

# FEBRILE URINARY TRACT INFECTION

## EXECUTIVE SUMMARY

Physician Owners: Nancy Knowles, M.D., and David Tolo, M.D.



### Primary Objective

Develop a pathway for treating febrile urinary tract infection (UTI) in Children's Physicians and Children's Urgent Care clinics that standardizes antibiotic selection, taking into account local antibiotic resistance patterns and imaging selection according to published literature and availability of resources.

### Recommendations

#### Inclusion Criteria

- Children  $\geq$  2 months of age  $\leq$  12 years of age with presumed or definite (UTI)

#### Exclusion Criteria:

- Toxic appearing
- Prior history of UTI (defined as  $>$  2 febrile UTIs)
- Chronic kidney disease as defined by estimated glomerular filtration rate (GFR), by the original Schwartz Formula  $<$  80 mL/min/1.73m<sup>2</sup>
- Genitourinary abnormalities, including: previous GU surgery (other than circumcision), neurogenic bladder conditions, known obstructive uropathy, known high-grade vesicoureteral reflux (Grades III-V)
- Septic shock
- Immunocompromised host
- Pregnancy
- Recent history of sexual abuse
- Children  $<$  2 months of age or  $>$  12 years of age
- Patients requiring admission to the PICU
- Premature infants

#### Diagnosis:

- A febrile urinary tract infection is defined as a fever  $\geq$  38°C with a urine colony count or urine culture with a single pathogen of  $\geq$  50,000 colony forming units (CFU)/ml.
- If a clinician decides that a febrile infant with no apparent source requires antimicrobial therapy because of ill appearance or another pressing reason, the clinician should ensure that a urine specimen is obtained for both urinalysis and culture before an antimicrobial agent is administered.<sup>2,3</sup>
- If the clinician determines the febrile infant to have a low likelihood of UTI, then clinical follow-up monitoring without testing is sufficient.<sup>3</sup>
- The strongest clinical predictor of UTI in infants and non-toilet trained children are: fever, fever for greater than 24 hours, fever without apparent source, ill appearance, abdominal pain and suprapubic tenderness.<sup>25</sup>

#### Signs and symptoms suggestive of UTI:

##### **Age 2 months of age - 2 years of age:**

- Poor feeding
- Vomiting
- Irritability
- Strong-smelling urine
- Abdominal pain
- Jaundice

##### **Children $>$ 2 years of age:**

- Hematuria
- Vomiting
- Strong smelling urine
- Abdominal pain
- Enuresis/incontinence
- Urinary symptoms
  - o Urgency
  - o Frequency
  - o Dysuria

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### Physical Findings Suggestive of UTI:

#### **Related to UTI:**

- Abdominal tenderness to palpation
  - Suprapubic
  - Palpable bladder
- Costovertebral angle (CVA) tenderness to percussion

#### **Related to Abnormal Anatomy:**

- Dribbling
- Poor stream
- Straining to void
- Hypertension
- Sacral dimple or hair patch

### Alternative Diagnoses to Consider:

- |                   |                                |
|-------------------|--------------------------------|
| • Appendicitis    | • Prostatitis                  |
| • Gastroenteritis | • Urethritis                   |
| • Pinworms        | • Pregnancy                    |
| • Vulvovaginitis  | • Urolithiasis                 |
| • Epididymitis    | • Bladder or bowel dysfunction |
| • Orchitis        | (voiding dysfunction)          |

### Urine Sample Collection:

- A urine sample should be obtained on all children in whom the clinician is suspicious of a febrile UTI. Refer to either PC 07 (Procedure for clean catch urine) or PC 32 (Specimen collection: urinary catheterization) for detailed sample collection procedures.
- It is not the policy of Children's Physicians clinics or Children's Urgent Care clinics to obtain urine samples through the use of bag collection methods. Bag collection may be suitable for urinalysis, but it is less appropriate for culture. If the child's genitalia are not cleaned adequately and culture is delayed, there can be a high incidence of false positive results (95-99%).<sup>1</sup>

### Laboratory Studies:

#### **Urinalysis:**

- Urine specimens will first be tested by urine dipstick. Urine specimens must be fresh (< 1 hour after voiding with maintenance at room temperature or < 4 hours after voiding with refrigeration).
  - Urine dipsticks are appealing because they provide rapid results, do not require microscopy and are eligible for a waiver under the Clinical Laboratory Improvement Amendments.<sup>2</sup>
  - Urine dipsticks indicate the presence of leukocyte esterase (as a surrogate marker for pyuria) and urinary nitrite (which is converted from dietary nitrates in the presence of most Gram-negative enteric bacteria in the urine).<sup>2</sup>
  - The conversion of dietary nitrates to nitrites by bacteria requires approximately 4 hours in the bladder.<sup>2</sup>
  - Clinicians should recognize that a negative urinalysis does not rule out a UTI with certainty.<sup>3</sup>  
A urine dipstick test may be falsely negative if the bladder is emptied frequently or if an organism that does not metabolize nitrate (including all Gram-positive organisms) is the cause of the infection.<sup>21</sup>
  - It is recognized that pyuria is a hallmark of true UTI and helps distinguish UTI from asymptomatic bacteriuria. It is the host's inflammatory response that results in scarring; therefore, the presence of white blood cells is an important feature of true UTI.<sup>22</sup>

