Clinical Practice Guideline:
Does the Urine Dipstick and/or the Urine Microanalysis Correlate with a Culture Positive UTI in Febrile Children? (2/14/10)

Reviewed and approved by the AAEM Clinical Practice Committee.

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1. Define the Issue and State the Question

A. Topic Area: _____Pediatric fever_____

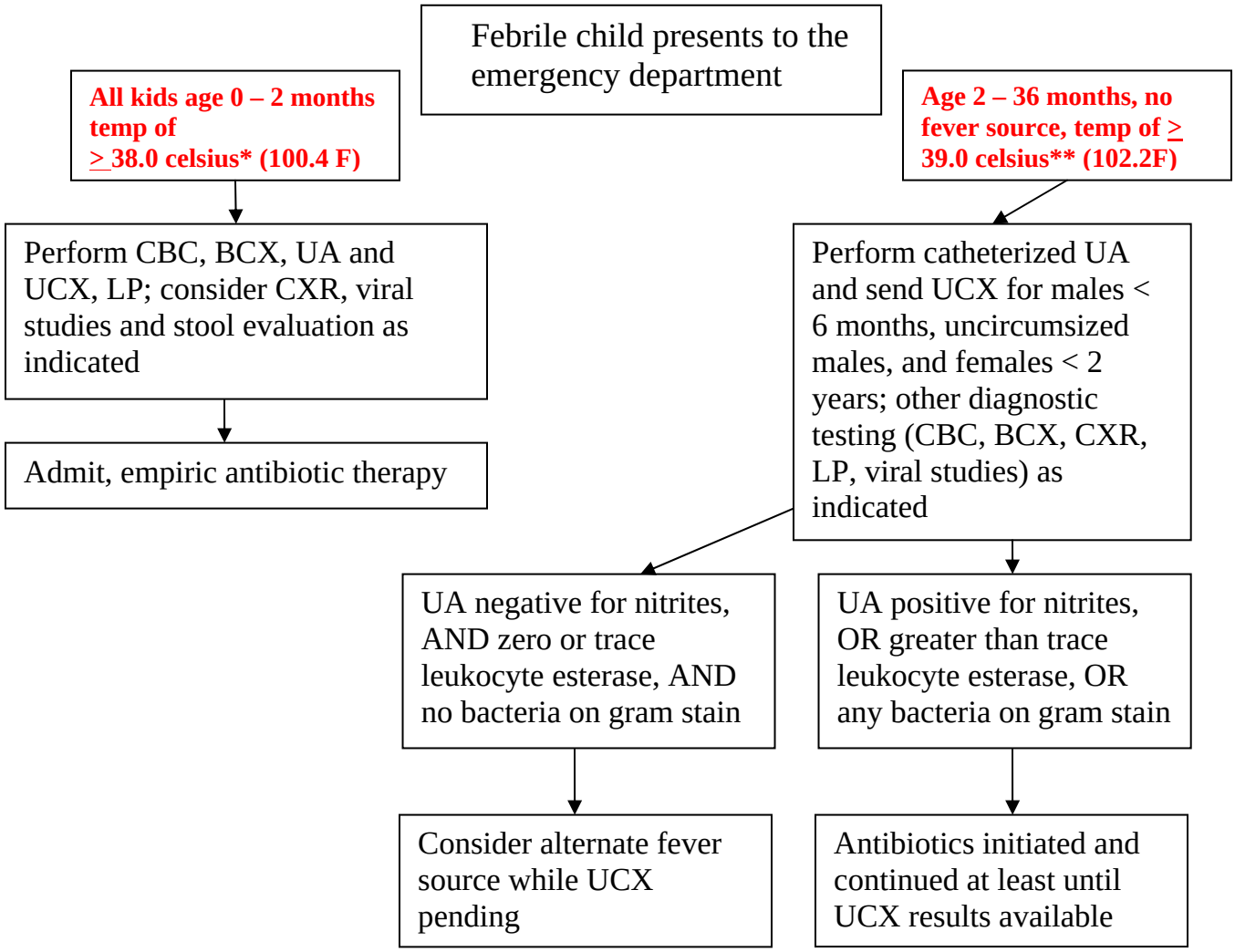
B. General Issue: __Urinary tract infection _____

C. Specific Question: _Does the urine dipstick and or the urine microanalysis correlate with a culture positive UTI in febrile children?

