INTRODUCTION

Diagnosing urinary tract infections in febrile infants and children: when evidence-based medicine and clinical practice collide

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ABSTRACT: The management of febrile pediatric patients is challenging, and the literature is replete with articles describing diverse diagnostic and therapeutic strategies. As many as 5% of infants and young children presenting with fever will be diagnosed with urinary tract infection. Many controversies exist concerning the management of these infections, the most important being: how to make the diagnosis. The financial and time costs of emergency department management must be balanced against the potential future costs of investigations and complications.

RÉSUMÉ : La prise en charge des patients pédiatriques fébriles représente un défi, et la littérature regorge d'articles décrivant diverses stratégies diagnostiques et thérapeutiques. Jusqu'à 5 % des bébés et des jeunes enfants atteints de fièvre recevront un diagnostic d'infection urinaire. Il existe de nombreuses controverses concernant la prise en charge de ces infections, la plus importante étant : comment poser le diagnostic. Les coûts en termes d'argent et de temps pour la prise en charge de ces infections à l'urgence doivent être comparés aux coûts ultérieurs potentiels liés aux investigations et aux complications.

Introduction

The American Academy of Pediatrics (AAP) recently published practice parameters for the evaluation and treatment of urinary tract infections (UTIs) in febrile children from 2 months to 2 years of age.[1] These highlight 4 specific issues: the recognition of children at risk for UTI, the diagnosis of UTI, the short-term treatment of UTI and the use of imaging modalities in infants with proven UTI.

Subcommittee participants, including pediatricians with expertise in epidemiology, informatics, infectious diseases, nephrology, radiology and urology, developed 11 recommendations (Table 1), which were subsequently reviewed by office-based practitioners. The document[1] contains 2 non-referenced statements of particular interest to emergency physicians.

1: "Urinary tract infections are important because they cause acute morbidity and may result in long-term medical problems, including hypertension and reduced renal function."

This statement is qualified later in the document when the authors note, "the relationship between UTI in infants and young children and reduced renal function in adults has been established but is not well characterized in quantitative terms. Estimates of undesirable outcomes in adulthood, such as

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Table 1. Recommendations of the American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection

1. The presence of UTI should be considered in infants and young children 2 months to 2 years of age with unexplained fever. (strength of evidence: strong)
2. In infants and young children 2 months to 2 years of age with unexplained fever, the degree of toxicity, dehydration and ability to retain oral intake must be carefully assessed. (strength of evidence: strong)
3. If an infant or young child 2 months to 2 years of age with unexplained fever is assessed as being sufficiently ill to warrant immediate antimicrobial therapy, a urine specimen should be obtained by SPA or transurethral bladder catheterization. The diagnosis of UTI cannot be obtained or be established by a culture of urine collected in a bag. (strength of evidence: good)
4. If an infant or young child 2 months to 2 years of age with unexplained fever is assessed as not being so ill as to require immediate antimicrobial therapy, there are two options. (strength of evidence: good)
   - Option 1 – Obtain and culture a urine specimen collected by suprapubic aspirate (SPA) or transurethral bladder catheterization.
   - Option 2 – Obtain a urine specimen by the most convenient means and perform a urinalysis. If the urinalysis suggests a UTI, obtain and culture a urine specimen collected by SPA or transurethral bladder catheterization; if urinalysis does not suggest a UTI, it is reasonable to follow the clinical course without initiating antimicrobial therapy, recognizing that a negative urinalysis does not rule out a UTI.
5. Diagnosis of UTI requires a culture of urine. (strength of evidence: strong)
6. If the infant or young child 2 months to 2 years of age with suspected UTI is assessed as toxic, dehydrated or unable to retain oral intake, initial antimicrobial therapy should be administered parenterally and hospitalization should be considered. (strength of evidence: opinion/consensus)
7. If the infant or young child 2 months to 2 years of age who may not appear ill but who has a culture confirming the presence of UTI, antimicrobial therapy should be initiated parenterally or orally. (strength of evidence: good)
8. Infants and young children 2 months to 2 years of age with UTI who have not had the expected clinical response with 2 days of antimicrobial therapy should be re-evaluated and another urine specimen should be cultured. (strength of evidence: good)
9. Infants and young children 2 months to 2 years of age, including those whose treatment initially was administered parenterally, should complete a 7–14 day antimicrobial course orally. (strength of evidence: strong)
10. After a 7–14 day course of antimicrobial therapy and sterilization of the urine, infants and young children 2 months to 2 years of age with UTI should receive antimicrobials in therapeutic or prophylactic dosages until the imaging studies are completed. (strength of evidence: good)
11. Infants and young children 2 months to 2 years of age with UTI who do not demonstrate the expected clinical response within 2 days of antimicrobial therapy should undergo ultrasonography promptly and either voiding cystourethrography (VCUG) or radionucleide cystography (RNC) should be performed at the earliest convenient time. Infants and young children who have the expected response to antimicrobials should have a sonogram and either VCUG or RNC performed at the earliest convenient time. (strength of evidence: fair)

