Texas Children's Hospital

DATE: December 2015

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
First Febrile Urinary Tract Infection (UTI)
Evidence-Based Guideline

Definition: The presence of a pure growth of more than 100,000 colony-forming units (cfu) of bacteria per milliliter of urine in a patient with clinical signs and laboratory values suggestive of UTI (positive urinalysis required). Lower counts of bacteria may be clinically important, especially in boys and specimens obtained by catheterization or suprapubic aspiration. [1,2]

Pathophysiology: The disease is usually caused by a bacterial infection. *Escherichia coli* is the most common bacterial species identified. Other common gram negative species include *Klebsiella, Proteus, Enterobacter*, and *Citrobacter*. Gram positive species include *Staphylococcus saprophyticus* and *Enterococcus*. Pyelonephritis results from bacterial infection of the kidney.

Inclusion Criteria [1-3]
- 1 month - 12 years
- Prepubertal children
- First episode of UTI
- Febrile

Exclusion Criteria [1-3]
- Afebrile
- Conditions in which immunity may be compromised (e.g., transplant recipient [solid organ or hematopoetic], chronic renal insufficiency/kidney disease)
- Known major genitourinary anomalies
- Toxic-appearing
- Sepsis with shock or meningitis
- PICU or NICU 3/4 admission
- Extended-spectrum beta-lactamase (ESBL) producing bacteria
- Other severe comorbid conditions

Differential Diagnosis

Renal abscess	Discitis
Kidney stones	Trauma
Sacroiliitis	Fever
Vertebral osteomyelitis	Gastroenteritis
Appendicitis	Vaginitis/Urethritis

Diagnostic Evaluation: Children with urinary tract infections have a risk of progressing to septic shock. Clinicians should immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic appearance, ill appearance, altered mental status, and/or compromised perfusion with abnormal vital signs.

Vital Sign Changes of Sepsis [4]

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0d - 1m	>205	>60	<60	<36 or >38
>1m - 3m	>205	>60	<70	<36 or >38
>3m - 1y	>190	>60	<70	<36 or >38.5
>1y - 2y	>190	>40	<70 + (age in yr x 2)	<36 or >38.5
>2y - 4y	>140	>40	<70 + (age in yr x 2)	<36 or >38.5
>4y - 6y	>140	>34	<70 + (age in yr x 2)	<36 or >38.5
>6y - 10y	>140	>30	<70 + (age in yr x 2)	<36 or >38.5
>10y - 13y	>100	>30	<90	<36 or >38.5
>13y	>100	>20	<90	<36 or >38.5

Signs and Symptoms of Shock [4]

Exam Abnormalities			
	Cold Shock	**Warm Shock**	**Non-Specific**
Peripheral Pulses	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

Clinical history, physical examination, and labs are used to diagnose UTI.

History: Assess for
- Urinary symptoms (incontinence, lack of proper stream, withholding maneuvers, frequency, urgency, dysuria)
- Previous UTIs
- Vesicoureteral reflux (VUR)
- Previous undiagnosed febrile illnesses
- Family history of frequent UTIs, VUR, and other genitourinary abnormalities
- Constipation
- Sexual history

Physical Examination
Complete routine vital signs including blood pressure

Assess for
- Toxic appearance, irritable
- Fever
- Disinterested in feeding
- Lethargic
- Poor tone (floppy)
- Poor perfusion
- Sluggish capillary refill
- Tachycardia or bradycardia
- Tachypnea or apnea
- Sunken fontanelle
- Dry mucous membranes
- Jaundice
- Vomiting
- Suprapubic tenderness
- Abdominal/Flank tenderness
- Abdominal mass
- Failure to thrive

Laboratory Tests [5]
Urinalysis is positive if the sample is positive for leukocyte esterase (LE) or nitrites or microscopy is positive for WBC (≥5 WBCs per high-power field) or bacteria. UTI is unlikely (<0.3%) if the urinalysis is negative.

Sensitivity and Specificity of Urinalysis Components [1,6-8]

Consider empiric treatment until culture results are available.

	Sensitivity	Specificity	*LR +	*LR -
Dipstick	70%	98%	35	0.3
Dipstick & Micro	80%	64%	2.2	0.3
Dipstick & Micro				
0-1 mos	82%	92%	10	0.2
>1-3 mos	82%	94%	13	0.07
Bag LE	76%	84%	4.75	0.29

If nitrites are positive, diagnosis of UTI is very likely.

*LR+: a positive test increases the odds that a patient has the disease by this factor

LR-: a negative test decreases the odds that a patient has the disease by this factor

Positive Urine Culture [1,3]

Catheterization/Suprapubic Aspiration	≥50,000 cfu/mL
Midstream Clean Catch	≥100,000 cfu/mL

Urine specimens should be processed as expediently as possible. If the specimen is not processed promptly, then it should be refrigerated to prevent the growth of organisms. Urine specimens with ≥3 different colony types above the threshold will not be evaluated.

