Cincinnati Children's Hospital Medical Center

Health Policy & Clinical Effectiveness Program

Evidence-Based Care Guideline

Fever of Uncertain Source

In infants 60 days of age or less[a]

Revised Publication Date(s): October 27, 2010; June 6, 2003
Original Publication Date: May 15, 1998

Target Population

Inclusions:

- Infants, 60 days of age or less, presenting as outpatients with a fever of uncertain source.

Exclusions:

- 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

Target Users

Include but are not limited to (in alphabetical order):

- Clinicians caring for inpatients
- Emergency Medicine physicians
- Patient Care staff, including:
  - nurse practitioners
  - nurses
- Patients and families
- Primary care providers
- Residents

[a] Please cite as: **FUS Team, Cincinnati Children's Hospital Medical Center:** Evidence-based clinical care guideline for fever of uncertain source in infants 60 days of age or less, http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm, Guideline 02, pages 1-14, October 2010

Introduction

References in parentheses ( ) Evidence level in [ ] (See last page for definitions)

The differential diagnosis involving fever in neonates and young infants 29 to 60 days of age includes both infectious and noninfectious causes. Although self-limited viral infections are the most common cause of fever, the incidence of serious bacterial infections (SBI) may be higher in this population compared to older children; neonates have been shown to be at particularly high risk *(Laupland 2009 [4a], Caviness 2008b [4b])*. Approximately 12% to 28% of neonates presenting to a pediatric emergency department (ED) with fever have serious bacterial illness *(Ishimine 2007 [5b])*. Serious bacterial infections include bacteremia (e.g., sepsis), gastroenteritis, cellulitis, osteomyelitis, septic arthritis, meningitis, pneumonia, and urinary tract infection (UTI) *(Poehling 2006 [3a], Byington 2003 [3a])*. Among these, UTI is the most common type of SBI *(Byington 2003 [3a])*.

Among bacterial pathogens causing SBI in infants less than 90 days of age, Gram-negative bacteria are most frequently identified. *Escherichia coli* and *Klebsiella* species accounted for 69% of all SBI cases in febrile infants (<90 days) presenting to one pediatric ED *(Byington 2003 [3a])*. The most common Gram-positive pathogens isolated include *Staphylococcus aureus* (8%), group B *Streptococcus* (6%), and *Enterococcus* (6%) *(Byington 2003 [3a])*.

Neonatal herpes simplex virus (HSV) is an important consideration in infants 0-28 days of age. Neonates with cutaneous vesicles, seizures, and/or elevated transaminases present a high index of suspicion for HSV infection; however, it is rare for a neonate with HSV to present with fever of uncertain source (FUS). Nine cases of neonatal HSV infections were admitted to Cincinnati Children's Hospital Medical Center (CCHMC) over a 2-year period (2001-2002), and only one of these nine infants presented with FUS. Earlier therapy may improve outcomes in neonates with HSV, and physicians need to remain aware of neonatal herpes in the development of their differential diagnoses *(Kimberlin 2005 [5a], James 2009 [5b])*.

Because the clinical exam alone is unable to reliably predict serious illness in neonates and young infants 29 to 60 days of age with FUS and culture results are not immediately available, clinicians must often approach management of patients with fever by relying on a combination of history, physical examination findings, and diagnostic screening tests. It can be a challenge to balance the minimization of risk for serious illness with

costs and morbidity of testing and treatment for patients who present with FUS *(Ishimine 2006 [5b])*.

The objectives of this guideline are to:

- Identify appropriate diagnostic studies
- Identify appropriate antimicrobial therapy
- Improve the efficiency of care
- Improve parent and family satisfaction with care

See Table 1 for definitions of terms used in this guideline.

Table 1: Definitions

Term	Definition
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	Rectal temperature ≥ 38ºC (100.4 ºF)
Neonates	Children birth to 28 days of age
Young infants	Children between 1 month and 2 months of age
Previously healthy	Born at term (≥ 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 *(Gomez 2010 [4b])*
Cerebrospinal fluid (CSF) pleocytosis	Neonates age 0-28 days: cerebrospinal fluid white blood cell count >19/μL *(Kestenbaum 2010 [4b])*
	Young infants 29-60 days: cerebrospinal fluid white blood cell count >9/μL *(Kestenbaum 2010 [4b])*

Guideline Recommendations

Assessment and Diagnosis

Clinical Assessment

1. It is recommended that a rectal temperature be measured to establish fever ≥ 38º C for the purpose of this guideline *(Claudius 2010 [5b])*.

