ARTICLE

Clinical Decision Rule to Identify Febrile Young Girls at Risk for Urinary Tract Infection

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Objective: To develop a clinical prediction rule to identify febrile young girls needing urine culture for evaluation of urinary tract infection (UTI).

Design: Prospective cohort study.

Setting: Urban children's hospital emergency department.

Patients: All girls younger than 2 years (N = 1469) presenting to the emergency department with fever (temperature ≥38.3°C) and without an unequivocal source of fever during a 12-month period.

Main Outcome Measures: The outcome of interest was UTI, defined as a catheterized urine culture with pure growth of 10^4 colonies/mL or greater. Candidate predictors included demographic, historical, and physical examination variables. Clinical prediction rules were developed using multiple logistic regression after screening variables for univariate association and reliability.

Results: The presence of 2 or more of the following 5 variables—less than 12 months old, white race, temperature of 39.0°C or higher, fever for 2 days or more, and absence of another source of fever on examination—predicted UTI with a sensitivity of 0.95 (95% confidence interval, 0.85-0.99) and a specificity of 0.31 (95% confidence interval, 0.28-0.34). In the study population, with an overall prevalence of UTI of 4.3%, the positive predictive value of a score of 2 or more was 6.4% and the negative predictive value of a score of less than 2 was 0.8%.

Conclusion: Using this clinical decision rule, a strategy of obtaining urine cultures from girls younger than 2 years with a score of 2 or more would lead to identification of 95% of children with UTI and elimination of 30% of unnecessary urine cultures.

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Editor's Note: I love these variable-roulette studies—they don't empty your pocket and will probably save a lot of discomfort.

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URINARY TRACT infection (UTI) is increasingly recognized as one of the most common specifically treatable causes of fever in young children.[1,2] Prompt recognition and treatment of children with UTI not only hastens resolution of the acute illness but might help reduce the incidence of renal scarring and long-term sequelae such as hypertension and renal failure associated with childhood pyelonephritis.[3] However, diagnosis of UTI depends on culture of a clean-collected urine specimen. In young, non–toilet-trained children, this typically requires an invasive procedure such as urethral catheterization or suprapubic bladder aspiration.[4] To avoid performing many unnecessary diagnostic tests, and to minimize inappropriate treatment of children with false-positive results, clinicians must identify those febrile children at particularly high risk of UTI for selective management.

Several authors have emphasized that the signs and symptoms of UTI are relatively nonspecific in infants and young children. Bauchner et al,[5] in a study of 208 girls younger than 5 years, found that all 6 with positive urine culture results had initially been given an alternative diagnosis, such as gastroenteritis or upper respiratory tract infection. Hoberman et al[1] obtained urine cultures for 945 febrile children in the first year of life; there was no significant association between UTI and several of the clinical findings studied, including vomiting, diarrhea, lethargy, and poor feeding. Conversely, these and other investigators have found that certain clinical

PATIENTS AND METHODS

PATIENTS

The study was conducted at an urban tertiary care children's hospital ED with an annual census of 55 000 visits per year. The study population has been described in detail previously.[2] Briefly, all boys younger than 1 year and all girls younger than 2 years who presented to the ED with fever (temperature ≥38.3°C) during a 12-month period were identified prospectively. (Because of the small number of UTIs in boys, this analysis is restricted to the girls.) The clinical policy in the ED was to obtain a catheterized urine specimen for culture in all such children without a definitive, or unequivocal, focus of infection to explain the fever. Such definitive sources of fever included confirmed bacterial infection (eg, meningitis, pneumonia by chest radiograph, cellulitis, and streptococcal pharyngitis), specific viral infections (eg, varicella, Coxsackie disease, and herpetic stomatitis), and recognizable febrile disease (eg, Kawasaki syndrome and Henoch-Schönlein purpura). Children with such definitive sources that were believed to explain the presence of fever did not routinely have urine cultures obtained and were therefore excluded from the study. Conversely, children with a possible, but not definitive, source of fever, such as upper respiratory tract infection, gastroenteritis, otitis media, or nonspecific viral syndrome, had urine cultures obtained and were included in the study. During the study, 83% of all eligible children had a urine culture obtained; of these, 89% had a questionnaire completed by the examining physician regarding the presence of various signs and symptoms. To allow measurement of interobserver reliability, a second clinician (usually the patient's primary nurse) completed the questionnaire independently in a subset of patients. The study protocol was reviewed and approved by the hospital's institutional review board.

