

The background of the slide is a soft-focus image of blue flowers, likely Delphiniums, with a light blue gradient overlay. The flowers are scattered across the frame, with some in sharp focus and others blurred.

Journal Reading

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Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months

Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management

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American Academy of Pediatrics

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Introduction

- After 1970s, effective conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*
 - Bacteremia and Meningitis ↓
- **Urinary tract** as the most frequent site of occult and serious bacterial infections
- Revision of American Academy of Pediatrics (AAP) in 1999

Introduction, cont.

- This guideline can be used in
 - Office
 - Emergency department
 - Hospital
- **Focus**
 - **Diagnosis** and **management** of initial urinary tract infections (UTIs) in febrile ($\geq 38.0^{\circ}\text{C}$) infants and young children (2–24 months of age;) [$\sim 5\%$ UTI]

Method

- Medline-listed literature over the past **10** years
 - Systematic review
- For recurrent febrile UTI in children with VUR
 - Antimicrobial prophylaxis trials published since 1993 (Antimicrobial v.s Placebo)
 - Contact with 6 RCT authors for raw data
- Formulated **7** recommendations
 - Assisted physician in decision making rather than guidance

Evidence Quality	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well designed RCTs or diagnostic studies on relevant population	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations;overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case-control and cohort design)	Option	
D. Expert opinion, case reports, reasoning from first principles	Option	No Rec
X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm	Strong Recommendation	



Outline

- **Diagnosis** recommendation
 - Action statement 1
 - Action statement 2
 - Action statement 3
- **Management** recommendation
 - Action statement 4
 - Action statement 5
 - Action statement 6
 - Action statement 7

Action statement 1

- A febrile infant without source for fever
- **Need** antimicrobial therapy (subjectively)
 - Ill appearance
 - Pressing reason
- **Ensure U/A and U/C before antimicrobial Tx**
 - Catheterization or SPA
- Urine collected in a bag **not reliable** (high false-positive rate)
- Evidence quality: A; strong recommendation

Suprapubic Aspiration(SPA)

- SPA has been considered a standard method for obtaining urine
 - Variable success rates for obtaining urine have been reported (23⁰%–90⁰%).
 - **Limited risks**
 - Technical expertise and experience required
 - Compared with catheterization many parents and physicians perceived **unacceptably invasive**
 - No alternative to SPA for boys with **moderate or severe phimosis** or girls with **tight labial adhesions**

Action statement 1

- Urine collect in bag

Prevalence of UTI	False positive result
5%(all)	88%
2%(boys)	95%
0.2%(circumcised boys)	99%

- Before Antimicrobial treatment, catheterization or SPA is required to establish the diagnosis of UTI.

Ensure U/A and U/C from catheterization or PSA before Abx

Aggregate quality of evidence	A (diagnostic studies on relevant populations).
Benefits	Renal scarring if left untreated Overdiagnosis: overtreatment and unnecessary and expensive imaging. After antimicrobial therapy: lost definitive diagnosis
Harms/risks/costs	Catheterization is invasive.
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	Once antimicrobial therapy has begun, the opportunity to make a definitive diagnosis is lost.
Role of patient preferences	No evidence of preferences for bag versus catheterized urine. Pain: bladder tap > urethral catheterization.
Exclusions	None
Intentional vagueness	Urgent antimicrobial therapy is not specified 1. Variability; 2. Individualized
Policy level	<u>Strong recommendation.</u>

Action Statement 2

- A febrile infant without source for fever
- **Not require immediate** antimicrobial therapy (not so ill)
- **Action Statement 2a** (low likelihood of UTI)
 - Clinical follow-up monitoring without testing
- **Action Statement 2b** (not in a low-risk)
 - **Option 1:** U/A and U/C from catheterization or SPA
 - **Option 2:** Get U/A from the most convenient means
 - Result suggested UTI, then do **Option 1**
 - **Leukocyte esterase test**
 - **Nitrite test**
 - **Microscopic** analysis results positive for **leukocytes or bacteria**
 - Otherwise, clinical observation
- Evidence quality: A; strong recommendation.

Individual Risk Factors: Girls
White race Age < 12 mo Temperature $\geq 39^{\circ}\text{C}$ Fever ≥ 2 d Absence of another source of infection

Individual Risk Factors: Boys
Nonblack race Temperature $\geq 39^{\circ}\text{C}$ Fever > 24 h Absence of another source of infection

Probability of UTI	No. of Factors Present
$\leq 1\%$	No more than 1
$\leq 2\%$	No more than 2

Probability of UTI	No. of Factors Present	
	Uncircumcised	Circumcised
$\leq 1\%$	a	No more than 2
$\leq 2\%$	None	No more than 3

FIGURE 2

Probability of UTI Among Febrile Infant Girls²⁸ and Infant Boys³⁰ According to Number of Findings Present. ^aProbability of UTI exceeds 1% even with no risk factors other than being uncircumcised.

