URINARY TRACT INFECTION PATHWAY

EXECUTIVE SUMMARY

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Primary Objective

Develop a pathway for management of urinary tract infection (UTI) that standardizes antibiotic selection local antibiotic resistance patterns, follow-up management, and imaging selection according to published literature and availability of resources.

Recommendations

Inclusion Criteria

- Children ≥ 2 months of age ≤ 18 years of age with presumed or definite UTI

Exclusion Criteria:

- Toxic-appearing or septic shock
- History of >2 febrile UTIs
- Chronic kidney disease as defined by estimated glomerular filtration rate (GFR), by the original Schwartz Formula < 80 mL/min/1.73m2
- Genitourinary abnormalities, including previous GU surgery (other than circumcision), neurogenic bladder conditions, known obstructive uropathy, known high-grade vesicoureteral reflux (Grades III-V)
- Immunocompromised status
- Pregnancy
- Recent history of sexual abuse
- Children <2 months corrected gestational age
- Patients requiring admission to the ICU

Diagnosis:

- A urinary tract infection is defined as signs and/or symptoms of UTI (see list below) with a urine colony count or urine culture with a single pathogen of ≥ 50,000 colony forming units (CFU)/mL for suprapubic aspiration or catheterization, or 100,000 CFU/mL in voided specimen.
- 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. (American Academy of Pediatrics), (Reaffirmation of AAP Clinical Practice Guideline)
- If the clinician determines the febrile infant to have a low likelihood of UTI, then clinical follow-up monitoring without testing is sufficient. (Reaffirmation of AAP Clinical Practice Guideline)
- 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. (Seattle Children's Hospital, Reaffirmation of AAP Clinical Practice guidelines), Shaw
- Infant boys that are not circumcised are at higher risk of UTI. Shaikh, Shoen

Sign and symptoms suggestive of UTI:

Age 2 months – 2 years of age

- Poor feeding
- Failure to thrive

Children > 2 years of age

- Hematuria
- Nausea or vomiting

- Vomiting
- Irritability
- Abdominal pain
- Jaundice
- Abdominal/suprapubic pain
- Flank pain
- Urinary symptoms: urgency, frequency, dysuria

Physical findings suggestive of UTI:
- Abdominal/suprapubic tenderness to palpation
- Costovertebral angle (CVA) tenderness to percussion

Alternative diagnoses to consider:
- Appendicitis
- Gastroenteritis
- Pinworms
- Vulvovaginitis
- Epididymitis
- Bladder or bowel dysfunction (voiding dysfunction)
- Prostatitis
- Urethritis
- Pregnancy
- Urolithiasis
- Orchitis

Urine Sample Collection:
- A urine sample should be obtained on all children in whom the clinician is suspicious of a UTI.
  - Refer to either Procedure for Clean Catch Urine or 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 using 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%). (Tekgul)

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 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).
  - Clinicians should recognize that a negative urinalysis does not rule out a UTI with certainty. (Reaffirmation of AAP Clinical Practice Guideline) A urine dipstick test may be falsely negative if the bladder is emptied frequently (e.g. infants) or if an organism that

does not metabolize nitrate (including all Gram-positive organisms) is the cause of the infection. (Robinson JL)

- 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. (Robert KB)

Urine Culture or Colony Count:

- A properly collected urine specimen should also be inoculated promptly on culture medium that will allow identification of urinary tract pathogens.
  - 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)/mL of a single uropathogen culture from an appropriately collected (suprapubic aspiration or catheterization) urine specimen, or 100,000 CFU/mL in voided specimen. (Reaffirmation of AAP Clinical Practice Guideline)
  - Susceptibility testing shall be performed on the isolated uropathogens to guide appropriate antibiotic therapy.
  - Urines with low colony counts, mixed growth or no pyuria are usually contaminated. (Robinson JL)

