Evidence-Based Care Guideline for Management of Infants 0 to 60 days with Fever of Unknown Source
Guideline 10

May 7, 2019

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INTRODUCTION / BACKGROUND

Infants presenting with fever of uncertain source (FUS) represent a common conundrum for clinicians, given the broad differential diagnosis. While viral infections remain the most common cause of fever in infants 0 to 60 days of age *(Ishimine, 2007 [5]; Woll, 2018 [5a]),* a systematic approach to evaluation is paramount in identifying infants at high risk for serious and invasive bacterial infections. Serious bacterial infections (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

Recommendation Strength
Moderate

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])*

Recommendation Strength ***Moderate***

- 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])*.

{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]).*

Recommendation Strength ***Weak***

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:

Recommendation Strength ***Moderate***

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

2) PCT is ≤ 0.5 ng/mL regardless of the ANC value *(Thomson, 2017 [4a]; Velasco, 2017 [4a]; Martinez, 2015 [4a]; Mintegi, 2014 [4a]; Schnadower, 2014 [4a]; Bressan, 2012 [4a]; Byington, 2012 [4a]; Paquette, 2011 [4a]; Schnadower, 2010 [4a]; Tebruegge, 2011 [4b]; Mintegi, 2010 [4b])*.

{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]).*

Recommendation Strength ***Weak***

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])*.

Statement Strength
Consensus

{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])*.

Statement Strength
Consensus

{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:

Statement Strength
Consensus

- 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])*.

Recommendation Strength
Moderate

{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])*.

Statement Strength
Consensus

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])*.

Statement Strength
Consensus

{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])*.

Recommendation Strength
Weak

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

Note 2: Document blood, urine and CSF culture review by the laboratory in the electronic health record before considering discharge (*Local Consensus, 2018 [5]).*

- CSF cultures are only reviewed by the microbiology lab once per day in the morning. A CSF culture preliminary read is only documented in the electronic medical record once (on the first day that the culture is reviewed). A final negative read is documented on day 5. Documentation is ONLY updated if the CSF culture is positive.
- Use clinical discretion in determining how this process impacts discharge time for hospitalized infants with FUS.

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

Note 4: Discharge criteria include:

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

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

{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])*.

Recommendation Strength
Strong

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])*.

Statement Strength
Consensus

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])*.

Recommendation Strength
Strong

{Evidence Discussion & Dimensions for Recommendations 13 through 17}

Care Recommendation Statement 16

Recommendation Strength
Moderate

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

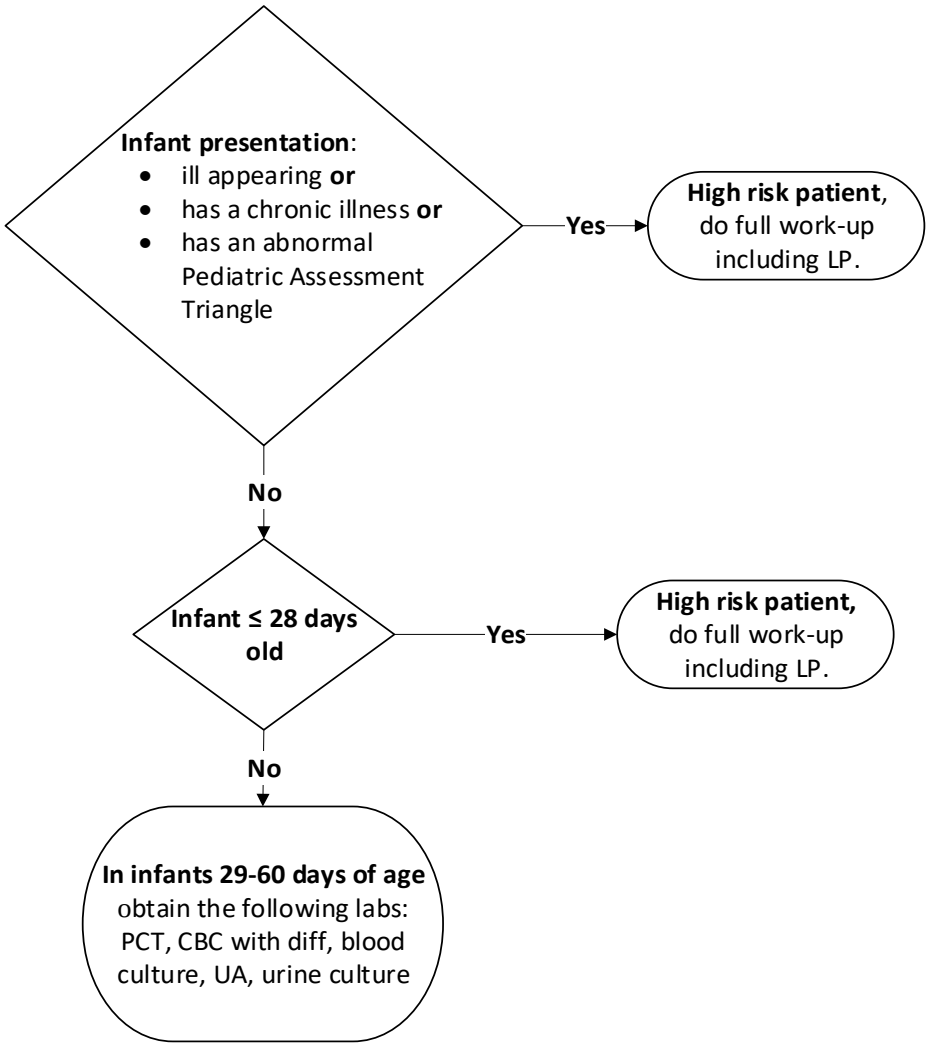
Statement Strength
Consensus

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



Low Risk	Intermediate Risk	High Risk	Abnormal UA

• Negative UA (UA with <10 WBC per hpf) **AND**
• Biomarkers below threshold:
  • PCT ≤ 0.5 ng/mL,
  • ANC ≤ 4,000/ mm³
	• Negative UA
	• PCT ≤ 0.5 ng/mL **BUT** ANC > 4,000/ mm³
		• Negative UA with
		• PCT > 0.5 ng/ml regardless of ANC value
			• Positive UA: (WBC ≥ 10 per hpf)

