DATE: September 2014

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Fever Without Localizing Signs (0-60 Days Old)
Evidence-Based Guideline

Definition: An acute febrile illness (temperature ≥100.4°F [38°C]) with uncertain etiology after completion of a thorough history and physical examination. [1-4]

Etiology: The most common cause of fever without localizing signs (FWLS) is a viral infection. The challenge lies in the difficulty of distinguishing serious bacterial illness (SBI) from viral illness in neonates and early infancy. [1,4-6]

Inclusion Criteria:
- Age 0-60 days (Term infants ≥37 weeks gestation)
- Neonates and infants without underlying conditions
- Actual rectal temp ≥100.4°F (38°C) OR reported temp (axillary or rectal) of ≥100.4°F (38°C) in home setting

Exclusion Criteria:
- History of prematurity
- Underlying conditions that affect immunity or may otherwise increase risk of SBI
- Toxic/Septic appearance
- Receiving antibiotic treatment for FWLS
- Routine vaccinations given within the previous 48 hours
- Presenting with seizures
- Requiring intensive care management
- Identified focus of infection (e.g., cellulitis, acute otitis media in infants >28 days old)

Differential Diagnosis:
Meningitis
Bone and joint infections
Pneumonia
Urinary tract infection
Sepsis/Bacteremia
Enteritis
Herpes Simplex Virus (HSV) infection
Enterovirus
Parechovirus

Toxic Criteria [7,8]
Infants that meet ANY of the toxic criteria should receive a full sepsis workup and be admitted to the inpatient area for antibiotic therapy and observation (See Tables 1 & 2).

Signs/Symptoms include:
Poor perfusion
Capillary refill time >2 seconds
Cyanosis
Lethargy
Unable to console
Tachypnea or bradypnea
Hypothermia (96.8°F/36°C)

Table 1. Signs and Symptoms of Shock [9,10]

	Cold Shock	Warm Shock	Non-specific
Pulses (central vs. peripheral)	Decreased or weak	Bounding	
Capillary refill (central vs. peripheral)	≥3 sec	Flash (<1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental status			Decreased, irritability, confusion inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

*↑ HR followed by ↓ HR with BP changes will be noted as shock becomes uncompensated.

Table 2. Vital Sign Changes of Sepsis [9,10]

Age	Heart Rate	Respiratory Rate	Systolic BP
0d - 1m	>205	>60	<60
>1m to 3m	>205	>60	<70

†BP changes are late signs of worsening condition. May also present with chills.

Diagnostic Evaluation: In this age group, bacterial pathogens associated with FWLS may include Gram-positive organisms (such as group B *Streptococcus*, *Enterococcus*, group A *Streptococcus*, *Staphylococcus aureus*, *Listeria monocytogenes*) and Gram-negative organisms (such as *Escherichia coli*, *Enterobacter*, *Klebsiella*). *Streptococcus pneumoniae* is more likely to occur in infants >30 days old. [11-12]

Viral pathogens, such as enterovirus, adenovirus, herpes simplex virus, influenza virus, and parainfluenza virus, are also a concern in this patient population. [13,14]

History: Assess for
Onset of fever
Immunization status [15]
Irritability
Poor feeding
Decreased urine output
Exposure to infectious agents
- Other sick contacts/family members
- Maternal fever at time of delivery

- Maternal Group B streptococcal vaginal colonization
- Maternal HSV infection

Physical Examination:
Rectal temperatures are preferred to axillary or other methods of temperature measurements.
A thorough clinical history and physical examination are essential to determine risk of SBI or identify focus of infection. (16,17)

