



# REVISED GUIDELINES FOR MANAGEMENT OF URINARY TRACT INFECTIONS IN INFANTS

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## INTRODUCTION

The American Academy of Pediatrics has finally published the first revision since 1999 of clinical practice guidelines for the diagnosis and management of initial urinary tract infections in febrile infants between 2-24 months of age (those with fevers of at least 100.4°F/38.0°C).<sup>1</sup> These long awaited guidelines are not intended to replace clinical judgment or to establish an exclusive protocol for all children with urinary tract infections. The update is intended for offices, hospitals, and emergency rooms for diagnosis and treatment of the approximately 5% of children in this age group who are affected by UTIs. These evidence-based guidelines are exceptionally well done, and the data underlying the recommendations are included in a companion technical report.<sup>2</sup> There is also an accompanying editorial by Dr. Thomas Newman of the University of California, San Francisco.<sup>3</sup>

Why is this subject so important? Because febrile UTIs can cause renal scarring, which later can lead to hypertension and end-stage renal disease. And although early intervention can prevent late complications, we still wish to avoid unnecessary, expensive, and potentially risky invasive tests unless they are proven to be helpful.

Management of these problems has been affected by the introduction of effective conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, which have dramatically decreased bacteremia and meningitis, resulted in a growing awareness that the urinary tract is the most frequent site of occult and serious bacterial infections.

## RECOMMENDATIONS

The AAP subcommittee formulated 7 recommendations as action statements. They are presented in the text that follows so a physician can use them in evaluating and treating a febrile infant, as well as in an algorithm form in the appendix which is reprinted here. I have included salient practical clinical comments under each of the action statements.

## ACTION STATEMENT I

**If a clinician decides that a febrile infant with no apparent source of fever required antimicrobial therapy to be administered because of ill appearance or another pressing reason, the clinician should ensure that a urine specimen is obtained for both culture and urinalysis before an antimicrobial agent is administered; the specimen needs to be obtained through catheterization or suprapubic aspiration (SPA), because the diagnosis of UTI cannot be established reliably through culture of urine collected in a bag (evidence quality: A; strong recommendation).**

SPA has been considered the standard method of obtaining urine that is uncontaminated by perineal flora. Success rates, however, for obtaining urine have been reported as low as 23% to as high as 90%. However, there may be no acceptable alternative to SPA for boys with moderate or severe phimosis or girls with tight labial adhesions.

Urine obtained for culture by catheterization has a sensitivity of 95% and specificity of 99%, compared with that obtained through SPA. Whether the urine is obtained through catheterization or as voided, the first few drops should be allowed to fall outside the sterile container, because they may be contaminated by bacteria in the distal urethra.

Cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate and are valid only when they yield negative results. With a prevalence of UTI of 5% and a high rate of false-positive results (specificity: 63%), a “positive” culture result for a urine collected in a bag would be a false-positive result 88% of the time! For febrile boys, with a prevalence of UTI of 2%, the rate of false-positive results is 95%. For circumcised boys, with a prevalence of a UTI of 0.2%, the rate of false-positive results is a whopping 99%! So in cases in which antimicrobial therapy will be immediately initiated, catheterization or SPA is required to establish the diagnosis of UTI.

**ACTION STATEMENT 2**

If a clinician assesses a febrile infant with no apparent source for the fever and the infant is not so ill as to require immediate antimicrobial therapy, then the clinician should assess the likelihood of UTI as discussed below.

**ACTION STATEMENT 2A**

If the clinician determines that the febrile infant has a low likelihood of UTI (as discussed below), then clinical follow-up monitoring without testing is sufficient (evidence quality: A; strong recommendation).

**ACTION STATEMENT 2B**

If the clinician determines that the febrile infant is not in a low-risk group (as discussed below), then there are two choices (evidence quality: A; strong recommendation).

Option 1 is to obtain a urine specimen through catheterization or SPA for culture and urinalysis.

Option 2 is to obtain a urine specimen through the most convenient means and to perform a urinalysis. If the urinalysis results suggest a UTI (positive leukocyte esterase test or positive nitrite test or microscopic analysis positive for leukocytes or bacteria), then a urine specimen should be obtained through catheterization or SPA and culture; if urinalysis is of fresh (< 1 hour since void) urine and yields negative leukocyte esterase and nitrite test results, then it is reasonable to monitor the clinical course without initiating antimicrobial therapy, recognizing that negative urinalysis results do not rule out a UTI with certainty.