This summary of the AAP recommendations is taken from *Pediatrics* (1999;103[4]:843-52) by permission of The American Academy of Pediatrics.

hypertension and end-stage renal disease are based on the mathematical product of probabilities at several steps, each of which is subject to bias and error." One wonders: Is the problem real or mathematical?

2: "Infants and young children with UTI are of particular concern because the risk of renal damage is greater in this age group and because the diagnosis is frequently challenging: The clinical presentation tends to be nonspecific and valid urine specimens cannot be obtained without invasive methods (suprapubic aspiration and transurethral catheterization)."

So how did the AAP committee reach their conclusions? The following discussion summarizes the strategies and rationale used to derive these practice guidelines.

Methodology

The AAP committee identified 2000 relevant articles and selected 430 for review. Article quality was variable and inter-rater reliability of quality scores was fair to poor.[2] Extracted data were recorded on evidence tables that included UTI probability, diagnostic tests performed, methods of specimen acquisition, culturing techniques, initial treatment, duration of therapy and prevalence of urinary tract abnormalities. The likely consequences of misdiagnosis, short- and long-term complications, need for imaging evaluations, and estimated costs were also considered in a formal decision analysis. The strength of the evidence was rated as strong, good, fair or opinion/consensus.

Decision analyses were performed to help clinicians weigh the overall risks and benefits of different strategies. Such analyses are helpful when deci-

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sions are made under conditions of uncertainty — that is, when published evidence is inconclusive.[3] Cost-effectiveness analysis was used to quantify the trade-off between cost and clinical effect among treatment strategies. In cost-effectiveness analysis, the additional cost per unit of improvement for different approaches is estimated based on available information. For example, in the case of a febrile child with a UTI, the least expensive strategy would be to neither diagnose nor treat (do nothing). Intuitively, this would also be the least effective strategy. Increasingly aggressive diagnostic and therapeutic strategies would add to both effectiveness and cost.

Results

Table 2 shows the estimated costs, number of untreated UTIs, number of imaging studies required and the likelihood of secondary hypertension, end stage renal disease (ESRD) and death associated with 6 UTI diagnostic strategies, assuming these strategies were applied to a hypothetical sample of 100,000 children with a 5% prevalence of UTI.

Using mathematical models, the committee concluded that culturing catheterized urine samples would provide the lowest risk of death due to sepsis or unnecessary treatment. The committee speculated that culturing bagged urine specimens would result in a slightly higher death rate related to unnecessary antibiotic therapy and imaging. This is based on the assumption that "bag" cultures are only 70% specific and that in a population with 5% prevalence 85% of positive cultures would be falsely positive. These false-positive tests would generate $47.2 million in "downstream" costs per 100,000 febrile infants, without improving clinical outcomes.

The committee also concluded that screening with leukocyte esterase (LE) or nitrite reagent strips would result in a small number of undiagnosed UTIs and would lead to 2.5 times as many imaging work-ups being obtained. Therefore, despite the lower initial cost, overall expense would be higher and clinical outcomes poorer.

