017</td>
<td>Retrospective cohort pediatric ED of an urban, tertiary care children's</td>
<td>1188</td>
<td>(1) Determine incidence of bacterial meningitis (BM) of all febrile young infants (FYI) undergoing LP in ED. (2) determine ratio of contaminants vs pathogens among those with positive CSF cultures.</td>
</tr>
</tbody>
</table>

• 75% of infants with pathogens detected at >24 hours were non-ill appearing; only 20% were non-ill appearing with normal laboratory parameters.
• Among infants <60 days old with bacteremia and/or bacterial meningitis, pathogens were commonly identified from bld or CSF within 24 & 36 hours.
• However, clinicians must weigh the potential for missed bacteremia in non-ill appearing infants discharged within 24 hours against the overall low prevalence of infection.

Application of the Rochester Criteria to Identify Febrile Infants with Bacteremia and Meningitis
- 5011 infants ≤ 60 days old who underwent blood culture in 8 EDs during 2-year study period, 85 (1.7%) had culture-positive bacteremia.
- Of 3381 infants who had CSF obtained, 10 (0.3%) had culture-positive bacterial meningitis, including 6 with concomitant bacteremia.
- 53/89 (59.6%) infants with IBI were ≤ 28 days & 36/89 (40.4%) 29 to 60 days of age.
- 9/10 (90.0%) of infants with meningitis were ≤ 28 days old. 7 were afebrile (hence why 82 infants were included).

- 53 (12.9%) true pathogens and 357 (87.1%) contaminant species
- Mean ± SD time to detection for true pathogens was 28.6 ± 16.8 hours (95% confidence interval, 24–33.2)
- Mean time (hours) to positivity for contaminant species was 68 ± 36.2 hours
- 43 true positive cases (81.1%) were positive in ≤36 hours.
- Most common pathogen was group B Streptococcus (51%), followed by Escherichia coli (13%) and Streptococcus pneumoniae (9%).

- 52/98 (53.1%) blood cultures were pathogenic and 46 (46.9%) were deemed contaminant, for a true prevalence of bacteremia of 1.5%.
- Collected from 96 infants (63 boys; 33 girls) with a mean age of 40.4 days (range, 3–89).
- At 24, 36, 48, and 50 hours, 87.8% (86 of 98), 96.9% (95 of 98), 99% (97 of 98), and 100% (98 of 98) of all cultures were positive.
- For pathogenic organisms, 96.1% (50 of 52) and 100% (52 of 52) were positive at 24 and 36 hours.
- Mean TTP for pathogens and contaminans was 14.40 and 23.18 hours, respectively (P < .001).
- Among infants with positive pathogenic blood cultures, 15/52 (28.8%) had isolated bacteremia. Other 37 incidences of bacteremia (71.1%) were associated with focal infections: 23 urinary tract infections, 8 meningitis, 2 septic arthritis and/or osteomyelitis, 1 cellulitis, and 1 polymicrobial bacteremia.
### Hospital (CHOP)

- **36-day-old infant** (36 wks gestation) brought to ED b/c febrile crying, described as “crying incoherently”, “very fussy”, distended abdomen; group B Strep isolated from blood & CSF.
- Most common contaminants were *Staphylococcus epidermidis* (n=16) and *Bacillus* species (n=4).
- Two pts (#34 & #37) had *Escherichia coli* isolation from CSF, organism traditionally considered to be a pathogen.
  - Pt #34 well-appearing, normal CSF tests including gram stain, WBC count, protein & glucose levels; failed low-risk criteria b/c/ abnormal WBC; hospitalized for empiric antibiotic therapy. E-Coli grew in enrichment broth, 29 hrs post LP. ID MD consulted & concluded organism was contaminant. Pt d/c/ed after 48 hrs, without antibiotics or sequelae.
  - Pt #37 completely normal evaluation @ initial ED encounter, normal screening laboratory & CSF tests, d/c/ed home without antibiotics. @ 24 hrs pt called back for positive CSF culture pending speciation. ID MD consulted concluded organism likely a contaminant given pt's initial presentation & normal laboratory test results. pt had been without antibiotics > 24 hrs & remained afebrile & well-appearing.

