JOURNAL OF ADOLESCENT HEALTH 1993;14:356–361

ORIGINAL ARTICLES

Screening for Urethral Infection in Adolescent and Young Adult Males

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We evaluated the urinary leukocyte esterase (LE) dipstick as a predictor of a positive urethral culture for *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* in adolescent and young adult males. Sexual and sexually transmitted disease (STD) histories were also analyzed to determine predictors of infection. Subjects were recruited from sexually active males attending an adolescent medicine clinic. Patients were interviewed regarding presence of symptoms of urethritis and a variety of clinical variables. First-voided urine for LE dipstick and urethral swabs for gonorrhea and *C. trachomatis* cultures were obtained. One hundred patients (mean age, 19.2 years) were asymptomatic; 50 patients (mean age, 19.0 years) had symptoms of urethritis. In asymptomatic patients, the sensitivity, specificity, predictive value positive (PVP), and predictive value negative (PVN) of the LE dipstick were 0.31, 0.92, 0.57, and 0.90, respectively. These values were 0.66, 0.71, 0.76, and 0.60, respectively, in symptomatic patients. In each patient group the dipstick was more sensitive in detecting, and a better predictor of, a positive culture for gonorrhea than *Chlamydia*. LE dipstick results and clinical variables were evaluated as correlates of infection using stepwise logistic regression. A positive LE dipstick and four additional variables increased the probability of obtaining a positive culture for one or both organisms from symptomatic patients. These variables were the following: sexual contact in the previous month with a partner diagnosed as having a sexually transmitted disease, having ever used a condom, five or more lifetime sexual partners, and more than one sexual partner in the past month. Only a positive LE dipstick entered the model as a predictor of infection in asymptomatic patients. We concluded that the LE dipstick is the only available noninvasive screening instrument for asymptomatic urethral infection. It can be used to identify asymptomatic, sexually active males for whom culture for STDs is appropriate. The sexual and STD history do not assist in predicting positive culture(s) in asymptomatic patients, although several variables were associated with infection in symptomatic patients. Symptomatic patients should be evaluated using standard techniques regardless of LE dipstick results.

KEY WORDS:
Urethritis
Gonorrhea
Chlamydia trachomatis

Routine screening and/or testing of sexually active adolescents of either gender for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* has been recommended (1–4). These organisms are the major causes of urethritis and epididymitis in males, and of endocervical infection and pelvic inflammatory disease in females. They are prevalent in sexually active adolescents (5). As many as 5% and 13% of asymptomatic male adolescents are infected with *N. gonorrhoeae* (6–9) and *C. trachomatis* (7–10), respectively. These young men represent an important reservoir of infection. Symptom-free intervals as long as 15–45 days may increase the likelihood of transmission (11–13). The need to detect asymptomatic

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Presented in part at the Annual Meeting of the Southern Society for Pediatric Research, New Orleans, Los Angeles, January 18, 1990.

Manuscript accepted December 29, 1992.

1054-139X/93/$6.00

Published by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010

infection is highlighted by the failure of a substantial proportion of symptomatic males to identify these symptoms as the reason for a clinic visit (14).

Gonorrhea cultures are simple and cost little. Cultures for *Chlamydia* are expensive, technically difficult, and logistically often not feasible. Data on the validity of noncultural antigen detection techniques in asymptomatic males are limited (15). Asymptomatic males, moreover, may reject endourethral swabs because of their significant discomfort (8).

Evaluation of urine provides an alternative to swabs (16–18). Pyuria in first-voided urine was found to be a more-sensitive indicator of asymptomatic nongonococcal infection than a urethral Gram stain (11,19). Recent interest has focused on the leukocyte esterase (LE) dipstick, which yields a visual, semiquantitative measure of pyuria (20). Two studies have evaluated the LE dipstick in screening asymptomatic adolescent males for *C. trachomatis* or *N. gonorrhoeae* (8,9). In a group of 13 symptomatic and 41 asymptomatic males, the dipstick was found to be good predictor of positive culture(s) (21).

Known exposure to a sexually transmitted disease (STD) slightly increased the ability to predict a positive culture (21). To date, the dipstick has not been studied in larger numbers of symptomatic and asymptomatic males, while controlling for relevant clinical, demographic, and behavioral variables. Such variables may be useful in identifying individuals at high risk for STD (22–26).

