Urinary Tract Infection (UTI) v11.0: Criteria and Definition

Approval & Citation

Summary of Version Changes

Explanation of Evidence Ratings

Inclusion Criteria

- Birth to 18 years with a postmenstrual age of at least 40 weeks
- Presumed or definite first-time or recurrent UTI in an otherwise healthy child

Exclusion Criteria

- Chronic kidney disease as defined by estimated glomerular filtration rate (GFR) by the original Schwartz formula < 80 mL/min/ 1.73m²
- Known OR suspected genitourinary abnormalities, including: previous genitourinary surgery (other than circumcision), neurogenic bladder conditions, obstructive uropathy, vesicoureteral reflux
- Septic shock
- Presumed or definite meningitis
- Conditions requiring Intensive Care Unit care
- Immunocompromised host
- Pregnancy
- Recent history of sexual abuse

Diagnosis

Outpatient Management

Inpatient Management

Imaging

Culture Results Decision Tree

Definition of a UTI

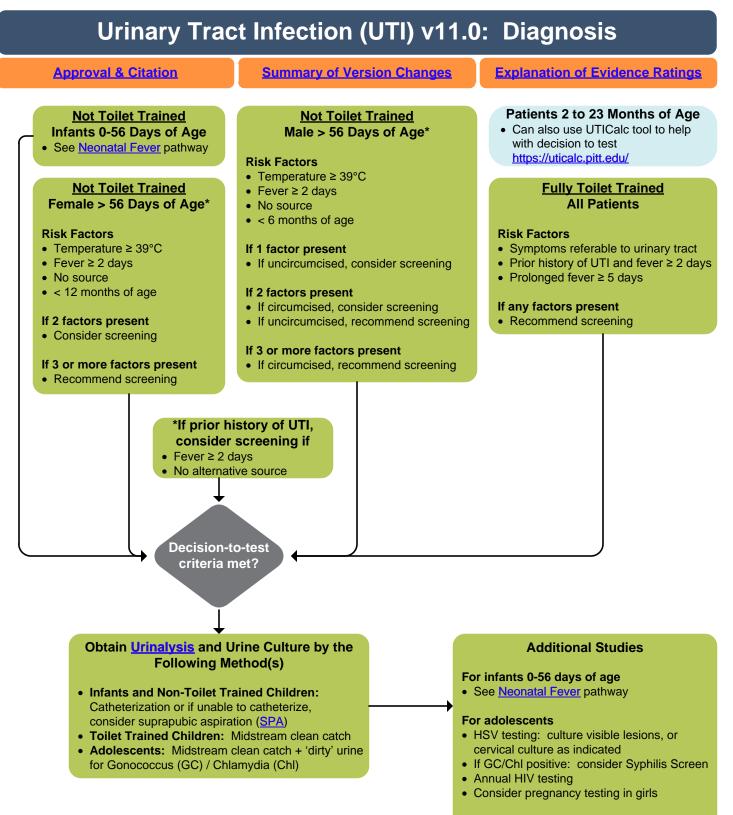
- Clinical signs and symptoms
- UA with pyuria and/or bacteriuria
- Growth of a urinary pathogen

<u>Specimen</u>	Possible	<u>Definite</u>				
Catheterization	≥ 10,000 cfu/mL	≥ 50,000 cfu/mL				
Clean-catch	≥ 50,000 cfu/mL	≥ 100,000 cfu/mL				



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If ill appearing

• See Septic Shock pathway

*Risk factors and screening recommendations are adapted from CHOP's UTI pathway (<u>www.chop.edu/clinical-pathway/urinary-tract-infection-uti-febrile-clinical-pathway</u>). This screening algorithm is intentionally not consistent with the American Academy of Pediatrics UTI guideline for risk assessment that includes race as a factor. The pathway team believes that there is little biological basis for including race as a UTI risk factor (NEJM 2020; 383:874-882). If using UTICalc to calculate pre/post-test probabilities, we recommend selecting 'non-black' for all patients.