### Thomson, 2017

- **Retrospective, cross-sectional**
  - 1737 infants had UTI, 9 had bacteremia both bacterial meningitis
  - Planned secondary analysis of a 23-center, retrospective, cross-sectional
  - Clinical and lab parameters examined for 9 pts with pos. CSF culture (contaminants excluded) Of the 1737 infants with UTI, 175 had growth of pathogenic organism on bld culture without concomitant bacterial meningitis (10.6%; 95% CI: 8.6%–11.6%). Most infants UTI & bacteremia had growth of same organism on bld cultu

### Velasco, 2017

- **Retrospective multicenter**
  - 391 febrile infants 90 days or younger with altered UA (leuks or nitrites)
  - 9 Spanish hospital ped EDs
  - Applied a predictive model this group had created in 2015 to these babies to validate the model "externally" – model tries to predict which babies with altered UA would have IBI

#### Clinical and lab parameters examined for 9 pts with pos. CSF culture (contaminants excluded) Of the 1737 infants with UTI, 175 had growth of pathogenic organism on bld culture without concomitant bacterial meningitis (10.6%; 95% CI: 8.6%–11.6%). Most infants UTI & bacteremia had growth of same organism from bld & urine cxn (n=170/175, 97.1%).

#### There is a low but not negligible incidence of meningitis in infants with positive urine cultures

- No data on clinical appearance of neonates.
- Only included infants with CSF obtained as part of the parent study (on neonatal HSV)