- Prevalence of UTI
 - Infant girls > boys (relative risk: 2.27)
 - Uncircumcised boys > circumcised boys: 0.2~0.4% (4 to 20 times)

For not so ill febrile patient, assessment for UTI likelihood

Aggregate quality of evidence	A (diagnostic studies on relevant populations).
Benefits	Prevent infection spread and renal scarring Avoid overdiagnosis: ↓ overtreatment; ↓ unnecessary and expensive imaging
Harms/risks/costs	A small proportion of febrile infants will not receive timely identification and treatment of their UTIs.
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	There is a risk of UTI sufficiently low to forestall further evaluation.
Role of patient preferences	Option 1 or 2 and the threshold risk of UTI warranting Parents' preference 1. Avoid urethral catheterization (bag urine: negative urinalysis) 2. Timely evaluation (through catheterization)
Exclusions	The precise threshold risk of UTI warranting obtaining a urine specimen is left to the clinician
Intentional vagueness	None
Policy level	Strong recommendation.

Action Statement 3

- To diagnose UTI
 - Urinalysis: **pyuria** and/or **bacteriuria**
 - Urine culture: **> 50 000** CFUs/mL of a uropathogen cultured through catheterization or SPA
- Evidence quality: C; recommendation

Action Statement 3

- Urine culture: At least **24** hours
- Urinalysis can be performed on any specimen, including fresh urine from a bag applied to the perineum
 - 1 hour after voiding with maintenance at room temperature
 - 4 hours after voiding with refrigeration
- **Prediction tests**
 - Leukocyte esterase
 - Nitrite (Gram negative enteric bacteria;; nitrate; 4hrs)
 - Urine microscopic examination for WBCs and bacteria

Urinalysis

TABLE 1 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite test positive	93 (90–100)	72 (58–91)
Microscopy, WBCs	73 (32–100)	81 (45–98)
Microscopy, bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase test, nitrite test, or microscopy positive	99.8 (99–100)	70 (60–92)

Nitrite Test

- Positive: **High specificity**
- Negative: Not rule out UTI
 - Not a sensitive marker for children
 - They empty their bladders frequently
 - Not all urinary pathogens reduce **nitrate** to **nitrite**

Leukocyte Esterase Test

- **Sensitivity > Specificity**
- Asymptomatic bacteriuria v.s True UTI
- Abx for asymptomatic bacteriuria: harm > good
- Definite pyuria: microscopic >5/HPF

Urine Culture

- Refrigerated
 - Be transported on ice
 - CFUs counted on culture medium
 - Adult woman: **>100000** CFUs/ml (morning collection)
 - Children or infants: **>50000** CFUs/ml (↑ se; ↓ sp)
 - Lactobacillus spp
 - coagulase-negative Staphylococci
 - Corynebacterium
- } Not relevant to healthy children

To Diagnose UTI by both 1. U/A; 2. U/C

Aggregate quality of evidence	C (observational studies)
Benefits	Prevent infection spread and renal scarring Avoiding overdiagnosis of asymptomatic bacteriuria or contaminated specimens.
Harms/risks/costs	Stringent diagnostic criteria may miss a small number of UTIs.
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	Treatment of asymptomatic bacteriuria may be harmful
Role of patient preferences	We assume that parents prefer no action in the absence of a UTI (avoiding false-positive results) over a very small chance of missing a UTI.
Exclusions	None
Intentional vagueness	None
Policy level	Recommendation



Outline

- Diagnosis recommendation
 - Action statement 1
 - Action statement 2
 - Action statement 3
- Management recommendation
 - Action statement 4
 - Action statement 5
 - Action statement 6
 - Action statement 7

Action Statement 4

- Action Statement 4a
 - 1. Abx orally or parenterally(toxic): equal efficacious
 - 2. According to local antimicrobial sensitivity patterns
 - 3. Adjust the choice according to sensitivity testing of the isolated uropathogen
 - Evidence quality: A; strong recommendation
- Action Statement 4b
 - Abx used for 7 to 14 days
 - Evidence quality: B; recommendation