VARIABLES

The outcome of interest was UTI, defined as a positive urine culture with pure growth of 10^4 colonies/mL or greater of a pathogenic species of bacteria. All urine specimens were obtained by urethral catheterization. The candidate predictor variables, classified as demographic, historical, or physical examination factors, are listed in the **Table**.

DATA ANALYSIS

Initially, univariate relative risks (RRs) with 95% confidence intervals (CIs) were calculated for the association with UTI of each of the clinical factors listed in the Table. We then attempted to develop a multivariate predictive model. Several strategies were used to reduce the number of potential predictors to the most parsimonious set that would adequately predict the risk of UTI. First, factors with a small ($0.8<RR<1.25$) and statistically nonsignificant (using a conservative significance level of $P<.3$) univariate association with UTI were excluded from further consideration. Next, we excluded factors whose measurement was insufficiently reproducible. Whenever a study form was completed by 2 clinicians, interobserver agreement was measured with the κ statistic, a measure of chance-corrected agreement. A value of $\kappa \geq 0.5$ was considered acceptable agreement beyond that expected by chance; those factors with a $\kappa<0.5$ were excluded as candidates for the predictive model. Finally, the remaining factors were entered into a multiple logistic regression model, with UTI as the outcome variable. A backward elimination modeling technique was used, with a significance limit for removal from the model of $P>.15$ using maximum likelihood estimation.

Those predictors remaining in the logistic regression model were then considered for the clinical decision rules. The goal was to create a simple linear score based on the presence or absence of each of the factors. A cutoff value would then be chosen to define a decision rule for identifying patients in whom urine testing should be performed. Alternative predictive models were created using different subsets of factors. In addition, the predictive models were evaluated with equal weighting (1 point for each factor present) and with weighting proportional to the coefficient for each factor in the logistic regression model. The overall discriminative ability of the resulting models was evaluated by the area under the receiver operating characteristic curve. At each possible cutoff value, a clinical rule was generated—culture for a score at or above the cutoff value, no culture for a score below the cutoff value. The discriminative ability of each rule was determined by calculating sensitivity, specificity, likelihood ratios, and predictive values (with 95% CIs) at each cutoff value. Statistical analyses were performed using Stata release 5.0 (Stata Corp, College Park, Tex).

factors are associated with a finding of UTI, including age, race, and height of fever.

The goals of this study were to evaluate a cohort of febrile young girls assessed in an emergency department (ED) to identify clinical factors predictive of a positive urine culture and to use these predictive factors to develop a clinical decision rule to distinguish children at low risk of UTI from those requiring further evaluation.

RESULTS

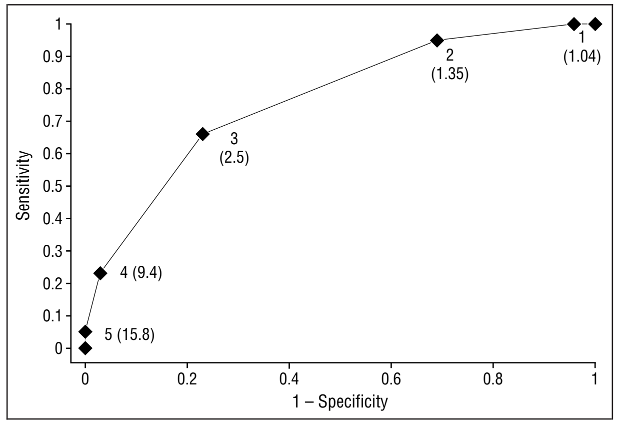
Urine cultures were obtained from 1469 girls, of which 63 were positive. The mean ± SD age of the girls was 11.0 ± 6.2 months. Eighty-four percent of the patients were African American, 12% were white, and 4% were another race or ethnicity. Most children were described as well appearing (68%) and had a potential source of fever on examination (77%).