Table 3. Laboratory Tests

	0-28 days	29 to 60 days
Complete blood count (CBC) with differential and platelets	X	X
Blood culture (BC) (obtain prior to antibiotic administration)	X	X
Enterovirus CSF PCR (during peak season of May – October)	X	X
Urinalysis (UA) with micro and culture (obtain specimen via cath or SPA† only)	X	X
Lumbar puncture* (LP) [gram stain, culture, cell count and diff, glucose, protein, viral culture‡]	X	Optional
Consider: (18-24)		
Stool for culture and presence of WBCs (if diarrhea present)		
Viral diagnostic testing or rapid tests (if respiratory symptoms)		
Chest X-ray (if respiratory symptoms; WBC >20,000/mm^3 or ANC >10,000/mm^3)		
Herpes simplex virus (HSV) if risk factors present or patient not improving on antibiotics		
Blood and/or CSF parechovirus PCR during peak season - May to October (if febrile and other viral/bacterial cultures negative)		

† Cath (transurethral catheterization) or SPA (suprapubic aspiration)
*LP should be performed prior to antibiotic administration
‡ Tube #1 Glucose, protein
Tube #2 Cell count & diff, Gram stain & culture
HOLD Tube #3 in virology lab

For infants with FWLS, laboratory evaluation for neonatal HSV infections should be reserved primarily for those with clinical findings suggestive of an HSV infection or a prior history of HSV. (25-28)

HSV Risk Factors (27)
- Maternal primary HSV infection
- Maternal fever
- Vaginal delivery
- Prematurity
- Neonatal seizures
- Vesicular rash
- CSF pleocytosis (monocytosis)
- Elevated hepatic enzymes

Signs/Symptoms of Systemic HSV (28)
- Skin, eye, and mouth lesions/disease
- Seizures, lethargy, and fever
- Disseminated form- neonate presents with multi-organ failure

The laboratory tests below are recommended if HSV suspected. (27,28)
- CSF specimen for HSV PCR (priority) and viral culture (if adequate specimen available)
- Blood PCR
- Blood viral culture
- Rectal viral culture
- Conjunctiva viral culture
- Nasopharyngeal (NP) viral culture
- ALT/AST

Critical Points of Evidence

Evidence Supports

- Consider administration of acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. [25,27,29,30] – Weak recommendation, low quality evidence
- The laboratory test that is most accurate in diagnosing HSV is the CSF HSV PCR in the presence of pleocytosis. [31-33] – Strong recommendation, low quality evidence
- Empiric antibiotic therapy of ampicillin and gentamicin for all neonates (0-28 days). If there is a concern for meningitis or CSF pleocytosis, cefTAZidime should be administered in lieu of gentamicin. [34,35] – Strong recommendation, low quality evidence
- The immunogenicity of influenza vaccine in former premature infants is lower than in full term infants. [36] – Strong recommendation, very low quality evidence
- Enterovirus testing should be utilized in addition to usual care in order to decrease length of stay. [37,38] – Strong recommendation, low quality evidence
- All infants 0-60 days with fever without localizing signs should be tested for enterovirus during peak season regardless of the presence of CSF pleocytosis (*TCH PCR positivity data plus expert consensus indicates that peak season will likely occur from May through October). [38-42] – Strong recommendation, low quality evidence
- Enterovirus CSF PCR should be used for testing when CSF specimen is available. (*This recommendation is also based on rapid turnaround time of CSF PCR as compared to serum PCR at TCH.) [18,42-44] – Strong recommendation, low quality evidence
- For enterovirus-positive infants 0-28 days old, they should have a minimum of 24 hours of hospital monitoring of bacterial cultures if low risk and 48 hours if high risk. [18,19,42] – Weak recommendation, low quality evidence
- For enterovirus-positive infants 29-60 days old, no further inpatient monitoring of bacterial cultures is needed once enterovirus result is known. If otherwise meeting discharge criteria, high risk 29-60 day old infants can be discharged with a dose of ceftriaxone and close pediatrician follow-up. For the low risk enterovirus infant 29-60 days old, they can be discharged as soon as result is known without antibiotics. (*Recommendations based on expert consensus plus epidemiologic evidence showing low rates of SBI. SBI seems more common in neonates and those that are high risk.) [18,19,42] – Weak recommendation, low quality evidence
- Consider CSF parechovirus testing during peak season (May to October) when other viral (e.g., enterovirus, HSV) and bacterial etiologies have been ruled out. [20-23,45,46] – Weak recommendation, low quality evidence