#### Thirty (7.7 %) developed IBI

- 26/30 (86.7 %) secondary to UTI (same bug in urine in blood or CSF)
- Prevalence of IBI: 2/104 (1.9 %; CI 95% 0.5–6.7) among low-risk pts vs 26/287 (9.7 %; CI 95% 6.8–13.7) among high-risk pts (p < 0.05).
- Sensitivity of model was 93.3 % (CI 95% 78.7–98.2) & negative predictive value 98.1 % (93.3–99.4) → lower than in their original study (both sensitivity & NPV were 100%) still good
<table>
<thead>
<tr>
<th>Study</th>
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<th>Descriptive Statistics</th>
<th>Methods</th>
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</table>
| **Chua, 2015** | Retrospective, administrative data review (PHIS) | 80,074 records | Febrile infants, 2 age groups 7-28 days and 29-56 days | Compared 7 groups with clin practice guidelines rec universal testing for all babies 29-56 days with 25 hospitals without this rec (control group) | • Further research should prove this hypothesis, but it appears that patients would benefit from a period of observation prior to discharge, no matter the ancillary test results  
• Applicable using same low risk criteria that we use with CRP and procalcitonin |
| **Martinez, 2015** | Prospective observational study – this was secondary analysis of a bigger study | 2362 babies | Babies less than 90 days with FUS in ED in Spain over 10 years | Define well-appearing, use pediatric assessment triangle (PAT) (appearance, work of breathing & circulation to skin) as assessed by doctor attending child within an hr of arriving at the PED  
Protocol is to get CSF in babies who:  
• all infants who are not well-appearing or have clinical manifestations suggestive of bacterial meningitis,  
• infants < 21 days  
• infants with abnormal bid test results (leukocytes <5000/μL or >15,000/μL, neutrophils >10,000/μL, CRP >20 mg/L or PCT ≥0.5 ng/mL) | • Proportion of older infants undergoing testing higher in the group that rec testing for all,  
• CPGs recommending universal CSF testing for older febrile infants were not associated with significant differences in adverse events  
• CPGs may encourage low-value applications of services without increasing their high-value applications |
| **Schroeder, 2015** | Observational Study – Retrospective Cohort – chart review | N = 245 (+115 random infants with neg. CX for specificity calculation) | Multicenter study – 11 hospital centers | Calculate sensitivity of UA in a multicenter sample of infants <3 months with bacteremic UTI  
*Sensitivity of Leukocyte esterase for bacteremic UTI was 97.6% (95% CI 94.5-99.2) and specificity was 93.9% (95% CI 87.9-97.5).  
*Sensitivity of pyuria (≥3 WBC/hpf) was 96.0% (95% CI 92.5-98.1) and specificity was 91.3% (95% CI 84.6-95.6) | • If looking for either LE OR pyuria, sensitivity was 99.5% (95% CI 98.5-100) & specificity for culture negative pts was 87.8 (95% CI 80.4-93.2)  
• Authors hypothesize higher sensitivities seen in this study compared to other studies was due to spectrum bias OR addition of asymptomatic bacteruria which was considered culture positive in the cohorts of patients used in previous studies  
• Limitations:  
  *Spectrum bias may have inflated the higher sensitivities  
  *One center in the study did not report method of urine collection, but infants were still included in study. This center routinely collects with catheterization |
<p>| <strong>Aronson, 2014</strong> | Retrospective cohort | 35,070 ED visits met inclusion criteria | Infants &lt; 90 days of age with diagnosis code of fever evaluated in 1 of 37 pediatric EDs; July, 2011 - June, 2013 Pediatric Health Information System (PHIS)- administrative database of inpt, ED ambulatory surgery, &amp; | Compared inter-hospital variation for 3-day revisits &amp; revisits resulting in hospitalization and testing, treatment, and disposition for patients in 3 distinct age groups: &lt; 29, 29 to 56, &amp; 57 to 89 days | • Pt- and hospital-level variation in testing, treatment, and disposition |</p>
<table>
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<tr>
<th>Study</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Main Findings</th>
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</table>
| Biondi, 2014  | Retrospective multicenter, cross-sectional | 392 pathogenic bid cultures after exclusion, 17 institutions Febrile infants ≤90 days admitted to general inpatient unit | • Time to positivity for blood cultures comparisons for those with fever (same TTP as with no fever), younger infants more likely to grow quicker than older ones.  
• Mean (SD) time to positivity was 15.41 (8.30) hrs.  
• By 24 hrs, 91% (95% CI 88.9-95) had turned positive.  
• By 36 hrs 96% (95%CI 95-98) & @ 48 hrs 99% (95%CI 97-100) become positive. |
| Mintegi, 2014 | Retrospective Comparison Study       | 1123 well appearing infants <3 months of age with fever without source (FWS) presenting to the PED | • Assess the accuracy of different blood biomarkers in diagnosing IBIs & SBIs; Low risk vs high risk; sequential approach to young febrile infants based on clinical & laboratory parameters, including procalcitonin, identifies better patients more suitable for outpatient management.  
• Compared to Lab Score and Rochester Criteria.  
• Sequential approach to young febrile infants like the step-by-step approach better identifies low-risk pts; more suitable for outpatient management; Procal 0.5 |
| Nosrati, 2014 | Retrospective cohort analysis        | 401 70% were 30-60d, 20.4% were 61-90d                                            | • Overall rate of SBI was 12% (90% had UTI, 3 bacteremia, one pneumonia, one meningitis).  
• ANC, platelets, BUN & CRP correlated with BSI.  
• CRP was most strongly correlated with risk for BSI.  
• CRP AUC = 0.89, Sens=79%, Spec = 84%, Neg Likelihood = 0.25, Pos likelihood = 4.9 |
| Schnadower, 2014 | Observational – Retrospective Chart Review | N = 1764 Multicenter trial – 19/20 clinical sites; one site excluded             | • Determine variation in pt disposition and clinical factors independently associated with outpatient.  
• Clinical site (OR=8.8; 95% CI 5.2-15.0), presence of URI symptoms (OR=1.8; 95% CI 1.1-2.9), absence of vomiting (OR=0.3; 95% CI 0.2-0.8), having fewer than 10 WBC per μL on
### Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

