Texas Children's Hospital

DATE: April 2021

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Fever Without Localizing Signs (2-36 Months)
Evidence-Based Guideline

Definition: An acute febrile (temperature ≥102.2°F [39°C]) illness lasting <7 days with uncertain etiology after completion of a thorough history and physical examination. [(1)]

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 this age group. Introduction of the *Haemophilus influenzae* type b (Hib) and heptavalent pneumococcal conjugate (PCV7) vaccines has dramatically decreased the incidence of SBI in infants and children. [(2-4)] In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 for routine administration to infants and children. PCV13 added six serotypes to the original serotypes of PCV7. [(5)] Since routine PCV13 immunization, invasive pneumococcal infections decreased 42% overall and 53% for children <24 months of age in 2011 compared with the average number of cases for 2007 to 2009 (year 2011, n = 124 vs. years 2007 to 2009, mean = 215). [(5)] In 2012, 23 out of 21,285 blood cultures were positive for pneumococcus at Texas Children's Hospital. The positivity rate for 2012 was approximately 0.1%.

Differential Diagnosis
Meningitis
Bone and joint infections
Urinary tract infection (UTI)
Sepsis/Bacteremia
Enteritis
Pneumonia

Inclusion Criteria
- Age 2-36 months
- Infants/Children without underlying conditions
- Actual rectal temp ≥102.2°F (39°C) OR reported temp of ≥102.2°F (39°C) in home setting

Exclusion Criteria
- Underlying conditions that affect their immunity or may otherwise increase risk of SBI (e.g., asplenia, sickle cell disease, prematurity, cancer)
- Toxic/Septic appearance [(6,7)]
- Currently receiving antibiotics
- Given routine vaccinations within the previous 48 hours
- Presenting with seizures
- Requiring intensive care management
- With an identified focus of infection (e.g., cellulitis, acute otitis media)
- With a suspicion of meningitis

Clinical Appearance
Toxic [(1,6,7)]

Infants who 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).

Lethargy
Hypothermia (96.8°F/36°C)
Capillary refill time >2 seconds
Tachypnea or bradypnea
Unable to console
Cyanosis
Poor perfusion
Suspicious of meningitis

Well-appearing
Playful, not irritable, feeding well, easily consoled by caregiver
No signs/symptoms (s/sx) dehydration
No compromise in peripheral perfusion
No s/sx respiratory distress

Ill-appearing
Less playful, irritable with crying, consolable by caregiver
S/Sx mild to moderate dehydration
Peripheral perfusion intact

Table 1. Shock Exam Abnormalities [(8)]

	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

Table 2. Vital Sign Changes of Sepsis (PALS) [(8)]

Age-specific Vital Signs			
Age	**Heart Rate**	**Resp Rate**	**Systolic BP**
>1m - 3m	>205	>60	<70
>3m - 1y	>190	>60	<70
>1y - 2y	>190	>40	<70 + (age in yr x 2)
>2y - 4y	>140	>40	<70 + (age in yr x 2)

Diagnostic Evaluation: A thorough clinical history and physical examination are essential to determine risk of SBI. [(9)] The most common bacterial infection in infants and young children is UTI. Risk factors for UTI are detailed in the laboratory section of the guideline. Pneumococcal bacteremia and meningitis prevalence has decreased since the introduction of the pneumococcal conjugate vaccines. [(10,11)]

History: Assess for
- Onset and duration of fever
- Use of antipyretics and response
- Immunization status [(12-20)]

- Presence of an underlying medical condition
- Irritability, lethargy, change in activity level
- Cough
- Tachypnea
- Vomiting with or without diarrhea
- Dysuria, frequency, abdominal pain, back pain
- New onset incontinence in toilet-trained children
- ↓ Urine output
- Poor feeding/decreased appetite
- Exposure to infectious agents
  - Other sick contacts/family members
  - Enrolled in daycare

Physical Examination

Subjective and objective findings should be utilized to determine the degree of illness. The sicker the child appears, the more likely the fever is the result of a SBI. Rectal temperatures are preferred to axillary or other methods of temperature measurement. Clinical appearance and risk should be utilized to determine laboratory work-up needs.

Laboratory Tests [2-4]

Viral infections are the most common etiology in this population. Most infants/children will not require laboratory testing.

Recognized Viral Sources of Fever [21-23]

Bronchiolitis	HSV
Chicken pox	Influenza
Croup	Stomatitis
Enterovirus	Viral exanthems (rashes)
Herpangina	

Upper respiratory infections (URIs) and acute gastroenteritis (AGE) are not acknowledged as viral sources.