D. Executive Summary:

Fever from a urinary tract source remains the predominant etiology of serious bacterial infection in the child who is 0-36 months of age. Our review of the available literature suggests that febrile children (≥ 38.0 celsius) who are 0-28 days old (and usually up to 60 – 90 days old) will still require a full septic work-up even if the urinalysis is strongly suggestive of a UTI due to the possibility of concomitant meningitis or bacteremia. In febrile children (≥ 39.0 celsius) 2-24 months of age with no obvious fever source, a urinary source should be investigated if the child is female, males < 6 months old, or any uncircumcised male. When collecting a urine sample from any child 0-36 months, obtain a catheterized specimen to minimize false positive results. A tentative diagnosis of UTI from this specimen can be made if the sample is positive for nitrites, has greater than trace leukocyte esterase, or has bacteria on gram stain. In these cases antibiotics should be initiated. A urine culture should be sent for all specimens; however if the urinalysis is negative for nitrites with zero or trace leukocyte esterase and no bacteria on gram stain, an alternate fever source should be considered while the urine culture is pending.

Algorithm of Executive Summary



*Literature supports full sepsis work-up, admission, and IV antibiotics in all children 0 – 28 days old with a temperature of ≥ 38.0 C (100.4 F); most institutions follow this protocol for infants 29 – 60 days old as well but there may be some variation in accepted clinical practices in this age group.

** Most pediatric literature supports a fever without a source evaluation at a temperature of ≥ 39.0 C (102.2 F) in children ages 3 months – 3 years; the 2 month to 3 month age range is a gray area, with varying evaluation and management strategies – please consult your institution's protocols and consider immunization status.

2. Search

- Define separate strategy for each database / search process used in this review.
- Attach additional search strategies for other database / search process in this review.

SEARCH _1_

A. Keywords used in search: UTI AND diagnosis

B. Database Searched / Process Performed (Ovid, BIOMEDNET, PubMed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____Pubmed_____

C. Dates searched: From 1/1/88 To 1/31/08 with # of references 1433

D. Limits applied

limit humans and English with # of references 1133

limit 0 – 18 years with # of references 578

limit randomized clinical trial, meta-analysis, clinical trial with # of references 79

E. Final Search Result with # of references____79_____

SEARCH _2_

A. Keywords used in search: Urinary tract infection AND diagnosis

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____Pubmed_____

C. Dates searched: From 1/1/88 To 1/31/08 with # of references 9160

D. Limits applied

limit humans and English with # of references__6902_____

limit 0 – 18 years with # of references 2918

limit randomized clinical trial, clinical trial, meta-analysis with # of references 298

E. Final Search Result with # of references 298

SEARCH _3_

A. Keywords used in search: urine microanalysis

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____Pubmed_____

C. Dates searched: From _1/1/88___ To _1/31/08____ with # of references___69____

D. Limits applied

limit _humans and English__ with # of references__35_____

limit __0 – 18 years_____ with # of references____2___

limit _____ with # of references_____

E. Final Search Result with # of references____35_____

A literature search of Pubmed was performed and limited to studies published from January 1988 to January 2008, involving human subjects ages zero to eighteen years, and written in the English language. Included studies were limited to randomized controlled trials, clinical trials, and meta-analyses. Using these parameters, the search term "urinary tract infection AND diagnosis," yielded 298 references. The term "urine microanalysis," yielded two references, and the term "UTI AND diagnosis," yielded 79 references. Combining these references resulted in 338 unique articles. The list of the titles of the 338 articles was assessed independently by two physicians, and a combined total of 61 articles were deemed appropriate to be pulled for review based on their suspected relevance to the clinical question. Of these 61 articles, the reference section of relevant articles was reviewed, and further articles were pulled for review. Independent review of the articles as well as discussion and joint review by the authors was undertaken to answer our clinical question. To date, 79 articles have been selected for potential review. Of these 79, 24 articles have been deemed suitable for comprehensive review. These articles include: meta-analyses (5), prospective cohort studies (12), retrospective cohort studies or case-control studies (4), review articles (2), and one article that was discarded on further review because it did not address either the urine dipstick or microanalysis.