<u>Reassessment When Urine Cultures are Available:</u>

Positive Cultures

- When positive culture results are received, clinicians should:
  - Review sensitivities
  - Assure appropriate antibiotics if not prescribed at initial visit
  - Start patient on appropriate antibiotic if they were not prescribed at initial visit
  - 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:
  - If >1 uropathogen is present, a new sample should be collected for testing (if antibiotics were not previously started)
  - Consider false negatives if CFU/ml do not meet positive threshold criteria
  - Discontinue antibiotic therapy
  - Manage patient care off pathway

<u>Antimicrobial Therapy</u>: **(AAP 2021 guidelines*)**

- **First Line**
  - Cephalexin: 25 mg/kg PO three times daily (usual adult dose 500 mg/dose twice daily.
    - 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 (TMP component) 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)
- Ceftriaxone 75 mg/kg/dose IM (max single dose 1 gram)
  - 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.
  - Children who are still significantly febrile or symptomatic at 24 hours may require additional parenteral doses before switching to oral therapy.

- **Second Line**
  - Cefixime: Infants and children weighing ≤ 45 kg: 8mg/kg/ PO once daily (usual adult dose 400 mg given once daily)
    - Children weighing > 45 kg and adolescents: 400 mg PO once daily.
  - Cefuroxime: 15 mg/kg PO twice daily (usual adult dose 250 mg PO twice daily)
- **Third line**
  - Cefdinir: 7mg/kg PO twice daily (usual adult dose 300 mg/ twice daily for 5-10 days)
    - Cefdinir does not concentrate in the urine as well as other beta-lactam antibiotics.

Cephalosporin-allergic Patients

- Bactrim: 4 mg/kg/ PO (TMP component) twice daily (usual adult dose 160 mg TMP twice daily, i.e., one double strength tablet two times a day)

<u>Notes about Antimicrobial Therapy:</u>

- 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. (Shaikh),(Bryce) *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*. Gram-positive bacterial pathogens include *Staphylococcus saprophyticus, Enterococcus* and, rarely, *Staphylococcus aureus*. (Edlin), (Yakubov)
- 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. (Roberts), (Smellie JM, Poulton), (Smellie JM, Ransley), (Hiraoka), (Doganis), (Fernández-Menéndez), (Oh MM, Kim), (Coulthard), (Shaikh N, Mattoo)

- Few studies are available to guide the duration of antimicrobial therapy in children with febrile UTIs. (Shaikh, Mattoo) The American Academy of Pediatrics (AAP) currently recommends 7 – 10 days as the duration of antimicrobial therapy. (Reaffirmation of AAP Clinical Practice Guideline)
- For acute cystitis treatment can be 3 day for Bactrim and 5 days of therapy for all other agents, while pyelonephritis is 7-10 days.(fox)

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. (American Academy of Pediatrics, Reaffirmation of AAP Clinical Practice Guideline) The United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines 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. (National Institute for Health and Care Excellence)

Imaging:

First Febrile UTI

- Renal Bladder Ultrasound (RBUS): Should be done after resolution of UTI for children ≥ 2 months old – 2 years old with first febrile UTI. RBUS should be done in 48-72 hours after treatment has been started if not responding to treatment.
  - Normal – manage in primary clinic and observe
  - Abnormal – consider voiding cystourethrogram (VCUG) and referral to Urology
- VCUG: A VCUG should be considered after first febrile UTI in children with abnormal RBUS, atypical causative pathogen, complex clinical course, or known renal scarring.

Second Febrile UTI

- RBUS: (after resolution of UTI) for older children with a recurrent febrile UTI (if not previously obtained).

- VCUG: A VCUG should be obtained in all children after recurrence of febrile UTI.

Notes about Imaging:

- Renal Bladder Ultrasound: The 2011 AAP guidelines recommend RBUS be performed in all infants (2–24 months) with first febrile UTI.34 Older children with recurrent UTIs may also benefit from an RBUS. The RBUS can be deferred until after resolution of the UTI but should be considered during the acute episode if the illness seems unusually severe or if high fevers persist beyond 48 to 72 hours of treatment34 ; such atypical course suggests complications, such as renal abscess or occult obstruction, that are well-seen on RBUS. A deferred RBUS permits more accurate interpretation of the

anatomy, without potential for false-positive findings associated with tissue edema or endotoxin-induced dilation.