Evidence Against

- AST and/or ALT lab tests should not routinely be used for screening for disseminated HSV in all infants 0-28 days with fever. If at any time the child has risk factors for HSV, CSF pleocytosis, appears ill, and/or has a persistent fever with negative bacterial cultures ≥48 hours, additional lab tests, including but not limited to HSV PCR, should be completed. [25,28,47-49] – Strong recommendation, low quality evidence
- Procalcitonin and/or C-reactive protein (CRP) should not be used as predictors of SBI in well-appearing children with FWLS. [50-58] – Strong recommendation, moderate quality evidence
  Remarks: Although the sensitivity of procalcitonin has shown to be higher than other biomarkers, there is not enough data to support changes in the clinical management of patients based upon this value alone. At this time, there is not a clearly defined cutoff in the literature for procalcitonin.

Condition-Specific Elements of Clinical Management

Treatment Recommendations [17, 47, 59-62]

Table 4. Low Risk Lab Criteria for 29-60 day old infants

CBC with d/p	WBC 5-15/mm^3 Absolute band count <1500/mm^3
UA with micro (cath or SPA specimen)	Clear Negative for nitrites & leukocyte esterase WBC <10/hpf
LP	**0-28 days** WBC cell count 0-22/mm^3 **≥29 days** WBC cell count 0-7/mm^3 Normal protein (0-30 days <100 mg/dL) (>1 month 15-45 mg/dL)

Table 5. Admission/Outpatient Management Criteria [7,8,18,19,42]

Admit
All infants ≤28 days old
High risk enterovirus negative 29-60 day old infants
Possible Outpatient Management
Enterovirus positive 29-60 day old infants
Low risk enterovirus negative 29-60 day old infants

Neonates (≤28 days):

If presenting in clinic setting, refer to EC.

Evaluate with a full sepsis workup, including enterovirus CSF PCR during peak season of May to October, and admitted to the inpatient area for antibiotic therapy and observation. [18,42-44]

Empiric antibiotic therapy of ampicillin and gentamicin should be initiated on all neonates. If there is a concern for meningitis or CSF pleocytosis, ampicillin and cefTAZidime should be administered. [34,35]

Consider administration of acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. [25,27,29,30]

Enterovirus-positive infants 0-28 days old should have a minimum of 24 hours of hospital monitoring of bacterial cultures if low risk and 48 hours if high risk. [18,19,42]

Infants ≥ 29 days:

If CBC or UA values do not meet low risk lab criteria, an LP is indicated (Table 4). Antibiotics should not be administered until ***after*** LP is obtained.

Enterovirus-positive infants 29-60 days old should be managed outpatient once enterovirus result is known if meeting all other discharge criteria (Table 5). [18,19,42]

- High risk 29-60 day old enterovirus-positive infants can be discharged with a dose of cefTRIAXone and close pediatrician follow-up.
- Low risk enterovirus-positive infants 29-60 days old can be discharged as soon as result is known without antibiotics.

A penicillin and a third generation cephalosporin are recommended as first-line therapy. For infants >6 weeks old, clinicians may consider third generation cephalosporin monotherapy.

Meningitic dosing should be initiated on all neonates and infants until CSF test results have been reviewed and CNS involvement has been ruled out.

Follow-up Care

Healthcare provider to follow up on blood and urine cultures (if discharged before 48 hours)

Healthcare provider to call lab for CSF culture interpretation prior to discharge.