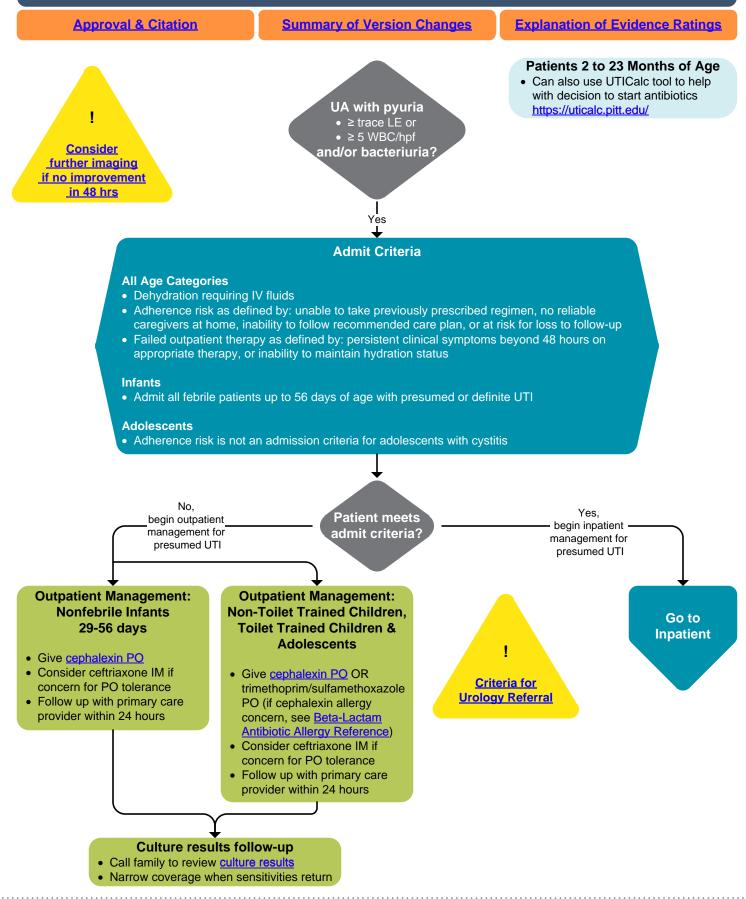
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Urinary Tract Infection (UTI) v11.0: Inpatient Management

Approval & Citation

Summary of Version Changes

Explanation of Evidence Ratings

Inpatient Management: Infants 0-28 days

• Give IV ampicillin + gentamicin

If E. coli

- Minimum 3 days IV antibiotics
- Consider switch to PO after 3 days if afebrile and back to baseline ≥24 hours, identification and sensitivities returned

If Non-E. coli

- *S. aureus* or *Pseudomonas*: consult ID
- Other non-*E. coli* pathogens: consider ID consult to discuss IV duration
- Total IV+PO duration: 14 days

Positive Blood Culture

If E. coli

- Repeat blood culture if not clinically improved within 48 hours of starting antibiotics
- Consider switch to PO after 3 days if meets criteria above, plus repeat blood culture negative x36 hours (if applicable)

If Non-E. coli

- *S. aureus* or *Pseudomonas*: repeat blood culture and consult ID
- Other non-*E. coli* pathogens: repeat blood culture and consider ID consult to discuss IV duration

Inpatient Management: Infants 29-56 days

- Give IV cefazolin **OR** ampicillin + gentamicin if cocci/ enterococcus is suspected
- Minimum 36 hours IV antibiotics
- Switch to PO after 36 hours if afebrile and back to baseline ≥24 hours, identification and sensitivities returned
- Total IV+PO duration: 14 days

Inpatient Management: Older Infants, Children & Adolescents

- Give IV cefazolin OR
 ampicillin + gentamicin if cocci/
 enterococcus is suspected
- No minimum IV duration
- Switch to PO if responding after identification and sensitivities return
- Total antibiotic duration: 7 days
 Consider longer total duration up to 14 days if <u>atypical clinical course</u>, non-*E. coli* UTI, or abnormal renalbladder ultrasound
- · Adolescents with cystitis: 3 days total