ACTION	**ACTION**	**ACTION**	**ACTION**
• No antimicrobials, discharge home with close follow up with PCP in next 24 hours • Family knowledgeable of when to call/return	• **Option 1: Proceed with LP**, send CSF studies and **consider empiric antimicrobials** • **Option 2: Defer LP** and **admit** for observation **OFF** antimicrobials	• Proceed with LP and CSF studies • Start empiric antimicrobials and admit to hospital	• **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

Cerebrospinal Fluid (CSF) pleocytosis	Neonates age 0 to 28 days: CSF white blood cell count ≥15/μL Infants 29 to 60 days CSF white blood cell count ≥ 9 uL.
Fever of uncertain source (FUS)	An acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical exam
Fever	Temperature ≥ 38ºC (100.4 ºF)
Invasive bacterial infection (IBI)	Bacteremia and/or bacterial meningitis in infants ≤ 60 days of age
Ill-appearing	Infant described as: “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” “irritable or any findings of the physical examination that indicates any clinical suspicion of sepsis
Neonate	Infant birth to 28 days of age
Previously healthy	Term Birth (≥ 37 weeks’ gestation) Not treated for unexplained hyperbilirubinemia Not hospitalized longer than mother No current or previous antimicrobial therapy No previous hospitalization No chronic or underlying illness
Serious bacterial infection (SBI)	A urinary tract infection, bacterial meningitis, bacteremia, bacterial pneumonia, gastroenteritis, cellulitis, osteomyelitis, or septic arthritis
Well appearing	Defined by a normal Pediatric Assessment Triangle (PAT): 3 components of the PAT are appearance, work of breathing, and circulation to the skin *(Horeczko, 2013 [4a]; Dieckmann, 2010 [5a])* *(See Appendix C)*
Young infant	Children 29 to 60 days of age

IMPLEMENTATION

Applicability & Feasibility Issues

Factors that will impact successful implementation of this guideline include:

Facilitators

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

Potential Barriers

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

Resource Implications

- Cost of additional testing (e.g. PCT)

Relevant CCHMC Tools

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

Outcome Measures

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

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

Process Measures

- Rate of FUS guideline adherence
- Rate of FUS order set use (in the ED and inpatient settings)
- Rate of discharges within 2 hours of meeting medically ready goals
- Emergency department length of stay for infants 0 to 60 days of age evaluated for FUS
- PCT result time

DISCUSSION / SYNTHESIS OF THE EVIDENCE *AND* TABLES OF DIMENSIONS FOR JUDGING RECOMMENDATIONS STRENGTH *BY* CARE RECOMMENDATION STATEMENT

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])*.

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.)

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

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 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-Cubells, 2012 [3a])*. Additionally, a combination of labs/ blood biomarkers may be more reliable in identifying infants with FUS who are at risk of IBI *(Woelker, 2012 [3a]; Diaz, 2016 [4b])*.

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

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.)

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**
2) PCT is ≤ 0.5 ng/mL regardless of the ANC value *(Thomson, 2017 [4a]; Velasco, 2017 [4a]; Martinez, 2015 [4a]; Mintegi, 2014 [4a]; Schnadower, 2014 [4a]; Bressan, 2012 [4a]; Byington, 2012 [4a]; Paquette, 2011 [4a]; Schnadower, 2010 [4a]; Tebruegge, 2011 [4b]; Mintegi, 2010 [4b])*.

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm *(Side Effects and Risks)*	☐ Minimal	☒ Moderate / Neutral		☐ Serious
2. Health benefit to patient	☒ 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.)

Care Recommendation Statement 5

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

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

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

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

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

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

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

Dimensions of Judging the Recommendation Strength for accurate diagnosis

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

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

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

The evidence of multiple studies suggests that the risk of meningitis in well-appearing infants age 28 days of age and greater is very low, including patients with concomitant UTI. In a study of 1975 infants with FUS over 21 days of age who were well-appearing, none were found to have had meningitis *(Martinez, 2015 [4a])*. Additional studies support the notion that well appearing infants over 28 days of age have a very low likelihood of meningitis *(Thomson, 2017 [4a]; Mintegi, 2014 [4a]; Bressan, 2012 [4a])*. Thomson, et al (2017,4a) did report that 2 (0.2%) patients over 28 days of age with UTI also had meningitis although both also had positive blood cultures and clinical appearance was not known *(Thomson, 2017 [4a])*. Paquette et al (2011, 4a) found that only one of 52 patients in their study had both UTI and meningitis; this infant was ill appearing at presentation and was also bacteremic *(Paquette, 2011 [4a])*. The negative predictive value of abnormal UA for meningitis was 98.2% in this study *(Paquette, 2011 [4a])*. Tebruegge et al (2011, 4b) reported concomitant bacterial meningitis in infants 0 to 28 days of age 0.9% of the time (95% CI 0.4%-1.8%) compared to 0 in infants 29 to 60 days of age *(Tebruegge, 2011 [4b])*.

Additionally, evidence suggests that UTI alone may result in CSF pleocytosis and thus, evaluation of CSF in well appearing infant with likely UTI may lead to concern for meningitis due to CSF cell counts alone. The concern over possible meningitis due to CSF pleocytosis has been shown to result in longer duration of IV antibiotic use compared to similar patients with UTI and no CSF pleocytosis *(Schnadower, 2011 [4a])*. Local consensus deemed that routine evaluation with LP is not warranted in this group of patients 29-60 days of age with UTI as likely source of SBI, due to the risk of additional unnecessary treatment, including longer hospitalization and IV antibiotic use.

Lastly, studies have recently evaluated outcomes related to clinical practice guidelines for management of FUS. The first study limited tested in those patients with likely UTI as source of fever and found lower admission rates, shorter lengths of stay and less antibiotic exposure without any increase in missed SBI *(Byington, 2003 [4b])*. A second study examined the impact of increased testing to include LP for evaluation of FUS for all patients up to 56 days. The outcomes included no decrease in adverse events including delay in diagnosis of meningitis *(Chua, 2015 [4a])*. Where there was insufficient evidence to make a recommendation, consensus was obtained (see consensus process below).
{Back to Statement 3, Statement 4, Statement 5, Statement 6, and Statement 7}

Management Recommendations
Emergency Department Discharge Criteria

Consensus Statement 8

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

- Low-risk clinical and laboratory criteria *(See FUS Algorithm)* have been met *(Irwin, 2016 [1b])*
- There is a collaborative discussion with:
  - The patient's PCP prior to discharge to ensure the family has an established follow up plan within the next 24 hours (e.g. appointment or phone call if no office hours available the next day)
  - The family to ensure they have a documented working telephone number and understand the importance of close follow up with the PCP and reasons to call/return to the ED *(Local Consensus, 2018-2019 [5])*.