The prevalence of UTI among febrile infant girls is more than twice that among febrile infant boys (relative risk: 2.27). The rate for uncircumcised boys is 4-20 times higher than that for circumcised boys, whose rate of UTI is only 0.2% to 0.4%. The presence of another, clinically obvious source of infection reduces the likelihood of UTI by 50%. In a series of studies, Gorelick, Shaw, and colleagues derived and validated a prediction model for febrile infant girls on the basis of five risk factors, namely white race, age less than 12 months, temperature of at least 39° C, fever for at least two days, and absence of another source of infection.<sup>4</sup>

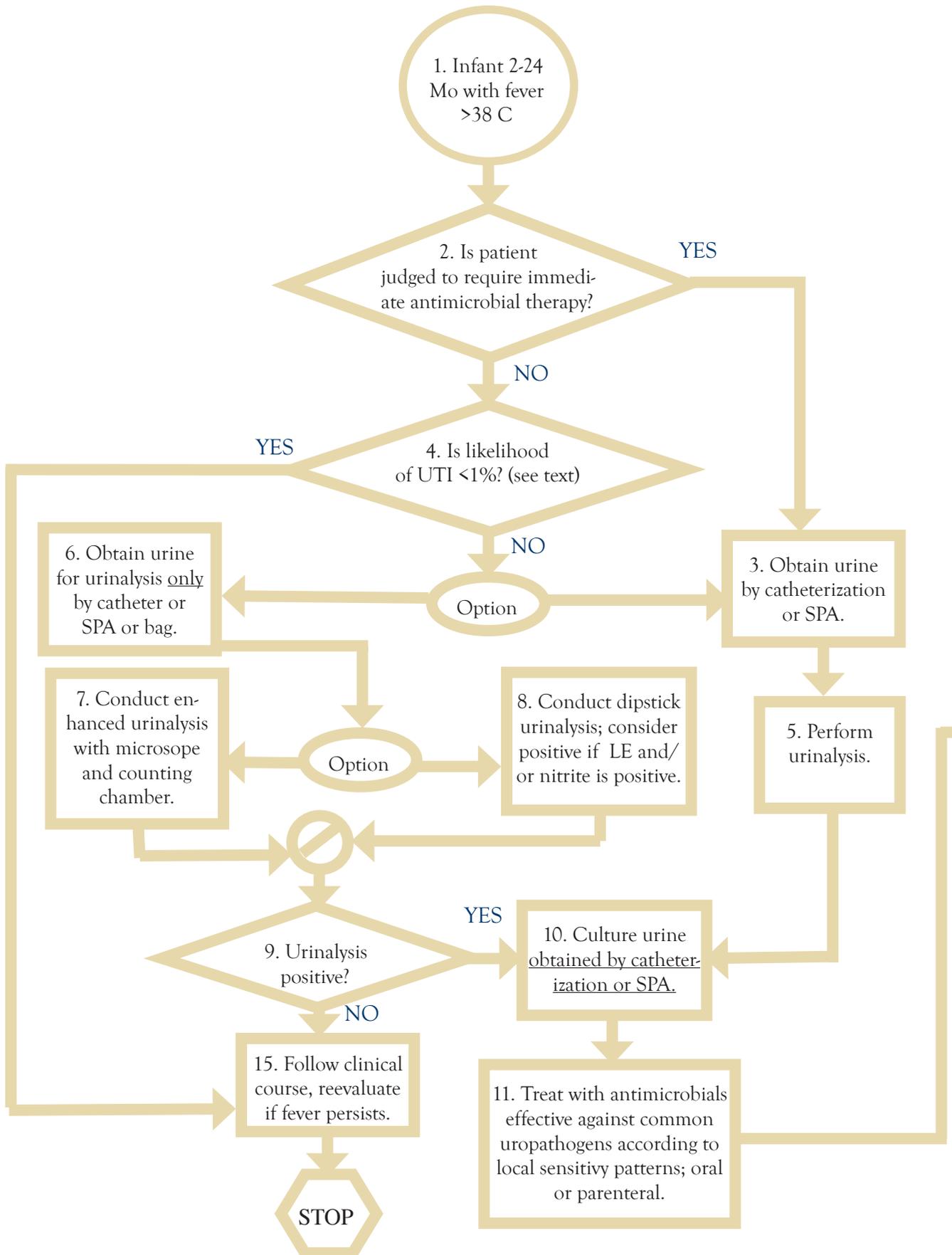
The major risk of UTI for febrile infant boys is whether they are circumcised. The probability of UTI can be estimated on the basis of four risk factors, namely, nonblack race, temperature of at least 39° C, fever for more than 24 hours, and absence of another

source of infection.<sup>2</sup> Remember that a “positive” culture from a specimen collected in a bag cannot be used to document a UTI, but a negative culture from a bagged urine can be used to rule out infection. Because there may be a substantial delay waiting for the infant to void for a second specimen, catheterization may be necessary if the urinalysis suggests the possibility of UTI. Many clinicians prefer to obtain a definitive urine specimen through catheterization initially.