Positive Blood Culture

If E. coli

- Repeat blood culture if not clinically improved within 48 hours of starting antibiotics
- Minimum 2 days IV antibiotics
- Consider switch to PO after 2 days if meets criteria above, plus repeat blood culture negative x36 hours (if applicable)

If Non-E. coli

- S. aureus or Pseudomonas: repeat blood culture and consult ID
- Other non-*E. coli* pathogens: repeat blood culture and consider ID consult to discuss IV duration

Consider further imaging if no improvement in 48 hrs

Criteria for Urology Referral

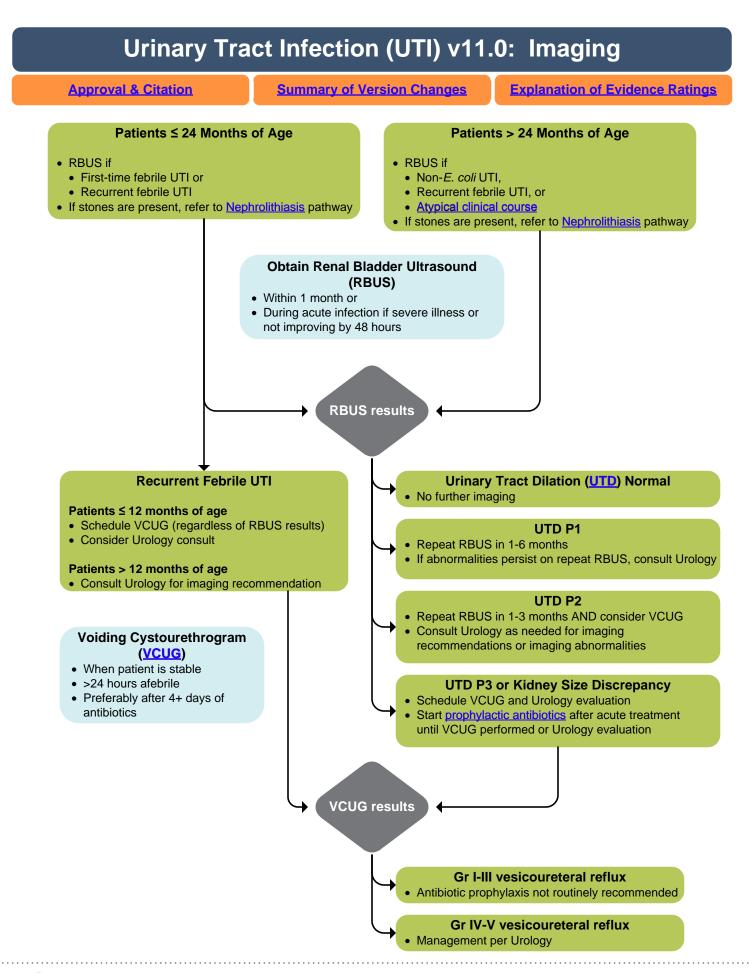
General discharge criteria for all patients

- Clinical response to therapy
- Social risk factors assessed and addressed
- Family education provided/completed
- Urine culture is negative on final report OR urine culture is positive and patient is on targeted antibiotics
- Other studies for bacteremia and meningitis are negative (if applicable), or if bacteremic have completed appropriate course of IV antibiotic therapy

Discharge Criteria

- If indicated, renal ultrasound completed or scheduled
- If indicated, VCUG scheduled
- Consultation (e.g., urology, nephrology, ID) completed if desired