- Voiding Cystourethrogram: In the last decade, the practice patterns have dramatically shifted, with far fewer patients undergoing voiding cystourethrogram (VCUG) after an initial UTI.79,80 This trend is consistent with many published guidelines, including those by the AAP.34,81,82 Part of the reason for this is that less than one-third of children with their first UTI have VUR, and of these, fewer than 10% have grade 4 to 5 VUR.7,83 A VCUG should be considered after first UTI in children with abnormal RBUS, atypical causative pathogen, complex clinical course, or known renal scarring.34,81,82,84 Patients with a family history of VUR or CAKUT can also be considered for VCUG after first febrile UTI. The interobserver variability in VUR grading must be kept in mind while making clinical decisions.85

https://publications.aap.org/pediatrics/article/147/2/e2020012138/36243/Contemporary-Management-of-Urinary-Tract-Infection

- 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. (Reaffirmation of AAP Clinical Practice Guideline)
- 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. (Economou G)

- 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. (Reaffirmation of AAP Clinical Practice Guideline)

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.

- 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.
- 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. (Shaikh)
- 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. (Reaffirmation of AAP Clinical Practice Guideline)
        - 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.(American Academy of Pediatrics) 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.(Jodal)
- 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. (Jodal)

<u>Referrals to Consider:</u>

- Clinicians should refer patients to Urology for any of the following:
    - Grade 3-5 VUR
    - ≥ Third febrile UTI all ages
    - Abnormal genitourinary anatomy
    - Any genitourinary surgery
    - Persistent VUR on follow-up imaging
- Clinicians should refer to Nephrology for any of the following:
    - CKD 2-5
    - Abnormal renal anatomy (e.g. solitary kidney, cystic disease, atrophy)
    - Hypertension
    - Proteinuria

Rationale

- Safety: will be improved by ensuring patients diagnosed with UTI receive the appropriate antibiotics and undergo renal bladder ultrasound within two weeks of first febrile UTI.
- Quality: will be improved by ensuring that antibiotics are only prescribed if testing confirms a bacterial cause for UTI.

- Cost: will be improved by instituting consistent terminology, testing, dosing and care between providers.
- Delivery:
  - Providing appropriate antibiotic therapy to patients with UTIs should reduce complications associated with the infection.
  - Ordering urine cultures on all patients that are prescribed an antibiotic to treat a 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

Emergency Medicine

1. Increase use of cephalexin or ceftriaxone to 85% as first line treatment of UTI by July 2024. (Process Metric)
2. Maintain urinalysis in conjunction with a urine colony count or urine culture will be performed ≥80% of all patients that receive antibiotics for UTI treatment by July 2024. (Outcome Metric)
3. Maintain proportion of urine cultures collected for infants (< 12 months) via urine catheterization >90% by July 2024. (Outcome Metric)
4. Monitor proportion of encounters with retreatment with another antibiotic within 14 days of initial antibiotic prescriptions. (Balancing Metric)
5. Monitor encounters prescribed antibiotics with negative urinalysis. (Balancing Metric)

Children's Physicians

1. Increase use of cephalexin or ceftriaxone to 80% as first line treatment of UTI by July 2024. (Process Metric)
2. Increase the number of people using the UTI smart set (CP) to 60% by July 2024. (Process Metric)
3. Maintain urinalysis in conjunction with a urine colony count or urine culture will be performed ≥80% of all patients that receive antibiotics for UTI treatment by July 2024. (Outcome Metric)
4. Maintain proportion of urine cultures collected for infants (< 12 months) via urine catheterization >80% by July 2024. (Outcome Metric)

5. Monitor proportion of encounters with retreatment with another antibiotic within 14 days of initial antibiotic prescriptions. (Balancing Metric)
6. Monitor encounters prescribed antibiotics with negative urinalysis. (Balancing Metric)

Supporting Documents

- Policy PC 07 Procedure for Clean Catch Urine
- Policy PC 32 Specimen Collection: Urinary Catheterization

Team Members

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Evidence

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