The present study was designed to evaluate the validity and predictive values of the LE dipstick in older adolescent males, with and without, symptoms of urethral infection. Additionally, the association of clinical variables with infection was investigated. It was hypothesized that factors such as previous STD, multiple sexual partners, and failure to use condoms would be associated with urethral infection.

Methods

Patients

Males, 18 years of age and older attending the adolescent medicine clinic at Children's Hospital of Oklahoma between July 31, 1989, and August 3, 1990, were recruited. This clinic provides primary care to adolescents 14 through 21 years of age, 80% of whom are female. There were 14,219 visits during fiscal year 1990. Most patients are of lower socioeconomic status; approximately 50% of visits are covered by Medicaid and 20% by private health insurance. The lower age limit for recruitment was based on previous requirements of the University of Oklahoma Institutional Review Board (IRB) for self-consent by adolescents and young adults. Patients were eligible if they had had sexual intercourse at least once and had not taken antibiotics in the previous 30 days. Patients were permitted to enroll twice if 6 months or greater separated each enrollment. Physicians (including house officers), fourth-year medical students, and a pediatric nurse practitioner recruited and examined patients, collected specimens and read urine dipsticks. In a 10-min presentation, the first author (J.J.) instructed recruiters on how to conduct the study. Patients were queried regarding presence of symptoms of urethritis (urethral discharge, dysuria, and/or itching at the distal end of the urethra), recent exposure to or prior STD diagnosed by a clinician, and other variables. Written informed consent was obtained. This study was approved by the IRB of the University of Oklahoma Health Sciences Center.

Sample Collection

Patients provided 15 mL of first-catch urine in a graduated 60 mL container or a 15 mL test tube. Urethral cultures for gonorrhea and *C. trachomatis* were then obtained by the recruiter on separate Type I calcium alginate swabs. The first swab, which was inserted 1–2 cm beyond the urethral meatus, was plated on modified Thayer-Martin agar for gonorrhea culture. If the patient was symptomatic, the swab was then smeared on a slide for Gram's stain. The second swab, which was inserted 2–3 cm beyond the meatus, was cultured for *C. trachomatis* using previously described techniques (27). Cultures were performed in the hospital laboratories. Within 5 min after collection, urine was tested by the examiner for leukocyte esterase with the Chemstrip-L dipstick (BioDynamics, Indianapolis, IN). The dipstick was read 60–120 sec later using the scale (−, trace, +, + +) provided by the manufacturer. Dipstick results were categorized as "positive" (+, + +) or "negative" (−, trace) in accordance with other authors (8,9). Patients with clinical indications and/or positive culture(s) were treated according to established guidelines (28).

Statistical Analysis

The 95% confidence limits (CL) for the validity and predictive values of the dipstick were calculated (29).

χ^2 analyses, Student's t tests, and stepwise logistic regression analyses were performed with SAS version 6.06 (30).

Stepwise logistic regression analysis was used to model the potential risk factors for positive culture results. In the SAS procedure LOGISTIC, the p value associated with a χ^2 statistic is used to determine the order of entry of the independent variables into the model. Entry into the model requires a p value of less than 0.05; variables are entered in order of the smallest p value (largest χ^2). Once in the model, the significance of the factor in the presence of variables already in the model is evaluated with a χ^2 statistic. If the p value is greater than 0.10, the variable is removed from the model. Interaction terms were not indicated for this model. All variables, including LE dipstick results, were considered for entry into the model.

The odds ratios and associated confidence intervals for the logistic regression analysis were calculated using the coefficient and standard errors provided by the final logistic model. The p values associated with each factor were determined from the Wald χ^2 statistic.

Results

Patient Enrollment

One-hundred fifty patients were properly enrolled with complete data collection. Twenty recruitment attempts failed, primarily because of patients' unwillingness to undergo specimen collection. These represent 10.8% of all recruitment contacts. Fourteen enrollments were excluded because of inappropriate duplicate enrollment or incomplete data. Two patients were appropriately recruited twice. Only data from these patients' first enrollment were used in logistic regression analysis. Hereafter, patient contacts are referred to as patients. Patients who had, or who in the previous 30 days had had, dysuria or urethral discharge were classified as symptomatic (n = 50). One hundred patients did not have symptoms (asymptomatic group).