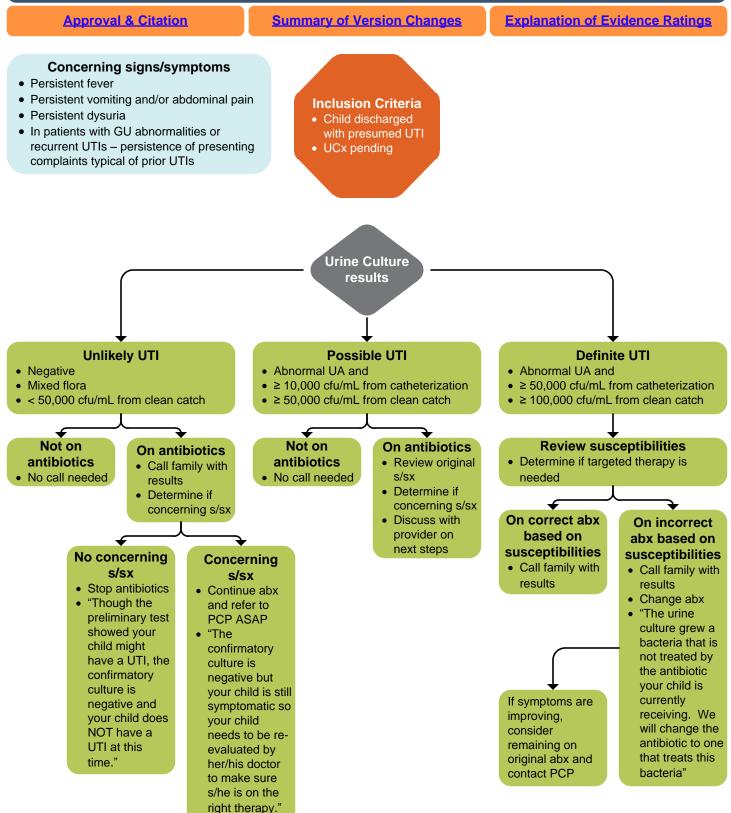




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Urinary Tract Infection (UTI) v11.0: Emergency / Urgent Care UTI Culture Results Decision Tree





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Urinalysis (UA) Post-Test Probability, Part 1

	(+) LE Trace or greater	(+) Nitrite	(+) gram stain	WBC > or = 5 per HPF		(-) LR Point estimate (95% Cl)	(-) LR GRADE	 (-) Post test probability (%) low prevalence estimate of 5% 	(-) Post -test probability (%) high prevalence estimate of 25%	(+) LR Point estimate (95% Cl)	(+) LR GRADE	 (+) Post test probability (%) low prevalence estimate of 5% 	(+) Post -test probability (%) high prevalence estimate of 25%
WBC > or = 10 per HPF or (+) Gram Stain (1 study, n = 3741)			(+) gram stain		WBC > or = 10 per HPF	0.0 (0.0- 0.1)			0 (0-3)	12.9 (11.5- 14.4)		40 (38-43)	81 (79-83)
Recommend (+) LE (trace or >), (+) nitrite and WBC > or = 10 per HPF (1 study, n = 4935)	(+) LE Trace or greater	NPV > 98% th	nreshold:		WBC > or = 10 per HPF	0.06 (0.04- 0.08)	-	() (()_())	0 (0-0)	7.6 (7.1- 8.2)		29 (27-30)	72 (70-73)
Nitrite or LE (trace or >) or WBC > 5 per HPF (1 study, n = 3470)	(+) LE Trace or greater	(+) Nitrite		WBC > or = 5 per HPF		0.07 (0.04- 0.10)	-	0 (0-1)	2 (1-3)	10.5 (9.4- 11.6)			78 (76-79)
(+) Nitrite or LE (trace or >) (2 studies, n = 3814)	greater	(+) Nitrite				0.09 (0.0- 0.15)	-	$() (()_{-1})$	3 (0-5)	14.8 (8.7- 25.2)		44 (31-57)	83 (74-89)