#### Guideline 10

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Design</th>
<th>Number</th>
<th>Details</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Byington, 2012</strong></td>
<td>Observational Quality improvement</td>
<td>8044</td>
<td>Well appearing febrile infants 1 to 90 days of age, Intermountain Healthcare System – various locations</td>
<td>Slight increase in admission rate of febrile infants, similar rate (with trends toward improvement) in admission of pts with meningitis &amp; bacteremia vs pre-implementation. Increased documentation of UTIs &amp; viral infections, Higher % of pts with SBI admitted after UTI detection, Decreased LOS, Appropriate use of recommended antibiotics, Considerable cost reduction</td>
</tr>
<tr>
<td><strong>Bressan, 2012</strong></td>
<td>Multicenter Retrospective</td>
<td>1098</td>
<td>7 pediatric emergency departments in Spain and Italy; FWS in well-appearing &lt;3 months of age</td>
<td>AUC for IBI prediction was 0.85 (CI 0.62-0.86) NOT significantly different than AUC for PCT or CRP but significantly higher than for WBC. Notably, 30% (7 patients) with IBI were missed by Lab-score with cutoff of 3. Lab-score was more useful for ruling in, than ruling out SBI, and accuracy for IBI prediction was unsatisfactory</td>
</tr>
<tr>
<td><strong>Gomez, 2012</strong></td>
<td>Retrospective cohort</td>
<td>1112</td>
<td>Infants &lt; 3 months old, well appearing, FUS who had a blood cx &amp; PCT 5 EDs in Spain, 2 EDs in Italy</td>
<td>• Of 1764 infants with UTIs, 132 (7.5%) d/c’ed home. 29/132 (22%) pts subsequently hospitalized (5 with bacteremia). 0/107 with known outcomes after d/c had adverse outcomes. Clinical site, presence of URI symptoms, absence of vomiting, &amp; having fever than 10 WBC per ul on CSF examination were all independently associated with discharge from ED. Clinical site most highly associated with likelihood of d/c’ed from ED when comparing top quartile of sites compared to the lower 3 quartiles (OR=8.8; 95% CI 5.2-15.0). <strong>Limitations</strong> *30 pts discharged from ED with UTI do not have initial outcome data. All 30 were seen within 1 year of d/c with no indication of serious adverse event, but no immediate outcome data available for analysis. Study identified patients via microbiology lab, meaning patients with concerning UAs but no cultures were not part of this study.</td>
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</table>

**Use of Evidence Based Care Process Model to reduce cost.**

- SBI = pathogen from blood, urine, CSF or stool
- IBI = pathogen from blood or CSF
- PCT: OR for IBI 21.7 (7.9-59.23)
- PCT reduces post-test prob to 0.5% AUC 0.83
- OR for SBI is not as good.
- 23/1112 (2.1%) had positive blood or CSF culture (IBI).
| Gomez, 2012b | Retrospective, cross sectional descriptive study | 1365 infants with WBC count performed | Infants < 3 mo of age with FUS; retrospective data from 2003-2010 in peds ED | (a) to assess the prevalence of leukopenia (b) to analyze the relationship between leukopenia and the risk of SBI | 295 infants (21.6%) were diagnosed with an SBI | 4a |
| Paquette, 2011 | Retrospective | 392 infants – 57 with abnormal UA | Babies 30-90 days Montreal ED 2001-2005 with FUS who are found to have abnormal UA | Looked at babies with pos UA to describe if they had meningitis | One baby with pos UA had meningitis but also had bacteremia & low WBC of 2.9 & ill looking; WBC count was associated with risk of CSF pleocytosis | 4a |
| Schnadower, 2011 | secondary analysis (ie, subanalysis) of data from a retrospective review | 1190 infants analyzed | Infants 29 - 60 days old with temp ≥ 38.0°C & culture-proven UTIs who underwent nontraumatic LP from 1995 - 2006 & present to any of 20 North American EDs in Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) | Definite bacterial meningitis - growth of known pathogen in CSF Probable bacterial meningitis = meeting any of the following criteria: Combination of sterile CSF pleocytosis & positive bld cx result & tx consistent with bacterial meningitis (14 days of abx); Combination of +CSF Gram stain result or + latex agglutination test results & treatment consistent with bacterial meningitis or Combination of pretreatment with antibiotics before LP, CSF pleocytosis (WBC count, 10/µL), & tx consistent with bacterial meningitis. | CSF pleocytosis present in 18% of infants with UTI (cutoff is set at 10). | 4a |