The participants represent 13.9% of potentially eligible male patients. Clinic patients diagnosed during the study period as having gonorrhea or nongonococcal urethritis were assumed to be symptomatic. Of those patients, 5.8% of whites and 4.6% of non-whites were recruited (χ^2 = 0.68, df = 1, p > 0.05). Of patients with all other diagnoses, 15.9% of non-whites but only 6.3% of whites were recruited (χ^2 = 23.8, df = 1, p < 0.0005).

Table 1. Sexual and Sexually Transmitted Disease Histories

	Patient category				
	Symptomatic (n = 48)			Asymptomatic (n = 100)	
Characteristic	n	(%)	p[a]	n	(%)
First intercourse <12 years	9	(19)	0.65	22	(22)
<2 partners prior month	26	(54)	0.02	73	(74)[b]
≥5 partners lifetime	42	(88)	0.48	83	(83)
Used condom prior month	17	(37)[c]	0.31	28	(29)
Ever used condom	41	(85)	0.02	68	(68)
Recent STD exposure	14	(29)	0.03	14	(14)
Ever had STD	27	(52)	0.05	35	(35)

[a]Denotes p value for χ^2 analysis.
[b]n = 99.
[c]n = 45.

Patient Characteristics

Mean ages of the patient groups were: asymptomatic, 19.2 (SD = 1.2; range, 18–24) years; symptomatic, 19.0 (SD = 1.1; range, 18–20) years (p > 0.05, unpaired Student's t test). Fewer whites were symptomatic (36% versus 14%; χ^2 = 9.14, df = 1, p = 0.002). All patients were heterosexual. Their sexual and STD histories are summarized in Table 1.

Culture Results and LE Dipstick Characteristics

Culture results for *N. gonorrhoeae* and *C. trachomatis* are compared to dipstick results in Table 2. Patients

Table 2. Cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

	Symptomatic patients[a] (n = 50)[b] LE dipstick[d]		Asymptomatic patients (n = 100)[c] LE dipstick[d]	
Organism cultured	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)
N. gonorrhoeae	16 (32)	7 (14)	3 (3)	2 (2)
C. trachomatis	4 (8)	5 (10)	1 (1)	8 (8)
Neither	6 (12)	15 (30)	3 (3)	84 (84)

[a]Patients with symptoms were more likely to have a positive dipstick (χ^2 = 36.72, df = 1, p < 0.0005) and to have a positive culture for one or both organisms (χ^2 = 33.48, df = 1, p < 0.0005).
[b]One symptomatic patient with a positive dipstick had positive cultures for both *N. gonorrhoeae* and *C. trachomatis*; two symptomatic patients with negative dipsticks had positive cultures for both organisms.
[c]One asymptomatic patient with a positive dipstick had positive cultures for both *N. gonorrhoeae* and *C. trachomatis*.
[d]LE dipstick, leukocyte esterase dipstick.

Table 3. Validity and Predictive Values

	Validity and predictive values positive (PVP) and negative (PVN)			
	Sensitivity (95% CL)	Specificity (95% CL)	PVP (95% CL)	PVN (95% CL)
Dipstick and symptoms compared with culture[a] (all patients, n = 150)				
LE dipstick[b]	0.55 (0.38, 0.71)	0.92 (0.84, 0.97)	0.72 (0.53, 0.87)	0.85 (0.76, 0.91)
Symptoms	0.69 (0.52, 0.83)	0.80 (0.71, 0.88)	0.58 (0.43, 0.72)	0.87 (0.78, 0.93)
Dipstick compared with culture (symptomatic patients, n = 50)				
NG[c] and/or CT[d]	0.66 (0.45, 0.83)	0.71 (0.47, 0.89)	0.76 (0.54, 0.91)	0.60 (0.38, 0.79)
NG[c]	0.70 (0.47, 0.87)	0.67 (0.46, 0.84)	0.64 (0.42, 0.83)	0.72 (0.50, 0.88)
CT[d]	0.44 (0.14, 0.79)	0.49 (0.32, 0.65)	0.16 (0.05, 0.36)	0.80 (0.59, 0.94)
Dipstick compared with culture (asymptomatic patients, n = 100)				
NG[c] and/or CT[d]	0.31 (0.09, 0.62)	0.97 (0.90, 0.99)	0.57 (0.18, 0.91)	0.90 (0.82, 0.96)
NG[c]	0.60 (0.14, 0.95)	0.96 (0.88, 0.99)	0.43 (0.09, 0.82)	0.98 (0.92, 1.00)
CT[d]	0.11 (0.00, 0.49)	0.93 (0.86, 0.98)	0.14 (0.00, 0.58)	0.91 (0.83, 0.97)