   Note 1: Patients who had a reliable rectal temperature measured at home undergo the same evaluation as if the temperature was measured in the office or emergency department *(Claudius 2010 [5b], Ishimine 2007 [5b])*.

   Note 2: Parental report of fever via palpation is unreliable as a sole method of determining fever *(Katz-Sidlow 2009 [4b], Callanan 2003 [4b])*.

   Note 3: A response to antipyretic medication does not change the likelihood of an infant having a serious bacterial infection *(American College of Emergency Physicians Clinical Policies Committee 2003 [5a])*.

2. It is recommended that a clinical assessment include a thorough history and physical exam *(Baraff 2008 [5b])*.

   Note: Include questions about recent symptoms, vaccinations, exposure to sick contacts, and the child's birth history in the patient history *(Thompson 2006 [4a], Sur 2007 [5b])*.

Laboratory Studies: Neonates

3. It is recommended that the following laboratory studies be performed in neonates with FUS *(Bilavsky 2009 [3b], Gomez 2010 [4b], American College of Emergency Physicians Clinical Policies Committee 2003 [5a], Baraff 2008 [5b], Sur 2007 [5b])*:
   - complete blood count (CBC), differential, blood culture
   - urinalysis (UA) and urine culture
     Note: Urethral catheterization and, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens *(American College of Emergency Physicians Clinical Policies Committee 2003 [5a])*
   - cerebrospinal fluid (CSF) studies:
     Tube 1: protein and glucose
     Tube 2: culture, sensitivity, Gram stain
     Tube 3: cell count and differential
     Tube 4: hold for additional studies
   - stool culture if diarrhea is present *(Ishimine 2007 [5b])*

4. It is recommended that CSF HSV polymerase chain reaction (PCR) testing **not** be routinely performed in neonates who present with FUS and no other evidence of an HSV infection *(Caviness 2008c [1a], Shah 2010 [4b], Local Consensus [5b])*.

5. It is recommended that CSF HSV PCR be considered in neonates with CSF pleocytosis and a negative Gram stain *(Caviness 2008c [1a], Caviness 2008b [4b], Local Consensus [5b])*.

Laboratory Studies: Young infants 29-60 days of age

6. It is recommended that the following laboratory studies be performed in young infants 29 to 60 days of age with FUS *(Bilavsky 2009 [3b], Gomez 2010 [4b], Kourtis 2004 [5a], American College of Emergency Physicians Clinical Policies Committee 2003 [5a], Ishimine 2007 [5b])*.
   - complete blood count, differential, blood culture
   - urinalysis and urine culture
     Note: Urethral catheterization and, although rarely performed, suprapubic aspiration are preferred methods for obtaining urine specimens. High rates of contamination occur with bagged specimens *(American College of Emergency Physicians Clinical Policies Committee 2003 [5a])*.
   - stool studies for white blood cell (WBC) count and culture if diarrhea is present *(Ishimine 2007 [5b])*.

   Note: C-reactive protein (CRP) and procalcitonin (PCT) have been studied in infants less than 90 days presenting with fever of uncertain source *(Maniaci 2008 [3a], Bilavsky 2009 [3b], Olaciregui 2009 [4a])*. Inclusion in a diagnostic evaluation of FUS does not improve our confidence in ruling out SBI at this time. See appendix for likelihood ratios from diagnostic studies evaluated.