- Supports adding procalcitonin /CRP to lab evaluation of febrile infants to identify IBI
- Multivariate analysis. PCT was only independent risk factor for IBI (odds ratio 21.69; 95% CI 7.93–59.28 for PCT $0.5 ng/mL).
- Positive likelihood ratios for PCT≥2 ng/mL & C-reactive protein (CRP) ≥40 mg/L = 11.14 (95% CI 7.81–15.89) & 3.45 (95% CI 2.20–5.42), respectively.
- Negative likelihood ratios for PCT≤0.5 ng/mL & CRP <20 mg/L = 0.25 (95% CI 0.12–0.55) & 0.41 (95% CI 0.22–0.76).
- True bacterial pathogen grew in 30 cases (2.2%) bld cx
- Most commonly isolated bacterial pathogen Escherichia coli (12, all but 1 with positive urine culture), Streptococcus agalactiae (n = 5), & Streptococcus pneumoniae (n = 4).
- 81 cases (5.9%; 95% CI: 4.7%–7.3%) presented with leukopenia (range, 2500–4900/mm3)
- 939 (68.8%), a normal WBC count; 345 (25.3%), leukocytosis.
- Rate of SBIs in global sample: 14.8% those with leukopenia, 15.5% for those with a normal WBC count (P = 0.97), & 39.7% those with leukocytosis (P = 0.001).
- Only SBIs diagnosed in group of well-appearing infants with leukopenia were 4 UTI by E. coli, ¾ with a urine dipstick testing negative for leukocyturia & natriuresis. All 4 infants did well.
- There were no statistically significant differences when comparing the rate of SBIs in the groups with neutropenia and with a normal ANC (1000–10,000/mm3).
- One baby with pos UA had meningitis but also had bacteremia & low WBC of 2.9 & ill appearing
- Negative predictive value of an abnormal UA for meningitis was 98.2%.
- Median CSF WBC count was 4
- 214 pts with UTI had CSF WBC of ≥10 (18%). Proportion of pts with sterile CSF pleocytosis decreased to 8.1% & 5.5% when sterile CSF pleocytosis thresholds changed to WBC count of 16/µL or higher & 21/µL or higher, respectively.
- Presentation during enteroviral season, height of fever, peripheral WBC count, peripheral bld ANC, & peripheral blood and count were associated with presence of CSF pleocytosis
### Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

**Guideline 10**

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Sample</th>
<th>Methods</th>
<th>Findings</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **Schnadower, 2010** | Observational – Retrospective Chart Review; Retrospective Cohort Study | N = 1895 Multicenter trial – 20 clinical sites. | Develop prediction models to identify the risk for adverse events and bacteremia in febrile infants with UTIs who are considered low risk | • *Adverse events occurred in 51/1842 febrile infants with UTI (2.8%; 95% CI 2.1-3.6).*  
• Bacteremia occurred in 123/1877 febrile infants with UTI (6.5%; 95% CI 5.5-7.7).  
• 1 infant (0.1%) was misclassified & had an adverse event–bacterial meningitis (but, CSF studies had been lost & his clinical course was non-complicated)  
• *Pts were at low risk for bacteremia if not clinically ill in ED, did not have high PMH, bands < 1250/uL, & ANC <1500/uL with sensitivity of 77.2% (95% CI 68.4-84.1), NPV 96.8 (95% CI 95.3-97.8)*  