[a]Positive culture for *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*.
[b]LE dipstick, leukocyte esterase dipstick.
[c]*N. gonorrhoeae*.
[d]*C. trachomatis*.

with symptoms were more likely to have a positive dipstick reading (χ^2 = 36.72, df = 1, $p < 0.0005$) and to have a positive culture for one or both organisms (χ^2 = 33.48, df = 1, $p < 0.0005$). The LE dipstick and the clinical presentation are compared in Table 3. The dipstick predictive value positive (PVP = 0.72) was a slightly better predictor of a positive culture than was the presence of symptoms (PVP = 0.58). Asymptomatic non-whites were no more likely than whites to have a positive dipstick (χ^2 = 0.284, df = 1, p = 0.594) or a positive culture (χ^2 = 0.001, df = 1, p = 0.971). The same was true for symptomatic patients (dipstick, χ^2 = 0.166, df = 1, p = 0.684); culture, χ^2 = 0.766, df = 1, p = 0.381).

The validity and predictive values of the dipstick are classified by patient group and organism in Table 3. Overall the dipstick was more sensitive but less specific in symptomatic patients. In each patient group, the dipstick was more sensitive in detecting, and a better positive predictor of, a positive culture for gonorrhea than *Chlamydia*. For several of these values, the confidence limits overlapped.

Logistic Regression

Culture results were used to classify patients as infected or not infected for the dependent variable. Independent variables were (a) positive LE dipstick, (b) prior STD, (c) white race, (d) STD exposure in the previous month, (e) age younger than 12 years at first intercourse, (f) five or more lifetime sexual partners, (g) more than one recent sexual partner, (h) condom use in prior month, and (i) use of condoms at least once. Results are shown in Table 4. For symptomatic patients, having a positive LE dipstick and four additional variables contributed to the increase in the probability of a positive culture. Only the LE dipstick entered and remained in the model for asymptomatic patients.

Discussion

In heterosexual young adult males with urethral discharge and/or dysuria, a positive LE dipstick and the presence of four additional variables each independently increased the probability of a positive urethral culture for gonorrhea or *Chlamydia*. These variables included a history of recent STD exposure, ever having used condoms, five or more lifetime sexual part-

Table 4. Stepwise Logistic Regression Analysis

Independent variable	Odds ratio	95% CL	p[a]
Symptomatic patients (n = 48)			
Positive LE dipstick	7.0	1.0, 48.7	0.02
STD exposure	27.3	2.1, 358.9	0.01
Condom use	28.6	1.7, 469.9	0.02
≥5 lifetime sexual partners	21.4	0.9, 501.9	0.06
≥2 recent sexual partners	5.4	0.9, 32.7	0.06
Asymptomatic patients (n = 100)			
Positive LE dipstick	12.2	2.3, 63.1	<0.01

CL, confidence limits; LE, leukocyte esterase; STD, sexually transmitted disease.
[a]p value for Wald χ^2 statistic.

ners, and more than one sexual partner in the past month. In patients without symptoms of urethritis, however, only a positive dipstick was predictive of a positive urethral culture.

Having ever used a condom was associated with an increased likelihood of infection in symptomatic patients. Having had more than one recent, and five or more lifetime, sexual partners were also predictive of infection. We considered the possibility that patients who have had more sexual partners perceive themselves (or their partners) to be at risk for STD and are more likely to use condoms, at least occasionally. However, in symptomatic males, there was no association between "ever" use of condoms and either having had five or more lifetime partners, or more than one recent partner ($p > 0.05$). The association between condom use and infection in symptomatic patients is, thus, not readily explained.