3. Final Evidence Database – Grade of Evidence Review

- For each reference from step 2, assign a grade of evidence using reference focus, design and methodology.
- Attach list of final evidence database with assigned grade of evidence

Grade A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials),directly addressing the review issue

Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C	Prospective, controlled, non-randomized, cohort studies
Grade D	Retrospective, non-randomized, cohort or case-control studies
Grade E	Case series, animal / model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

4. Final Evidence Database – Quality Ranking

- Critically assess each reference with regards design and methodology.
- Design Consideration – of the reference under review, consider the focus, model structure, presence of controls, etc.
- Methodology Consideration -- of the reference under review, consider the methodology.
- Attach list of final evidence database with assigned quality of evidence

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with Possible Bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable / None	Questionable / None	No, either present

List #	Article Information	Grade	Quality
50	Zorc; Clinical and demographic factors associated with urinary tract infection in young febrile infants; Pediatrics, 2005	C – prospective cohort	Outstanding
62	Committee; Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children; Pediatrics, 1999	A – literature review	Poor
73	Crain; Urinary tract infections in febrile infants younger than 8 weeks of age; Pediatrics, 1990	C - prospective	Good
69B	Hoberman; Prevalence of urinary tract infection in febrile infants; J Pediatr, 1993	C	Good
47	Little; Developing clinical rules to predict urinary tract infection in primary care settings: sensitivity and specificity of near patient tests (dipsticks) and clinical scores; British Journal of General Practice, 2006	C/D?	Good

2	Kelly; Identification of non-infected urine specimens in children; British Journal of Nursing, 1995	C	Poor
68	Lammers; Comparison of Test Characteristics of Urine Dipstick and Urinalysis at Various Test Cutoff Points; Annals of Emerg Med, 2001	C	Good
69A	Lohr; Making a presumptive diagnosis of urinary tract infection by using a urinalysis performed in an on-site laboratory	C	Adequate
65	Lockhart; Use of urinary gram stain for detection of urinary tract infection in infants; Annals of Emerg Med, 1995	C	Good
46	Deville; The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy; BMC Urology, 2004	A	Poor
48	Sharief; Use of rapid dipstick tests to exclude urinary tract infection in children; British Journal of Biomedical Science, 1998	C	Adequate
66	Shaw; Prevalence of Urinary Tract Infection in Febrile Young Children in the Emergency Department; Pediatrics, 1998	D	Good
67	Shaw; Screening for urinary tract infections in infants in the emergency department: which test is best; Pediatrics, 1998	C	Outstanding
40	Gorelick; Screening tests for urinary tract infection in children: a meta-analysis; Pediatrics, 1999	A	Outstanding
70	Ginsburg; Urinary tract infections in young infants; Pediatrics, 1982	C	Poor
76	Craver; Dipstick only urinalysis screen for the pediatric emergency room; Pediatr Nephrology, 1997	C	Adequate
77	Herr; Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness	D	Outstanding
78	Shaikh; Does this child have a urinary tract infection; JAMA, 2007	A	Good

5. Assign the Reference Support of the Question

- Separate the references into 3 categories: supportive, neutral, opposed.
- Construct 3 tables assigning the references to the appropriate location using both Grade of Evidence and Quality of Evidence.
- Use lead author name, journal abbreviation, and year of publication as reference.

Supportive Evidence (Article # referenced)

Quality / Grade	A	B	C	D	E	F
Outstanding	40		67	77		
Good			73 69B 65			
Adequate			69A			
Poor	62 46		2			
Unsatisfactory						

Neutral Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good	78		68	66		
Adequate			48, 76			
Poor			70			
Unsatisfactory						

Explanations –
68 – not the study population
66 – does not answer the question directly
76 – weakly supports
78 – not our question

No opposing table.

6. Recommendation

- Answer the clinical question, if possible.
- Assign a level of recommendation.
- Make a recommendation.

A. Recommendation: Our goal in conducting this literature search was to identify whether the urinalysis or urine microscopy could definitively diagnose a urinary tract infection (UTI) before the return of the urine culture. In the zero to two month age group this requires a test that approaches 100% sensitivity to avoid the potential serious consequences of missing an occult serious bacterial infection (SBI.) There is a paucity of literature that directly addresses febrile infants less than two months of age. Most of the studies use subset analysis of this important age group and analyze varying components of the urinalysis or urine microscopy. Our literature search did not conclusively identify any component of either the urinalysis or the urine microscopy which would allow a practitioner to conclude definitively that the source of that infant's fever is a UTI.