Follow-up appointment with PCP 12-24 hours post-discharge

Return to PCP/EC if worsening symptoms

Inpatient/Observation Discharge Criteria

- Decreasing fever curves
- Well-appearing with no evolution of signs/symptoms
- Tolerating oral intake and maintaining hydration status
- One of the following clinical situations:
  - Negative cultures after 48 hours and clinically stable (applies only to inpatients)
  - Low risk enterovirus-positive infants 0-28 days with negative bacterial cultures after 24 hours of hospital monitoring [18,19,42]
  - Clinically stable infants 29-60 days old with positive urine culture (CSF & blood negative) after 23 hours of observation on PO antibiotics
- Reliable follow-up available 12-24 hours post-discharge
- Caregiver and PCP agree with plan
- Caregiver understands discharge education

Measures

Outcome

- Length of stay
- # of readmissions for same problem
- Type of follow-up post EC or Inpatient discharge (phone call vs. visit to PCP)
- # of infants >28 days with LP vs. no LP based on risk criteria
- EC treatment plan for infants after LP performed vs. infants without LP performed
- # of call backs for positive blood cultures
- # of call backs for positive urine cultures for patients with negative UA
- # of enterovirus positive patients with concomitant serious bacteria infection

Table 5. Antibiotic Dose Administration Table [63]
Infants 0-28 days
Consider insurance/Medicaid formulary restrictions

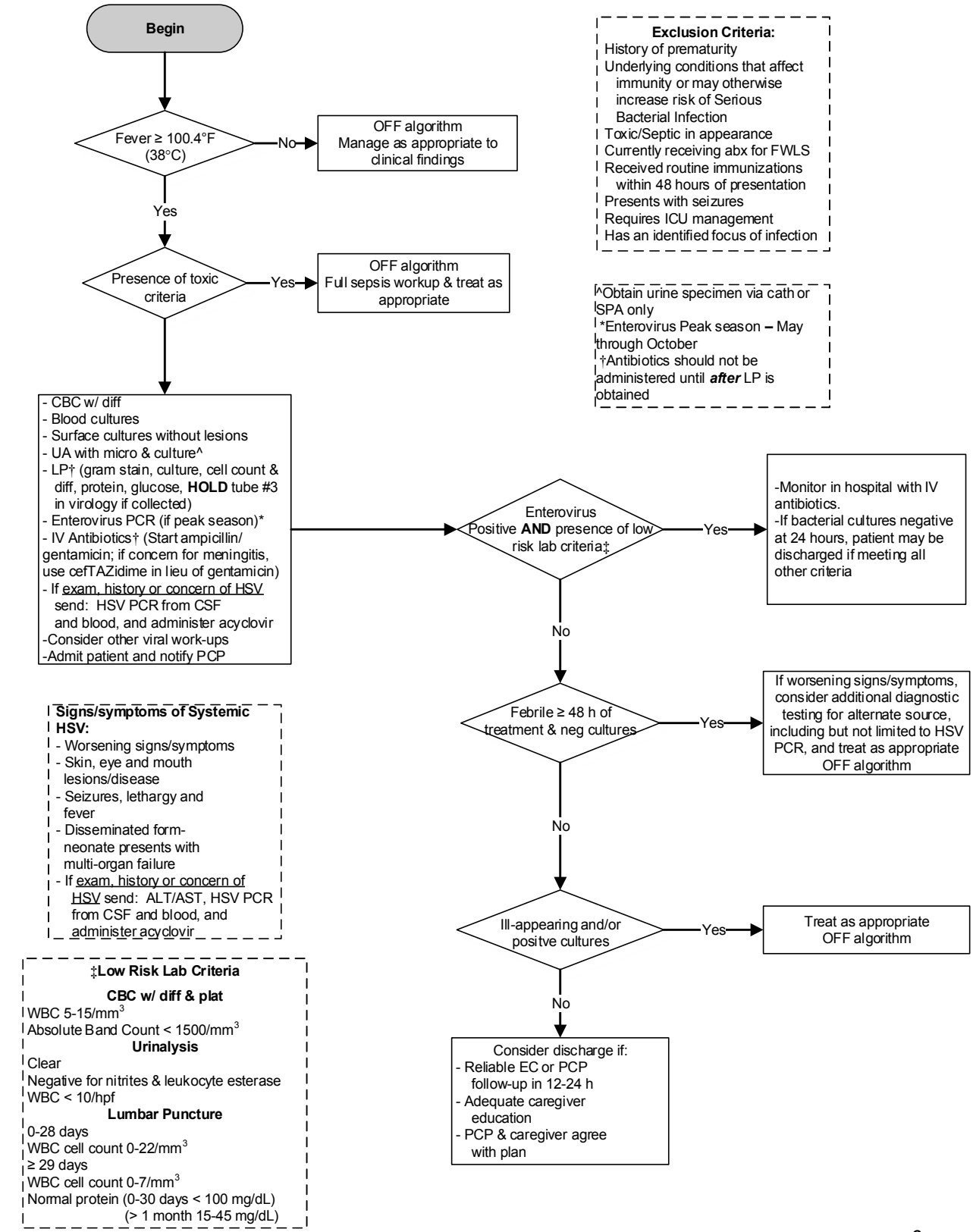
Drug	Dosing Guidelines
Empirical Parenteral Therapy (IV)	
Ampicillin	**≤7 days:** 100 mg/kg/dose every 12 h **>7 days:** 50 mg/kg/dose every 6 h If concern for meningitis: 75 mg/kg/dose every 6 hours
Gentamicin Sulfate	**Neonates:** 4 mg/kg/dose every 24 h
Use in lieu of gentamicin for suspected meningitis or CSF pleocytosis	
CefTAZidime	**Neonates:** **0-28 days:** 50 mg/kg/dose every 8 h **NOTE:** Recommended usage to: - Neonatal patients (defined as ≤44 weeks postmenstrual age OR neonates <1 month of age)
Treatment of choice for suspected *Staphylococcus* [11]	
Vancomycin	**<7 days old:** >2,000 g: 10 to 15 mg/kg/dose every 8 to 12 hours **≥7 to 28 days:** >2,000 g: 10 to 15 mg/kg/dose every 6 to 8 hours
Treatment of choice for Herpes Simplex Virus (HSV)	
Acyclovir	**Neonates and Infants:** 20 mg/kg/dose every 8 h