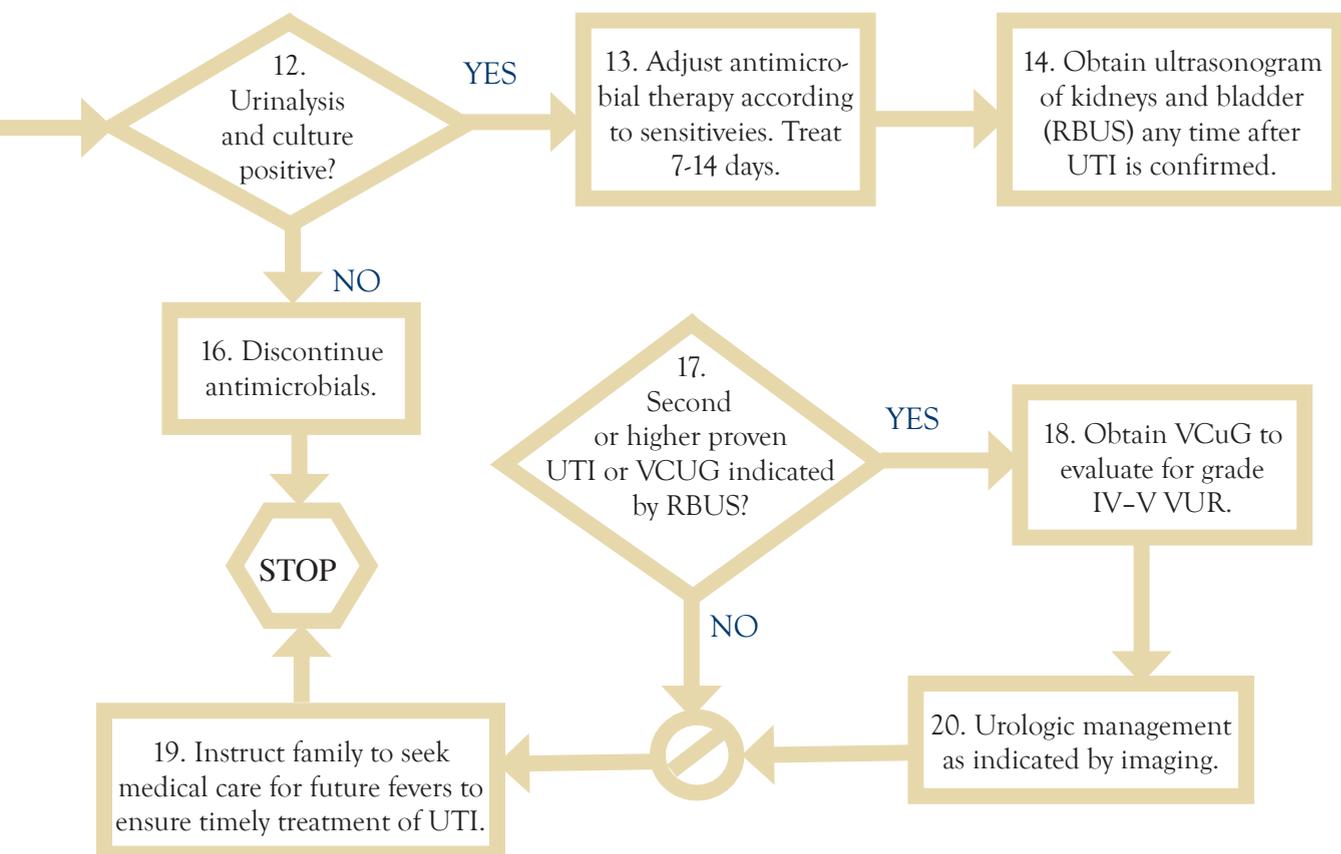
**ACTION STATEMENT 3**

To establish the diagnosis of UTI, the clinician should require both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 50,000 colony-forming units (CFUs) per mL of a uropathogen cultured from a urine specimen obtained through catheterization or SPA (evidence quality: C; recommendation).