Critical Points of Evidence*

Evidence Supports

- Obtain a urine specimen via transuretheral catheterization in non-toilet trained children and via midstream clean catch for toilet trained children. [9-14] – Strong recommendation, moderate quality evidence
- For rapid diagnosis of UTI, utilize LE and nitrite testing. [13,15-22] – Strong recommendation, moderate quality evidence
- Obtain a renal ultrasound (RUS) in children 1-24 months with their first febrile UTI. If RUS is normal, a voiding cystourethrogram (VCUG) is not needed. Consider a RUS based on clinical findings in children >24 months. [23-44] – Strong recommendation, moderate quality evidence
- Administer oral antibiotics (7-14 days total of effective antimicrobial therapy) to toilet trained children and/or children >60 days who are tolerating PO. [45-49] – Strong recommendation, moderate quality evidence
- Administer oral antibiotics (10-14 days total of effective antimicrobial therapy) and consider outpatient management for non-toilet trained children and/or children 31-60 days who meet the following criteria: no elevated inflammatory markers, tolerating PO, well-hydrated, not tachycardic, adequate transportation, ability to follow up with PCP within 24-48 hours. [45-51] – Weak recommendation, low quality evidence
- Utilize short-course IV antibiotics (3-4 days) followed by oral antibiotics (once afebrile and feeding adequately) in children who require admission. Total duration of effective antimicrobial therapy should be 10-14 days for non-toilet trained children and/or children 31-60 days and 7-14 days for toilet trained children or children >60 days. [45-49] – Strong recommendation, low quality evidence
- The health benefits of newborn male circumcision outweigh the risks and that the procedure's benefits justify access to this procedure for families who choose it (per the AAP's Circumcision Policy Statement). [52-55] – Strong recommendation, moderate quality evidence

Evidence Against

- Do not routinely administer prophylactic antibiotics to infants/children with their first febrile UTI with a normal renal ultrasound. [56-62] – Strong recommendation, moderate quality evidence
- Do not administer prophylactic antibiotics to infants/children with Grades I-III vesicoureteral reflux. [56-62] – Weak recommendation, moderate quality evidence

Evidence Lacking/Inconclusive

- A positive culture is indicated by >50,000 cfu/mL of a single urinary pathogen from a urine specimen obtained by catheterization or SPA. The cutoff for a clean-catch specimen from a child beyond toilet-training is >100,000 cfu/mL. The diagnosis of UTI requires both a positive culture and a urinalysis suggesting infection. [63,64] – Weak recommendation, very low quality evidence
- No evidence addressing whether the diagnostic accuracy of RUS is affected if taken within two days after UTI diagnosis versus several days after diagnosis.

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

Condition-Specific Elements of Clinical Management

Urine Specimen for Urinalysis and Culture† (9-14)
- Non-toilet trained children: transurethral catheterization
- Toilet trained children: midstream clean catch

Hydration
- IV fluids if not taking oral fluids adequately.

Imaging Studies (1,23-44)

Age	Imaging Study
1-24 months	Renal ultrasound (RUS) If RUS is normal, a VCUG is not needed.
>24 months	RUS at discretion of physician based on clinical findings

*VCUG may be performed as soon as fever is decreasing and culture-specific antibiotics are in use. There is no need to perform an additional urinalysis if the patient is on appropriate antibiotics.

Admission Criteria
- Unable to tolerate oral fluids (requires IV fluids for hydration)
- Failed outpatient therapy (requires IV antibiotics)

Inpatient Discharge Criteria
- A decreasing trend in daily maximal temperatures combined with physician discretion
- On culture-specific antibiotics
- Tolerating oral intake
- Patient/Caregiver discharge teaching completed on:
  - Discharge care
  - Signs and symptoms of concern
  - Risk of recurrence
  - Proper perineal care
  - Documentation of scheduled PCP follow-up

Parent Teaching
- Teach parents to recognize symptoms of UTI
- Clearly explain the course of necessary testing and treatment
- Explain strategies to prevent future recurrence (e.g., adequate hydration, frequent voiding, perineal hygiene, completion of antibiotic course)
- Pediatrician follow-up

Consults/Referrals
- Refer to urology if surgical intervention is being considered and/or if child has VUR.
- Refer to nephrology if child has VUR and associated renal insufficiency, hypertension, abnormal serum chemistries, or renal scarring.