Table 1 (page 1078) - raw statistics; Table 2 (1079) - Adverse events; Figure 2 (1080) - prediction model for adverse event outcome; Figure 3 (1081) - Prediction model for bacteremia  

Limitations:  
*Subjectiveness of clinical findings; bias of clinical documentation  
*Pts identified by querying laboratory databases, rather than identifying pts who had positive UAs in the ED which was not feasible in this study. | 4a |
| **Olaciregui, 2009** | Retrospective cohort | 347 (23% with SBI) Donostia Hospital, Spain. 4d to 3 mos. Enrollment: 2004 to 2006 Excl: fever > 7d, immunodeficiency, antibiotics prior | SBI versus no SBI. Included pneumonia based on 'infiltrate' on CXR as well as cellulitis, even if cultures negative. | • Overall BSI 23.6%. PCT, CRP, WBC, ANC higher in SBI grp.  
• PCT & CRP had approximately same AUC & better than WBC/ANC.  
• Serious /invasive SBI, PCT better AUC vs CRP, especially when < 12hr.  
• Overall AUC PCT 0.77, CRP 0.79 Invasive infection: PCT 0.84, CRP 0.68  

Table 1 (page 1078) - raw statistics; Table 2 (1079) - Adverse events; Figure 2 (1080) - prediction model for adverse event outcome; Figure 3 (1081) - Prediction model for bacteremia  

Limitations:  
*Pts identified by querying laboratory databases, rather than identifying pts who had positive UAs in the ED which was not feasible in this study. | 4a |
| **Lacour, 2008** | Retrospective | 202 25 d-26 yo, Texas Children’s Hospital Single university-based center over multi-years | 2/3 of patients in a derivation set and 1/3 of patients in a validation set | • Serotypes of adenovirus  
• Using a scoring system based on giving scores to changes in PCT, CRP, & urine dipstick,  
• Able to predict SBI with specificity of 81% and sensitivity of 94%.  

Table 1 (page 1078) - raw statistics; Table 2 (1079) - Adverse events; Figure 2 (1080) - prediction model for adverse event outcome; Figure 3 (1081) - Prediction model for bacteremia  

Limitations:  
*Pts identified by querying laboratory databases, rather than identifying pts who had positive UAs in the ED which was not feasible in this study. | 4a |
| **Diaz, 2016** | Retrospective descriptive | 318 Febrile (≥ 38C), < 90 d visiting pedi ER of tertiary teaching hospital, with no previous hospitalization involving antibiotic use, | IBI in 3.5% (11 patients) all of whom had bacteremia, none of whom had bacterial meningitis  
To be included, patients must have had CRP and PCT measured | • For IBI, Sensitivity for PCT >0.5 was 72.7% (CI 43.4-90.2) and for PCT >2.0 was 45% (CI 16-74.9)  
• 10/11 pts with IBI had abnormal values in at least one lab value and/or physical appearance,  
• 4/5 with IBI were well-appearing & had abnormal results in ≥ one lab values  

Table 1 (page 1078) - raw statistics; Table 2 (1079) - Adverse events; Figure 2 (1080) - prediction model for adverse event outcome; Figure 3 (1081) - Prediction model for bacteremia  

Limitations:  
*Pts identified by querying laboratory databases, rather than identifying pts who had positive UAs in the ED which was not feasible in this study. | 4b |
### Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source

**Guideline 10**

- **AUC for IBI was best for PCT (0.77), then CRP (0.54), ANC (0.53) and WBC (0.42)**
- **Pts with IBI had abnormal values in at least one lab value and/or physical appearance, or were well-appearing had abnormal results in one or more lab values**