7. It is recommended that delaying or omitting a lumbar puncture (LP) for CSF analyses be considered in young infants 29 to 60 days of age with FUS who meet all applicable low-risk clinical and laboratory criteria (See Table 2) *(Huppler 2010 [1b], Sur 2007 [5b], Local Consensus [5b])*.
   Note 1: If antimicrobial therapy will be initiated in infants who meet low-risk criteria, CSF specimens need to be collected prior to treatment. See note 2 below for details of CSF analyses.
   Note 2: If all applicable low risk clinical and laboratory criteria are **not** met, CSF analyses include:
   Tube 1: protein and glucose
   Tube 2: culture, sensitivity, Gram stain
   Tube 3: cell count and differential
   Tube 4: hold for additional studies

Table 2: Low-risk criteria *(Garra 2005 [2b], Gomez 2010 [4b], Baraff 2008 [5b], Dobson 2008 [5b])*

Low-risk clinical criteria	
• well-appearing • previously healthy • no focal source of infection	
Low-risk laboratory criteria	
Urinalysis	• ≤10 WBC/hpf • No bacteria on Gram's stain
CBC	• WBC 5,000 to 15,000/mm^3 • ≤1,500 band cells/mm^3
Chest radiograph (if obtained)	• No evidence of discrete infiltrate
Stool smear (when diarrhea is present)	• Negative for blood • ≤5 WBC/hpf

CBC=complete blood count; WBC=white blood cells; hpf=high-power field
Note: The likelihood ratio for ruling-out SBI in patients who meet low-risk clinical and laboratory criteria is 0.08 *(Garra 2005 [2b])*. See the appendix for further information.

8. It is recommended that testing for enteroviruses (EV), human herpesvirus 6, influenza A and B viruses, rotavirus, respiratory syncytial virus, and *Treponema pallidum* be selectively considered for infants with fever *(Benito-Fernandez 2006 [3a], Byington 2004 [3a], Rittichier 2005 [3b], Byington 2002 [4b])*.
   Note: PCR testing of both blood and CSF for enterovirus increased the diagnostic yield of EV infections by ~ 20% in one study *(Rittichier 2005 [3b])*.

Radiology Studies

9. It is recommended that a chest x-ray be performed in neonates and young infants 29 to 60 days of age who manifest one or more of the following clinical findings: tachypnea >60 breaths/min, crackles in the chest, retractions, nasal flaring, cyanosis, or oxygen saturation ≤ 95%. *(National Collaborating Centre for Women's and Children's Health 2007 [5a])*.

Management

Admission Criteria

10. It is recommended that all neonates with FUS be admitted to the hospital *(Gomez 2010 [4b], Claudius 2010 [5b], Baraff 2008 [5b], Ishimine 2007 [5b], Sur 2007 [5b])*.

11. It is recommended that young infants 29 to 60 days of age with FUS be admitted to the hospital when all relevant low risk clinical and laboratory criteria are **not** met (Table 2) and/or social or family concerns (e.g., transportation problems, lack of resources for

prompt medical follow-up) are present *(Ishimine 2007 [5b])*.

12. It is recommended that outpatient management of young infants 29 to 60 days of age with FUS be considered if **all** the following conditions are present *(Huppler 2010 [1b], Condra 2010 [3b], Baraff 2008 [5b], Local Consensus [5b])*:
    - low-risk clinical and laboratory criteria have been met (see Table 2)
    - available reliable follow-up in 12-24 hours
    - healthcare provider(s) confident that parent will use appropriate observational and follow-up skills
    - primary care physician (PCP) and family agree with plan of care

Medications: Neonates

13. It is recommended that neonates with FUS be treated with intravenous (IV) ampicillin plus a 3rd generation cephalosporin or gentamicin pending culture results *(Brown 2002 [1b], Baraff 2008 [5b], Dobson 2008 [5b], Ishimine 2007 [5b])*. See Table 3 for further information.

Table 3: Medication administration

Drug	Dose	Comments
Acyclovir	20 mg/kg IV every 8 hours	
Ampicillin	50 mg/kg IV every 6 hours Note: every 12 hours for < 7 days of age	
Cefotaxime (Claforan®)	50 mg/kg IV every 8 hours for presumed bacteremia 50 mg/kg IV every 6 hours for presumed meningitis Note: every 12 hours for < 7 days of age	
Ceftriaxone (Rocephin®)	50 mg/kg IV or IM every 24 hours for presumed bacteremia 100 mg/kg IV or IM every 24 hours for presumed meningitis	Contraindicated in neonates with hyperbilirubinemia and in neonates requiring or who may require IV calcium-containing solutions
Gentamicin	0-30 days: 3 mg/kg IV every 24 hours 31-60 days: 2.5 mg/kg IV every 12 hours	
Vancomycin	15 mg/kg IV every 12 hours	Consider in patients at risk for *S. aureus* infection

14. It is recommended that vancomycin rather than ampicillin be considered in neonates with FUS at risk for *S. aureus* *(Byington 2003 [3a], Local Consensus [5b])*.