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm *(Side Effects and Risks)*	☐ Minimal		☒ Moderate / Neutral		☐ Serious
2. Health benefit to patient	☐ 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 *(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 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 *(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.)

Inpatient Discharge Criteria

Care Recommendation Statement 12

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

Note 1: The countdown to 24 hours starts from the time of final culture collection *(Local Consensus, 2018 [5])*.
Note 2: Document blood, urine and CSF culture review by the laboratory in the electronic health record before considering discharge (*Local Consensus, 2018 [5])*.

- CSF cultures are only reviewed by the microbiology lab once per day in the morning. A CSF culture preliminary read is only documented in the electronic medical record once (on the first day that the culture is reviewed). A final negative read is documented on day 5. Documentation is ONLY updated if the CSF culture is positive.
- Use clinical discretion in determining how this process impacts discharge time for hospitalized infants with FUS.

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

Note 4: Discharge criteria include:

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

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

Dimensions of Judging the Recommendation Strength for admission discharge

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

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

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

Several studies considering the time to positivity of blood cultures contributed to this suggestion. Mean time to positivity for pathogens were noted to be 17.54 hours *(McGowan, 2000 [3a])*, 14.40 hours *(Lefebvre, 2017 [4a])* and 15.41 hours *(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

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.)

Care Recommendation Statement 16

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

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm *(Side Effects and Risks)*	☒ Minimal		☐ Moderate / Neutral		☐ Serious
2. Health benefit to patient	☒ 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 17

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

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

Dimensions of Judging the Recommendation Strength for accurate diagnosis

1. Safety / Harm *(Side Effects and Risks)*	☒ Minimal		☐ Moderate / Neutral		☐ Serious
2. Health benefit to patient	☒ 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 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.

Search Databases	Search Terms	Limits, Filters, & Search Date Parameters	Date of Most Recent Search
☒ MedLine via PubMed or Ovid ☒ CINAHL ☒ Cochrane Database for Systematic Reviews	• exp "Fever of Unknown Origin"/ or Fever/ or fever of unknown source.mp • workup.mp or Diagnosis, Differential/ or Diagnosis/ or diagnosis.mp. • Urinalysis/ or Urinary Tract Infections/ or urinanalysis.mp. • lumbar puncture.mp. or Spinal Puncture/ or spinal tap.mp. or Spinal Puncture/ • Blood Cell Count/ or CBC.mp.or CBC and Diff).mp. or diagnostic techniques and procedures"/ or blood cell count/ • UTI.mp. * • cerebrospinal fluid • "Bacterial Infections"/ or bacterial infection.mp. or Bacterial Infections/ bacteremia.mp. or Bacteremia/ • newborn.mp. or Infant, Newborn/ newborn infant.mp. or Infant, Newborn/ • management.mp. or treatment.mp. or Therapeutics/ " • Fever of Unknown Origin"[Mesh]) AND "Infant, Newborn"[Mesh] • anti-bacterial agent.mp. or Anti-Bacterial Agents/ antibiotic.mp.	Publication Dates or Search Dates: • 01/2000 to Present ☒ English Language ☒ Pediatric Evidence Only: • Infants 0 to 60 days • *Newborns 0 – 28 days* • *Infant 0-23 months* ☒ Other Limits or Filters: • Humans • clinical study or clinical trial, all or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation studies or government publications or guideline or meta-analysis or multicenter study or observational study or practice guideline or randomized controlled trial or systematic reviews)	9/25/2018

Search Results

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

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

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

TEAM MEMBERS & CONFLICTS OF INTEREST

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Christina Harding, Parent

Evidence-Based Care Recommendation Development Support

Methodologist, Consultant:

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Conflicts of Interest were declared for each team member and:

☒ No financial or intellectual conflicts of interest were found.
☒ No external funding was received for development of these recommendation statements.
Funding for development of this guideline was provided through Cincinnati Children's salaries.

☐ The following conflicts of interest were disclosed: no conflicts noted.
Conflict of interest declarations information is maintained in Cincinnati Children's ePAS *(electronic Protocol Administration System)*.

External Funding

☒ No external funding was received for development of this recommendation.
Recommendations were developed through hospital funding via salaries.

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?

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

Full tables of the LEGEND evidence evaluation system are available in separate documents:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality *(abbreviated table below)*
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation *(Evidence Discussion and Dimensions for Recommendations section)*

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

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

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

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

Grade	Definition
High	Good quality, High-level studies with consistent results
Moderate	Good quality, Lower-level OR Lesser quality, Higher-level studies with consistent* results
Low	Good or lesser quality, Lower-level with results that may be inconsistent
Very Low	Few Good or Lesser quality, Low-level studies that may have inconsistent results
Grade Not Assignable	Local Consensus

Table of Language and Definitions for Recommendation Strength *(see link above for full table)*:

Language for Strength	Definition
It is strongly recommended that… It is strongly recommended that… not…	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)
It is recommended that… It is recommended that… not…	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.
It is suggested that… It is suggested that… not…	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.
There is insufficient evidence to make a recommendation…	

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

Date	*Event*	*Outcome*
May, 2019	Revision	Revised Guideline
Oct, 2010	Revision	Revised Guideline
June, 2003	Revision	Revised Guideline
May, 1998	Original Publication	New guideline developed and published

Permission to Use the Guideline

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

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

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Notification to Cincinnati Children's (EBDMInfo@cchmc.org) is appreciated for all uses of any EBCG or its companion documents which are adopted, adapted, implemented, or hyperlinked.