TABLE 2 Some Empiric Antimicrobial Agents for Parenteral Treatment of UTI

Antimicrobial Agent	Dosage
Ceftriaxone	75 mg/kg, every 24 h
Cefotaxime	150 mg/kg per d, divided every 6–8 h
Ceftazidime	100–150 mg/kg per d, divided every 8 h
Gentamicin	7.5 mg/kg per d, divided every 8 h
Tobramycin	5 mg/kg per d, divided every 8 h
Piperacillin	300 mg/kg per d, divided every 6–8 h

TABLE 3 Some Empiric Antimicrobial Agents for Oral Treatment of UTI

Antimicrobial Agent	Dosage
Amoxicillin-clavulanate	20–40 mg/kg per d in 3 doses
Sulfonamide	
Trimethoprim-sulfamethoxazole	6–12 mg/kg trimethoprim and 30–60 mg/kg sulfamethoxazole per d in 2 doses
Sulfisoxazole	120–150 mg/kg per d in 4 doses
Cephalosporin	
Cefixime	8 mg/kg per d in 1 dose
Cefpodoxime	10 mg/kg per d in 2 doses
Cefprozil	30 mg/kg per d in 2 doses
Cefuroxime axetil	20–30 mg/kg per d in 2 doses
Cephalexin	50–100 mg/kg per d in 4 doses

- No evidence-based study compared 7, 10, and 14 days
- Evidence: 1–3 days courses <7–14 days
- The minimal duration selected should be 7 days.

Treat UTI, A. oral=iv; local sensitivity; uropathogen / B. 7-14 days Abx

Aggregate quality of evidence	A/B (RCTs)
Benefits	Outcomes of short courses (1–3 d) are inferior to those of 7- to 14-d courses.
Harms/risks/costs	Minimal harm and minor cost effects of antimicrobial choice and duration of therapy
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	<ol style="list-style-type: none"> 1. Adjusting antimicrobial choice on available data 2. Treating according to best evidence: minimize cost and consequences of failed or unnecessary treatment.
Role of patient preferences	Assume parents prefer the most-effective treatment and the least amount of medication that ensures effective treatment
Exclusions	None
Intentional vagueness	No evidence distinguishes 7 vs 10 vs 14 days benefit
Policy level	Strong Recommendation/Recommendation



Action Statement 5

- Febrile infants with UTIs should undergo renal and bladder ultrasonography (RBUS)
- Evidence quality: C; recommendation

Action Statement 5

- RBUS recommended: first 2 days of treatment
- Identify serious complications
 - renal or perirenal abscesses
 - pyonephrosis associated with obstructive uropathy
- Patient with clinical improvement: not need during the acute infection, even misleading
 - Animal studies: E. coli endotoxin induce dilation during acute infection, confused with hydronephrosis, pyonephrosis, or obstruction.

Febrile infants with UTIs undergo renal and bladder ultrasonography

Aggregate quality of evidence	C (observational studies)
Benefits	RBUS in this population will yield abnormal results in 15% of cases, and 1% to 2% will have abnormalities that would lead to action (eg, additional evaluation, referral, or surgery).
Harms/risks/costs	2-3% will be false-positive results, leading to unnecessary and invasive evaluations.
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	The seriousness of the potentially correctable abnormalities in 1% to 2%, coupled with the absence of physical harm
Role of patient preferences	Ultrasonography is noninvasive and poses minimal risk, we assume that parents will prefer RBUS
Exclusions	None
Intentional vagueness	None
Policy level	Recommendation

Action Statement 6

- Action Statement 6a
 - VCUG should not be performed routinely after the first febrile UTI
 - VCUG indication: RBUS reveals
 - Hydronephrosis
 - Scarring
 - High-grade VUR
 - Obstructive uropathy
 - Evidence quality B; recommendation
- Action Statement 6b
 - For recurrent febrile UTI: further evaluation conducted
 - Evidence quality: X; recommendation

TABLE 4 Recurrences of Febrile UTI/Pyelonephritis in Infants 2 to 24 Months of Age With and Without Antimicrobial Prophylaxis, According to Grade of VUR

6 RCT

Reflux Grade	Prophylaxis		No Prophylaxis		<i>P</i>
	No. of Recurrences	Total <i>N</i>	No. of Recurrences	Total <i>N</i>	
None	7	210	11	163	.15
I	2	37	2	35	1.00
II	11	133	10	124	.95
III	31	140	40	145	.29
IV	16	55	21	49	.14

TABLE 5 Rates of VUR According to Grade in Hypothetical Cohort of Infants After First UTI and After Recurrence

	Rate, %	
	After First UTI (<i>N</i> = 100)	After Recurrence (<i>N</i> = 10)
No VUR	65	26
Grades I–III VUR	29	56
Grade IV VUR	5	12
Grade V VUR	1	6