15. It is recommended that treatment for HSV be considered in neonates with FUS, CSF pleocytosis, and a negative Gram stain until an alternative diagnosis is established or CSF PCR is negative for HSV *(Caviness 2008c [1a], Claudius 2010 [5b], Baraff 2008 [5b])*. See Table 3 for dosing of acyclovir.

Medications: Young infants 29 to 60 days of age

16. It is recommended that young infants 29 to 60 days of age with FUS who do not meet low risk criteria (Table 2) be treated with a 3rd generation cephalosporin pending culture results *(Byington 2003 [3a])*.

17. It is recommended that IV ampicillin be considered as an addition to the antibiotic regimen for febrile infants 29 to 60 days of age who are severely ill or who have findings suggestive of urinary tract infection to assure coverage for rare organisms such as *Listeria monocytogenes*, gram-positive cocci or enterococcus. *(Brown 2002 [1b], Byington 2003 [3a])*.

18. It is recommended that vancomycin be considered in febrile young infants 29 to 60 days of age at risk for *S. aureus* *(Byington 2003 [3a], Local Consensus [5b])*.

19. It is recommended that a 3rd generation cephalosporin (such as ceftriaxone) be considered for young infants 29 to 60 days of age managed as outpatients after a LP is performed *(Dobson 2008 [5b])*.

Monitoring

20. It is recommended that fluid status be carefully monitored in all patients *(Local Consensus [5b])*.
    Note: Especially for patients on gentamicin and/or acyclovir, fluid replacement may be needed if the infant is dehydrated due to a risk of renal toxicity.

21. It is recommended that the duration of initial treatment cover a period of 36 hours until culture results are available *(Local Consensus [5b])*.
    Note 1: Cultures must be checked after a true minimum incubation period of 36 hours, which begins when the inoculated culture is placed in the incubator.
    Note 2: Approximately 90% of bacterial pathogens are identified within the first 24 hours of incubation *(Byington 2004 [3a])*.
    Note 3: The probability of identifying SBI in febrile infants (28-90 days) after 24 hours is

about 1.1% among all patients and 0.3% among low risk patients *(Kaplan 2000 [4b])*.
Note 4: In blood cultures of infants 0-6 months of age, mean time to positivity for true pathogens is about 17.5 hours and for contaminants is about 27.9 hours *(McGowan 2000 [4a])*. Median time to positivity for urine and CSF cultures are 16 and 18 hours, respectively, in febrile infants age 28-90 days *(Kaplan 2000 [4b])*.

22. It is recommended that in patients with FUS who are not responding to antimicrobial therapy, the clinician consider additional evaluation and treatment options, including:
    - alternative antimicrobial therapy for resistant organisms *(Byington 2003 [3a], Local Consensus [5b])*
    - (in neonates only) CSF HSV PCR (if not completed previously) and empiric treatment with acyclovir *(Caviness 2008a [4b], Sur 2007 [5b])*

Discharge Criteria

23. It is recommended that discharge be considered in patients with negative cultures after a true minimum incubation period of 36 hours *(Local Consensus [5b])*. See Table 4 for discharge criteria.

Table 4: Discharge Criteria

- Well-appearing
- Eating well
- Antimicrobial therapies complete or can be continued in the home
- Culture results negative
- Infant observed without antibacterial treatment is well-appearing at 24 hours
- Family:
  a. has participated in the discharge planning and decision process
  b. understands and agrees to any prescribed therapies or follow-up needs
  c. confident in ability to care for infant at home
- Home environment considered appropriate for continuing care
- Follow-up physician:
  a. identified
  b. has participated in generating the discharge plan
  c. agrees with the discharge plan

Follow-up

24. It is recommended that young infants 29 to 60 days of age managed as outpatients be examined by their health care provider within 12 to 24 hours for follow-up and a second dose of ceftriaxone (if applicable) *(Dobson 2008 [5b])*.