Please cite as

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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 EBDMinfo@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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Evidence Level in [ ], Table of Evidence Levels in LEGEND section above

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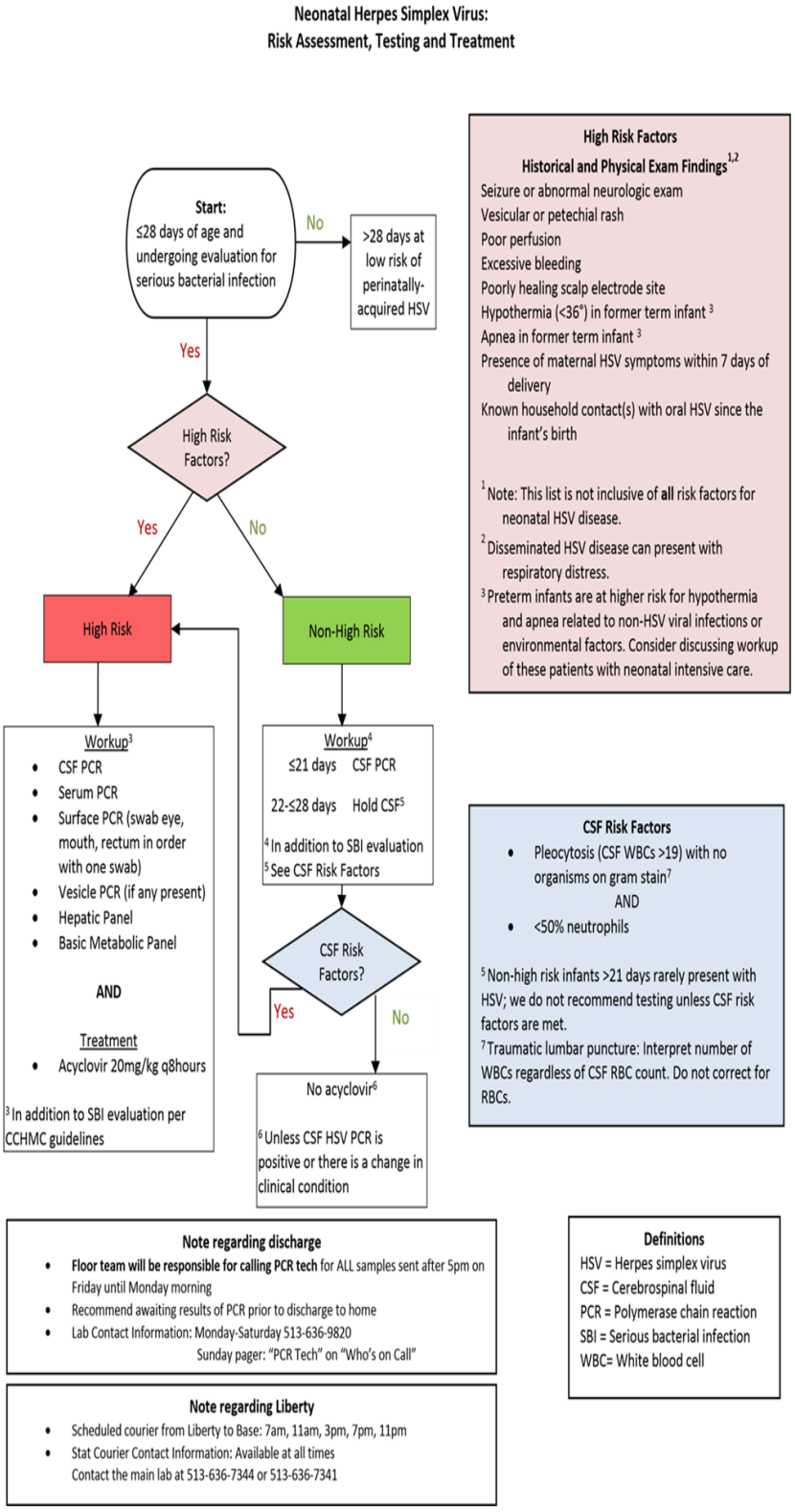
Appendix A



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/mm^3

Management Options:

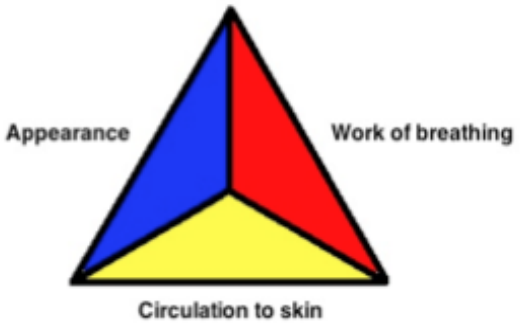
	Defer CSF Studies	Obtain CSF Studies
Benefits	• No pain from lumbar puncture procedure	• Ability to evaluate CSF for signs of infection and obtain CSF culture
Risks	• Missed meningitis Note: In one prospective cohort, multicenter study, 0.8% of infants with a negative UA and an ANC > 4090/mm^3 had meningitis.	• Traumatic lumbar puncture • 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 If blood culture becomes positive or infant becomes ill-appearing, obtain CSF studies and initiated antibiotics.	Consider initiating empiric antibiotics and admit to the hospital.

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. *Pedriatr 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	
Characteristic	**Normal features**
T one	Move spontaneously, resists examination, sits or stands (age appropriate)
I nteractiveness	Appears alert/engaged with clinician or caregiver, interacts well with people/environment, reaches for objects
C onsolability	Stops crying with holding/comforting by caregiver, has differential response to caregiver vs. examiner
L ook/gaze	Makes eye contact with clinician, tracks visually
S peech/cry	Uses age-appropriate speech

Work of breathing	
Characteristic	**Abnormal features**
Abnormal airway sounds	Snoring, muffled/hoarse speech, stridor, grunting, wheezing
Abnormal positioning	Sniffing position, tripoding, prefers seated posture
Retractions	Supraclavicular, intercostal, or substernal, head bobbing (infants)
Flaring	Flaring of the nares on inspiration

Circulation to skin	
Characteristic	**Abnormal features**
Pallor	White/pale skin or mucous membranes
Mottling	Patchy skin discoloration due to variable vasoconstriction
Cyanosis	Bluish discoloration of skin/mucous membranes