The Table shows the results of the univariate analysis for each of the potential risk factors. Using the conservative criteria specified in the "Patients and Methods" section, the presence of any gastrointestinal symptoms and the absence of ill contacts were eliminated from further consideration for inclusion in the prediction rule at this stage. For the continuous variables, a cutoff point was selected to permit use of a dichotomous variable for prediction. First, the assumption of a linear relationship between categories of the predictor and the outcome was tested by a χ^2 test for trend.[6] Then, sev-

Clinical Factors Associated With Urinary Tract Infection in Girls Younger Than 2 Years*

Variable	Relative Risk (95% Confidence Interval)	*P*	κ
Demographic			
Age (<12 vs ≥12 mo)	2.82 (1.6-5.1)	.001	NA
Race (white vs nonwhite)	6.0 (3.7-9.5)	<.001	NA
Race (adjusted for residence and insurance type)	9.7 (5.2-18.3)	<.001	NA
Historical			
Duration of fever ≥2 d	1.5 (0.9-2.6)	.10	0.75
Any gastrointestinal tract symptoms	0.86 (0.5-1.5)	.58	0.65
Any urinary symptoms	3.5 (1.5-8.1)	.004	0.31
Past history	2.5 (0.9-6.4)	.07	0.57
Absence of ill contacts	1.19 (0.7-2.1)	.54	0.65
Physical examination			
Temperature ≥39°C	1.7 (0.9-3.1)	.09	NA
Ill general appearance	2.3 (1.4-3.8)	<.001	0.38
Any tenderness	3.4 (1.2-10.1)	.02	0.38
Absence of an alternative source of fever	1.9 (1.1-3.2)	.01	NA

*NA indicates not applicable.



Receiver operating characteristic curve showing sensitivity (true-positive rate) vs 1 – specificity (false-positive rate) at each score of the clinical decision rules. The number next to each point represents the number of positive items, and the likelihood ratio at that cutoff value is shown in parentheses.

eral possible cutoff points for each variable were chosen on the basis of clinical sensibility. Two cutoff points for dichotomizing age—6 or 12 months—were chosen a priori. The RRs for UTI were similar at the 6-month (RR = 2.3) and 12-month (RR = 2.8) cutoff values, so the latter was used to categorize age in further analyses. Similarly, 3 temperature cutoff values were considered: 39.0°C or higher, 39.5°C or higher, and 40.0°C or higher. The risk of UTI was similar in all 3 of the higher temperature subgroups (4.4%, 3.6%, 4.3%, respectively) and higher than in the lowest temperature subgroup (2.8%). Therefore, the cutoff value of 39.0°C or higher was chosen to dichotomize temperature for all analyses. Finally, for duration of fever, cutoff points of 2 or more, 3 or more, and 4 or more days were considered. The RR was 1.5 using a cutoff value of either 2 or more or 3 or more days, so the former was chosen for use in the prediction model.

White race was one of the strongest univariate predictors of a positive urine culture. To explore the possibility of confounding by socioeconomic status or referral status (ie, referred to ED for evaluation by primary care provider vs self-referral) as the explanation of the observed association of race with UTI, adjustment was made for insurance type (medical assistance or self-pay vs commercial insurance) and ZIP code of residence (within the primary catchment area of the hospital vs outside), with no resulting change in the RR.

Interobserver reliability was determined for 267 pairs of observations of clinical factors (see the Table). The following factors were not considered to be subject to interobserver variability and were therefore not subjected to reliability analysis: age, race, sex, and temperature in the ED. In addition, because the second observer did not usually perform a thorough assessment for the presence of an alternative source of fever (eg, otitis media or pharyngitis), we were unable to evaluate the interobserver reliability for this clinical factor. Based on κ<0.5, general appearance, presence of any abdominal or flank tenderness, and report of any urinary symptoms were eliminated from further consideration for the predictive model.

Candidate predictor variables remaining after the screening process were included in a logistic regression model, with backward stepwise elimination using a remove limit of $P>.15$. There were 1151 girls (with 56 UTIs) with complete data for all variables included in the regression analysis. Five predictors remained in the final model: white race (adjusted odds ratio [AOR] = 7.5), age younger than 12 months (AOR = 3.0), temperature of 39.0°C or higher (AOR = 2.6), absence of another potential source of fever (AOR = 2.4), and duration of fever of 2 days or longer (AOR = 2.0). Medical history of UTI or urinary tract anomaly was dropped from the model ($P = .26$).