<table>
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<tr>
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<th>Design</th>
<th>Sample Size</th>
<th>Outcome Description</th>
<th>Methods/Results</th>
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<tr>
<td>Hassoun, 2014</td>
<td>Retrospective chart review</td>
<td>1192</td>
<td>Febrile infants &lt;28 days presenting to one of two EDs for SBI evaluation</td>
<td>Describing pathogens in febrile infants</td>
</tr>
<tr>
<td>Biondi, 2013</td>
<td>Retrospective review - descriptive</td>
<td>177 infants</td>
<td>Febrile infants &lt;90 days across 6 hospitals over 6 years</td>
<td>No comparisons – describing pathogens</td>
</tr>
<tr>
<td>Greenhow, 2012</td>
<td>Retrospective review – descriptive</td>
<td>4255 blood cultures</td>
<td>Prev healthy babies 1wk to 3 mos with bld culture drawn at Kaiser 2005-2009</td>
<td>No comparisons – describing pathogens in bacteremia</td>
</tr>
<tr>
<td>Tebruegge, 2011</td>
<td>Retrospective cohort</td>
<td>735 pts, with 163 &lt; 28 days &amp; 499 &gt; 29 days to 12 months</td>
<td>Large ped referral hospital in Victoria, Australia. Pt 1 d - 16 yrs of age with a pos. urine culture &amp; CSF sample collected w/in 48 hrs of urine sample, UTI patients with or without positive CSF culture</td>
<td>Two pts –with UTI co-existing bacterial meningitis, 1-15 days (fever, poor feed, irritable, lethargy – S aureus, other 19 days (fever, poor feed, irritable, lethargy – E Coli)</td>
</tr>
</tbody>
</table>

- **Cultures were positive in 6% of neonates undergoing SBI workup.**
- **Listeria was a rare cause of SBI 2% of 72 organisms grown from 1192 patients. Enterococcus is more prevalent cause of SBI (22%), which still necessitates the use of ampicillin or penicillin in children ≤ 28 days of age.**
- **Limitations: May not have captured the entire SBI rule-out population.**

- **Pathogens:**
  - 7% of E. coli bacteremia had meningitis;
  - 3% with E. coli UTI + bacteremia had meningitis
  - Bacteremia more likely in non-low-risk bacteremic infants by modified Rochester criteria (term, did not require treatment of hyperbilirubinemia)
  - 80% of bacteremic infants non-low risk

- **Could be useful in not doing empiric ampicillin?**
- **E. coli top pathogen, GBS second**
- **S.pneumo in older infants**
- **No Listeria**
- **Very rare Enterococcus (4%) – if assume 2% bacteremia, rate of Enterococcus <01%**

- **Findings supports not doing empiric ampicillin for Listeria**
- **Note: UTI = WBC 5+ WBC /hpf**
- **Not necessarily febrile: 86/92 infants with bacteremia had temperature documented, 6/86 no history of fever or documentation of fever (so included afebrile & hypothermic);**
- **1/10 infants with meningitis was afebrile & 7/10 were described as ill appearing**

- **Rate of definite co-existing meningitis with UTI was significantly higher in neonates than in infants outside the neonatal period (p =0.013).**
- **Cannot exclude with absolute certainty the possibility of some pts having not received antibiotics prior to the CSF sample being obtained, thereby potentially rendering their CSF culture false negative. No data regarding the timing of the lumbar puncture and the initiation of antibiotic treatment.**
- **Concomitant bacterial meningitis was more common in infants 0–28 days of age (n = 7/803, 0.9%; 95% CI: 0.4%–1.8%) compared with infants 29–60 days of age (n = 2/934, 0.2%; 95% CI: 0%–0.7%). All cases of concomitant bacterial meningitis and bacteremia with same organism and UCx and CSFcx**
- **Study indicates low but not zero incidence of meningitis in UTI patients**
### Evidence-Based Care Guideline for Management of Infants