Diagnostic Studies for Accurate Serious Bacterial Infection Diagnosis

Study Citation	Study Type	N Sample Size	Population (Setting, Patients)	Intervention / Comparison Groups	Outcomes	Evidence Level
	Significant Results and Conclusions Including estimates with associated precision *(e.g., Odds Ratios or NNT with Confidence Intervals) as well as* Limitations / Risk of Bias, Gaps, Applicability, Consistency, or other Notes					
England, 2014	Meta-analysis	3217	7 studies involved infants <91 days with fever ≥ 38C, with use of procalcitonin in initial assessment,	Cutoffs for PCT included 0.3, 0.12, and 0.5 ng/mL depending on the study. SBI was defined in each study and included infection of blood, CSF, urine or joint spaces	• 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%	**1a**
	• 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					
Hu, 2017	Systematic review Meta-analysis	17 articles included – 1415 pts total	5 studies included our age (<3 months) in varying ranges	Diagnostic value of PCT and CRP (separately) a figuring out if SBI in patients with FUO	In meta-analysis: • PCT & CRP both higher in pts with SBI: ○ Higher sens for PCT than CRP ○ No diff in sensitivity btwn PCT & CRP ○ Higher AUC for PCT than CRP	**1b**
	• 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					
Leazer, 2016	Meta-analysis – rates of Enterococcus and Listeria among febrile infants	<90 days febrile infants 16 studies	Studies conducted in US published between 1998-2014	Describing rates of Listeria and Enterococcus – no comparisons	• 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 • Total - 3 infants with L. monocytogenes infections: • 2 with bacteremia & meningitis, • 1 with meningitis alone. • No reported cases of L-monocytogenes after 2001	**1b**
	• 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					
Irwin, 2016	Review of multiple prospective studies via medline and Cochrane	33 studies were reviewed. 14 of these involved infants < 3 months	In the 0-3 months group (14 studies) Rochester and Philadelphia criteria were used.	Review evaluated both Rochester and Philadelphia criteria to see when infants under 3 months can be safely discharged from the ER after fever.		**1b**
	• Combo of both criteria could safely be used to predict d/c.					
Brown, 2002	Systematic Review	14 studies 5247 infants with bacteremia and/or meningitis	Studies assessing febrile infants <3 mo in outpt setting (ED, clinic, etc) for presence of SBI. Studies reported prevalence of *L. monocytogenes* & enterococci.	Describe prevalence of infections requiring ampicillin in febrile pts <3 mo of age undergoing ruleout for SBI, with cultures.	• Prevalence of Listeria/Enterococcus per 1000 febrile infants • Patients **with bacteremia and/or meningitis:** Month of Life / n / Prevalence 1 / 1754 / 4.0% (95%CI 1.6 - 8.2) 2 / 3088 / 0.6% (95%CI 0.1 - 2.3) 3 / 405 / 2.7% (95%CI 0.6 -17.2) Month of Life / Number Needed to Cover 1 / 251 (95%CI 122 to 623)	**1b**

					2 1544 (95%CI 428 to 12755) 3 203 (95%CI 57 to 1671) • Patients **with bacteriuria (all Enterococcus):** Month of Life / n / Prevalence 1 1379 7.3% (95%CI 3.5 -13.3) 2 2632 1.9% (95%CI 0.6 - 4.4) 3 356 5.6% (95%CI 0.7 -20.1) Month of Life / Number Needed to Cover 1 138 (95%CI 55 to 566) 2 527 (95%CI 226 to 1621) 3 178 (95%CI 50 to 1469)	
	• Listeriosis has not decreased in prevalence over time from included studies, but has remained an infrequent event • Ampicillin for treatment of L-monocytogenes & enterococcal infections in CSF or blood has a number needed to cover of 251 (1 month) 1544 (2 months) & 203 (3 months) children. • Enterococcal urinary infections are more prevalent, with a number needed to cover of 138 (1 month), 527 (2 month), 178 children 3 months of age, res • Limitations**:** Checks for heterogeneity and publication bias were not performed; authors used non-traditional statistical methods in place of a Meta-Analysis.					
Kuppermann, 2019	Prospective observational multicenter study	1821	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)	Prospectively examined rates of bacteremia, meningitis or UTI (SBI) Subanalysis looking at just IBI 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	For prediction rule: - UA + - ANC >4090 - PCT > 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 bactermia. Repeat cx prior to abx was negative. Uneventful course	**3a**
	• 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 the1821 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 <28 days (aged 10, 12, 20 days) & had +CSF for HSV; the other was 33 days & had HV detected in nasal swab only.					
Cruz, 2017	Prospective Observational Multicenter	4313	Febrile (≥ 38C), previously healthy, full-term infants <60 days old who visited a pediatric ER & had blood cultures drawn.	97 (2.2%) had bacteremia or bacterial meningitis (IBI). Specifically, 1.7% had isolated bacteremia. 0.6% had bacterial meningitis.	• 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	**3a**
	• ANC did best, all AUCs were classified as poor discriminatory value (<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.					
Gomez, 2016	Retrospective cohort	1112 Infants	Infants < 3 months, well appearing, fever without	SBI = pathogen from blood, urine, CSF or stool IBI = pathogen from blood or CSF -	• PCT: OR for IBI 21.7 (7.9-59.23)	**3a**

			source had bld cx & PCT sent; 5 EDs in Spain, 2 in Italy	Cutoffs: PCT 0.5 ng/mL, CRP 20 mg/L, WBC 15K, ANC 10K	• PCT reduces post-test prob to 0.5% AUC 0.83
					• OR for SBI not as good.
					  • 289 (26%) had SBI
					  • 23 (2.1%) had 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, leukocyteria, 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					

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.	• SBI: AUC 0.80 vs 0.81 • IBI: AUC 0.91 vs 0.77 • 1 pt with IBI had procal < 0.3 (83d old with 4h fever & otitis media, blood cx + strep pneumo • Procal better than CRP in infants <28d, & fever < 6h	**3a**
	• Study supports using procalcitonin, although cutoffs can be discussed further. • Need to discuss: only 1258 had blood cx drawn? 1326 had LP					
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, Appear Non-well OR1.82 CI 0.79–4.96, CRP > 20 mg/L OR 3.82 CI 1.27–11.42, PCT > 0.5 ng/mL OR 3.32 CI 1.46–7.56	**3a**
	• 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					
Luaces-Cubells, 2012	prospective, observational study	868	Infants (2-36months) 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 ng/mL, sensitivity 86.7%, specificity 90.5%), • AUC for C-reactive protein was 0.79 (optimum cutoff 91 mg/L, 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	**3a**