Linear combinations including some or all of the remaining variables were generated, and sensitivity and specificity were calculated at each cutoff score. The overall discriminative ability of models containing 3, 4, or all 5 variables, and with equal or proportional weighting, was similar (areas under the receiver operating characteristic curves, 0.73-0.77). Because many clinicians and parents place a high value on sensitivity, particularly when the diagnostic test is relatively inexpensive and noninvasive, we sought to define decision rules with the highest possible sensitivity. All scores had a sensitivity of 1.0 if any of the predictors were present; however, all such rules had extremely high false-positive rates and would eliminate few, if any, unnecessary urine cultures. The score with the best performance in girls was one including all 5 of the remaining variables, with 1 point assigned for each (**Figure**). The presence of any 2 or more of these risk factors (ie, a score of ≥2) predicted a positive urine culture with a sensitivity of 0.95 (95% CI, 0.85-0.99), a specificity of 0.31 (95% CI, 0.28-0.34), and a likelihood ratio of 1.35 (95% CI, 1.21-1.43) for a positive result and a likelihood ratio of 0.18 (95% CI, 0.06-0.49) for a negative result. In the derivation population, the probability of UTI in girls with a score of 2 or higher was 6.4% (95% CI, 4.8%-8.3%), whereas the risk of UTI in those with a score of less than 2 was 0.8% (95% CI, 0.2%-2.5%). Obtaining a urine culture from only girls with a score of 2 or more would have resulted in missing only 3 UTIs (5%), and 349 negative urine cultures would have been avoided (30% of the total). A cutoff value of 3 points or more results in a gain in specificity but a corresponding loss in sensitivity; thus, restricting urine culture to girls with a score of 3 or more leads to fewer unnecessary cultures (984 [67% of the total]) but more missed UTIs (21 [33%]).

COMMENT

Evaluation of the young child with fever is complicated by the possibility of clinically "occult" bacterial infections, with traditional emphasis on occult bacteremia.[7] Recently, however, there has been increased recognition of UTI as a source of infection in otherwise well-appearing febrile infants, even without signs or symptoms referable to the urinary tract and even in the presence of another possible source of fever such as otitis media or upper respiratory tract infection.[1,2] Concern about possible long-term sequelae of untreated UTI has led to recommendations for more liberal testing for UTI in this group of patients.[4,7,8]

We formulated a decision model, derived from a small number of easily observed clinical factors, that might permit a more selective approach to urine testing in febrile young girls. Although developed using mathematical modeling techniques, the score is clinically sensible and easy to use, important characteristics of a decision rule designed to assist clinicians in making diagnostic and therapeutic decisions.[9] The choice of a threshold score, above which a urine specimen is obtained, will depend at least in part on the perceived relative costs and benefits to clinicians and parents of prompt diagnosis of UTI vs possibly unnecessary testing. Clinicians can use the information on likelihood ratios at different cutoff scores, combined with their own and the parents' preferences and knowledge of the overall prevalence of disease in their patient population, to guide their decisions.

In proposing a score of 2 or more as a threshold for obtaining urine culture, we sought to create a rule with high sensitivity so that few, if any, children with UTI would be missed and with reasonable specificity to decrease the number of unnecessary laboratory tests performed. Many physicians, particularly those working in an ED setting where follow-up may be problematic, place a premium on sensitivity to avoid missing an important diagnosis.[10] Our decision rule, with culture obtained from any girls with 2 or more of the 5 predictors, correctly identified 95% of girls with UTI. Although the sensitivity of the rule is less than 100%, the action prescribed by the rules corresponds with clinicians' thresholds for obtaining a culture as documented by Roberts et al.[11] In their study, only 10% of clinicians believed that a urine culture is indicated if the probability of UTI is less than 1%, whereas 80% to 90% would obtain a culture with a probability of disease of 3% to 5% and all would do so if the probability exceeds 5%. The probability of UTI in children with a negative decision rule in this study is 0.8%; the probability in those with a positive decision rule is 6.4%. More important, the sensitivity of the decision rules represents an improvement over current general practice. A published guideline[7] for the management of young children with fever recommends obtaining urine culture only from boys younger than 6 months and girls younger than 2 years with a temperature of 39.0°C or higher and no other source of fever. In our study population, following this recommendation would have led to detecting only 21% of the UTIs. Use of the decision rule, on the other hand, while correctly identifying most girls needing urine culture, would eliminate 30% of negative cultures. With approximately 4 million infants born in the United States each year, and an average of at least 3 febrile illnesses during the first 2 years of life,[8] substantial savings could be realized using a selective, rule-based strategy to guide management.