Table 1 summarizes the AAP recommendations.[1] Despite these, the committee acknowledged that, in circumcised boys less than 1 year of age, the invasive strategy's benefit is equivocal and that, in children over 1 year of age, its benefit is unsupported (hence that bag urine specimens may be used for screening). The committee also suggested that in children who are not acutely ill a screening urine sample may be obtained by the "most convenient means," but that if this sample suggests infection an aspirated or catheterized specimen should be cultured.[1]

Are the recommendations valid?

In assessing the validity of these recommendations, three questions should be addressed.

1. Were all important diagnostic and therapeutic strategies considered?

The AAP committee reviewed several common strategies and considered most major complications and adverse events. Interestingly, however, they did not model a strategy that many clinicians might prefer — that of analyzing "bag" urine and obtaining suprapubic aspiration or transurethral specimens only if the initial bag urine suggests infection.

2. Were critical determinants derived from credible sources and were primary assumptions valid?

Unfortunately, the quality of the source articles was variable and the committee's agreement on article quality was only fair to poor. The authors failed to provide information

Table 2. Predicted costs and outcomes for different diagnostic strategies

Strategy	US$ costs (millions)	Untreated UTI, *n*	Imaging work-ups, *n*	Hypertension cases, *n*	End-stage renal disease, *n*	Deaths, *n*
Treat all patients	19.7	0	0	49.5	23.7	1.7
Culture suprapubic aspiration or transurethral sample	25.3	0	5,000	42.4	20.3	0.7
Culture "bag" urine	72.5	0	33,500	42.4	20.3	1
Screen leukocyte esterase or nitrite	33.7	580	13,050	43.1	20.6	2.1
Screen urinalysis; culture if (+)	24.3	0	5,000	42.4	20.3	2.1
Observe	19.0	5,000	0	49.5	23.7	10

Footnote: In comparing the performance of different diagnostic tests, suprapubic aspiration was considered the "gold standard." Cost estimates were provided by the Accounting Department, University of North Carolina Hospital, and are based on the following assumptions: urinalysis ($6.77), urine culture ($21.53), renal ultrasound ($304), voiding cystourethrogram ($323), amoxicillin or sulfamethoxazole/trimethoprim ($10), broader spectrum antibiotic ($40), intramuscular ceftriaxone ($125), complications of therapy ($100), recurrent infection ($612), hospitalization for sepsis ($10,000), end-stage renal disease ($300,000).
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regarding the precision of sensitivity and specificity assumptions for the diagnostic tests analyzed. In addition, the cost data upon which the model was built are probably not relevant in the Canadian setting. Importantly, the core assumption — that employing a suboptimal screening test will lead to undiagnosed childhood UTI, which in turn will lead to adult hypertension and end-stage renal disease — may be questionable. Certainly, the incidence of these late sequelae as related to delayed or missed diagnosis of childhood UTI is ill defined. All these factors raise doubt about the validity of the model used to derive the AAP guidelines.

3. Was the impact of uncertainty considered?
Sensitivity analyses, which allow clinicians to explore the effect of uncertainty around model assumptions, were presented in the technical report.

How will the AAP recommendations influence ED practice?

Clinical guidelines are often not followed. The most common barriers to guideline adoption are lack of agreement with guidelines, lack of awareness of guidelines and difficulty performing the recommended behaviour.[4] Other barriers included a lack of time and resources to stay abreast of the large volume of clinical information, limited guideline accessibility, discomfort with "cookbook medicine," the presence of contradictory guidelines and a perceived increase in liability. Along these lines, emergency physicians often view urinary catheterization and bladder aspiration as invasive, uncomfortable and time consuming. Many are unfamiliar with SPA, concerned about its potential complications, and aware of its variable success rate (from 23% to 90%).[1] In the end, the penetration of the AAP recommendations into Canadian EDs will depend on how they are viewed by the physicians working there.

The following article,[5] by Anna Jarvis and Dennis Scolnik from the Hospital for Sick Children in Toronto, describes an approach to childhood UTI.

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