Consults and Referrals

25. It is recommended that a consult with an infectious disease specialist be considered for *(Local Consensus [5b])*:
    - an unusual presentation or clinical course of disease
    - questions regarding acyclovir treatment
26. It is recommended that a consult with Lactation Services be considered for breastfed patients who are feeding poorly *(Local Consensus [5b])*.

Education

27. It is recommended that parent and family education include the following *(Local Consensus [5b])*:
    - knowledge of illness
    - worrisome signs to report to medical care provider
    - when and how to measure child's temperature
    - administration of medications
    - nutrition and fluids

Health Topics on CCHMC's website[b]:
- Fever
- Fever in a Newborn
- Temperature Taking

Future Research Agenda

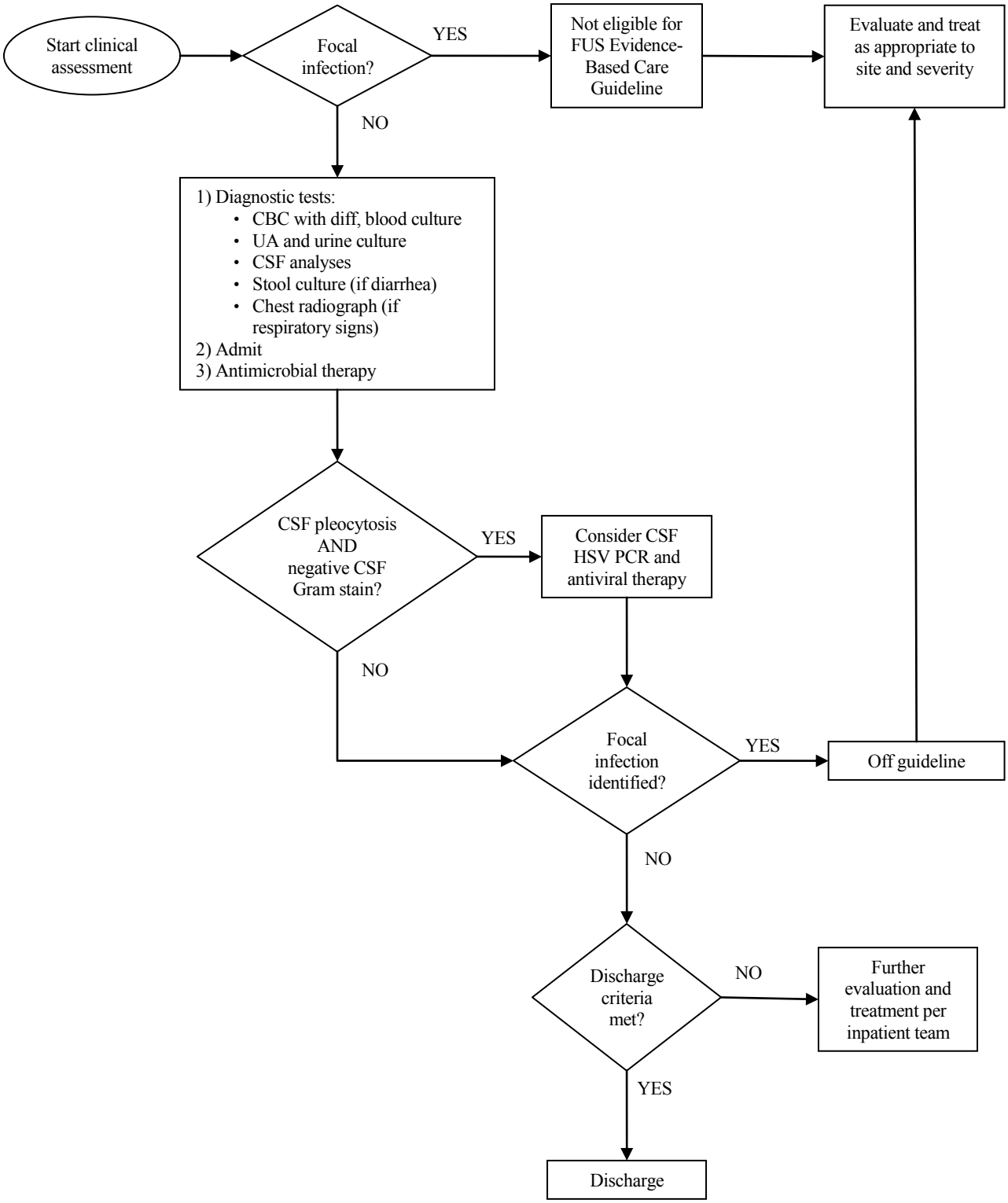
- In children 0 to 60 days of age with fever of uncertain source, which laboratory test or combination of tests (procalcitonin, C-reactive protein, IL-8, sTREM-1, urine dipstick) best predict serious bacterial infection? *(Sanders 2008 [1b], Chen 2009b [3b], Chen 2008 [3b], Andreola 2007 [3b], Galetto-Lacour 2003 [3b], Lacour 2008 [4b], Fernandez Lopez 2003 [4b])*
- In children 0 to 60 days of age with fever of uncertain source, what risk factors best predict the presence of serious bacterial infection? *(Chen 2009a [4a], Schwartz 2009 [4a], Shin 2009 [4b])*
- In children 0 to 60 days of age with fever of uncertain source, does rapid viral testing in the Emergency Department affect the treatment of