Laboratory screening tests are often used to decide on need for culture or institution of empirical treatment. As a screen for the need for culture, the sensitivity of the prediction rules compares favorably with that of urine dipstick (60%-91%)[12] and enhanced urinalysis (95%).[13,14] Because these urine screening tests have lower false-positive rates than the decision rules, they have greater potential for reducing the number of unnecessary urine cultures. However, unlike the dipstick and enhanced urinalysis, the decision rule requires no urine specimen, eliminating the need for an invasive procedure such as catheterization, or the unproven and frequently unsuccessful urine bag technique, in many children.

There are several limitations that must be addressed. The most important is that although the decision rule performed extremely well in the population in which it was derived, it has not been prospectively validated in a different population. Such validation is crucial because prediction rules generally fail to perform as well when subsequently applied to different groups of patients.[9,15] Although we acknowledge the need to validate this rule, there are several reasons to believe that our decision rule will perform well in an independent sample. First, the usual reason for this failure to validate is overfitting of a multiple regression model, or overstating the importance of some factors because of idiosyncrasies in the derivation sample.[16] Overfitting is minimized when the ratio of outcomes to predictors in the model is at least 10:1[15]; in our regression analysis, there were 56 outcomes and 6 predictor variables. In addition, the RRs for several of the variables included in the rules are remarkably similar to those found by other investigators. For example, 16.9% of white female infants with a temperature of 39.0°C or higher studied by Hoberman et al[1] in Pittsburgh had a UTI compared with 17.8% in this study. The RR for lack of another source of fever was 2.3 in boys and girls combined in the study by Hoberman et al and 2.2 in this study.

Another limitation is that although we believe that the decision rules are clinically sensible, clinicians might be surprised at some of the variables not included in the model. For example, children with a history of UTI are at higher risk and usually have testing done with a febrile illness.[3] In our population, however, such children were always identified by the presence of other risk factors. In another population, a clinician might be influenced to obtain a urine culture in a child with a history of UTI even in the absence of other indications for testing. Similarly, we did not find a parental report of urinary symptoms such as malodorous or cloudy urine to be helpful, at least in part because such symptoms were not consistently reported to examiners.

We did not examine children believed to have an unequivocal source of fever, such as varicella, radiographically documented pneumonia, or cellulitis. Hoberman et al[1] found the prevalence of positive cultures in such children to be low, and current practice does not generally support testing for UTI in such children. However, the results of this study cannot be extrapolated to such children.

The definition of UTI used in this study is subject to some debate. Although our definition has been used in various other studies,[3] some investigators have proposed different criteria for diagnosis of UTI, including different colony counts considered positive and the requirement that pyuria also be present.[3,8] Our definition of pure growth of 10^4 colonies/mL or higher from a catheterized specimen might be considered too liberal, leading to some false-positives. Only 7 of 80 cultures had fewer than 5×10^4 colonies/mL, and 3 of these had significant pyuria. None of the children with lower colony counts and no pyuria would have been classified as positive according to the decision rule. Thus, eliminating these from the analysis would actually increase the sensitivity of the rule to 100% (52/52).

In summary, we developed a clinical prediction model to aid in identifying febrile girls younger than 2 years who are at risk for UTI. The model has excellent sensitivity, although further work is necessary to validate the results in different patient populations. When sensitivity is of paramount importance, we recommend obtaining urine culture if any 2 or more of the 5 risk factors are present. Such a strategy leads to identification of 95% of affected children and elimination of the need for a substantial proportion of unnecessary tests. We are currently conducting a formal economic analysis to compare the cost-effectiveness of various screening strategies for UTI in febrile young children.

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