#### 0 to 60 days with Fever of Unknown Source

**Guideline 10**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez, 2010</td>
<td>Retrospective cohort</td>
<td>1018</td>
<td>&lt;3 mo with FUS with blood culture over 5-year period to Peds ED from 2003 to 2008 in Spain</td>
<td>Assess rate of bacteremia in febrile infants &lt; 3 months of age admitted to a pediatric emergency department at a tertiary hospital; Describe the bacteria isolated; Analyze factors related to increased probability of having a positive blood culture</td>
</tr>
<tr>
<td>Mintegi, 2010</td>
<td>Descriptive, retrospective?</td>
<td>685 included</td>
<td>Babies less than 90 days with FUS who did not have LP in Spain over 4 years</td>
<td>Descriptive Rec LP if less than 15 days, careful consideration 15-28 days, consider based on appearance over 28 days</td>
</tr>
<tr>
<td>Byington, 2003</td>
<td>Retrospective chart review</td>
<td>105 pathogens</td>
<td>Febrile infants &lt;90 days of age presenting to tertiary pediatric referral center ED</td>
<td>Describing pathogens in febrile infants</td>
</tr>
<tr>
<td>Roberts, 2012</td>
<td>Guideline Revision</td>
<td>NA</td>
<td>Infants and young children two to 24 months of age with unexplained fever</td>
<td>• Bacteremia or meningitis organisms: Resistant to Ampicillin Pathogen N (%) N (%) E coli 7 (22) 2 (29) S aureus 6 (19) 6 (100) GBS 5 (16) 0 (0) Salmonella 3 (9) 1 (33) Gm (-) 7 (22) 6 (86) Gm (+) 4 (12) 2 (50) Total 32 (100) 17 (53)</td>
</tr>
</tbody>
</table>

**Findings (continued):**

- Low risk = previously healthy – 0.6% positive blood cs in low risk. 1.6% in high risk
- Infant, well-appearing, urine dipstick testing without leukocyturia or nitriuria, WBC between 5000 & 15,000/mm3, ANC - 10,000/mm3, no pleocytosis if LP performed, & staying several hours in the Observation Unit with normal clinical evaluations.

**Mintegi, 2010**

- Adds support to similar findings that unlikely to find meningitis in well-appearing > one month
- Unnecessary to do LP routinely in babies > 1 month of age. Decision can be individualized without adverse outcomes…may underdiagnose non-bacterial meningitis”

**Byington, 2003**

- Ampicillin still covers GBS and enterococci but does not cover gram-negative isolates well.
- SBI in febrile infants 1-90 days is 8%. 53% (17 of 32) of pathogens causing bacteremia or meningitis were resistant to ampicillin, reaffirming it is not suitable as monotherapy for SBI.
- Limitations: The authors showed surprise that multiple pts with S. aureus isolates were gentamicin “susceptible” in vitro failed treatment with a regimen including gentamicin.

**Roberts, 2012**

- Both urinalysis & culture should be performed to assure a diagnosis of true UTI rather than asymptomatic bacteriuria in a child whose fever is unrelated to the urinary tract
- Urine specimen for both culture & urinalysis should be obtained by catheterization, because diagnosis of UTI cannot be established reliably by a culture of urine collected in a bag. (Evidence Quality A; Strong Recommendation) Only urine obtained by catheterization (or SPA) is suitable for culture. SPA is not recommended unless necessary, because it produces more distress than catheterization
- Urine specimen should be obtained for both culture & urinalysis before an antimicrobial is administered
- To establish diagnosis of UTI, clinicians should require both urinalysis results that suggest infection (pyuria or bacteriuria) AND the presence of at least 50,000 colony-forming units/mL of a uropathogen cultured from a urine specimen obtained by catheterization or suprapubic aspiration. (Evidence Quality C; Recommendation)