#### **Urine Culture or Urine Colony Count:**

- A properly collected urine specimen should also be inoculated promptly on culture medium that will allow identification of urinary tract pathogens. If the patient is seen in clinic a urine colony count is utilized. If the patient is seen in Urgent Care, a urine culture is utilized.

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- o Clinicians should require both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 50,000 colony forming units (CFU) per milliliter of a single uropathogen cultured from an appropriately collected (clean catch or catheter) urine specimen.<sup>3</sup>
- o Susceptibility testing shall be performed on the isolated uropathogens to guide appropriate antibiotic therapy.
- o Urines with low colony counts, mixed growth or no pyuria are usually contaminated.<sup>21</sup>

### Reassessment When Urine Cultures are Available:

#### **Positive Cultures**

- When positive culture results are received, clinicians should:
  - o Review sensitivities
  - o Assure appropriate antibiotics if not prescribed at initial visit
  - o Start patient on appropriate antibiotic if they were not prescribed at initial visit
  - o Instruct caregiver(s) to follow up with clinician if the child is not afebrile or showing improvement within 48 hours

#### **Negative Cultures**

- When negative cultures are received, clinicians should:
  - o If >1 uropathogen is present, a new sample should be collected for testing (if antibiotics were not previously started)
  - o Consider false negatives if CFU/ml do not meet positive threshold criteria
  - o Discontinue antibiotic therapy (if warranted)
  - o Manage patient care off pathway

### Antimicrobial Therapy:

#### **First Line**

- **Cephalexin:** 75 mg/kg/day PO in three divided doses (usual adult dose 1000 mg/day in two divided doses) for 7 – 14 days
  - o Dosing frequency in children must be more frequent than in adults in this setting due to difference in drug metabolism.
- **Bactrim:** 8 mg/kg/day PO in two divided doses (usual adult dose 320 mg/day divided two times a day, i.e. one double strength tablet two times a day) for 7-14 days

#### **Second Line**

- **Cefixime:** Infants and children weighing ≤ 45 kg: 8mg/kg/day PO in one dose (usual adult dose 400 mg given once daily) for 7-14 days
  - o Children weighing > 45 kg and adolescents: 400 mg PO in one dose for 7-14 days
- **Cefuroxime:** 30 mg/kg/day PO in two divided doses (usual adult dose 500 mg/day in two divided doses) for 7-14 days

#### **Third Line**

- **Cefdinir:** 14 mg/kg/day PO in one dose (usual adult dose 600 mg/day given once daily) for 7-14 days
  - o Cefdinir does not concentrate in the urine as well as other beta-lactam antibiotics.
- **Ceftriaxone 75 mg/kg/dose IM (max single dose 1 gram)**
  - o For children who are hydrated, but may be unable to tolerate oral medication, or unlikely to be adherent to the initial doses of antibiotic. If clinical improvement is observed at 24 hours, an oral antibiotic can be substituted to complete the course of therapy.
  - o Children who are still significantly febrile or symptomatic at 24 hours may require additional parenteral doses before switching to oral therapy.

### **Notes about Antimicrobial Therapy:**

- Patients that test positive for leukocyte esterase and/or nitrite should start antimicrobial therapy
- Empiric antibiotic therapy for UTI in infants and children should include an antibiotic that provides adequate coverage for *E. coli*.<sup>9, 10</sup> *Escherichia coli* is the most common bacterial cause of UTI; it accounts for approximately 80 percent of UTI in children. Other gram-negative bacterial pathogens include *Klebsiella*, *Proteus*, *Enterobacter* and *Citrobacter*. Grampositive bacterial pathogens include *Staphylococcus saprophyticus*, *Enterococcus* and, rarely, *Staphylococcus aureus*.<sup>7,8</sup>