	• 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	**3a**
	• PCT at least as good as RC in detecting children at risk of 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%	**3a**
	• 95% critical pedi pathogens: Streptococcus pneumoniae, Salmonella & other Enterobacteriaceae, Neisseria meningitidis, & groups A & B streptococci were detected <24 hours.					
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	**3b**
	• Id SBI, sensitivity of a score ≥3 was 86% (95% CI 77% to 92%) and specificity 83% (95% CI 79% to 87%). • Area under receiver operating characteristic curve for Lab-score (0.91) was significantly superior to that of any single variable: 0.71 for WBC, 0.86 for CRP and 0.84 for PCT. • The Lab-score performed better than other laboratory markers, even when applied to children of different age groups (<3 months, 3–12 months and >12 months). • The results obtained in this validation set population were comparable with those of the derivation set population. • This study validated the Lab-score as a valuable tool to identify SBI in children with FWS.					
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: ○ 87.8% within 24 hours ○ 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: ○ 88.7% within 24 hours ○ 95.2% within 36 hours	**4a**
	• 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 at >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)					

	• 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.					
Aronson, 2018b	Multicenter Retrospective cohort study	82 infants with IBI	febrile infants ≤ with invasive bacterial infections evaluated at 8 pediatric Eds, July, 2012, - June, 2014 Invasive bacterial infection - growth of pathogenic bacteria from blood or CSF cx	Main outcome measure: invasive bacterial infection - either bacteremia or bacterial meningitis Potential IBI cases - Id'ed from PHIS using ICD 9 dx codes for bacteremia, meningitis, UTI, & fever. Med. records reviewed confirm presence IBI & evaluate Rochester criteria: medical history, symptoms or ill appearance, UA results, CBC, CSF testing (if obtained), & blood, urine, & CSF cx.	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%) 6 infants with bacteremia, including one neonate with meningitis, met low risk criteria	**4a**
	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)					
Leazer, 2017	Retrospective	410 CSF cultures	Infants < 90 days with CSF cx drawn over 13 yrs 2000-2013, 5 children's hospitals Central site: Children's Hospital of The King's Daughters	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.	• 87% contaminants, 13% true pathogens • Contaminants grew at 68 hours, • True pathogens grew at 28 +/- 17 hrs → over 80% positive by 36 hours • CSF parameters helpful but cannot rule out meningitis • GBS most common pathogen (unlike bld cx)	**4a**
	• 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 68.1 ± 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%).					
Lefebvre, 2017	Retrospective	3559 blood cultures → 96 infants 98 positive	Infants < 90days in Quebec ED tertiary care pediatric center 2008-2013 – continuous blood culture monitoring system used	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	• 52 pathogenic, 46 contaminants • All cx: At 24, 36, 48, & 50 hours, 87.8% (86 of 98), 96.9% (95 of 98), 99% (97 of 98), & 100% (98 of 98) of all cultures were positive. • Pathogens: 96.1% (50 of 52) and 100% (52 of 52) were positive at 24 and 36 hours. • TTP: Mean TTP for pathogens14.40 hrs & contaminants 23.18 hrs, (P < .001).	**4a**
	• 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 contaminants 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					
Scarfone, 2017	Retrospective cohort pediatric ED of an urban, tertiary care children's	1188	Infants 29–56 days old with fever and who had an LP in the ED. (July 2007 – April 2014)	(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	1/1188 (0.08%) FYI had bacterial meningitis; pt did not meet low-risk criteria. 40 (3.4%) had positive CSF cultures; all contaminants.	4a

	Hospital (CHOP)			(3) determine proportion of study subjects who met low-risk criteria in absence of CSF analysis (4) determine # of infants meeting low-risk criteria with BM. Data extracted from clinical pathway QI registry. Data extracted: medical record #, encounter identification, date of birth, date/time of ED arrival, disposition from ED (admission vs discharge), date/time of hospital d/c & CSF results.	Sub-analysis of 1/3 of study population revealed that 45.6% met low-risk criteria; most common reasons for failing low-risk classification = abnormal wbc count or urinalysis	
	• 36-day-old infant (36 wks gestation) brought to ED b/c febrile crying, described as "crying inconsolably", "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. o 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. o Pt #37 completely normal evaluation @ initial ED encounter, normal screening laboratory & CSF tests, d/c'd 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 9 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 from bld & urine cxs (n =170/175, 97.1%	• All 9 bacterial meningitis cases had the same organism isolated from blood and from urine (all with >100 K in urine). • Concomitant bacterial meningitis was present in 9 infants (0.5%; 95% CI: 0.2%–1.0%)	**4a**
	• There is a low but not negligible incidence of meningitis in infants with positive urine cultures • No available data on antibiotic pretreatment prior to LP. • No data on clinical appearance of neonates. • Only included infants with CSF obtained as part of the parent study (on neonatal HSV					
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 Baby is low risk for IBI in the model if: well-appearing, over 21 days of age, procal less than 0.5, CRP less than 20 (2 for us)	• 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 28/287 (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	**4a**
	• Validation of a predictive model for identifying febrile young infants with altered urinalysis at low risk of invasive bacterial infection • Invasive Bacterial Infection secondary to Urinary Tract Infection: isolation of the same pathogen in blood or CSF culture as in urine culture. • Sensitivity of the model was 93.3 % (CI 95% 78.7–98.2), with a negative predictive value of 98.1 % (93.3–99.4). • Two patients in the low-risk group had an IBI. Both patients had occult bacteremia without UTI. One was an 87-day-old girl, with 3 h of fever, who grew • Streptococcus pneumoniae in the blood culture. This patient was discharged after one dose of parenteral antibiotic, • and afebrile when she was re-evaluated after arrival of the blood culture result. • The other one was a 28-day-old boy who presented fever at arrival in the PED and grew Moraxella catarrhalis in the blood culture. He was admitted with parenteral antibiotic. All patients had good outcome, without any deaths or sequelae. • Two false negative patients, both with occult bacteremias. When analysed one had a blood culture growing S. pneumoniae & had PCT and CRP blood levels of 0.4 ng/ml and 18 mg/L, respectively. These values are very close to cut-off values, which suggest that accuracy of the model may improve as time of evolution increases.					