To document the presence of UTI, urinalysis cannot substitute for urine culture but needs to be used in conjunction with culture. Urinalysis can be performed on any specimen, including one collected from a bag applied to the perineum, but the specimen must be fresh (<1 hour after voiding with maintenance at room temperature or <4 hours after voiding with refrigeration) to ensure sensitivity and specificity of the urinalysis. Leukocyte esterase and nitrite tests using a rapid dip stick method and urine microscopic examination for white blood cells (WBCs) and bacteria are the tests that have received the most attention. Leukocyte esterase is a surrogate marker for pyuria, and urinary nitrite is converted from dietary nitrates in the presence of most Gram negative enteric bacteria in the urine. The conversion of dietary nitrates to nitrites by bacteria requires approximately 4 hours in the bladder, so nitrite is not a sensitive marker in children, particularly infants, who empty their bladders quite frequently. Therefore, negative nitrite test results have little value in ruling out UTI in children. A positive test, however, is highly specific, as there are few false positive results. Sensitivity of the leukocyte esterase test is 94% when it is used in the context of clinically suspected UTI. With numerous conditions other than UTI, however, including fever resulting from other conditions (eg, streptococcal infections or Kawasaki disease), and after vigorous exercise, WBCs may be found in the urine. Therefore, a finding of pyuria does not confirm that infection of the urinary tract is present. On the other hand, the absence of pyuria



1. Risk of urinary tract infection (UTI) is ~5%.
2. A clinician may decide that a febrile infant requires antimicrobial therapy to be administered because of ill appearance or other pressing reason.
3. A urine sample suitable for culture should be obtained before initiating antimicrobials.
4. See text and tables below for girls and boys.
5. A urinalysis helps interpret the results of the urine culture, distinguishing UTI from asymptomatic bacteria.
6. Suprapubic aspiration (SPA) is not recommended unless necessary, because it produces more distress than catheterization.
7. UA that includes microscopy with a hemocytometer has higher sensitivity and specificity but may not be available.
8. Urine dipstick is slightly less sensitive, but satisfactory if microscopy is not available. Positive leukocyte esterase (LE) or nitrites or microscopy positive for white blood cells (WBCs) or bacteria is a positive urinalysis.
9. If urinalysis is negative, UTI is unlikely (<0.3%).
10. Satisfactory culture is necessary to document a true UTI and to guide antimicrobial management. Only urine obtained by catheterization (or SPA) is suitable for culture.
11. Sensitivities vary by region and time. Base route on practical consideration, e.g. unable to retain oral fluids.
12. Pure growth of  $\geq 50,000$  CFUs/mL of a uropathogen and urinalysis demonstrating bacteria or pyuria.
13. Antimicrobial sensitivities of isolated bacteria should be used to adjust antimicrobial choice.
14. Look for anatomic abnormalities that require further evaluation.
15. Follow-up in 1-2 days is important to ensure risk factors have not emerged that would increase UTI risk.
16. Discontinuation of antimicrobials assumes that urine culture was obtained before any antimicrobials were started. Unnecessary antimicrobials can contribute to antimicrobial resistance and may increase risk of UTI.
17. "Proven UTI" means a positive urine culture obtained by suprapubic tap or catheterization. RBUS indications for voiding cystourethrography (VCUG) should be judged by the clinician.
18. After a second UTI, the risk of grade IV-V vesicoureteral reflux (VUR), i.e. hydronephrosis, is estimated to be 18%.
19. Evaluation ideally within 48 hours. Early detection and treatment of febrile UTI may reduce the risk of renal scarring.



is rare in children with true UTIs. Children who are being evaluated because of fever should realistically already have WBCs in their urine. The standard method of assessing pyuria has been centrifugation of the urine and microscopic analysis, with a threshold of 5 WBCs per high-power field (25 WBCs/  $\mu$ L). The key to distinguishing a true UTI from asymptomatic bacteriuria is the presence of pyuria.

In most instances, an appropriate threshold to consider bacteriuria “significant” in infants and children is the presence of at least 50,000 CFUs/ml of a single urinary pathogen.<sup>5</sup> Organisms such as *Lactobacillus* spp, coagulase-negative staphylococci, and *Corynebacterium* spp are not considered clinically relevant urine isolates for otherwise healthy, 2 to 24 month-old children. Because the proposed criteria for UTI now include evidence of pyuria in addition to positive culture results, infants with “positive” culture results alone will be recognized as having asymptomatic bacteriuria rather a true UTI.

#### ACTION STATEMENT 4

##### ACTION STATEMENT 4A

When initiating treatment, the clinician should base the choice of route of administration on practical considerations. Initiating treatment orally or parentally is equally efficacious. The clinician should base the choice of agent on local antimicrobial sensitivity patterns (if available) and should adjust the choice according to sensitivity testing of the isolated uropathogen (evidence quality: A; strong recommendation).

##### ACTION STATEMENT 4B

The clinician should choose 7 to 14 days as the duration of antimicrobial therapy (evidence quality: B; recommendation).