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- The ultimate choice of antimicrobial therapies should be based on local susceptibility patterns for initial treatment, with further tailoring based on the organism isolated when culture results are available. 93 percent of *E. coli* isolated by the Children's Hospital & Medical Center lab are susceptible to cephalexin, making it the most appropriate first line antibiotic treatment in our region. Antimicrobial susceptibilities are reviewed annually and treatment guidelines will be reviewed at that time each year to update these empiric recommendations.
- Early and aggressive antibiotic therapy (e.g., within 72 hours of presentation) is necessary to prevent renal damage. Delayed therapy has been associated with increased severity of infection and greater likelihood of upper tract disease and renal damage in experimental, retrospective, prospective and small randomized studies.<sup>11-19</sup>
- Little evidence is available to guide the duration of antimicrobial therapy in children with febrile UTIs. <sup>5</sup>The American Academy of Pediatrics (AAP) currently recommends 7 – 14 days as the duration of antimicrobial therapy. Further delineation of treatment duration has not been forthcoming, but a randomized controlled trial is currently under way comparing the effectiveness of 5 days versus 10 days of treatment. <sup>3</sup>

### Prophylactic Antibiotics:

- The 2011 AAP practice guideline (reaffirmed in 2016) does not recommend prophylactic antimicrobials following the first febrile UTI in children ages 2 to 24 months. <sup>2,3</sup> The United Kingdom's National Institute for Health and Care Excellence (NICE) guideline for UTI in children indicates that antibiotic prophylaxis should not be routinely recommended in infants and children following their first UTI, but may be warranted after recurrent UTI.<sup>6</sup>

### Imaging:

#### **First Febrile UTI**

- Renal Bladder Ultrasound (RBUS): within 1-2 weeks for children  $\geq$  2 months old – 2 years old with first febrile UTI and for older children who fail to respond to antibiotics with first febrile UTI <sup>2,3,5</sup>
  - Normal – manage in primary clinic and observe
  - Abnormal – consider voiding cystourethrogram (VCUG) and referral to Urology
- VCUG:
  - Clinicians should consider obtaining a VCUG to evaluate for posterior urethral valves in infant boys  $\leq$  1 year of age.

#### **Second Febrile UTI**

- RBUS: within 1-2 weeks for older children with a recurrent febrile UTI <sup>6,24</sup>
- VCUG: within a few weeks of diagnosis, for children  $\geq$  2 months of age – 2 years with a recurrent febrile UTI <sup>2,3,5</sup>
  - Clinicians are encouraged to observe and manage  $\leq$  grade 3 vesicoureteral reflux (VUR) found on VCUG in primary care.
  - Children with abnormal VCUG or  $\geq$  grade 4 VUR should be referred to Urology.

### **Notes about Imaging:**

#### **RBUS:**

- For infants and young children with unusually severe illness or failure to improve as expected after initiation of antimicrobial therapy, RBUS should be performed as soon as possible during the acute phase of illness to identify complications (e.g. renal or perirenal abscess, pyonephrosis).<sup>5</sup>
- RBUS is a noninvasive test that can demonstrate the size and shape of the kidneys, the presence of duplication and dilation of the ureters and the existence of gross anatomic abnormalities. <sup>5</sup>
- For infants and young children who respond as expected to antimicrobial therapy, RBUS should be performed after the acute phase to reduce the risk of false positive results secondary to renal inflammation during the acute episode.<sup>5</sup>
- Concern has been raised that RBUS is not effective to detect VUR, and is frequently normal in infants with low-grade VUR and even in some who have high grade VUR. Low grade VUR is generally not considered of concern for renal damage. Although RBUS is not invariably abnormal in infants with grades IV and V VUR, it does identify most, and of particular importance, an abnormal RBUS is a major risk factor for scarring.<sup>3</sup>

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- Widespread application of prenatal ultrasonography clearly has reduced the prevalence of previously unsuspected obstructive uropathy in infants, but the consequences of prenatal screening with respect to the risk of renal abnormalities in infants with UTIs have not yet been well defined. There is considerable variability in the timing and quality of prenatal ultrasonograms, and the report of “normal” ultrasonographic results cannot necessarily be relied on to dismiss completely the possibility of a structural abnormality unless the study was a detailed anatomic survey (with measurements), was performed during the third trimester and was performed and interpreted by qualified individuals.<sup>26</sup>

### **VCUG:**

- VCUG should not be performed routinely after first febrile UTI. Instead, they should be reserved for a recurrence of a febrile UTI.<sup>3</sup>
- VCUG is only indicated after first febrile UTI if RBUS reveals hydronephrosis, scarring or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances.<sup>3</sup>
- Early imaging (as early as the first week) does not appear to falsely increase the detection of VUR.<sup>5</sup>
- VCUG should be done when patient is stable, more than 24 hours afebrile and prior to the end of antibiotic therapy if possible. If not possible to schedule prior to completion of antibiotic therapy, the child should be placed on a prophylactic antibiotic dose until the VCUG is completed.<sup>25</sup>
- Since the publication of the 2011 guideline, multiple studies have demonstrated that abnormalities are missed by the selective imaging recommended in the guideline; however, there is no evidence that identifying these missed abnormalities is of sufficient clinical benefit to offset the cost, discomfort and radiation associated with performing VCUG after the first febrile UTI.<sup>3</sup>