	• 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 procal					
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) Difference in difference analysis: interaction between age comparisons and groups with the guidelines saying to LP all older babies vs not	• Primary outcome: adverse event (delayed dx of meningitis, in-hospital mortality, place CVC, mech ventilation, ECMO) • No difference in younger or older febrile infants between intervention & control groups (-0.02% in young, 0.33% in old; 95% CI -0.32 - 0.95, p=0.29)	**4a**
	• 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					
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 bld test results (leukocytes <5000/µLor >15,000/µL, neutrophils >10,000/µL, CRP >20 mg/L or PCT ≥0.5 ng/mL)	• 11 infants with bacterial meningitis – 9 were less than 21 days, the 5 were ill-appearing • None of the 1975 babies over 21 days who were well-appearing had bacterial meningitis	**4a**
	• Appropriate to get LP on babies < 21 days or those ill-appearing; but recommendation of systematically performing CSF analysis in well-appearing infants 22–90 days old based on analytical criteria alone must be reevaluated • Described findings, no real comparisons					
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)	**4a**
	• 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					
Aronson, 2014	Retrospective cohort	35 070 ED visits met inclusion criteria	infants < 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, &	Compared inter-hospital variation for 3-day revisits & revisits resulting in hospitalization and testing, treatment, and disposition for patients in 3 distinct age groups: < 28, 29 to 56, & 57 to 89 days	• Pt- and hospital-level variation in testing, treatment, and disposition	**4a**

			observation data from 44 pedi. hospitals in US affiliated with Children's Hospital Association (hospitals located in 26 states & DC representing 85% freestanding children's hospitals)			
	• The proportion of pts who underwent comprehensive evaluation, defined as urine, serum, & CSF testing, decreased with increasing pt age: 72.0% (95% CI, 71.0–73.0) of neonates ≤ 28 days, 49.0% (95% CI, 48.2–49.8) infants 29 to 56 days, and 13.1% (95% CI, 12.5–13.6) of infants 57 to 89 days. • Significant inter-hospital variation was demonstrated in testing, treatment, & hospitalization rates overall & across all 3 age groups, with little inter-hospital variation in outcomes. • Hospitalization rate in the overall cohort did not correlate with 3-day revisits (R2 = 0.10, P = .06) or revisits resulting in hospitalization (R2 = 0.08, P = .09). • Substantial patient- and hospital-level variation was observed in the ED management of the febrile young infant, without concomitant differences in outcomes.					
Biondi, 2014	Retrospective multicenter, cross-sectional	392 pathogenic bld cultures after excls	17 institutions Febrile infants ≤ 90 days admitted to general inpatient unit	Determine 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, 88-93) had turned positive. • By 36 hrs 96% (95%CI, 95-98) & @ 48 hrs 99% (95%CI, 97-100) become positive	**4a**
	• Findings supports how long to watch febrile infants → consider rec 24 hours					
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.	• Of 1123 infants (IBI 48; 4.2%), 488 (43.4%) were classified low-risk criteria according to step by step approach (vs 693 (61.7%) with Lab-score & 458 (40.7%) with Rochester criteria). • Prevalence of IBI in low-risk criteria pts was 0.2% (95% CI 0% to 0.6%) using step by step approach; 0.7% (95% CI 0.1% to 1.3%) using Lab score; 1.1% (95% CI 0.1% to 2%) with Rochester criteria • Using step by step approach, 1 pt with IBI was not correctly classified (2.0%, 95% CI 0% to 6.12%) vs 5 using Lab-score or Rochester criteria (10.4%, 95% CI 1.76% to 19.04%).	**4a**
	• Sequential approach to young febrile infants like the step-by-step approach better identifies low-risk pts; more suitable for outpt management; Procal 0.5 • Identification of young febrile infants with low-risk criteria for IBI can be improved using a sequential approach including PCT					
Nosrati, 2014	Retrospective cohort analysis	**401** 70% were 30-60d, 20.4% were 61-90d	Dana-Dwek Children's, Tel Aviv. < 3 mos with fever (> 38C). Excl: preterm birth, chronic dz, antibiotics. Enrollment: 2006 to 2008 (prior to PCV13)	SBI versus no SBI as defined by well-described characteristics.	• 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	**4a**
	• Overall rate of SBI was 12% (UTI in 90 Caveats; mostly > 30 days. High rate of SBI • CRP was most strongly correlated with risk for BSI. Highly superior to clinical characteristics, ANC, and WBC.					
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 fever than 10 WBC per uL on	**4a**

	Retrospective Cohort Study		because they referred most pts to larger center	management of febrile infants in the emergency room diagnosed with UTI	CSF examination (OR=0.4; 95% CI 1.1-2.9) were all independently associated with discharge from ED	
	• 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, & 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). • Limitations *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					
Bressan, 2012	Multicenter Retrospective	1098	7 pediatric emergency departments in Spain and Italy; FWS in well-appearing <3 months of age	287 (28.3%) were diagnosed with SBI (isolation of a bacterial pathogen from the blood, CSF, urine, or stools). 23 (2.1%) were diagnosed with IBI (isolation of a bacterial pathogen from blood or CSF) Lab-score was calculated as follows: 2 points for PCT $\geq$ 0.5 ng/mL or CRP $\geq$ 40 mg/L, 4 points for PCT $\geq$ 2 ng/mL or CRP $\geq$ 100 mg/L, 1 point for positive urine dipstick (positive nitrite or leukocyte esterase)	• For SBI, sensitivity 16% (CI 12-21), specificity 100% (CI 99-100) for Lab-score > 7, ranging to sensitivity of 52% (CI 46-58), specificity 95% (CI 93-96) for Lab-score > 3. • AUC for SBI prediction 0.83 (CI 0.80-0.86), significantly higher than for individual elements of Lab-score. • For IBI, sensitivity 39% (CI 20-62) specificity of 96% (CI 95-97) for Lab-score $\geq$ 7, ranging to sensitivity 70% (CI 49-84), specificity 84% (CI 81-86) for Lab-score $\geq$ 3.	**4a**
	• AUC for IBI prediction was 085 (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					
Byington, 2012	Observational Quality improvement	8044	Well appearing febrile infants 1 to 90 days of age. Intermountain Healthcare System – various locations	Use of Evidence Based Care Process Model to reduce cost.	• Slight increase in admission rate of febrile infants, similar rate (with trends toward improvement) in admission of pts with meningitis & bacteremia vs pre-implementation. • Increased documentation of UTIs & viral infections, • Higher % of pts with SBI admitted after UTI detection, d • Decreased LOS, • Appropriate use of recommended antibiotics, • Considerable cost reduction	**4a**
	• Viral testing on all infants, our los much shorter • No missed SBI • Although hospital admissions were shortened by 27%, there were no cases of missed SBI. Health Care costs were also reduced, with the mean cost per admitted infant decreasing from $7178 in 2007 to $5979 in 2009 (-17%, P < .001).					
Gomez, 2012	Retrospective cohort	1112 infants	Infants < 3 months old, well appearing, FUS who had a blood cx & PCT 5 EDs in Spain, 2 EDs in Italy	SBI = pathogen from blood, urine, CSF or stool 289 (26%) had SBI IBI – pathogen from blood or CSF 23 (2.1%) had IBI Cutoffs used: PCT 0.5 ng/mL, CRP 20 mg/L, WBC 15K, ANC 10K.	• 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).	**4a**