Measures

Structure
- Location of radiologic studies (inpatient or outpatient setting)

Process
- Utilization of the order set(s)
- Frequency of completed radiologic studies
- Time frame to complete radiologic studies

Outcome
- Use of prophylactic antibiotics with documented reflux
- EC visit within 14 days and reason for visit
- Documented use of prophylactic antibiotics
- Length of stay
- Organisms and their resistance patterns
- Rate of positive/negative RUS, radionuclide cystogram, and VCUG

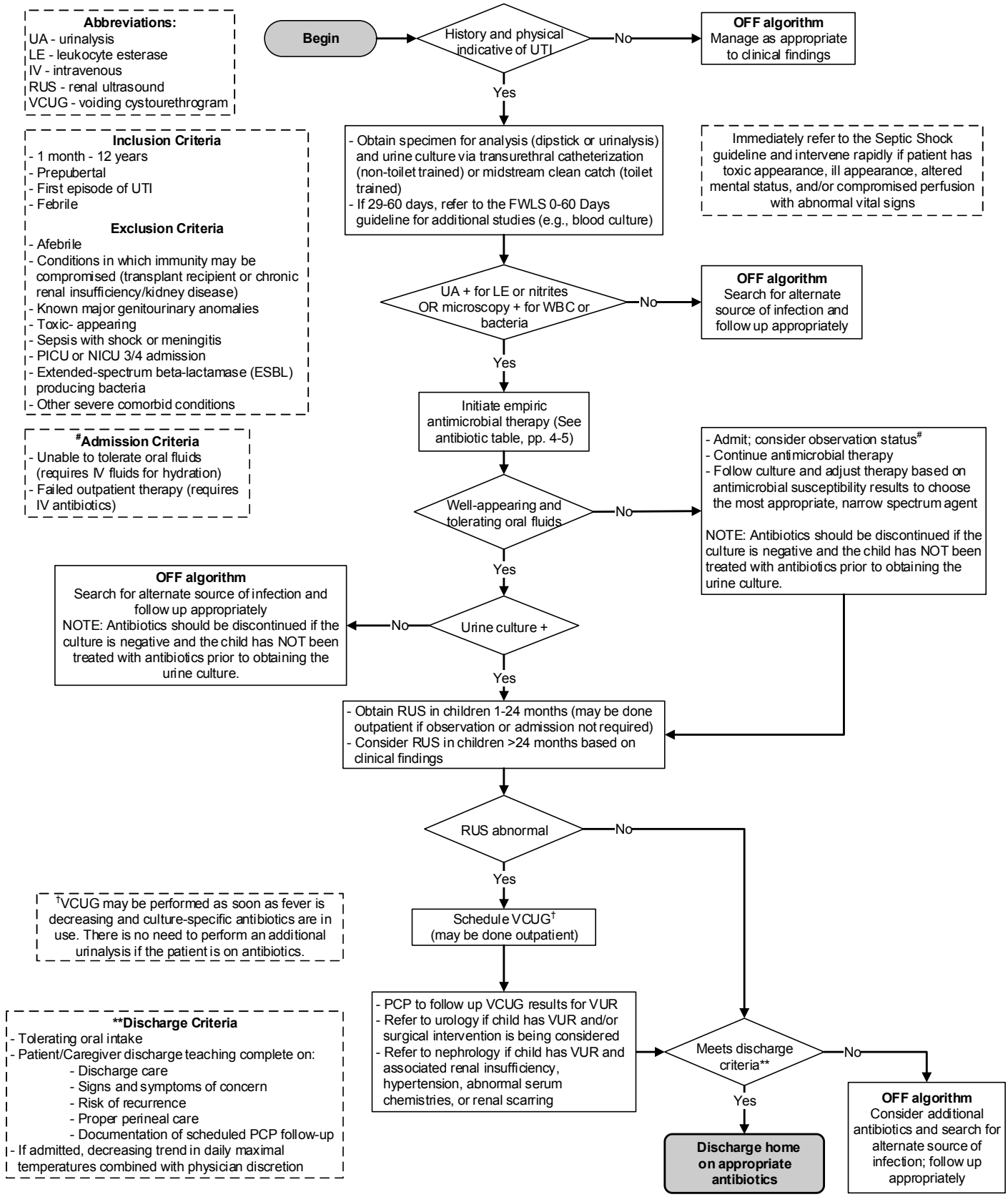
Antibiotic Therapy [65]

Consider insurance/Medicaid formulary restrictions.