Well-appearing children with an unremarkable history may be observed at home without initial lab testing in the presence of the following conditions:

- Availability of reliable follow-up
- Adequate caregiver education
- Primary Care Physician (PCP) and caregiver agree with plan

UA with micro & culture [2-4,24]

UTI is the most common SBI in this age group.

Risk factors for UTI:

- Male: ≤6 months
  >6 months to 12 months and uncircumcised
- Female: <24 months

Specimen collection recommendations:
Non-toilet trained children via cath or SPA
Toilet trained via midstream clean catch

If urine dipstick is positive for nitrites or leukocyte esterase OR the microscopy is positive, then UTI is very likely.

When UTI is suspected, refer to the Texas Children's Hospital First Febrile Urinary Tract Infection Clinical Guideline for management and treatment recommendations.

CBC with differential/platelet count & blood culture [2,18,25,26]

Not recommended in well-appearing children.

Recommended in ill-appearing children and those at risk for occult bacteremia.

Risk factors include:

- Incomplete PCV13 series for age [17-19,25]
- Ill-appearing
- Fever >104°F (40°C)
- Known meningococcal contact

Table 3. Reference Lab Values [27]

CBC with d/p	ANC <10,000/mm^3
UA with micro	Clear Negative for nitrites & leukocyte esterase WBC <10/hpf

Critical Points of Evidence*

Evidence Supports

- Children with FWLS at risk for SBI (received less than two doses of PCV13 and/or ill-appearing) with an ANC ≥10,000 should be treated with ceftriaxone. [5,28,29] – Strong recommendation, moderate quality evidence
- There is a decreased incidence of pneumococcal-related bacteremia in the post-PCV13 era. [5,15,30-35] – Strong recommendation, low quality evidence
- Two doses of PCV13 are reliable to decrease the risk of pneumococcal infections. [12,36-39] – Strong recommendation, low quality evidence
- CBC and blood culture should be conducted in ill-appearing children. [9,40-44] – Strong recommendation, moderate quality evidence
- Consider a CBC and blood culture in children that have not received two doses of PCV13. [9,40-44] – Strong recommendation, moderate quality evidence

Evidence Against

- Rapid viral testing is unnecessary in most cases for infants/children with FWLS. [45-50] – Weak recommendation, low quality evidence
- Well-appearing children with FWLS should not have a procalcitonin or C-reactive protein (CRP) performed to predict the risk of SBI. [51-58] – Strong recommendation, moderate quality evidence
- Caregiver knowledge is not a reliable method to ascertain immunization status of infant/child with FWLS. [13,14,59] – Weak recommendation, low quality evidence
- Children with at least two doses of PCV13 that present with FWLS should not have a CBC and blood culture obtained. [9,40-44] – Strong recommendation, moderate quality evidence

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

Treatment Recommendations [2,6,21,60]

Clinical assessment and H&P indicative of a source-refer to the appropriate TCH Guideline and treat as appropriate (e.g., acute otitis media, community-acquired pneumonia, enteritis, urinary tract infection).

In addition to clinical findings the following factors should be considered prior to treatment:

- Availability of reliable follow-up
- Adequate caregiver education
- PCP and caregiver agree with plan

Viral Syndromes & Well-appearing

No antibiotics indicated. In most cases, rapid viral testing is not necessary. Consider UA with micro and culture. Treat symptomatically.

Educate caregiver/patient on symptom management and PCP follow-up.

Antibiotic Recommendations [35,60]

Not recommended in well-appearing infants/children without a focus of a bacterial infection and in the absence of a laboratory workup. Monitor clinically.

Consider administration of IM ceftriaxone [28,61] if:

- CBC abnormal and/or ANC ≥10,000/mm^3
- No viral signs/symptoms and unable to identify a bacterial source on exam

Recommended dose: 50 mg/kg/dose IM once

Consider insurance/Medicaid formulary restrictions.

Observation Criteria

- Unable to tolerate oral intake or maintain hydration status
- Hypoxemia
- Respiratory distress
- Clinical concern
- Reliable follow-up unavailable

Discharge Criteria

- Tolerating oral intake and maintaining hydration status

Follow-Up Care

Follow up on CSF, blood and urine cultures (if done and discharged prior to **48 hours-** MD to call lab for CSF reading)