### Follow-up:

- Patients should follow up via telephone and/or in their primary care physician’s office within 48 hours to assess clinical response to therapy.
- Several observational studies suggest there is little utility in repeating the urine culture in children with UTI who are treated with an antibiotic to which their uropathogen is susceptible. Accordingly, it is not necessary to routinely obtain repeat urine cultures during antimicrobial therapy to document sterilization of the urine.<sup>5</sup>
- Clinicians should offer children and caregiver(s) advice and education on:
  - The strong link that exists between bowel and bladder dysfunction and the development of UTI.
  - The importance of avoiding constipation
  - The importance of timed and double voiding
  - Seeking prompt medical evaluation (ideally within 48 hours) for future febrile illnesses after the first febrile UTI.<sup>3</sup>
    - Prompt diagnosis and effective treatment of recurrent febrile UTI and treatment of bowel and bladder dysfunction that predisposes many children to UTI may be more important than identifying anatomic or functional genitourinary abnormalities after the first febrile UTI in preventing renal scarring. <sup>2</sup>The risk of renal scarring increases with recurrent episodes of pyelonephritis, from approximately 5 percent after the first episode to 10 percent after the second, 20 percent after the third, 40 percent after the fourth and 60 percent after the fifth.<sup>20</sup>
- Primary care follow-up for infants and young children who have had a febrile UTI should include regular monitoring of height, weight and blood pressure.<sup>20</sup>
- Clinicians should encourage caregiver(s) to avoid giving nonsteroidal anti-inflammatory drugs (NSAIDs) to infants and children with a febrile UTI and instead use acetaminophen-based antipyretics.

### Referrals to Consider:

- Clinicians should refer patients to Urology for any of the following:
  - Grade 4-5 VUR
  - ≥ Third febrile UTI all ages
  - Abnormal anatomy
  - Surgical consideration
  - Recent or history of genitourinary surgery

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### Rationale

- **Safety:** Will be improved by ensuring patients diagnosed with febrile UTI receive the appropriate antibiotics and undergo renal bladder ultrasound within two weeks of first febrile UTI.
- **Quality:** This pathway will improve the quality of care patients receive by ensuring that antibiotics are only prescribed if testing confirms a bacterial cause for febrile UTI.
- **Cost:** Will be improved by instituting consistent terminology, testing, dosing and care between providers.
- **Delivery:**
  - Providing appropriate antibiotic therapy to patients with febrile UTIs should reduce complications associated with the infection.
  - Ordering urine cultures on all patients that are prescribed an antibiotic to treat a febrile UTI will ensure that bacterium present is sensitive to the antibiotic prescribed.
  - Providing appropriate therapy to patients that test negative for the presence of bacteria in urine will help reduce antibiotic resistance.
- **Engagement:** Is created and supported by the involvement of a multidisciplinary team in the development and maintenance of the pathway.
- **Patient/Family Satisfaction:** Shall be improved by providing the highest quality care based on established guidelines and the latest evidence available in the literature.

### Implementation Items

Algorithm

Epic UTI SmartSet which includes: order set, note template and diagnosis options

### Metrics Plan

1. Urinalysis in conjunction with a urine colony count or urine culture will be performed on 100 percent of all patients that receive antibiotics for febrile UTI treatment.
2. Children identified with febrile UTI and their caregiver(s) will receive appropriate education regarding the association of constipation and urinary tract infection and the importance of timed, frequent voiding in the prevention of further urinary tract infection at least 90 percent of the time.
3. Monitor the number of patients that receive a renal bladder ultrasound after initial febrile UTI diagnosis.
4. Monitor prophylactic antibiotics prescribed when associated with previous diagnosis of vesicoureteral reflux.
5. Monitor VCUGs ordered.

### Supporting Documents

Policy PC 07 Procedure for Clean Catch Urine

Policy PC 32 Specimen Collection: Urinary Catheterization

### Team Members

Nancy Knowles, M.D., David Tolo, M.D., Debra Tomek, M.D., Christopher Youngman, M.D. (general pediatrics), Andrea Green-Hines, M.D., Jessica Snowden, M.D. (infectious disease), Carlos Villaneuva, M.D., Tara Goesch APRN (urology), Teri Mauch, M.D. (nephrology), Jen Zwiener (pharmacy), Jess Bender (performance improvement)

### Evidence

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