					• 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).	
	• Supports adding procalcitonin /CRP to lab evaluation of febrile infants to identify 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 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).	**4a**
	• 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 & natriuria. 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).					
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 U/A	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-appearing • Negative predictive value of an abnormal UA for meningitis was 98.2%.	**4a**
	• LP not necessary if well-appearing and with reassuring labs • Negative predictive value of an abnormal urinalysis for meningitis was 98.2%. • Consistent with above two studies, was low numbers					
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 pleocytosais present in 18% of infants with UTI (cutoff is set at 10). • Found WBC was only factor independently associated with risk of CSF pleocytosis (inflammatory response) • Presence of sterile pleocytosis affects clinical decision making (20% of low risk infants with UTIs & sterile CSF pleocytosis received ≥ 7 days of IV abx despite rapid resolution of fever)	**4a**
	• Sterile CSF Pleocytosis in Young Febrile Infants with Urinary Tract Infections • 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 pleocutosis					

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)	**4a**
	• Pts were at low risk for adverse events if not clinically ill in ED and did not have high risk PMH with sensitivity of 98.0% (95% CI 88.2-99.9) & NPV of 99.9% (95% CI 99.5-100%). • Pts were at low risk for bacteremia if not clinically ill in ED, 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 post-laboratory results *Pts identified by querying laboratory databases, rather than identifying pts who had positive UAs in the ED which was not feasible in this study.					
Olaciregui, 2009	Retrospective cohort	347 (23% with SBI)	Donosotia 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	**4a**
	• Overall BSI rate 23.6% (high - 84% UTI). PCT & CRP better than WBC & ANC. PCT better than CRP in invasive infection (not UTI, cellulitis, pneumonia)					
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%.	**4a**
	• 4.3% were positive for adenovirus with Adenovirus 1 2, 3 were most common types (none were Adenovirus 14) • Using scoring system (Table 2), Procalcitonin, CRP, and urine dipstick had sensitivity of 94% (95% CI 82-99) and specificity of 81 (95% CI 72-88). • Alone, Procalcitonin was most significant predictor of SBI (OR 37.6, 95% CI 5.8-243) with sensitivity 94% & specificity 68%. (cutoffs for OR not specify, based on other data likely used cutoff of 0.5) • CRP OR 7.8 (95% CI 2-30.4) and urine dipstick OR 23.2 (95% CI 5.1-104.8)					
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	**4b**

	• 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					
Hassoun, 2014	Retrospective chart review	1192 screened	Febrile infants <28 days presenting to one of two EDs for SBI evaluation	Describing pathogens in febrile infants	TABLE 1. Frequency of Different Causes of SBI Bacteremia / UTI / Meningitis / Total E. coli 8 (36) / 30 (56) / 2 (67) / 34 (47) GBS 6 (27) / 0 (0) / 1 (33) / 6 (8) S. aureus 2 (9) / 4 (7) / 0 (0) / 6 (8) Listeria 1 (5) / 0 (0) / 0 (0) / 1 (2) Enterococcus 1 (5) / 15 (28) / 0 (0) / 16 (22) Salmonella 2 (9) / 0 (0) / 0 (0) / 2 (3) Other 2 (9) / 5 (9) / 0 (0) / 7 (10) Total 22 (100) / 54 (100) / 3 (100) / 72 (100) Values are presented as n (%).	**4b**
	• 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.					
Biondi, 2013	Retrospective review - descriptive	177 infants 181 total pos blood cultures	Febrile infants <90 days across 6 hospitals over 6 years	No comparisons – describing pathogens	• 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	**4b**
	• 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%					
Greenhow, 2012	Retrospective review – descriptive	4255 blood cultures 160,818 infants	Prev healthy babies 1wk to 3 mos with bld culture drawn at Kaiser 2005-2009	No comparisons – describing pathogens in bacteremia	• 2% positive (93/4255) for pathogens – • E-coli 1st GBS 2nd, S. aureus 3rd • No Listeria No meningococcemia • One case Enterococcus	**4b**
	• 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					
Tebruegge, 2011	Retrospective cohort	735 pts, with 163 < 28 days & 499 > 29 days to 12 months	Large ped referral hospital in Victoria, Australia. Pt 1 d - 16 yrs of age with a pos. urine culture & CSF sample collected w/in 48 hrs of urine sample.	UTI patients with or without positive CSF culture	• 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)	**4b**
	• 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					

Gomez, 2010	Retrospective cohort	1018	<3 mo with FUS with blood culture over 5-year period to Peds ED from 2003 to 2008 in Spain	Assess rate of bacteremia in febrile infants < 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	• 23 positive blood cultures: 9 bacteremia 8 UTI+bacteremia 4 meningitis • 0 - 1 mo 8/243; 3.29% (1.04%–5.53%) 2/243; 0.82% (0%–1.95%) • 1–2 mo 9/417; 2.15% (0.76%–3.55%) 3/417; 0.71% (0%–1.53%) • 2–3 mo 6/358; 1.67% (0.34%–3.00%) 4/358; 1.11% (0.02%–2.20%)	**4b**
	• 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 nitrituria, 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	Descriptive, retrospective?	685 included	Babies less than 90 days with FUS who did not have LP in Spain over 4 years	Descriptive Rec LP if less than 15 days, careful consideration 15-28 days, consider based on appearance over 28 days	LP in 198 babies – 2 under 15 days with bacterial meningitis 487 without LP: 69 were admitted (46 had UTI), 418 discharged, with 38 of those having had "unscheduled revisits" to ED (4 were aseptic meningitis)	**4b**
	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	Retrospective chart review	105 pathogens	Febrile infants <90 days of age presenting to tertiary pediatric referral center ED	Describing pathogens in febrile infants	• 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)	**4b**
	• 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	Guideline Revision	NA	infants and young children two to 24 months of age with unexplained fever		• Accurate diagnosis	**5a**
	• 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)					