Empirical Oral Therapy - Outpatient				
	Age & Weight Parameters	**Dose and Frequency**	**TCH Formulary**	**Cost $-$$$$**
Cefixime	Infants and children ≤45 kg	8 mg/kg/dose PO every 24 h (**MAX:** 400 mg/DAY)	No	$$$$
	Children >45 kg and adolescents	400 mg PO every 24 h		
Cefdinir If available, cefixime is the preferred oral antibiotic for the empiric treatment of UTI since it concentrates better in the urine compared to cefdinir.	Children ≥6 months to 12 years	14 mg/kg/dose PO every 24 h (**MAX:** 600 mg/DAY)	Yes	$$$
	Adolescents	600 mg PO every 24 h		
Empirical Parenteral Therapy (IV/IM) - Emergency Center or Inpatient				
	Age & Weight Parameters	**Dose and Frequency**	**TCH Formulary**	**Cost $-$$$$**
CefTRIAXone **NOTE:** Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site *Use cefTAZidime as an alternative	Infants and children ≥2 months and adolescents	50 mg/kg/dose IV every 24 h (**MAX:** 2 grams/DAY)	Yes	N/A
CefTAZidime *Use cefTRIAXone as an alternative	Infants, children, and adolescents	50 mg/kg/dose IV every 8 h (**MAX:** 6 grams/DAY)	Yes	
Gentamicin* *Not typically first-line monotherapy	Infants, children, and adolescents	2.5 mg/kg/dose IV every 8 h (**MAX:** 3 mg/kg/dose **not to exceed** 120 mg/dose)	Yes	
Directed Oral Therapy (Based on Lab Results)				
	Age & Weight Parameters	**Dose and Frequency**	**TCH Formulary**	**Cost $-$$$$**
Cefixime	Infants and children ≤45 kg	8 mg/kg/dose PO every 24 h (**MAX:** 400 mg/DAY)	No	$$$$
	Children >45 kg and adolescents	400 mg PO every 24 h		
Cefdinir If available, cefixime is the preferred oral antibiotic for the empiric treatment of UTI since it concentrates better in the urine compared to cefdinir.	Children ≥6 months to 12 years	14 mg/kg/dose PO every 24 h (**MAX:** 600 mg/DAY)	Yes	$$$
	Adolescents	600 mg PO every 24 h		
Amoxicillin	Infants and children <40 kg	13 mg/kg/dose PO every 8 h (**MAX:** 500 mg/dose)	Yes	$
	Children and adolescents ≥40 kg	500 mg PO every 8 h		
Trimethoprim and Sulfamethoxazole (TMP/SMX)	Children 2-24 months	3-6 mg TMP/kg/dose PO every 12 h (**MAX:** 160 mg TMP/dose)	Yes	$
	Children >24 months and adolescents	4 mg TMP/kg/dose PO every 12 h (**MAX:** 160 mg TMP/dose)		
Directed Parenteral Therapy (IV) - Inpatient (Based on Micro Results)				
	Age & Weight Parameters	**Dose and Frequency**	**TCH Formulary**	**Cost $-$$$$**
CefTRIAXone **NOTE:** Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site *Use cefTAZidime as an alternative	Infants and children ≥2 months and adolescents	50 mg/kg/dose IV every 24 h (**MAX:** 2 grams/DAY)	Yes	N/A

CefTAZidime *Use cefTRIAXone as an alternative	Infants, children, and adolescents	50 mg/kg/dose IV every 8 h (**MAX:** 6 grams/DAY)	Yes	
Ampicillin	Infants and children	25-50 mg/kg/dose IV every 6 h (**MAX:** 100 mg/kg/dose **not to exceed** 2 grams/dose or 12 grams/DAY)	Yes	
Gentamicin	Infants and children	2.5 mg/kg/dose IV every 8 h (**MAX:** 3 mg/kg/dose **not to exceed** 120 mg/dose)	Yes	

TCH Evidence-Based Outcomes Center
Clinical Algorithm for Children with First Febrile Urinary Tract Infection (UTI)



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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 Internal and External Guidelines
   - Cincinnati Children's First Urinary Tract Infection in Children ≤12 Years; American Academy of Pediatrics' Urinary Tract Infection: The Diagnosis and Management of Initial UTI in Febrile Infants and Children 2 to 24 Months; National Institute of Health and Clinical Excellence Urinary Tract Infection in Children
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Collaboration, CINAHL, Google
4. Critically Analyze the Evidence
   - 13 meta-analyses, 3 randomized controlled trials, and 39 nonrandomized studies
5. Summarize the Evidence
   - Materials used in the development of the guideline, evidence summary, and order sets are maintained in a UTI 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 first febrile UTI in children. 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
May 2008	Originally completed
Jan 2012	Updated
Dec 2015	Updated
Aug 2017	Added a note indicating preference of cefixime to cefdinir
Jan 2019	Revised the 'Vital Sign Changes of Sepsis' table, replaced cefotaxime with ceftazidime, and changed the dosing of ceftriaxone