Table 6. Antibiotic Dose Administration Table [63]
Infants 29-60 days
Consider insurance/Medicaid formulary restrictions

Drug	Dosing Guidelines
Outpatient or Emergency Center Empirical Therapy (IM/IV)	
CefTRIAXone	**Infants >28 days:** 50 mg/kg/dose once
Empirical Parenteral Therapy (IV)	
Ampicillin†	**Infants >28 days and children:** *Mild to Moderate Infection*: 100-150 mg/kg/**DAY** divided every 6 hours **MAX** daily dose: 4000 mg/**DAY** *Meningitis or Severe Infection*: 200-400 mg/kg/**DAY** divided every 6 hours; **MAX** daily dose: 12g/**DAY**
CefTRIAXone†	**Infants >28 days:** 100 mg/kg/dose every 24 h **NOTE:** Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site Not for use in infants <44 weeks postmenstrual age OR neonates <1 month of age *Use cefTAZidime as an alternative
Treatment of choice for suspected *Staphylococcus* [11]	
Vancomycin	**Infants >28 days to 60 days:** 15 mg/kg/dose every 8 hours

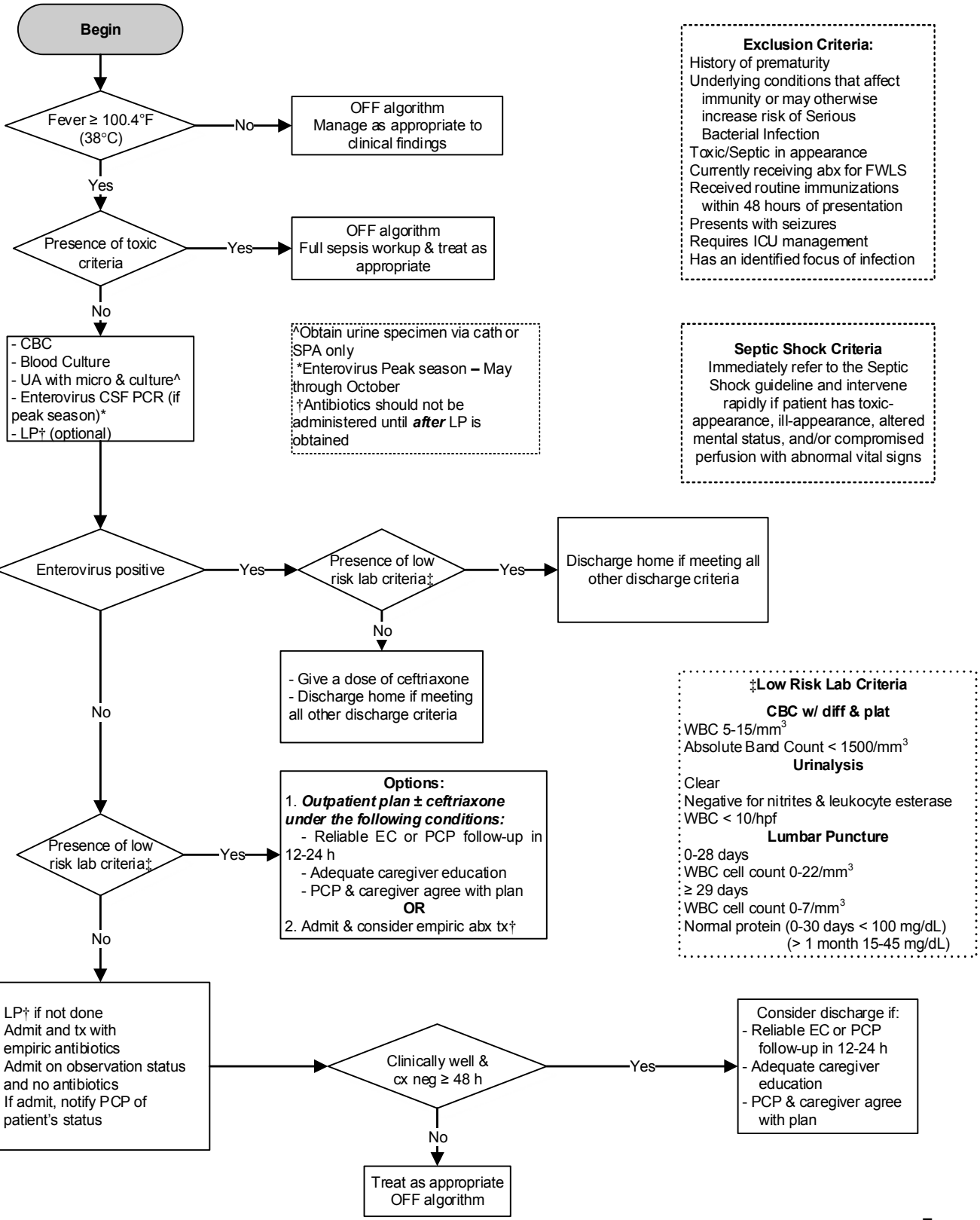
†Reduce antibiotics to general dosing for suspected infection once meningitis ruled out.

TCH Evidence-Based Outcomes Center Clinical Algorithm
Neonates & Infants with Fever Without Localizing Signs (FWLS)
0-28 days



DATE: September 2014

TCH Evidence-Based Outcomes Center Clinical Algorithm
Neonates & Infants with Fever Without Localizing Signs (FWLS)
29-60 days



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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - A published guideline from a children's hospital
3. Literature Review of Relevant Evidence
   - Searched: Medline, Cochrane, AHRQ, Cinahl, Trip, Best BETS, AAP, BMJ Clinical Evidence, Google Scholar
4. Critically Analyze the Evidence
   - Cincinnati Guideline, Emergency Medicine Clinical Policy for Children Younger than Three Years Presenting with Fever, 2 meta-analyses, 42 non-randomized studies, and 4 review articles
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a FWLS 0-60 Days manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence.*
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the management of FWLS in infants 0-60 days. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
Mar 2009	Originally completed
Sep 2014	Updated
Jul 2015	Revision: Literature search on procalcitonin
Jun 2016	Revision: Antibiotic selection
Feb 2017	Revision: Antibiotic selection