See PCP 12-24 hours post discharge

Return to PCP/EC if worsening symptoms

Measures

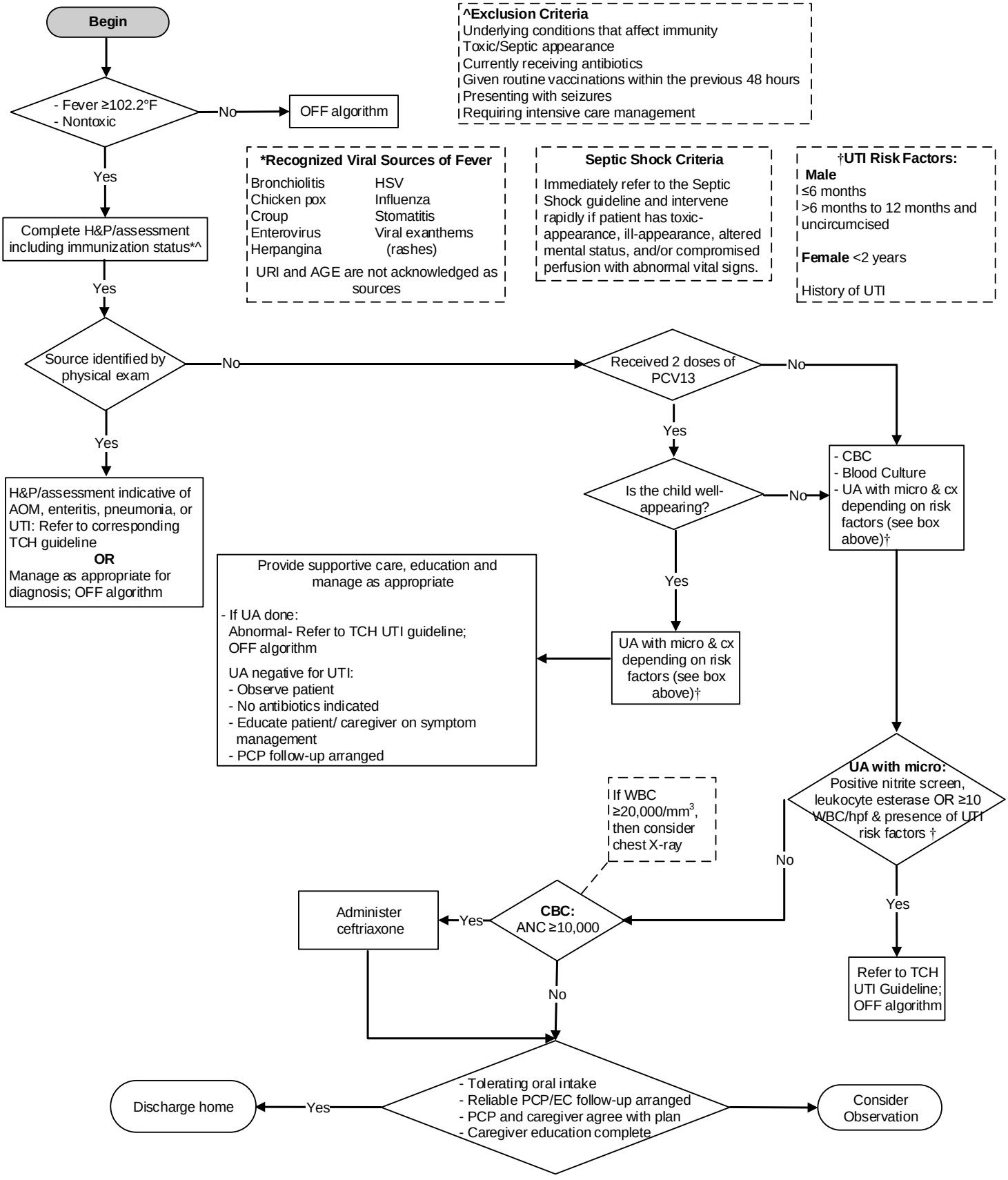
Process

- Contamination Rate
- Type of follow-up post EC or discharge from observation (phone call vs. visit to PCP)
- If return to EC, # of infants/children that received antibiotics on first visit
- # of callbacks for positive blood cultures
- # of callbacks for positive urine cultures of infants/children with negative UA

Outcome

- Length of stay
- Readmission rate

TCH Evidence-Based Outcomes Center
Clinical Algorithm for Fever Without Localizing Signs (FWLS)
2-36 Months



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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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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
   - Fever of Uncertain Source in 2-36 months of age, Cincinnati Children's Hospital Medical Center; Clinical Policy for Children Younger Than Three Years Presenting with Fever, American College of Emergency Physicians; Feverish Illness in Children: Assessment and Initial Management in Children Younger Than 5 Years, NICE Clinical Guideline

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
   - 1 meta-analysis, 2 systematic reviews, 2 randomized controlled trials, and 32 nonrandomized studies.

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Fever Without Localizing Signs (2-36 Months) evidence-based review 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 diagnosis/management of fever without localizing signs in children 2-36 months of age. 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	Action	Comments
Mar 2009	Originally completed	
Aug 2013	Updated	
April 2021	Reaffirmed	