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Continue to Part 2



Urinalysis (UA) Post-Test Probability, Part 2

	(+) LE	(+) Nitrite	(+) gram	WBC > or =						(-) Post	(+) LR Point	• •	(+) Post	(+) Post
Results (#	Trace or		stain	5 per HPF	10 per HPF	per HPF	estimate	GRADE	-test	-test		GRADE	-test	-test
	greater						(95% Cl)		probability	probability	(95% Cl)		probability	probability
Gold									(%) low	(%) high			(%) low	(%) high
Standard:									•	prevalence			prevalence	prevalence
Urine										estimate of			estimate of	estimate of
Culture									5%	25%			5%	25%
Recommended based on PPV > 50% threshold														
WBC > or =														
10 per HPF														
and (+)			(+) gram		WBC > or =		0.12 (0.09-	-	1 (()_1)	4 (3-6)	104.3 (74.3-		85 (80-89)	97 (96-98)
Gram Stain			stain		10 per HPF		0.18)	certainty	1 (0-1)	+ (3-0)	146.3)	certainty	05 (00-03)	37 (30-30)
(1 study, n=														
4007)														
WBC > or =														
5 per HPF				WBC > or =			0.29 (0.18-	+2 Low	2 (1-2)	9 (6-13)	13.9 (11.7-	+4 High	42 (38-46)	82 (80-85)
(4 studies,				5 per HPF			0.46)	certainty	2 (1-2)	3 (0-13)	16.4)	certainty	42 (30-40)	02 (00-03)
n = 7003)														
WBC > or =								+1 Very				+3		
10 per HPF					WBC > or =		0.26 (0.07-	-		8 (2-25)	16.3 (10.4,	Hoderate	46 (35-57)	84 (78-90)
(4 studies,					10 per HPF		1.02)	low	``'	0 (2-25)	25.6)	certainty	40 (35-57)	64 (76-90)
n=10068)								certainty				certainty		
(+) LE														
(trace or >)	(+) LE						0.13 (0.05-	+2 Low	1 (0, 0)	4 (0.40)	19.3 (12.0,	+4 High	50 (20, 02)	07 (00.04)
(2 studies,	Trace or						0.34)	certainty	1 (0-2)	4 (2-10)	31.2)	certainty	50 (39-62)	87 (80-91)
n = 3899)	greater													
WBC > or =														
5 per HPF														
and > 1														
bacteria per							0 54 /0 05	+3			004/10-	+3		
HPF in				WBC > or =		> 1 bacteria	``	Moderate		15 (11-19)	22.1 (10.6,		54 (36-71)	88 (78-94)
unspun				5 per HPF		per HPF	0.72)	certainty		, ,	45.9)	certainty	. ,	,
sample (1								Í Í						
study, n =														
388)														

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Suprapubic Aspiration (SPA)

- SPA is an available option if there is difficulty obtaining a catheterized specimen
- Additionally, UAs may be falsely (+) in uncircumcised infant boys
- SPA may be offered to parents and performed in the following circumstances:
 - Uncircumcised infant boy with positive cath screening tests (urinalysis, microscopy)
 - Operationally difficult to obtain a catheterized specimen
- The following criteria must be met prior to performing SPA:
 - Provider with demonstrated competency available (consult Urology, Nephrology, or Neonatology for teaching or help performing SPA)
 - Ultrasound guidance available
 - With agreement of family after discussion of risks/benefits

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UTI: Typical vs. Atypical Clinical Course

- Approximately 80-90% of first-time UTI is due to E. coli
- Patients on appropriate treatment typically improve clinically by 48 hours
- Atypical clinical course may have one or more of the following features:
 - Seriously ill
 - Poor urine flow (oliguria not due to dehydration)
 - Elevated creatinine
 - Failure to respond to treatment with suitable antibiotics within 48 hours
- In patients who have not improved by 48 hours or have an atypical clinical course, recommend renal bladder ultrasound (RBUS) during the acute infection to assess for abscess or other condition that may require acute surgical intervention
 - If RBUS negative and continued clinical concern for abscess, consider CT scan (the gold standard)
 - Consult Radiology as needed to discuss imaging options
- In the United Kingdom's NICE UTI Guidelines, non-*E. coli* UTI and bacteremic UTI are considered "atypical UTI" because of concerns that there is a higher prevalence of urinary tract abnormalities in these patients, especially younger infants. The AAP's UTI Guideline does not make this distinction.