[b] CCHMC Health Topic website: www.cincinnatichildrens.org/health/info

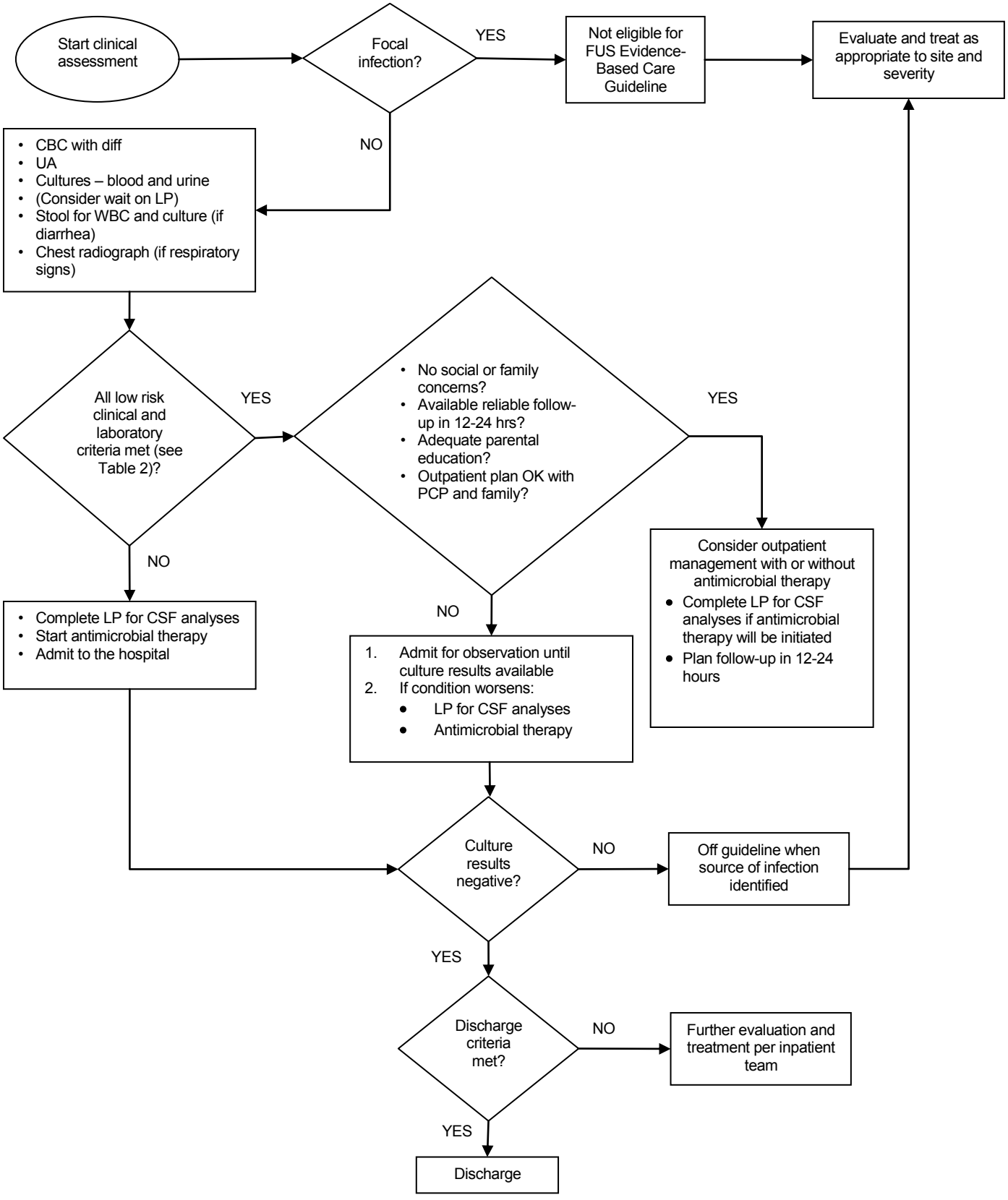
children with fever? *(Doan 2009 [1a], Iyer 2006 [2b], Benito-Fernandez 2006 [3a], Vega 2005 [5b])*