Our recommendation for febrile infants less than two months of age is that a catheterized urine specimen be sent for urinalysis, urine microscopy, and culture. The presence of any nitrites on urinalysis is strongly predictive of a UTI. The absence of nitrites is not helpful for excluding the diagnosis because infants less than two months void frequently, limiting urine stasis and decreasing nitrite formation. The presence of any urinary nitrites, leukocyte esterase, bacteria on gram stain, or greater than five white blood cells (WBCs) per high-powered field make the diagnosis of UTI more likely but do not allow the clinician to forego the remainder of the septic work-up in this age group. We recommend that all febrile infants less than 30 days of age also be evaluated with a lumbar puncture, complete blood count, blood culture, and other testing as indicated by the clinical presentation (eg. chest radiograph, stool studies, RSV swab.) Most infants 30-60 days of age will also require a complete septic work-up, however there are some institutional variations in the accepted clinical work-up of this age group. The literature demonstrates that even the strong likelihood of a UTI on urinalysis and microscopy does not exclude another SBI (eg. Meningitis). Furthermore, even the confirmation of a viral illness (e.g. RSV or influenza) does not preclude a concurrent SBI as demonstrated by the 2006 study by Hsiao et al. In this study of febrile infants two to six months of age, 4.9% of febrile infants had a SBI as well as a positive nasal swab for a viral respiratory infection. (12)

There is a relative abundance of studies looking at the source of infection in febrile children ages two months to two years. One of the most recent studies by Rudinsky et al in 2009 demonstrated that there is a 13.1% incidence of SBI in febrile children 0-24 months of age. It is notable that

79% of all enrolled patients in the Rudinsky study had received at least one pneumococcal vaccination. (11) Most studies in the last few decades have shown that UTI is typically the most common source of SBI in the two month to two year age group with a prevalence in most studies that is approximately 5%. Shaikh et al in 2007 reported an incidence of UTI of up to 7% in this age group based on their large meta-analysis which included a large proportion of fully-immunized children. (10) There are potential advantages of early diagnosis of a UTI in this age group. The patient could receive more directed antibiotic therapy, reducing community resistance to valuable broad spectrum antibiotics. A potentially traumatic lumbar puncture could be averted and hospital admission may become unnecessary.

In any child less than 2 years old who requires a diagnostic evaluation for fever, we recommend that a catheterized urine specimen be obtained. A urinalysis and urine culture should be performed on the catheterized specimen. If the results show any one of the following then the diagnosis of UTI may be made: 1) nitrites 2) greater than trace leukocyte esterase 3) bacteria on gram stain of uncentrifuged urine specimen. One large study (n=3873) of febrile children less than two years old presenting to the ED found a positive likelihood ratio (LR) for the diagnosis of UTI of 26 for greater than trace leukocyte esterase or nitrites on urinalysis, with a negative LR of 0.22 if neither were present. (5) Additionally, a meta-analysis revealed that the presence of any bacteria on gram stain has a positive LR of 18 for UTI, with a negative LR of 0.07 if bacteria are absent. (8) Antibiotics should be continued for a minimum of 48 hours until the culture results are available. Local sensitivity patterns should be referenced to guide the choice of antibiotics.

B. Level of recommendation:__Class B1_____

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A recommended with outstanding evidence	• Acceptable • Safe • Useful • Established / definitive	• Level A / B grade • Outstanding quality • Robust • All positive
Class B acceptable & appropriate with good evidence	• Acceptable • Safe • Useful • Not yet definitive	• Level A / B grade lacking • Adequate to Good quality • Most evidence positive • No evidence of harm
Class B 1	• Standard approach	• Higher grades of evidence • Consistently positive
Class B 2	• Optional or alternative approach	• Lower grades of evidence • Generally, but not consistently, positive
Class C not acceptable or not appropriate	• Unacceptable • Unsafe • Not useful	• No positive evidence • Evidence of harm
Class Indeterminate Unknown	• Minimal to no evidence	• Minimal to no evidence

7. List all conflicts of interest:

No conflicts of interest for any committee members

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8. Discussion

- Discuss the clinical question -- Address the issue
- Make a recommendation -- Succinctly discuss the rationale and evidence supporting the recommendation.