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Empiric Antibiotic Choice

- Overuse of broad spectrum antibiotics has led to emergence of resistant *E. coli* and other Gramnegatives
- ~80% of first-time UTIs are due to E. coli
- 3rd generation cephalosporins, such as oral cefixime, are NOT recommended as first-line empiric therapy
- Narrow spectrum (1st generation) cephalosporin, such as cephalexin, is recommended
 - Cephalosporins should not be used where enterococci are suspected, due to intrinsic resistance
 - If cephalexin allergy concern, see <u>Beta-Lactam Antibiotic Allergy Reference</u>
 - Also recommended for adolescent patients with pyelonephritis, per ID and ASP based on peer institution and local clinical experience
- Antibiotic therapy should always be targeted to the sensitivities of the organism when those sensitivities are known

Rationale for Cephalexin

- Cephalexin is highly concentrated in the urine (~100 fold)
- Cephalexin is approximately 10 times less expensive than 2nd and 3rd generation cephalosporins
- Most *E. coli* are susceptible to cephalexin (=cefazolin) in the urine, even when susceptibility testing based on treatment for bloodstream infections report intermediate or resistant susceptibility
- Some children would be expected to respond to treatment with cephalexin even when their urinary isolate was reported intermediate or resistant to cefazolin
- Questions can be directed to the ID service if questions about antibiotic choice for resistant organisms

MIC Breakpoints for Cefazolin

- In January 2011, the Clinical and Laboratory Standards Institute (CLSI) published new minimum inhibitory concentration (MIC) breakpoints for cefazolin against Enterobacteriaceae
- These new breakpoints were largely based on data from bloodstream infections in adults
- Following adoption of this new standard in March 2011, Seattle Children's antibiograms gave the false impression that intrinsic resistance of *E. coli* to cefazolin was increasing
- Because of this, the Microbiology lab now includes a comment for *E. coli* isolates from the urine discussing this issue

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Criteria for Urology Referral

- Children with recurrent febrile UTIs
- Abnormal imaging: anatomic abnormality detected on ultrasound or VCUG, including complex congenital urologic problems such as:
 - Renal parenchymal loss or kidney size discrepancies
 - Ureterocele
 - Bladder or cloacal exstrophy
 - Any grade vesicoureteral reflux with febrile UTI
 - Posterior urethral valves
 - Other structural abnormalities of genitourinary development, such as persistent genitourinary sinus or cloacal abnormalities
- If uncertain if patient's medical condition requires Urology management, please consult Urology to discuss further
- DMSA Scan is an imaging study used to assess renal scarring approximately 12 months post-UTI and if needed, should be ordered via consultation with Urology

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Urinary Tract Dilation (UTD) Classification

- The UTD grading system classifies findings seen on renal bladder ultrasounds
 See <u>https://www.jpurol.com/article/S1477-5131(14)00310-6/fulltext</u>, Figure 6
- Voiding cystourethrogram is needed for definitive evaluation and grading of vesicoureteral reflux (VUR)

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Antibiotic Prophylaxis Prior to VCUG

- For patients with UTD P3 results or kidney size discrepancy on RBUS, clinicians should prescribe antibiotic prophylaxis for patients until VCUG is performed or Urology evaluation has occurred
- Patients < 2 months of age
 - Amoxicillin
- Patients 2 months to 18 years of age
 - Trimethoprim-sulfamethoxazole or
 - Nitrofurantoin

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Voiding Cystourethrogram (VCUG)