- In neonates 0 to 28 days of age does empirical treatment with acyclovir for patients with CSF pleocytosis improve outcomes related to morbidity or mortality from neonatal HSV infection? *(James 2009 [5b])*
- In infants 30 to 60 days of age does a clinical prediction rule for serious bacterial infection help the clinician decide to ambulatory follow a child without starting antibiotic treatment? *(Bleeker 2007 [2a])*
- Does continuous automated monitoring of CSF cultures allow earlier hospital discharge?

Algorithm for managing fever of uncertain source in neonates (age 0 to 28 days)



Algorithm for managing fever of uncertain source in young infants (age 29 to 60 days)

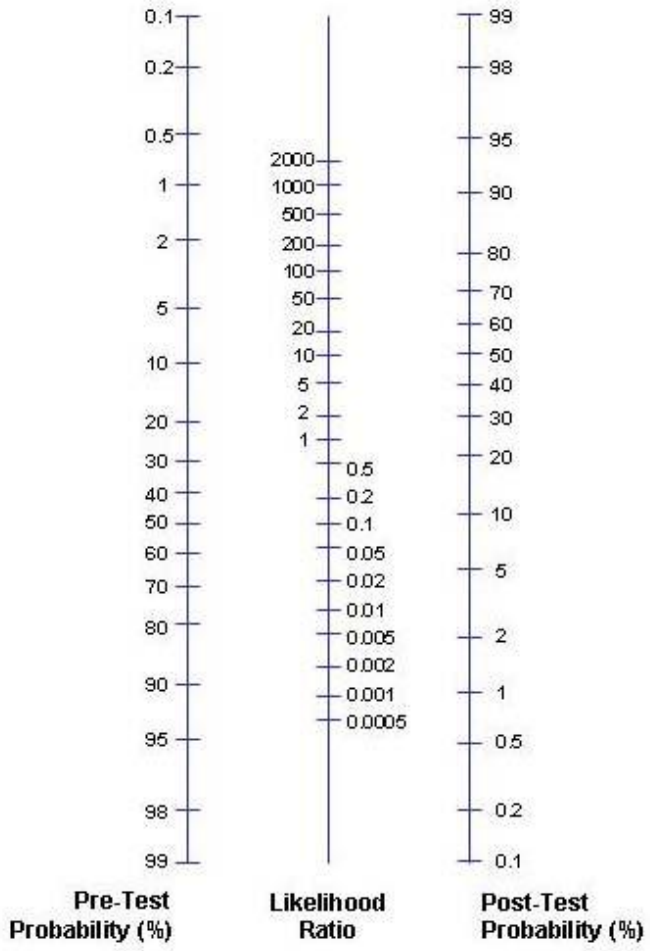


Appendix: Likelihood ratios (LR) for diagnostic tests to detect serious bacterial infection

Probability Worksheet for your own use[c]

1. Based on _____ **(Prior Factors Considered)**,

   my estimate of the **pre-test probability** is ____ % that this child has a serious bacterial infection.
2. The sign or symptom I found, _____, has a **LR** of _____.
3. Using the nomogram, I calculate that the **post-test probability** is ____% that this child has a serious bacterial infection.
4. Repeat steps 1 to 3, as desired, for each additional sign or symptom observed (shortcut: multiply LRs before starting).
5. The final **post-test probability** is _____ % that this child has a serious bacterial infection.