Agents that are excreted in the urine but do not achieve therapeutic concentrations in the blood stream, such as nitrofurantoin, should not be used to treat febrile infants with UTIs because parenchymal and serum antimicrobial concentrations may be insufficient to treat pyelonephritis or urosepsis. There is evidence that 1-3 day courses for febrile UTIs are inferior to courses in the recommended range; therefore, the minimal duration selected would be 7 days. Whether the initial route of administration of the antimicrobial agent is oral or parenteral (then changed to oral), the total course of therapy should be 7-14 days.

#### ACTION STATEMENT 5

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

When the clinical illness is unusually severe or substantial clinical improvement is not occurring, RBUS is recommended during the first 2 days of treatment to identify serious complications such as renal or perirenal abscesses or pyonephrosis associated with obstructive uropathy. For febrile infants with UTIs who demonstrate substantial clinical improvement, however, early imaging during the acute infection is unnecessary and can even be misleading as *E. coli* can produce dilatation during acute infection which can cause an erroneous interpretation of the results.

#### ACTION STATEMENT 6

##### ACTION STATEMENT 6A

A voiding cystourethrogram (VCUG) should not be performed routinely after the first febrile UTI; VCUG is indicated 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 (evidence quality B; recommendation).

##### ACTION STATEMENT 6B

Further evaluation should be conducted if there is a recurrence of febrile UTI (evidence quality: X [exceptional situation]; recommendation).

The proportion of infants with high-grade vesicoureteral reflux (VUR) among all infants with febrile UTIs is small. Data adapted from current studies indicate that only 1 of 100 of a hypothetical cohort of infants with febrile UTIs has grade V VUR. By waiting for a second UTI before performing VCUG, only 10 of the 100 would undergo the procedure, and the 1 with the Grade V VUR would be identified. Furthermore, the 1 infant might have been identified after the first UTI on the basis of an abnormal RBUS. A national study (The Randomized Intervention for Children with Vesicoureteral Reflux study) is currently in progress to identify the effects of a prophylactic antimicrobial regimen for children 2 months to 2 years of age who have experienced a UTI, and it should provide additional important data.<sup>6</sup>

#### ACTION STATEMENT 7

After confirmation of UTI, the clinician should instruct parents or guardians to seek prompt medical

evaluation for future febrile illnesses (ideally within the first 48 hours), to ensure that recurrent infections can be detected and treated promptly (evidence quality: C; recommendation).

Early treatment limits renal damage better than late treatment, and the risk of renal scarring increases as the number of recurrences increases. For these reasons all infants who have sustained a febrile UTI should have a urine specimen obtained at the onset of subsequent febrile illnesses (even if a UTI is not suspected), so that a UTI can be diagnosed and treated promptly.

In the accompanying editorial, Dr. Thomas Newman<sup>3</sup> made additional comments in response to five clinical questions addressed in the guideline and technical report. These include the following:

1. Which children should have their urine tested? The new guideline recommends selective urine testing based on the probability of prior UTI, which Dr. Newman agrees is an important improvement over the 1999 practice parameter.

2. How should the urine samples be obtained? Dr. Newman applauds the new guidelines for continuing the option of noninvasively obtaining urine for urinalysis. But he is not convinced that the bag urine can never be used for culture, because the prior probability may sometimes be in a range where the bag culture will be useful. For example, the technical report calculates that “with a prevalence of 5% and specificity of 70%, the positive predictive value

of a positive culture obtained by bag would be 15%.” However, with the same 5% pretest probability, a positive nitrite test would raise the probability of UTI to ~75% (using the median sensitivity [58%] and specificity [99%] in the technical report). This is high enough to make the positive culture on bag urine convincing (and perhaps unnecessary).

3. How should UTIs be treated? Dr. Newman agrees with the recommendation that regional variation and antimicrobial susceptibility patterns should dictate the choice of initial treatment. He suggests adjusting the choice based on the clinical course rather than on sensitivity testing of the isolated uropathogen.

4. What imaging and follow up are recommended after a diagnosis of UTI? The recommendation that most dramatically differs from the 1999 guideline is that the VCUG not be routinely performed after the first febrile UTI. Accumulation of evidence casts doubt on the benefit of making a diagnosis of VUR. Operative ureteral reimplantation was standard treatment for VUR until randomized trials found it to be no better than prophylactic antibiotics at preventing renal scarring.

5. How should children be monitored after a UTI has been diagnosed? Dr. Newman concurs in not recommending prophylactic antibiotics to prevent UTI recurrences, because meta-analyses have revealed no significant reduction in symptomatic UTI from such prophylaxis regardless of whether VUR was present.

## REFERENCES

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