- VCUG is the definitive test for vesicoureteral reflux (VUR)
- Although VCUG is felt to be the best imaging study for detection of VUR, it is no longer necessary for most patients (*Guideline, AAP 2016*)
 - Approximate prevalences of VUR among girls 0-18 years of age
 - Grade I: 7%
 - Grade II: 22%
 - Grade III: 6%
 - Grade IV: 1%
 - Grade V: < 1%
 - Antibiotic prophylaxis is not felt to be helpful for patients with no reflux or grade I-III reflux (AAP 2016, Chand 2003)
 - This suggests that over 30 VCUGs would need to be performed to find a patient with high grade (IV-V) reflux
- VCUG is not a good study for detection of acute pyelonephritis or to delineate renal parenchymal anatomy
- VCUG is an invasive test that involves fluoroscopy; children may need sedation to tolerate the procedure

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Antibiotic Prophylaxis if Vesicoureteral Reflux (VUR) is Found

- Ongoing antibiotic prophylaxis IS NOT routinely recommended for patients with first-time febrile UTI or with low grade (I-III) VUR
- Multiple randomized trials examined the relationship between the effectiveness of antibiotic prophylaxis in different patient populations; this recommendation was reaffirmed by the 2014 RIVUR study (level of evidence: +4 high certainty)
- Children with high grade VUR should be referred to Urology

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Summaries of Literature Evidence for VUR Antibiotic Prophylaxis

- A trial of 338 randomized children with first febrile UTI showed no benefit of prophylaxis (Montini et al. 2008)
- A trial of 100 randomized patients showed no benefit in children under 30 months of age with grade II-IV reflux (Pennesi et al. 2008)
- A study of 225 randomized patients 1 month to 3 years of age with grade I-III reflux show no benefit of prophylaxis (Roussey-Kesler et al. 2008)
- A retrospective review suggested that recurrent UTIs were associated with high grade (IV-V) reflux, Caucasian race, and 3-5 years of age and that antibiotic prophylaxis was associated with increasing resistance of organisms (Conway et al. 2007)
- A prospective randomized study of 218 children 3 months to 18 years of age suggests that grade I-III reflux does not increase the incidence of UTI / pyelonephritis and that antibiotic prophylaxis does not appear to prevent the recurrence of UTI nor the development of renal scarring (Garin et al. 2006)
- The RIVUR study was a randomized control study that assigned children 2 to 71 months of age with grade I-IV reflux to receive placebo vs. antibiotic prophylaxis
 - The study found fewer symptomatic recurrences in the placebo group (RR: 0.55; 95% CI: 0.38-0.78) but no significant difference in renal scarring at 2 years of follow-up
 - Antimicrobial resistance rates were higher in the prophylaxis group compared to placebo (63% vs. 19%) (Hoberman et al. 2014)



CSW Urinary Tract Infection Pathway Approval & Citation

Approved by the UTI Pathway team for February 20, 2020, go-live

CSW Urinary Tract Infection (UTI) Pathway Team:

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Clinical Effectiveness Leadership:

Medical Director Operations Director Darren Migita, MD Karen Rancich Demmert, BS, MA

Retrieval Website: http://www.seattlechildrens.org/pdf/UTI-pathway.pdf

Please cite as:

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Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children's. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are *downgraded* if studies:

- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:

- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Certainty of Evidence:

High: The authors have a lot of confidence that the true effect is similar to the estimated effect
 Moderate: The authors believe that the true effect is probably close to the estimated effect
 Low: The true effect might be markedly different from the estimated effect
 VOO Very low: The true effect is probably markedly different from the estimated effect
 Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team
 Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies).