Diagnostic test/criteria and age group	Test value	LR+	LR-
PCT *(Maniaci 2008 [3a])* Infants < 90 days of age	0.12 ng/ml	1.28	0.19
PCT-Q *(Olaciregui 2009 [4a])* Infants < 90 days of age	>0.5 ng/ml	4.8	0.42
CRP *(Olaciregui 2009 [4a])* Infants < 90 days of age	≥ 3 mg/dl	5.4	0.46
CRP *(Bilavsky 2009 [3b])* Infants ≤ 90 days of age; hospitalized infants	> 8 mg/dl	13.3	0.8
	>4 mg/dl	5.6	0.6
	>2 mg/dl	3.1	0.5
WBC *(Olaciregui 2009 [4a])* Infants < 90 days of age	> 15,000/µl	2.4	0.74
WBC *(Bilavsky 2009 [3b])* Infants ≤ 90 days of age; hospitalized infants	> 15,000/ µl or < 5,000/ µl	2.3	0.6
WBC, CRP, PCT, good general state, and urine dipstick *(Olaciregui 2009 [4a])* Infants < 90 days of age	WBC 5,000/ µl - 15,000/ µl CRP <3 mg/dl PCT <0.5 ng/ml Urine negative	1.48	0.11
Rochester criteria *(Garra 2005 [2b])* Infants <56 days of age	Low risk based upon Rochester criteria: • Appears well • Previously healthy • No evidence of skin, soft tissue, bone, joint, or ear infection • Normal labs (WBC, ANC, urine, stool [if applicable])	1.60	0.08

[c] Rule of thumb:
LR > 10 greatly increases diagnostic certainty
LR = 1 test result is not helpful in diagnosis
LR <0.2 greatly helps rule out condition

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All Team Members and Clinical Effectiveness support staff listed above have signed a conflict of interest declaration and none were found.

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Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual; a Team Binder maintains minutes and other relevant development materials. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic search and critical appraisal of the literature, using the Table of Evidence Levels described following the references, and examined current local clinical practices.

To select evidence for critical appraisal by the group for this guideline, the Medline, EmBase and the Cochrane databases were searched for dates of January, 2003 to February, 2010 to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to fever of uncertain source and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. December, 2002 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

Tools to assist in the effective dissemination and implementation of the guideline may be available online at http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm . Experience with the implementation of earlier publications of this guideline has provided learnings which have been incorporated into this revision.

Once the guideline has been in place for three years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

The guideline was externally appraised by two reviewers[d] using the AGREE instrument and the results by domain are:

- Scope and Purpose 56%
- Stakeholder Involvement 67%
- Rigor of Development 52%
- Clarity and Presentation 56%
- Applicability 13%
- Editorial Independence 100%

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.

The guideline has been reviewed and approved by clinical experts not involved in the development process, distributed to senior management, and other parties as appropriate to their intended purposes.

The guideline was developed without external funding. All Team Members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest and none were identified.

Copies of this Evidence-based Care Guideline (EBCG) and its any available implementation tools 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/svc/alpha/h/health-policy/ev-based/default.htm Examples of approved uses of the EBCG include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care guidelines;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the EBCG may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

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NOTE: These 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 in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about this guideline, its supporting evidences and the guideline development process, contact the Health Policy & Clinical Effectiveness office at: 513-636-2501 or HPCEInfo@cchmc.org .

References

Note: When using the electronic version of this document, ☜ indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

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Note: Full tables of evidence grading system available in separate document:

- 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 (abbreviated table below)

Table of Evidence Levels (see note above)

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
5	Other: General review, expert opinion, case report, consensus report, or guideline

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

Table of Recommendation Strength (see note above)

Strength	***Definition***
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