The validity and predictive values of the LE dipstick in symptomatic males were lower than expected. The PVP of the dipstick (0.72) was slightly higher than the PVP of symptoms (0.58). The confidence intervals overlapped, suggesting that this difference is not significant. The negative predictive values of the LE dipstick and of symptoms were virtually identical. In both symptomatic and asymptomatic patients, the dipstick was more sensitive in detecting, and a better positive predictor of, gonorrhea than *Chlamydia*. For several of these values, the confidence limits overlapped.

The specificity and predictive values of the dipstick in asymptomatic patients were quite similar to those reported by others (8,9). Inadequate sampling techniques may have contributed to the relatively low proportion of positive *Chlamydia* cultures in the present study. However, the prevalence of *C. trachomatis* in females attending our clinic (31,32) has been consistently lower than that reported in most studies of adolescent females (5). This may reflect regional differences in the prevalence of *Chlamydia*.

The dipstick's sensitivity for asymptomatic patients in the present study (0.31) was considerably lower than the value of 0.72 in a larger study (8). In that study, however, almost one-half of those who had undergone urinary screening refused culture. The authors calculated that, the sensitivity of the dipstick would have been .56, had the prevalence of culture-documented infection in the non-participants been the same as that in the participants (8). This falls within the broad confidence limits (0.09, 0.62) of the present study.

The low sensitivity of the dipstick in the present study might reflect the inexperience of some examiners. Other authors have suggested that suboptimal interobserver reliability might affect the validity of the dipstick (8).

"False" positive dipsticks may have resulted from pyuria of other etiologies including: renal disease, urinary tract infection (33), trichomonas and *Ureaplasma urealyticum*. The LE dipstick may appear falsely positive because *Chlamydia* cultures are less than 100% sensitive (15). Finally, the dipstick itself may have been the source of error, in yielding a positive reading in patients who were not infected.

Although the refusal rate was low, only 14% of potentially eligible patients were recruited for the study. This convenience sample reflected clinic patient flow and recruiter availability rather than a systematically biased sample. Asymptomatic non-white patients were recruited more than twice as often as whites. This potentially represented recruitment bias. However, asymptomatic non-white males were no more likely to be infected than were asymptomatic white patients. Race did not enter into the regression equation for predicting a positive urethral culture. Thus, oversampling of non-white patients does not appear to have affected study results.

At present, the LE dipstick is the only available noninvasive screening instrument for asymptomatic urethral infection. Its low sensitivity in this study—particularly for *Chlamydia*—and its moderately low PVP in several studies (8,9), are offset clinically by its high specificity and PVN. Although predictive values vary with the prevalence of infection in a given population, the prevalence of asymptomatic infection has been similar in different cohorts (8,9). The prevalence is relatively low, so that a screening test would need to be quite sensitive to have a high PVP. The small number of infected patients in this study limits its generalizability. Most importantly, there appears to be a 90% (present study) to 96% (8) likelihood that an asymptomatic patient with a negative dipstick will have negative cultures. The PVP of the dipstick is not high enough to justify treatment of asymptomatic patients based on a positive dipstick alone.

The dipstick can be cost saving, both as a screening instrument prior to culture (8) or as a substitute for diagnostic testing (34). If used as a surrogate test for *C. trachomatis*, however, it would not lower overall costs (including those of resultant pelvic inflammatory disease in females) unless the prevalence of *Chlamydia* were higher than 21% (34).

In symptomatic patients, the PVN of the dipstick is relatively low. These patients should be evaluated using Gram-stain and diagnostic testing in accor-

dance with current recommendations (35) regardless of dipstick results. The LE dipstick should be used to screen sexually active adolescent and young adult males. Patients with positive dipsticks should undergo conventional culture testing. The sexual and STD history does not assist in predicting positive culture(s) in asymptomatic patients.

This study was funded in part by Presbyterian Health Foundation (Oklahoma City, OK) grant no. 73.

Doxycycline and erythromycin were provided at no cost by Parke-Davis, Inc.

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