To Bibliography



Summary of Version Changes

- Version 1.0 (12/2011): Go live.
- Version 2.0 (12/3/2011): Expanded recommendation for empiric outpatient antibiotics to include oral cephalexin or oral cefuroxime.
- Version 2.3 (4/3/2013): Removed race from the decision to treat parameter. Included information on timing of obtaining a VCUG. Expanded discussion about cephalexin still being first-line treatment for *E. coli* in UTI.
- Version 3.0 (6/3/2014): Added additional content/information regarding the VCUG and SFU grade with a link to the SFU grade training slide.
- Version 4.0 (4/8/2015): Periodic review go live. Completed full literature search. Made multiple changes to this document and PowerPlan.
- Version 4.1 (7/6/2015): Updated bibliography formatting.
- Version 5.0 (9/29/2015): Updated inclusion/exclusion criteria to coincide with Nephrolithiasis pathway go live. Added to imaging page, specifically renal ultrasound to consider Nephrolithiasis pathway if stones are present.
- Version 6.0 (1/20/2016): Performed CSW value analysis, including review of positive blood culture recommendation.
- Version 7.0 (2/26/2016): Updated thresholds for positive urine cultures to better align with most recent AAP Guidelines.
- Version 7.1 (11/22/2016): Updated approval page to include Laboratory.
- Version 8.0 (10/31/2018): Updated UTI diagnosis criteria to include UA results and added UA's false negative rate and LR from literature review.
- Version 9.0 (4/4/2019): Changed cephalexin approximate daily dosing to Q8H instead of QID. This change is supported by recognition of actual practice in antibiotic frequency ordering and evidence that reducing frequency of antibiotic dosing is effective per pharmacy consultation.
- Version 10.0 (2/20/2020): Periodic review go live. Overhauled entire document: modified inclusion criteria to include recurrent UTI; added CFU criteria to include possible UTI; and extensively revised the screening and management algorithms to align with 2011 and 2016 AAP Guideline and current literature, including age group classification, risk factors for screening, IV antibiotic duration in neonates, and when to obtain imaging.
- Version 10.1 (4/14/2020): Clarified admit criteria for infants.
- Version 11.0 (10/30/2020): Added indication for cephalexin. Added explanation for not including race as a UTI risk factor.



Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children's Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.



Bibliography

Literature Search Methods:

For this update, we revised the search strategies in line with current Library practices. Literature searches were conducted in July 2019. The search targeted synthesized literature on urinary tract infections from 2014 to current, and was executed in Ovid Medline, Embase, Cochrane Database of Systematic Review (CDSR), and Turning Research into Practice database (TRIP).

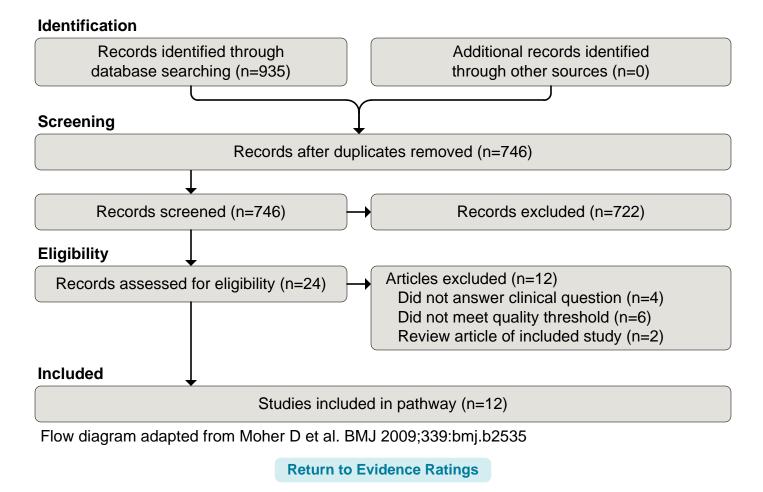
Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers independently screened abstracts and included guidelines and systematic reviews that addressed optimal diagnosis, treatment, and prognosis of patients who meet pathway inclusion/exclusion criteria. One reviewer screened full text and extracted data and a second reviewer quality checked the results. Differences were resolved by consensus.

Literature Search Results:

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The search retrieved 935 records. No additional records were included from other sources. Once duplicates had been removed, we had a total of 746 records. We excluded 722 records based on titles and abstracts. We obtained the full text of the remaining 24 records and excluded 12; twelve articles were used for this review. The flow diagram summarizes the study selection process.



Included Studies

- Reaffirmation of AAP Clinical Practice Guideline: The Diagnosis and Management of the Initial Urinary Tract Infection in Febrile Infants and Young Children 2-24 Months of Age. (2016). Pediatrics, 138(6). doi:10.1542/peds.2016-3026
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