Urinary tract infection (UTI) is consistently the number one cause of serious bacterial infection in young febrile children. (2) Typical urinary pathogens include Escherichia coli, Klebsiella pneumoniae, and members of the Enterobacter, Citrobacter, and Pseudomonas species. (2) The prevalence of UTI in febrile children ages 2 months to 2 years presenting without an obvious source of fever is approximately 5%. (1) This prevalence increases to 8% in girls ages one – two years old, and declines to 2% in boys in this age group. (1) In one study of 442 patients less than eight weeks old presenting to an emergency department (ED) with a temperature of at least 38 degrees Celsius(100.4 F), 7.5% had a positive urine culture. (3) Certain epidemiologic factors have been associated with a higher prevalence of UTI in febrile children less than two years. These include white females (16%) and uncircumcised boys (8.0%). (5) However, in young children, symptoms such as poor feeding, vomiting, irritability, diarrhea, cough, and ear pulling were present in children with and without positive urine cultures, making an accurate clinical pre-test probability from history difficult to establish. (4,5)

Current pediatric guidelines advocate performing a urine culture on all febrile children less than two months of age as part of the fever work-up. For children age two months to two years with unexplained fever, testing for UTI should be considered. (1) These same guidelines advocate that while a urinalysis cannot replace a urine culture obtained by suprapubic aspiration or by transurethral bladder catheterization for the definitive diagnosis of UTI, the urinalysis and microscopy can increase the post-test probability of UTI when it is positive for leukocyte esterase or nitrites or white blood cells or bacteria. (1) This raises the primary question addressed by our literature review: does the urine dipstick and/or the urine microanalysis correlate with a positive urine culture in children ages zero – two months and/or children from two months to two years of age?

This question is important for several reasons. First and foremost, given that urine culture is the gold standard for the diagnosis of UTI, we would want to make sure that we do not miss children who may have a negative urine microanalysis and microscopy evaluation but who do in fact have a UTI. Second, given that a urine culture takes time to become positive, could a reliable presumptive diagnosis of UTI be made by dipstick or microanalysis, thus facilitating early initiation of antibiotics and potentially decreasing the likelihood of renal scarring and its associated complications? (9) Third, if a presumptive diagnosis of UTI can be made by urine dipstick or microanalysis in a febrile child, could this potentially decrease the number of lumbar punctures obtained as part of the fever evaluation? Fourth, there is the issue of cost. Cost of a bedside urine dipstick in one study performed from 1994 to 1996 was $0.32. The cost of the dipstick and microscopic urinalysis in that same study was $5.20 when performed by the lab, exceeding the $1.15 cost of a negative urine culture, but dwarfed by the cost of a contaminated specimen ($15.05) and a positive culture ($23.05). (6) Finally, in addition to the early initiation of antibiotic therapy, current guidelines advocate evaluation of the urinary tract in every febrile infant or child less than two years old with a positive urine

culture. (1) This evaluation should include both a renal ultrasound to evaluate for anatomic abnormalities such as hydronephrosis or ureterocele, and testing for vesicoureteral reflux (VUR), which occurs in 50% of children under age one with a UTI . (1) This can be accomplished by either voiding cystourethrography (VCUG), which is preferred for initial diagnosis, or radionuclide cystography. (1) In the ED population which may have limited follow-up, but in otherwise well young children who do not require hospital admission, there would be value in giving parents a strong presumptive diagnosis of UTI by dipstick or microanalysis and perhaps arranging follow-up studies prior to ED discharge.

Other considerations that should be mentioned regarding this topic include the fact that the threshold for a positive urine culture varies in the literature, with certain studies supporting the diagnosis of UTI when at least 10,000 colony-forming units (CFU's) per milliliter (mL) of a urinary pathogen grow after transurethral bladder catheterization. (5,6) Other studies define a positive UCX as growth of at least 50,000 CFU's per mL or at least 10,000 CFU's per mL plus a positive dipstick or urinalysis. (2) Similarly, various studies reviewed use different thresholds for identifying the dipstick and urinalysis as positive. The nitrite test is always interpreted as either positive or negative, as the production of nitrites occurs because of the reduction of nitrate by enteric bacteria. (7) Leukocyte esterase is produced by the patient's polymorphonuclear cells in response to infection and can be measured on the dipstick as none, trace, small, moderate, or large. (7) However, these tests are not perfect. Dipstick interpretation may be automated but often is done by the clinician at the bedside and thus is subject to human error. Also, in infants there is less time for the pathogenic bacteria to declare themselves by reducing nitrates to nitrites because of the infants' frequent voiding. (8) The majority of the studies reviewed considered microscopic urinalysis positive if any organisms were detected on Gram stain, but varied in the cut-off for white blood cells per high power field, ranging from five to ten. (8)

References

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