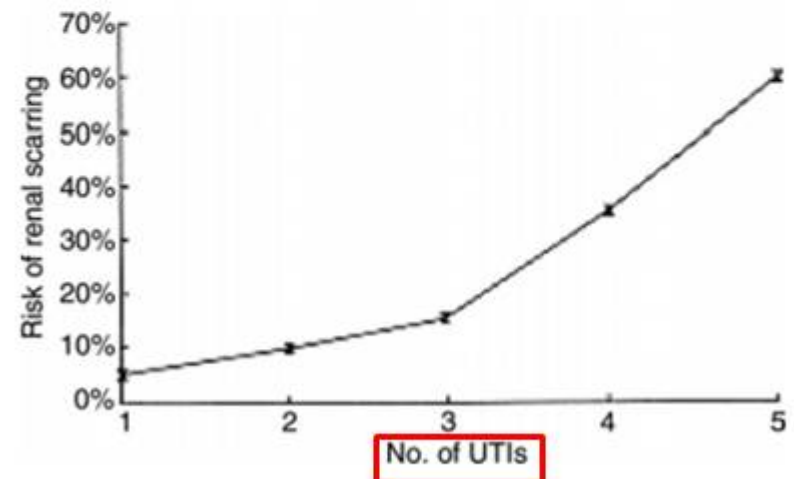


FIGURE 4 Relationship between renal scarring and number of bouts of pyelonephritis. Adapted from Jodal.⁵⁹

VCUG: not routine; indicated for active findings from RBUS

Aggregate quality of evidence	B (RCTs).
Benefits	This avoids radiation exposure, expense, and discomfort.
Harms/risks/costs	Detection of a small number of cases of high-grade reflux and correctable abnormalities is delayed
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	The risks associated with radiation for most patients outweigh the risk of delaying the detection of the few with correctable abnormalities until their second UTI.
Role of patient preferences	VCUG is an uncomfortable procedure involving radiation exposure. <ol style="list-style-type: none">1. Some prefer even the benefit is small and uncertain.2. Antimicrobial prophylaxis: ineffective in preventing recurrence of febrile UTI/pyelonephritis3. Some may want to avoid VCUG even after the second UTI.4. Committee: <u>VCUG is indicated after the second UTI.</u>
Exclusions	None
Intentional vagueness	None
Policy level	Recommendation

Recurrent UTI: further evaluation needed

Aggregate quality of evidence	X (exceptional situation).
Benefits	VCUG after a second UTI should identify infants with very high-grade reflux
Harms/risks/costs	VCUG: uncomfortable, cost, radiation (the ovaries of girls)
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	Committee: high-grade reflux may benefit from interventions to prevent further scarring.
Role of patient preferences	VCUG is an uncomfortable procedure involving radiation exposure. <ol style="list-style-type: none">1. Some prefer even the benefit is small and uncertain.2. Benefits of treatment of VUR remain unproven3. Some may want to avoid VCUG even second UTI. Benefit of identifying high-grade reflux is still in some doubt4. Committee: VCUG is indicated after the second UTI
Exclusions	None
Intentional vagueness	None
Policy level	Recommendation



Action Statement 7

- After confirmation of UTI, we should instruct parents or guardians to seek prompt medical evaluation (<48 hrs) for future febrile illnesses
- Evidence quality: C; recommendation

Education parents and guardians about fever

Aggregate quality of evidence	C (observational studies).
Benefits	Studies suggest that early treatment of UTI reduces the risk of renal scarring.
Harms/risks/costs	Additional costs and inconvenience to parents with more-frequent visit for fever.
Benefit-harms assessment	Preponderance of benefit over harm.
Value judgments	None
Role of patient preferences	Parents will ultimately make the judgment to seek medical care.
Exclusions	None
Intentional vagueness	None
Policy level	Recommendation

Summary

- Diagnosis for 2-24 mo unexplained fever
- Abx: yes → U/A and U/C by catheterization or SPA
- Abx: uncertain
 - OBS(low risk)
 - U/A and U/C(not low risk) or U/A first
- UTI
 - U/A: pyuria(+/- bacteriuria)
 - U/C: pathogen >50000 CFUs/ml

Summary, cont.

- Abx IV or PO: equal efficacious
- Give/Adjust Abx according to
 - Local antimicrobial sensitivity patterns
 - Isolated uropathogen
- Antibiotics course: 7 to 14 days
- Febrile infants with UTIs should undergo RBUS
- VCUG indication
 - Hydronephrosis
 - Scarring
 - High-grade VUR
 - Obstructive uropathy
 - Recurrent UTI



Thanks for Attention